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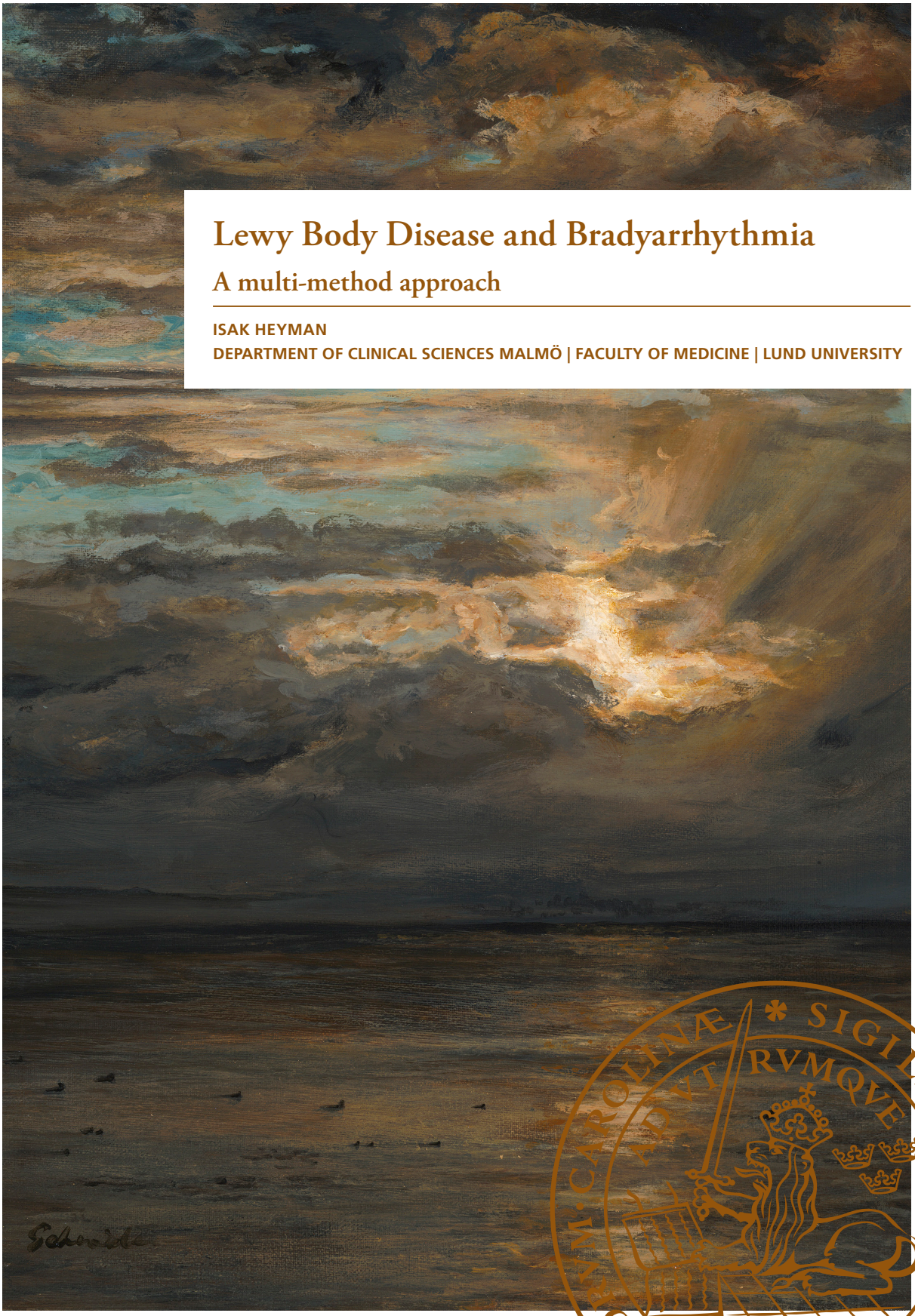

Lewy Body Disease and Bradyarrhythmia

A multi-method approach

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Abstract:

Dementia with Lewy bodies (DLB) and Parkinson's disease are collectively called Lewy body disease (LBD), reflecting their shared alpha-synuclein neuropathology. LBD may involve cardiac autonomic nerves, theoretically predisposing to bradyarrhythmia. Such arrhythmias (e.g. sick sinus syndrome) often manifest as syncope, which is also a feature of DLB. This thesis aimed to explore if bradyarrhythmia could represent an under-recognized and manageable feature of DLB.

Paper I (qualitative case study, n=4) used repeated interviews to explore how individuals with DLB experienced daily life following pacemaker implantation to manage their symptoms of bradyarrhythmia. The participants experienced less syncope, increased wakefulness and improved physical stamina following pacemaker implantation, which was perceived to have increased their overall well-being.

Paper II (cross-sectional study, n=28) investigated the prevalence of undetected bradyarrhythmia in individuals with DLB by ambulatory heart rate monitoring. Three (10.7%) participants were diagnosed with sick sinus syndrome, of whom two received pacemaker implants. Most participants had features suggestive of cardiovascular autonomic dysfunction.

Paper III (case-control study, n=73,619) investigated the occurrence of bradyarrhythmia requiring pacemaker implantation in individuals with DLB compared to other dementia subtypes. Pacemaker implantation due to sick sinus syndrome was more common in individuals with DLB compared to individuals with Alzheimer's disease (2.2% versus 1.5%, p=0.008). An association between sick sinus syndrome and DLB (odds ratio, 1.49; 95% confidence interval: 1.11–2.01) was observed in adjusted models.

Paper IV (cross-sectional study, n=95) investigated the prevalence of cardiac alpha-synuclein pathology in various neuropathological categories of LBD, also at a presymptomatic stage. Cardiac alpha-synuclein pathology was evident in 67 of 72 (93.1%) individuals with LBD (even early in the disease process). Eight (11.1%) individuals with LBD had sick sinus syndrome.

In conclusion, our findings suggest that bradyarrhythmia (i.e. sick sinus syndrome) represents an under-recognized and potentially manageable feature of DLB.

Key words: alpha-synuclein, bradyarrhythmia, dementia with Lewy bodies, Lewy body disease, sick sinus syndrome.

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To my wife Ylva

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Paper II

Heyman I, Persson T, Haglund M, & Londos E. Exploring the prevalence of undetected bradyarrhythmia in dementia with Lewy bodies. Clinical autonomic research. 2023;33(4): 433–442. DOI: 10.1007/s10286-023-00962-w

Paper III

Heyman I, Haglund M, Eriksdotter M, & Londos E. Sick sinus syndrome and high-degree atrioventricular block in dementia with Lewy bodies and other dementia subtypes: A study of ≈ 73,000 patients with dementia. Alzheimer's & dementia (New York, N. Y.). 2025; 11(1), e70053. DOI: 10.1002/trc2.70053

Paper IV

Heyman I, Londos E, Englund E. Cardiac alpha-synuclein is evident in various neuropathological categories of Lewy body disease. Unpublished manuscript.

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Thesis at a glance

Paper and Approach	Aims	Methods	Conclusion
I **Qualitative approach**	To explore how people with DLB experience daily life following a pacemaker implant to manage associated symptoms of bradyarrhythmia.	Two men with DLB and their wives were recruited for repeated interviews within a year after receiving a pacemaker implant to manage sick sinus syndrome.	Reduction in syncope, increased wakefulness and improved physical stamina following pacemaker implantation were perceived to have increased their overall well-being.
II **Clinical approach**	To explore the prevalence of undetected bradyarrhythmia in people with DLB.	Twenty-eight individuals with DLB were enrolled to conduct ambulatory heart rate monitoring and examinations of cardiac autonomic dysfunction.	The prevalence of SSS was notably higher compared to estimates in the general population.
III **Registry-based approach**	To investigate the occurrence of SSS and HAVB in patients with DLB compared to other dementia subtypes.	The Swedish Dementia Registry was used to identify 73,619 individuals diagnosed with dementia. Pacemaker implantation data were obtained from the Swedish Pacemaker Registry.	SSS (but not HAVB) was more common in individuals with DLB compared to those with Alzheimer's disease. SSS (but not HAVB) was associated with DLB in adjusted models.
IV **Neuropathological approach**	To elucidate the prevalence of cardiac alpha-synuclein pathology in various neuropathological categories of Lewy body disease.	Eighty-two individuals with suspected Lewy body disease and 18 assumed controls were included at autopsy. Brain and heart samples were checked for alpha-synuclein pathology.	Cardiac alpha-synuclein pathology was evident in most individuals with Lewy body disease, even early in the disease process.

DLB, dementia with Lewy bodies; SSS, sick sinus syndrome; HAVB, high-degree atrioventricular block

Author's contribution to the papers

Paper I–II

Partly designed the projects. Partly wrote ethics applications. Collected and analyzed data. Wrote the manuscripts. Formatted and submitted the manuscripts. Responded to reviewers' comments.

Paper III

Partly designed the project. Wrote the ethics application. Retrieved and analyzed registry data. Wrote the manuscript. Formatted and submitted the manuscript. Responded to reviewers' comments.

Paper IV

Partly designed the project. Partly wrote the ethics applications. Partly collected tissue samples and analyzed data. Wrote the manuscript.

Abbreviations and acronyms

α-syn	Alpha-synuclein
DLB	Dementia with Lewy bodies
ECG	Electrocardiogram
HAVB	High-degree atrioventricular block
LBD	Lewy body disease
MIBG	Metaiodobenzylguanidine
RBD	Rapid-eye-movement sleep behavior disorder
RMSSD	Root mean square of successive differences
SSS	Sick sinus syndrome
SveDem	Swedish Dementia Registry

Populärvetenskaplig sammanfattning

Demens innebär stort lidande för drabbade och anhöriga. Världshälsoorganisationen räknar med att antalet människor med demens i världen kommer tredubblas till 2050. Efter Alzheimers sjukdom och vaskulär demens, är Lewy Body-demens den tredje vanligaste orsaken till demens bland äldre.

Lewy body-demens orsakas av skadliga proteinansamlingar i hjärnans nervceller, vilket påverkar hjärnans funktioner. Dessa proteinansamlingar ses också vid Parkinsons sjukdom och dessa två sjukdomar benämns ofta gemensamt som Lewy body-sjukdom.

Vid Lewy body-demens är det vanligt att vara mycket trött, ha sämre rumsuppfattning och svårigheter att omvandla tanke till handling. Minnesproblematiken kommer ofta senare. Andra vanliga kännetecken är stela och långsamma rörelser, synhallucinationer och störd drömsömn. Sjukdomen kan också orsaka blodtrycksfall, svimningar och att man ramlar.

De skadliga proteinansamlingarna vid Lewy Body-sjukdom påverkar inte bara hjärnan, utan även nerver till andra organ som urinblåsan och tarmarna, vilket kan leda till urininkontinens och förstoppning. Även hjärtats nerver påverkas, men idag vet vi inte om dessa individer får några symptom av detta. I teorin skulle dock skador på hjärtats nerver kunna leda till onormalt långsam hjärtfrekvens.

Tidigare studier har antytt att Lewy Body-sjukdom kan ge liknande symtom som ses vid tillstånd som innebär en onormalt långsam hjärtfrekvens, däribland ett tillstånd som kallas sjuk sinusknuta. Sjuk sinusknuta och andra tillstånd som ger en onormalt långsam hjärtfrekvens ger vanligtvis symptom som yrsel, trötthet, svimningar och att man ramlar. Om onormalt långsam hjärtfrekvens ger mycket symptom kan det ofta behandlas med en pacemaker. Sjuk sinusknuta är ett av de vanligaste tillstånden som ger onormalt långsam hjärtfrekvens, och drabbar ungefär 0,17% av hjärtsjuka personer över 65 år. Tillståndet diagnosticeras vanligen genom långtidsövervakning med EKG.

Denna avhandling syftade till att undersöka om onormalt långsam hjärtfrekvens (till exempel sjuk sinusknuta) skulle kunna vara en förbisedd och behandlingsbar aspekt av Lewy body-sjukdom. Avhandlingen består av fyra studier.

I den första studien intervjuade vi två personer med Lewy Body-demens före och efter pacemakerinsättning för sjuk sinusknuta, tillsammans med sina fruar. Paren upplevde att pacemakern minskade benägenheten att falla, vilket ökade en känsla av kontroll i deras vardag. De upplevde även en klarare tankeförmåga, vilket

underlättade socialt umgänge. Intervjuerna gav också en inblick i de vardagliga utmaningar som Lewy Body-demens innebär.

I den andra studien genomgick 28 personer med Lewy Body-demens långtidsövervakning av hjärtfrekvensen med EKG i hemmet. Av dessa diagnostiserades tre (10,7%) med sjuk sinusknuta, varav två fick pacemaker för att minska symtom förknippade med långsam hjärtfrekvens. I studien var alltså förekomsten av sjuk sinusknuta märkbart högre än de 0,17% som vanligen anges i den äldre hjärtsjuka befolkningen.

I den tredje studien samkörde vi svenska pacemakerregistret med svenska demensregistret för att undersöka hur många personer med en demensdiagnos i Sverige som också fått en pacemaker på grund av långsam hjärtfrekvens. Totalt ingick 73 619 personer med olika demensdiagnoser. Studien visade att pacemaker på grund av sjuk sinusknuta var vanligare vid Lewy Body-demens än vid Alzheimers sjukdom.

I den fjärde studien undersökte vi vävnadsprover från hjärta och hjärna hos 95 avlidna personer för att med mikroskop leta efter de skadliga proteinansamlingar som orsakar Lewy Body-sjukdom. Majoriteten av dessa 95 personer misstänktes ha Lewy body-demens eller Parkinsons sjukdom. Totalt konstaterades vi att 72 personer hade Lewy body-sjukdom, allt från lindriga fynd av proteinansamlingar i hjärnan som inte antas orsaka symtom till mer uttalade fynd in hjärnan som orsak till demens. Totalt hade 67 av dessa 72 (93,1%) personer även proteinansamlingar i hjärtats nerver. Åtta av dessa 72 (11.1%) personer hade även fått diagnosen sjuk sinusknuta när de levde. Intressant nog hade även 8 av 18 (44.4%) personer utan Lewy body-sjukdom proteinansamlingar i hjärtats nerver. Studien visade således att hjärtats nerver kan drabbas tidigt vid Lewy Body-sjukdom.

Sammantaget pekar avhandlingen åt att de skadliga proteinansamlingar som ses vid Lewy Body-sjukdom är vanligt förekommande i hjärtat och sannolikt påverkar hjärtats funktion, vilket kan leda till onormalt långsam hjärtfrekvens. Detta kan möjligen bidra till trötthet, svimningar och att man ramlar, och där pacemaker kan ge en viss symptomlindring.

Om resultaten bekräftas kan riktlinjerna för utredning och behandling av personer med Lewy body-sjukdom komma att ändras, till exempel genom mer frikostig långtidsövervakning med EKG i hemmet för att hitta och behandla samtidig onormalt långsam hjärtfrekvens.

Introduction and background

Dementia

The word ‘dementia’ is derived from the Latin ‘*demens*’, which roughly translates to ‘being out of one’s mind’. A more accurate and less stigmatizing term to describe this condition would be ‘cognitive disorder’. However, for simplicity the term ‘dementia’ will be used to discuss this concept throughout this thesis.

As a clinical syndrome, dementia is defined by a progressive and persistent decline in one or several cognitive domains sufficient to interfere with individuals’ functional independence[1]. These domains are typically categorized as memory, complex attention, social cognition, language, executive function and visuo-perceptual function[1].

In 2015, the World Health Organization reported that dementia is an underdiagnosed condition globally, which is often recognized in its advanced stages, when it is difficult to preserve functional independence[2]. It is estimated that a new individual is diagnosed with dementia approximately every 4 seconds. From 2015 to 2050, the number of individuals living with dementia is predicted to triple globally[2]. Importantly, dementia not only impacts the lives of diagnosed individuals, but also their close family members[2].

In public, the word ‘dementia’ is often used interchangeably with ‘Alzheimer’s disease’, as it is the most common underlying cause of dementia. However, dementia can result from various other diseases, including vascular dementia, frontotemporal dementia and dementia with Lewy bodies (DLB)[1]. Mixed forms are also common, especially Alzheimer’s disease with concurrent vascular lesions[1].

Among older individuals, DLB is widely recognized as the second most common neurodegenerative cause of dementia globally, after Alzheimer’s disease[3,4].

Dementia with Lewy bodies

Historical perspective

While working at the University of Munich during the early 1900s, Emil Kraepelin and Alois Alzheimer discovered the neuropathological hallmarks associated with Alzheimer's disease[5]. During the early 1910s, Friedrich Lewy, a young neurologist at the University of Munich, discovered neuronal inclusion bodies in the dorsal vagal nucleus and substantia innominata in the brains of individuals with clinical Parkinson's disease[5]. Parkinson's disease was clinically defined as 'paralysis agitans' by James Parkinson a century earlier. However, the neuropathology of Parkinson's disease had been unknown until Lewy's discovery[6].

A few years after Lewy's discovery, neuropathologist Konstantin Tretiakoff related his findings of these inclusion bodies in the substantia nigra with Parkinson's disease[5]. He would eponymously call them 'Lewy bodies' after their original discoverer. However, Lewy and Tretiakoff disagreed on the sites where these inclusion bodies would cause Parkinson's disease[5]. During the 1930s, Rolf Hassler confirmed the substantia nigra as the main site of neurodegeneration seen in Parkinson's disease[7].

During the early 1960s, Dutch scientists described the widespread occurrence of Lewy bodies in the autonomic nervous system among individuals with Parkinson's disease[8]. Meanwhile, Haruo Okazaki presented neuropathological examinations of two autopsy cases of individuals with dementia and parkinsonism, and revealed widespread findings of Lewy bodies in their brains[9]. Furthermore, in 1976, Japanese psychiatrist Kenji Kosaka described an autopsy case of Lewy bodies in the brain of an individual with unclassifiable dementia[10]. However, such findings were thought to be rare.

Following advances in immunostaining during the 1980s, scientists from Japan, the United States and Europe discovered Lewy bodies in their autopsies of individuals with dementia[6]. When reviewing these individuals' medical records, they observed a consistent pattern of clinical features, including visual hallucinations, fluctuating cognition and parkinsonism[11]. However, the influence of Lewy body co-pathology in Alzheimer's disease was still debated globally and many names were given to this 'new' type of dementia. These names would sometimes emphasize the presumed importance of Alzheimer's disease co-pathology, including 'diffuse Lewy body disease', 'senile dementia of Lewy body type' and 'Lewy body variant of Alzheimer's disease'[6].

In 1995, the newly formed International DLB Consortium established an international agreement to use the term 'dementia with Lewy bodies' to describe this type of dementia. The first diagnostic criteria for DLB were then established in

1996[11]. In 1997, alpha-synuclein (α-syn) was discovered to be the main component of Lewy bodies[12].

Terms and conditions

The clinical syndrome of DLB is caused by neurotoxic accumulations of the misfolded protein α-syn in the central and peripheral nervous system[13]. Syndromes caused by α-syn pathology are collectively known as synucleinopathies. Besides DLB, other synucleinopathies include Parkinson's disease (with or without dementia), multiple system atrophy, rapid-eye-movement sleep behavior disorder (RBD) and pure autonomic failure[14] (see Figure 1).

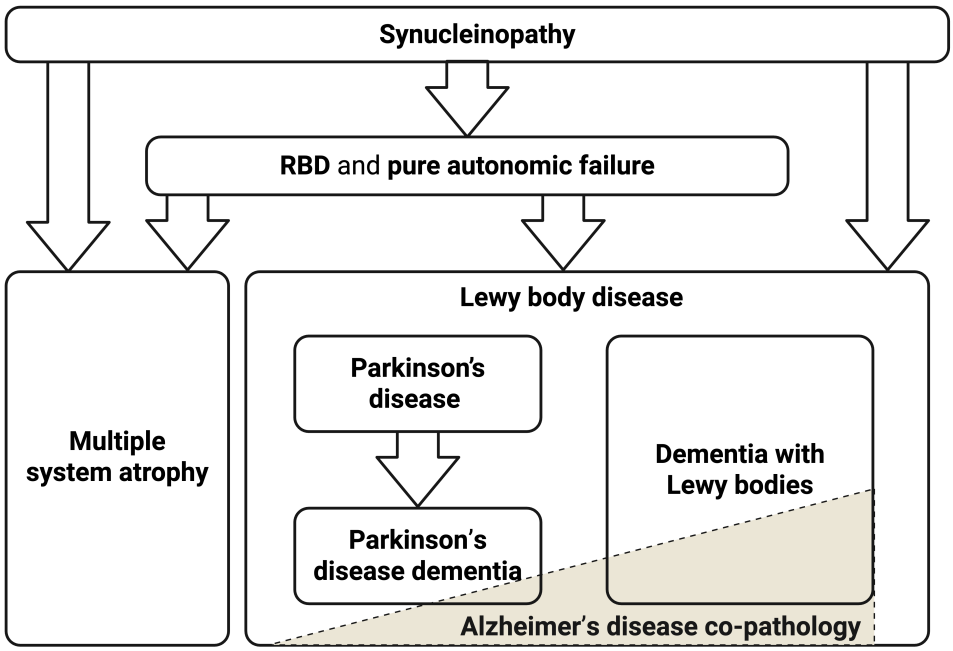

Figure 1. Illustration of clinical diseases caused by alpha-synuclein pathology and their interconnections. RBD, rapid-eye-movement sleep behavior disorder. Created in BioRender.com.

Due to their overlapping features and similar underlying α-syn pathology, Parkinson's disease and DLB are often collectively referred to as Lewy body disease (LBD), while the α-syn pathology of multiple system atrophy differs[14]. LBD and multiple system atrophy are sometimes preceded by RBD or pure autonomic failure[15,16]. When an individual with RBD or pure autonomic failure develops additional symptoms associated with LBD or multiple system atrophy, this is known as phenoconversion[15,16].

Alzheimer's disease co-pathology is common and seems to be more prevalent among individuals with DLB compared to those with Parkinson's disease, with up to 89% of individuals with DLB having some degree of Alzheimer's disease co-pathology[17].

Epidemiology

Today, DLB is widely recognized as the second most common neurodegenerative cause of dementia after Alzheimer's disease among the older adults[6]. The estimated prevalence of DLB among individuals with dementia varies between 2.2–9.6% in clinical studies[4,18-21] and 15–20% in neuropathological research[11]. These differences are likely due to clinical underdiagnosis and misdiagnosis of DLB[4]. Interestingly, population-based post-mortem studies suggest that 9% of individuals aged 50 years or older and one-third of those aged 65 years or older exhibit some degree of α-syn pathology in the central and/or peripheral nervous system[22,23].

The average age of onset of cognitive symptoms among individuals with DLB is between 70 and 80 years[24,25]. Overall mortality after diagnosis seems higher among individuals with DLB compared to those with Alzheimer's disease[26,27]. A large English cohort study showed that survival from first presentation with cognitive symptoms was 3.72 versus 6.95 years in individuals with DLB compared to those with Alzheimer's disease[24]. Furthermore, women tend to live slightly longer when adjusted for comorbidities and prescription of antipsychotic drugs[24]. DLB seems to be more common among men, but this may depend on geographical location, a higher degree of Alzheimer's disease co-pathology among women and/or differences in clinical presentation making DLB diagnoses more uncertain[28].

Clinical features and biomarkers

Clinical diagnosis

The latest consensus criteria for clinical diagnosis of DLB were issued in 2017 by the International DLB Consortium[29] (see Figure 2). These criteria are based on global consensus regarding common dementia features, core clinical features and indicative biomarkers of dementia. Additionally, the presence of supportive features and biomarkers may be helpful in recognising individuals with DLB but lack diagnostic specificity[29]. However, a diagnosis of DLB can only be fully ascertained upon post-mortem neuropathological verification of disease-specific α-syn pathology[29].

As of 2017, the consensus criteria had incorporated four core clinical features and three indicative biomarkers. For individuals with dementia, probable DLB (i.e. higher degree of certainty) may be diagnosed by the presence of two or more core

clinical features, or one core clinical feature and one or more indicative biomarkers. Possible DLB (i.e. lower degree of certainty) may be diagnosed by either one core clinical feature or one indicate biomarker alone[29].

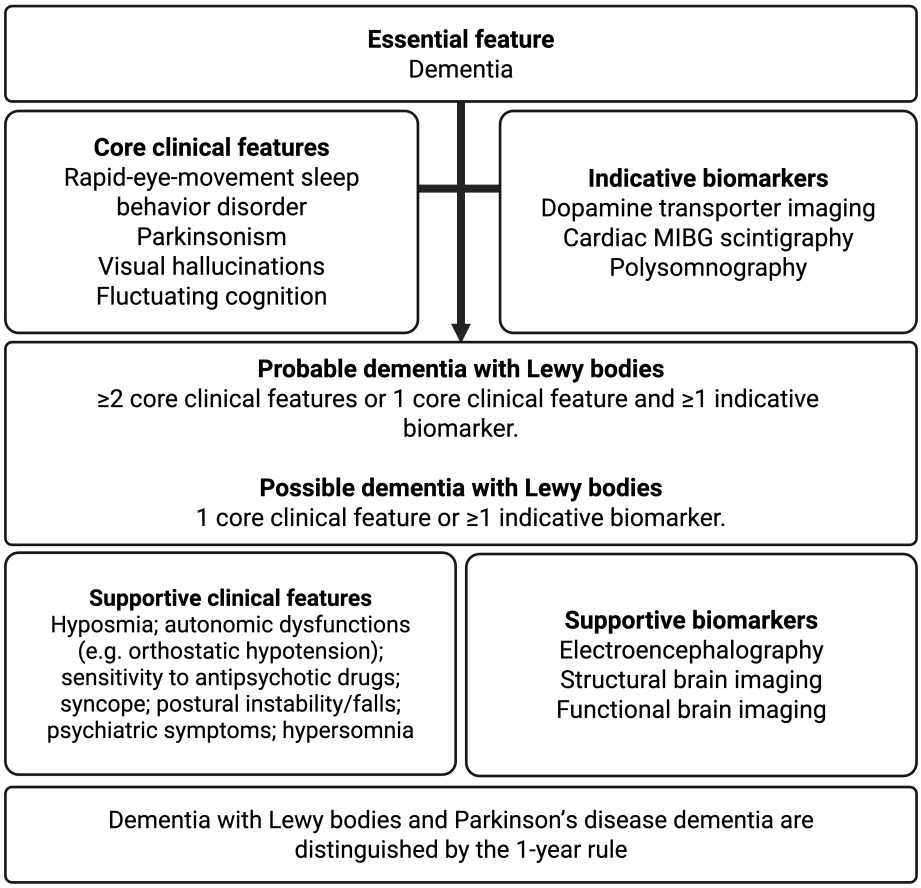

Figure 2. Latest consensus criteria (2017) for dementia with Lewy bodies. MIBG, metaiodobenzylguanidine. Created in BioRender.com.

The chronological onset of core clinical features can vary among individuals and between men and women[25]. For example, RBD seems to precede cognitive impairment for a longer period in men, while visual hallucination seems to occur among women earlier in the disease course[25]. Furthermore, if core clinical features and indicative biomarkers are present for a person with mild cognitive impairment, the term 'mild cognitive impairment with Lewy bodies' is used[30].

In addition, prodromal DLB is a pre-dementia stage characterized by early features suggesting the potential future development of DLB, which includes not only mild

cognitive impairment but also various non-cognitive clinical features, such as motor symptoms, sleep disorders, autonomic dysfunction and neuropsychiatric disturbances[30].

Furthermore, Parkinson's disease dementia is distinguished from DLB if parkinsonism occurs before 1 year prior to the onset of cognitive symptoms, a framework dubbed the '1-year rule'[29]. Likewise, the 1-year rule may be helpful in distinguishing between mild cognitive impairment with Lewy bodies and Parkinson's disease with mild cognitive impairment[30]. One-fourth of individuals with Parkinson's disease develop Parkinson's disease dementia within a decade[31].

Essential feature of dementia

Dementia is essential when diagnosing DLB and is caused by neurodegeneration of cortical and subcortical structures of the brain, due to α-syn pathology. In DLB, this neurodegeneration causes attention and executive dysfunctions, as well as visuo-perceptual impairments. These cognitive domains are usually more affected than short-term memory loss, at least early in the disease course[29]. Some differences in the presentation of cognitive symptoms may be attributed to co-pathologies, such as Alzheimer's disease and/or vascular lesions[29].

Rapid-eye-movement sleep behavior disorder

As a parasomnia characterized by the absence of normal sleep paralysis when dreaming[32], RBD often precedes other core features by several years or even decades and serves as a significant indicator of phenoconversion to clinical DLB, Parkinson's disease or multiple system atrophy[14,25]. About half of individuals with RBD are estimated to phenoconvert to either DLB or Parkinson's disease within a decade[15]. RBD is believed to originate from α-syn pathology affecting specific areas of the brainstem responsible for regulating muscle paralysis during rapid-eye-movement sleep[32].

Fluctuating cognition

Spontaneous fluctuations in attention and alertness are also characteristics of DLB that persist throughout the progression of the disease[33]. These cognitive fluctuations occur in about 70% of individuals with DLB and can range in duration from a few seconds up to several weeks[33]. Cognitive fluctuations do not typically follow a strict daily pattern, and differs from the predictable night-time variations seen in other forms of dementia (e.g. Alzheimer's disease and vascular dementia)[34]. The cause of cognitive fluctuations in LBD could be due to disturbed 'switching' of the brain that upholds an otherwise continuous pattern/cycle of sleep and wakefulness[35]. This is likely due to deficits in the cholinergic and noradrenergic systems in the brain caused by α-syn pathology[35].

Parkinsonism

Spontaneous features of parkinsonism in individuals with DLB are usually less prominent compared to the motor symptoms seen among individuals with Parkinson's disease[29]. Parkinsonism is caused by α-syn pathology affecting the substantia nigra, causing dopaminergic deficits[29]. By the time cognitive impairment in DLB is identified, it is estimated that about one-fourth of men and one-fifth of women have parkinsonism[25], which is a common cause of falls among individuals with DLB[36].

Visual hallucinations

Visual hallucinations are present in up to 70% of individuals with probable DLB and may occur early in the disease course, especially among women[25,37]. Moreover, visual hallucinations are a common non-motor feature affecting approximately 40% of individuals with Parkinson's disease[38]. Visual hallucinations might be caused by a combination of impaired sensory input (due to degeneration of neuronal tracts that connect the occipital and temporal lobes) and an over-reliance on abnormally constructed prior visual expectations[38-42].

Supportive features

Several clinical features may support a diagnosis of DLB in individuals with dementia, especially if persistent over time and in combination with each other. However, these features lack diagnostic specificity[30]. Supportive clinical features may sometimes present in prodromal DLB, sometimes preceding cognitive and motor symptoms by several decades[14]. Thus, they are often difficult to differentiate from other conditions. Two such features are hyposmia and constipation, caused by α-syn pathology in the olfactory bulb and enteric nerves, respectively. Other supportive features are caused by neurodegeneration of autonomic nerves resulting in autonomic dysfunction, including urinary incontinence, dysphagia and orthostatic hypotension[43]. Moreover, supportive features also include severe sensitivity to neuroleptics, excessive daytime sleepiness, transient episodes of unresponsiveness, syncope and repeated falls[29].

Indicative biomarkers

The current diagnostic framework distinguishes between clinical symptoms and disease biomarkers[29]. For DLB, biomarkers serve as objective indicators of neurodegeneration, but do not reliably confirm α-syn pathology. However, they may suggest dopaminergic or noradrenergic dysfunctions associated with α-syn pathology[29]. However, many studies of biomarkers lack neuropathological confirmation of specific dementia diagnosis and do not account for Alzheimer's disease co-pathology[44]. Additionally, the role of most biomarkers in prodromal DLB remains uncertain[45].

First, polysomnography may be used to confirm RBD. If RBD is confirmed for an individual with either dementia, parkinsonism or autonomic dysfunction, the predictive likelihood to determine the presence of underlying α-syn pathology is 98%[46]. Second, reduced dopamine transporter binding in the basal ganglia can be demonstrated with either single-photon emission computed tomography or positron emission tomography. The effectiveness of dopamine transporter imaging in differentiating DLB from Alzheimer's disease has a sensitivity and specificity of 78% and 90%, respectively[47].

Third, intravenously administered metaiodobenzylguanidine (MIBG) was first used in 1988 to assess cardiac sympathetic denervation in individuals with myocardial infarction using cardiac scintigraphy[48,49]. In 1994, cardiac sympathetic denervation was observed among individuals with Parkinson's disease[50]. In 2001, cardiac MIBG scintigraphy was described as a useful tool in differentiating DLB from Alzheimer's disease[51]. Cardiac MIBG scintigraphy has a sensitivity and specificity of 69% and 87%, respectively, for differentiating between DLB and Alzheimer's disease[52,53]. In subgroups of individuals with milder dementia, however, both sensitivity and specificity are equal to that of dopamine transporter imaging[52].

As an inactive analogue of the adrenergic blocking agent guanethidine, MIBG shares a similar molecular structure with noradrenaline[54]. As such, cardiac sympathetic denervation (as visualized by cardiac MIBG scintigraphy) is a biomarker of peripheral noradrenergic insufficiency. Post-mortem examinations have shown that the α-syn pathology of postganglionic cardiac sympathetic nerves results in decreased tyrosine hydroxylase immunoreactivity[54]. Tyrosine hydroxylase is an integral enzyme for noradrenaline synthesis.

Supportive biomarkers

Three additional biomarkers that may support a diagnosis of DLB are listed in the latest consensus criteria: (a) relative sparing of medial temporal lobe structures on structural brain imaging, (b) generalized low uptake or reduced occipital perfusion/metabolism using functional brain imaging and (c) prominent slow-wave activity observed using electroencephalography[29].

Disease heterogeneity

As emphasized above, individuals with DLB may experience various symptoms, including cognitive impairment, motor symptoms, psychiatric disturbances and autonomic dysfunctions[29]. As not everyone exhibits every symptom, DLB often presents as a highly heterogeneous disease (see Figure 3). Due to the varying disease presentation and fluctuating symptoms over time, it can be challenging for clinicians to ascertain the correct diagnosis[25]. Thus, most individuals with DLB may see multiple physicians across several appointments before receiving an accurate diagnosis[55]. Interestingly, an American survey found that 78% of individuals with

DLB were initially diagnosed with other conditions, including Parkinson's disease, Alzheimer's disease or mental illness[56]. Furthermore, as mentioned previously, the chronological onset of core clinical features seems to vary between men and women, adding another layer of diagnostic difficulty[25].

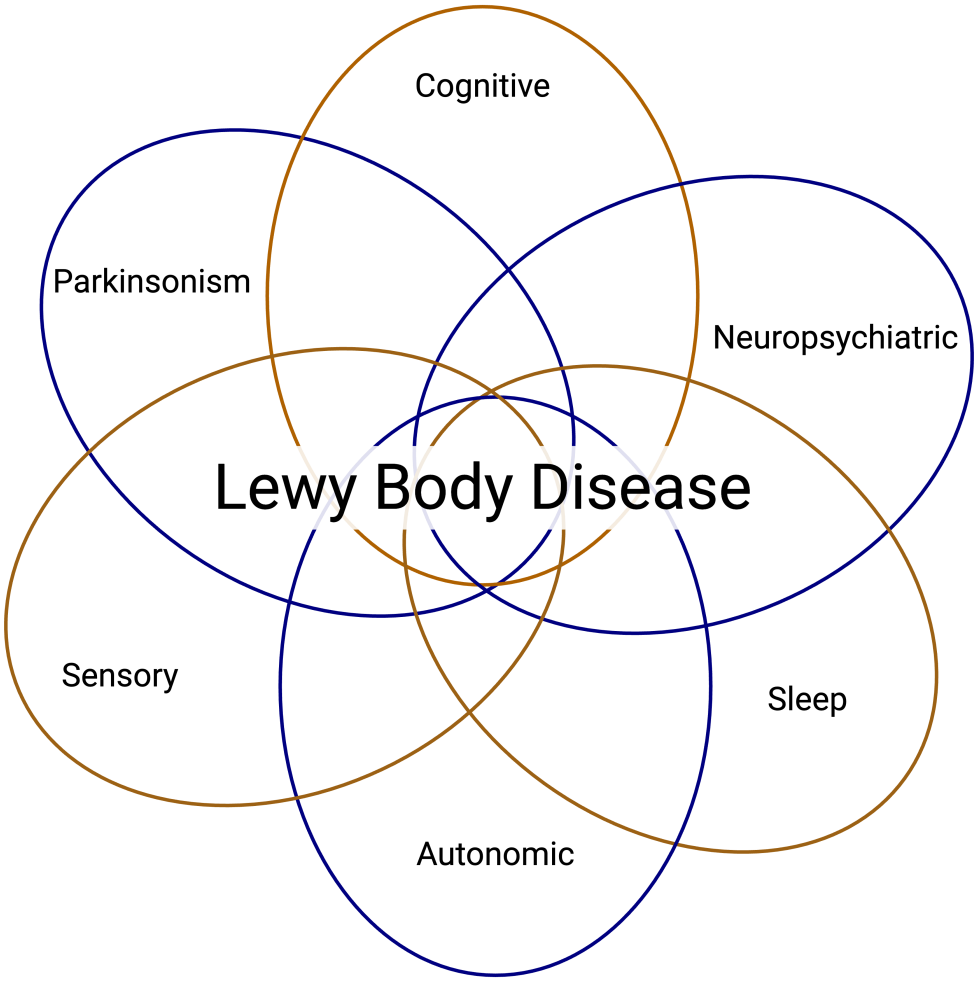

Figure 3. Illustration of the clinical heterogeneity of Lewy body disease. Created in BioRender.com.

Cardiovascular comorbidity

Both epidemiological and post-mortem studies have shown that individuals with DLB have comparable rates of cardiovascular comorbidity to individuals with Alzheimer's disease and cognitively unimpaired older controls[57-62]. However, some epidemiological studies suggest that ischaemic stroke is more common among

individuals with DLB compared to those with Alzheimer's disease and cognitively unimpaired controls[63,64]. Atrial fibrillation, a well-known cause of ischaemic stroke, might be more common among individuals with DLB compared to those with Alzheimer's disease[57,58,65]. Current evidence for Parkinson's disease does not support an increased risk of atrial fibrillation[66]; however, individuals newly diagnosed with Parkinson's disease seem to be at higher risk of ischaemic stroke compared to those without Parkinson's disease[67].

Therapy and management

Pharmacological therapies

No disease-modifying therapies are currently available for synucleinopathies. For individuals with DLB, symptomatic therapies include cholinesterase inhibitors and memantine, both of which are also used to treat Alzheimer's disease[29]. Cholinesterase inhibitors act by inhibiting the reuptake of acetylcholine in neurons, which increases their duration of action in cholinergic receptors[68]. Memantine is a glutamate receptor antagonist that reduces the amount of glutamate in neurons to counteract excessive brain stimulation[68]. These therapies are mainly used to improve both global cognitive functioning and functional independence[69,70].

Several other pharmacological therapies may be used to address non-cognitive symptoms and enhance quality of life. For instance, parkinsonism can be managed with levodopa, orthostatic hypotension with midodrine, RBD with melatonin and depression with venlafaxine[43]; however, each added prescription should be carefully considered to avoid polypharmacy[71].

Non-pharmacological interventions

Besides the above pharmacological therapies, a wide range of non-pharmacological interventions have been designed to decrease symptom burden and improve quality of life; however, studies of these interventions have generally included few participants[72]. For orthostatic hypotension, treatment may include increased fluid and salt intake, sleeping with the head elevated and use of compression garments[73]. For parkinsonism, physiotherapy may enhance balance and strength, which may reduce the risk of falls and enhance functional independence[74,75].

First-hand perspectives

In the literature, DLB is associated with detriments to the daily life of those affected and their family carers. Compared to individuals living with Alzheimer's disease, individuals with DLB commonly experience a lower quality of life, more apathy, greater functional impairments, higher levels of caregiver distress and increased risk of hospitalization[36,76-80]. Most studies investigating the experiences of individuals

living with DLB have used quantitative methodologies and mostly included family carers[81].

Besides difficulties in obtaining a correct diagnosis, family carers often experience difficulties in finding physicians with in-depth knowledge of disease management and receiving timely and adequate support[56,82,83]. In addition, family carers often experience fears regarding uncertain disease trajectories and prognosis, in addition to frustration due to the lack of interprofessional communication between health-care providers[84-86]. Moreover, individuals living with DLB and their family carers have reported distress regarding hallucinations, apathy and the risk of falling[87]. Furthermore, the need to maintain an active social life despite these physical, cognitive and psychiatric difficulties has been highlighted in prior studies[81].

Neuropathology

This section describes α-syn pathology, how its presence in the central nervous system can be categorized post-mortem in LBD and the current theories about how α-syn pathology may propagate through the peripheral and central nervous system.

Alpha-synuclein pathology

As mentioned previously, a diagnosis of DLB (and Parkinson's disease) can only be fully ascertained upon post-mortem neuropathological verification of disease-specific α-syn pathology. First discovered in 1988, α-syn is a membrane-bound protein primarily found in the axonal terminal of neurons and is associated with the storage, recycling and release of various neurotransmitters[88]. Like other proteins associated with neurodegenerative diseases (e.g. amyloid-β), α-syn is an intrinsically disordered protein, that is, its three-dimensional structure varies dynamically[89].

For as-yet unknown reasons, α-syn may sporadically misfold and aggregate, forming neurotoxic oligomers and fibrils[90]. These aggregates are contained in the nerve cell bodies, forming the inclusions known as Lewy bodies[90]. Moreover, α-syn aggregates in axons and dendrites are known as Lewy neurites. Lewy bodies and neurites are the neuropathological microscopic hallmarks of DLB and Parkinson's disease (see Figure 4). In multiple system atrophy, misfolded α-syn is enclosed in oligodendrocytes instead of neurons, forming glial cytoplasmic inclusions instead of Lewy bodies[91].

This neuropathology may result in various synaptic function impairments, ultimately resulting in neurodegeneration of both the central and peripheral nervous systems. As mentioned previously, this neurodegeneration impairs neural pathways

and dysregulates cholinergic, dopaminergic and noradrenergic signalling[92]. Indication of this neurodegeneration may be visually observed during autopsy as depigmentation of the two monoaminergic brainstem nuclei: the substantia nigra and locus coeruleus[93].

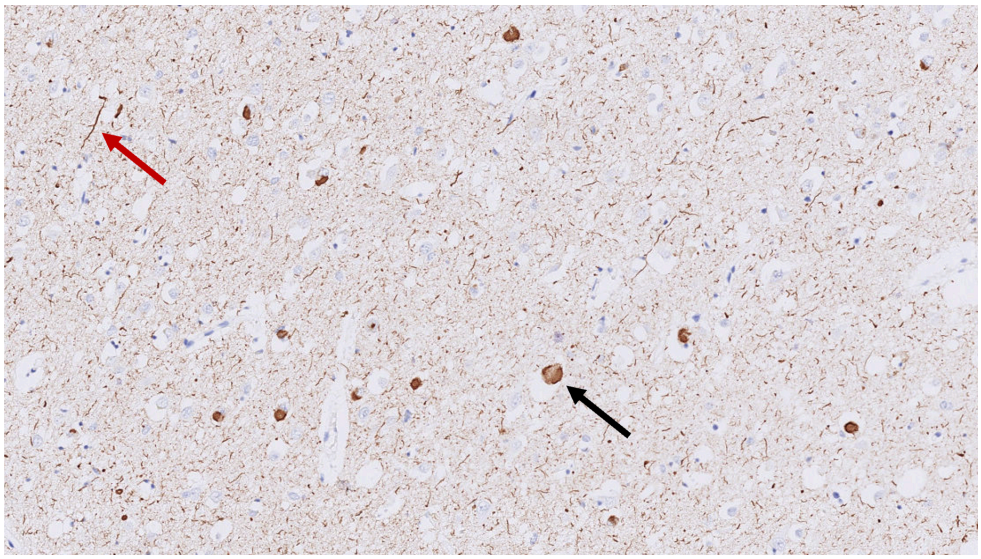

Figure 4. Lewy body (black arrow) and Lewy neurite (red arrow) in the neocortex of a deceased person with Lewy body disease. Source: the author.

Neuropathological categorization

A neuropathological diagnosis of LBD may be categorized according to various staging systems, which may be helpful to determine the possibility of α-syn pathology translating to clinical disease if other co-pathologies are present (e.g. Alzheimer's disease or vascular lesions)[29]. If Lewy bodies or neurites are identified post-mortem in individuals with neither documented cognitive nor motor symptoms, the condition is termed 'incidental LBD'[94].

In 2003, German anatomist Heiko Braak and colleagues proposed a neuropathological staging system for Parkinson's disease based on post-mortem findings of Lewy bodies and neurites in various regions of the brain (i.e. the Braak staging system)[95]. In 2005, the third consensus report of the International DLB Consortium proposed a separate system for categorizing the extent of α-syn pathology for individuals with DLB[96]. These systems share similarities in terms of the affected brain regions and increasingly severe symptoms when more brain regions are involved. However, both systems have been subjected to criticism, as many individuals have remained unclassifiable[97,98]. Therefore, the fourth consensus report of the International DLB Consortium added 'amygdala-predominant' and

'olfactory bulb only' categories to incorporate most α-syn pathology findings[29]. These additional categories and the brainstem predominant type are considered low likelihood of translating to clinical DLB[29].

In 2021, the 'Lewy pathology consensus criteria' were published to categorize LBD based on neuropathological examinations with similar categories to those proposed in the fourth consensus report[99]. These categories are (1) olfactory only, (2) amygdala predominant, (3) brainstem predominant, (4) limbic and (5) neocortical.

Neuropathological propagation

In 2007, Braak and colleagues suggested that α-syn misfolding might start with a neurotropic pathogen entering the body through the olfactory and gastrointestinal mucosa, which they termed as the 'dual-hit hypothesis'[100]. This hypothesis was supported by autopsy cases of relatively isolated findings of α-syn pathology in the olfactory bulb and enteric nerves[100]. They further postulated that α-syn might propagate from the olfactory bulb to the temporal lobes and from enteric nerves to the autonomic nervous system and brainstem. However, Braak and colleagues noted that not all individuals with Parkinson's disease demonstrated this propagation pattern and did not include individuals diagnosed with clinical DLB[100].

More recent neuropathological research suggests that LBD can be divided into two distinct propagation patterns with separate sites of origin: a brain-first amygdala-predominant type originating in the olfactory bulb or a body-first type originating in the enteric nerves (see Figure 5)[101]. The brain-first type seemingly propagates mostly ipsilaterally in a rostro-caudal (i.e. 'downwards') direction before involving autonomic nerves, whereas the body-first type propagates mostly bilaterally in a caudo-rostral (i.e. 'upwards') direction before involving autonomic nerves and the brain[101]. The body-first type seems to constitute two-thirds of clinical DLB cases and one-third of clinical Parkinson's disease cases, and vice versa for the brain-first type[101].

Individuals with a body-first type more often exhibit prodromal cardiac sympathetic denervation and autonomic dysfunctions compared to those with a brain-first type[101]. Interestingly, those with a body-first type also seems to get dementia earlier[101]. Moreover, the body-first type might be further subdivided into either sympathetic- or parasympathetic-predominant subtypes[102].

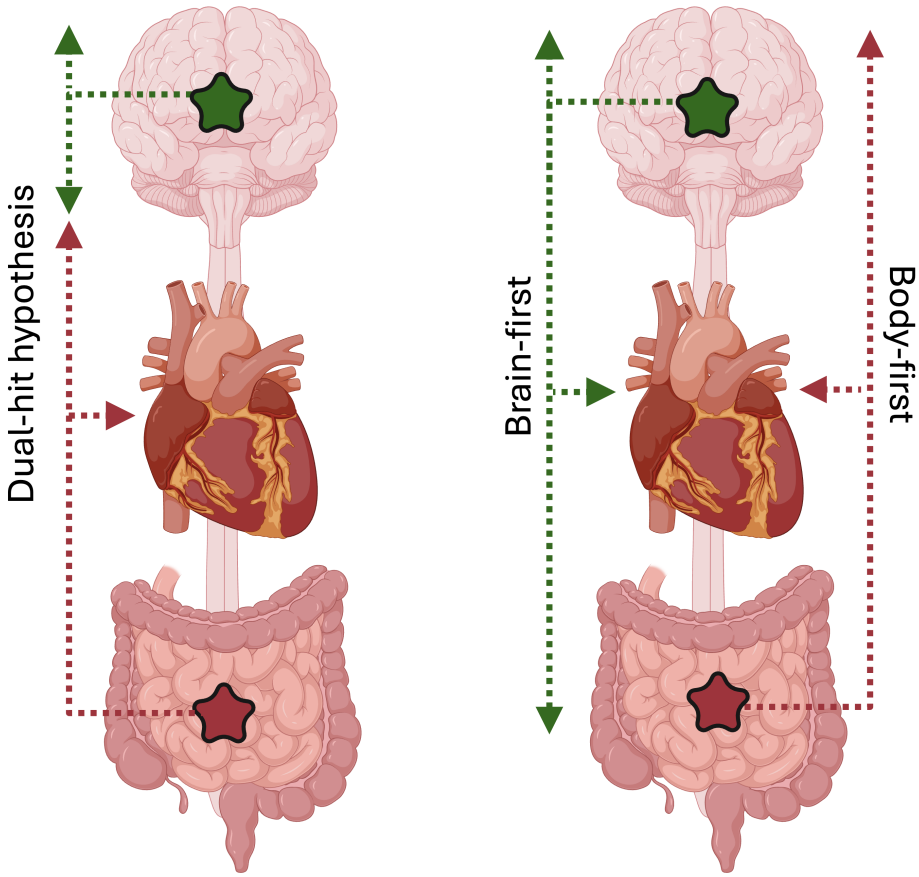

Figure 5. Illustration of the dual-hit hypothesis and the brain-first versus body-first theory. Green and red stars illustrate where the alpha-synuclein pathology is thought to begin. The dual-hit hypothesis suggests that alpha-synuclein pathology begins simultaneously in the olfactory bulb and enteric nerves, while the brain-first versus body-first theories propose that it starts in the brain or the body, respectively. Created in BioRender.com.

Cardiac autonomic nervous system

This section describes how heartbeats are generated within the cardiac conduction system and how the autonomic nervous system influences the heart rate. Furthermore, the presence of α-syn pathology in these structures will be detailed.

Cardiac conduction system

The cardiac conduction system is a network composed of specialized myocytes responsible for initiating, propagating and coordinating each heartbeat[103] (see Figure 6). The sinus node is the most densely innervated part of the cardiac conduction system and contains a cluster of pacemaker myocytes[104,105]. These myocytes do not have a resting potential and will immediately depolarize after repolarization, which continuously and rhythmically generates electrical impulses[106]. These impulses propagate from the sinus node to both atria, causing them to contract and fill both ventricles with blood.

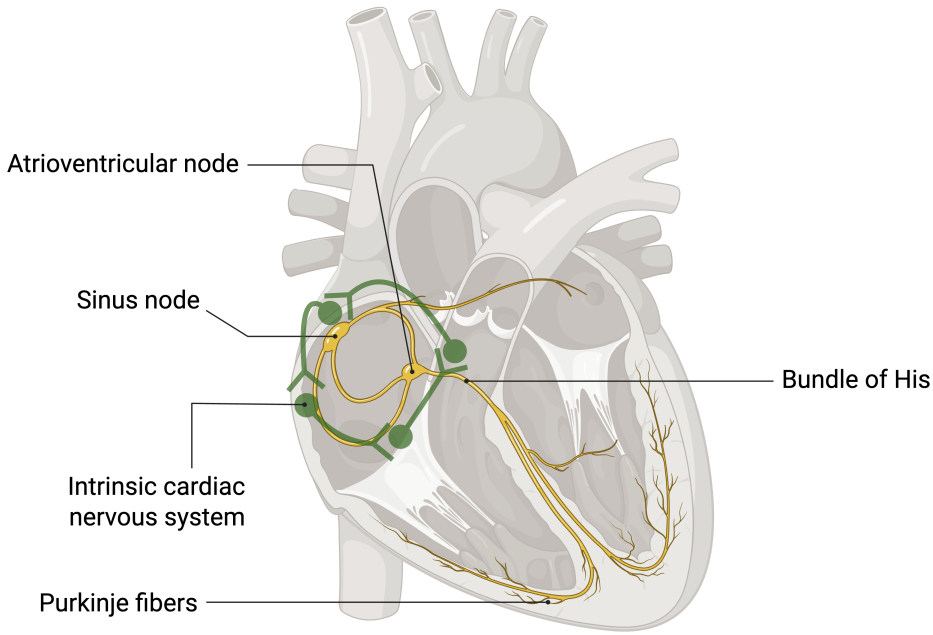

Figure 6. Schematic illustration of the cardiac conduction system with its main structures (yellow). The sinus node is responsible for rhythmically initiating each heartbeat. Green neurons represent the intrinsic cardiac nervous system. Created in BioRender.com.

The electrical impulses then reach the atrioventricular node, where they are briefly delayed, allowing for sufficient blood to fill both ventricles. Through specialized conducting fibres known as the bundle of His and Purkinje fibres, these impulses are then rapidly relayed to each ventricle to trigger a coordinated ventricular contraction, pumping blood to the pulmonary arteries and aorta[103].

The cardiac conduction system is innervated by a poorly understood and complex intrinsic cardiac nervous system, sometimes called the ‘little brain’ of the heart[107].

This system is made of several interconnected clusters of intracardiac neurons that modulate heart functions by innervating the cardiac conduction system and fine-tuning external sympathetic and parasympathetic influences[107]. Most of these neurons have cholinergic parasympathetic properties, but 40–50% seems to have a cholinergic–noradrenergic co-expression[108]. The role of the intrinsic cardiac nervous system in arrhythmia is unknown[107].

By itself, the sinus node could generate a heart rate of approximately 100 beats per minute[109]; however, as the parasympathetic nervous system is active upon rest, the normal resting heart rate typically falls between 60 and 100 beats per minute[109]. A heart rate below 60 beats per minute is referred to as bradycardia, while a heart rate exceeding 100 beats per minute is known as tachycardia[110]. If bradycardia or tachycardia is due to a non-physiological cause they are referred to as either bradyarrhythmia or tachyarrhythmia[111].

Sympathetic and parasympathetic nerves

Physiological adaptation of the heart rate is produced through continuous output from the autonomic nervous system influencing the sinus node in particular[112,113]. These nerves originate in the cardiovascular centre of the brainstem, which receives input from baroreceptors, chemoreceptors and the hypothalamus to adapt the heart rate to ensure adequate blood pressure[113]. Depending on this collective input, signals will relay to either the cardioacceleratory or cardioinhibitory divisions of the cardiovascular centre. The former originates in the caudal and rostral ventrolateral medulla, and the latter in the nucleus ambiguous and dorsal vagal nucleus[113,114] (see Figure 7). These structures may be affected by α-syn pathology[115].

The parasympathetic vagus nerve exits the brainstem, branches and synapses with neurons close to or embedded within the heart[113] (see Figure 8). When activated, these neurons release acetylcholine to muscarinic receptors mainly at the sinus node, which slows the heart rate[113].

Sympathetic cardiac nerves exit the brainstem and synapses with postganglionic sympathetic nerves in the uppermost parts of the sympathetic trunk[113]. These nerves then convey with branches of the vagus nerve to form the cardiac plexus[113]. Postganglionic sympathetic nerves then accompany blood vessels to innervate most of the epicardium and myocardium, including the sinus node[109]. These nerves release noradrenaline to adrenergic receptors, which increases heart rate and cardiac contractions[109].

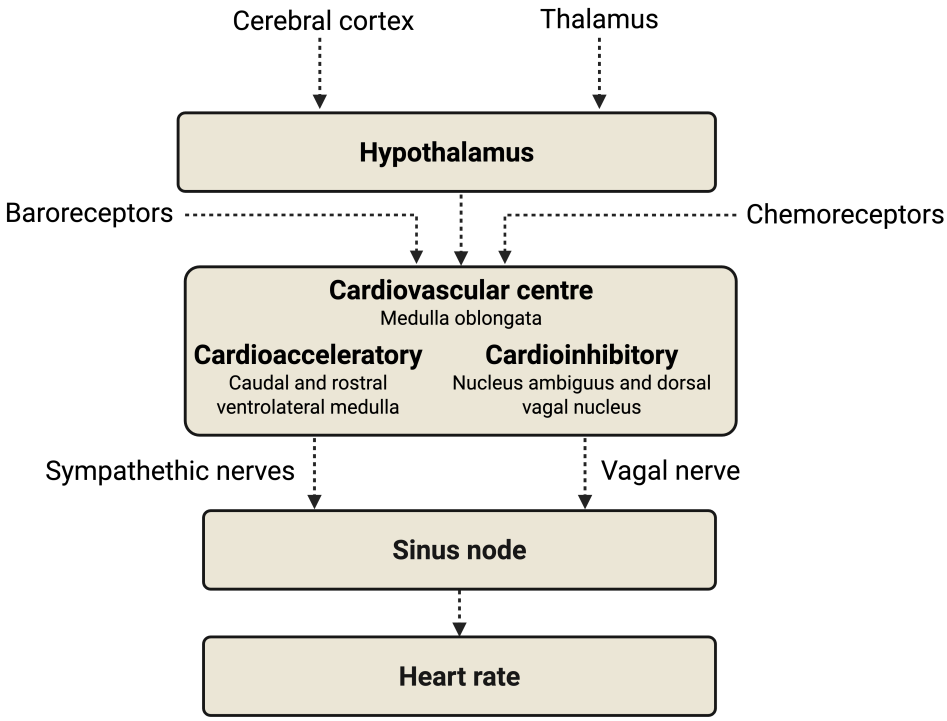

Figure 7. The cardiovascular centre of the brainstem receives input from baroreceptors, chemoreceptors and the hypothalamus. This collective input is conveyed to either the cardioacceleratory or cardioinhibitory parts of the brainstem. Sympathetic output from the former increases the heart rate, while parasympathetic (vagal) output from the latter decreases the heart rate by influencing the sinus node. Created in BioRender.com.

Cardiac alpha-synuclein pathology

Neuropathological studies have demonstrated that the epicardial nerves of the cardiac plexus are affected by α-syn pathology in 3.2–100% of individuals with LBD[94,116-121]. These differences are likely due to variations in sampled cardiac regions and immunostaining techniques.[120,122]. Mostly, these nerves are postganglionic cardiac sympathetic nerves, identified post-mortem by their decreased immunoreactivity to tyrosine hydroxylase[118,121]. Furthermore, a few studies have observed the presence of α-syn pathology in intracardiac nerves of the sinus node[123-125].

As mentioned previously, depletion of tyrosine hydroxylase can be visualized as cardiac sympathetic denervation using cardiac MIBG scintigraphy as a biomarker of DLB[54]. Moreover, heart rate variability may be used to assess sympathetic and parasympathetic influences on the sinus node[126]. Heart rate variability refers to natural fluctuations in the time between consecutive heartbeats as measured by an

electrocardiogram (ECG)[126]. There is some research supporting the use of heart rate variability as a biomarker to distinguish between DLB and Alzheimer's disease, especially during the early disease stages[127,128]. Increased parasympathetic innervation relative to sympathetic innervation of the sinus node results in increased heart rate variability[126], which is quantified by measuring either time or frequency domains. Time domains measure beat-to-beat time variations, such as the root mean square of successive differences (RMSSD)[126].

Besides heart rate variability, potential electrophysiological cardiac alterations due to cardiac α-syn pathology have not yet been determined. However, some studies have theorized that cardiac α-syn pathology might contribute to arrhythmia and potential associations with sudden cardiac death has been described previously[65,123,129-131].

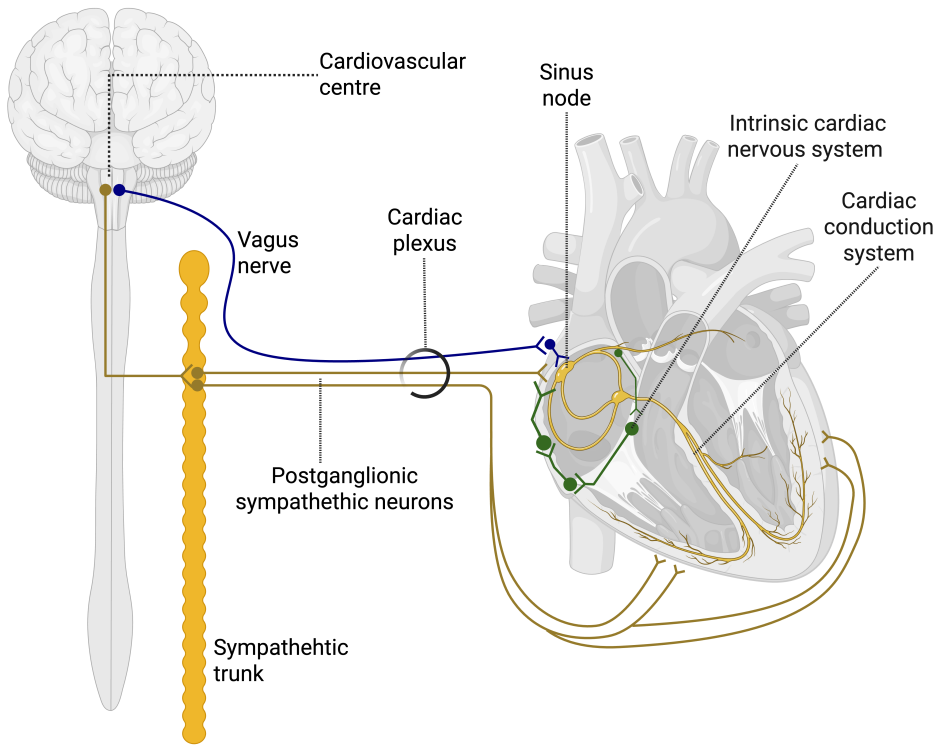

Figure 8. Schematic illustration of cardiac sympathetic nerves and the parasympathetic vagus nerve originating in the cardiovascular centre, synapsing and targeting the heart (including the sinus node). Created in BioRender.com.

Syncope

Syncope and repeated falls are both supportive features of DLB[29]. Among individuals with dementia, unexplained falls are often attributed to syncope, and falls are a major cause of hospitalization for individuals with DLB[132]. Syncope is caused by transient global cerebral hypoperfusion caused by sudden hypotension[133]. Beside syncope, transient global cerebral hypoperfusion may cause dizziness, lightheadedness and fatigue. There are three main types of syncope based on the underlying cause: reflex syncope, orthostatic hypotension and cardiac syncope[134] (see Figure 9).

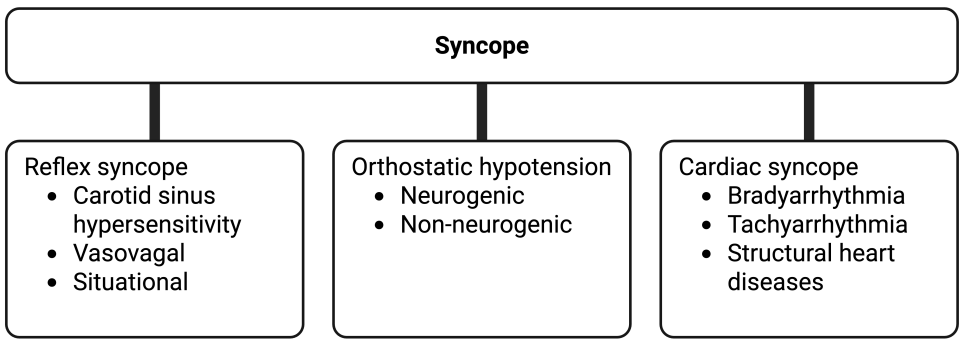

Figure 9. Syncope classifications based on the underlying mechanisms resulting in transient global cerebral hypoperfusion. Created in BioRender.com.

Reflex syncope

Reflex syncope is often benign and represents the most common cause of syncope in the general population[133]. This type can be further divided into three subtypes: carotid sinus hypersensitivity, vasovagal and situational syncope[133]. Carotid sinus hypersensitivity is an exaggerated response of the autonomic nervous system when exerting pressure on the carotid sinus (which is then falsely perceived as high blood pressure)[133]. In response, this may cause excessive vasodilation and bradycardia (i.e. sympathetic decrease and vagal increase) leading to sudden hypotension. Interestingly, carotid sinus hypersensitivity has been reported to be more prevalent among individuals with DLB compared to those with Alzheimer's disease[135], possibly due to neurodegeneration of the cardiovascular centre[136]. Furthermore, emotional stress and certain situations (e.g. urinating) may cause the cardiovascular centre to increase vagal tone and decrease sympathetic activity, resulting in vasovagal and situation syncope, respectively[133]. The underlying mechanisms for these types of syncope are still unknown[134].

Orthostatic hypotension

In individuals with LBD, syncope is mostly attributed to orthostatic hypotension[137,138]. When standing upright from a lying position, gravity causes blood to pool in the lower extremities, resulting in sudden hypotension. To compensate, the baroreflex is activated, which increases the heart rate and instigates vasoconstriction, helping to stabilize blood pressure[113]. This response is driven by increased sympathetic activity targeting the heart and blood vessels[139]. If this mechanism fails to properly regulate blood pressure, it will cause hypotension when standing, a condition known as orthostatic hypotension[139], which is defined as a sustained fall in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg after 3 minutes of standing[140].

Orthostatic hypotension can be divided into neurogenic orthostatic hypotension and non-neurogenic orthostatic hypotension[141]. The latter is often due to dehydration, anaemia or atherosclerosis, while the former is caused by cardiovascular autonomic dysfunction (the type seen in synucleinopathies)[141]. In synucleinopathies, sympathetic denervation affects the body's ability to properly activate the baroreflex, resulting in both an insufficient increase in heart rate and vasoconstriction when standing[141]. As a result, the body cannot effectively compensate for the sudden hypotension[141].

Individuals with more peripheral (i.e. postganglionic) cardiac sympathetic denervation (i.e. LBD) seems to have less increase in heart rate upon standing compared to those with multiple system atrophy who primarily have central autonomic lesions[119,142]. The presence of neurogenic orthostatic hypotension is examined by dividing the heart rate difference by the difference in systolic blood pressure at baseline and after 3 minutes of standing. A ratio <0.5 in the presence of orthostatic hypotension is suggestive of neurogenic orthostatic hypotension[142].

Up to half of those with DLB and about one-third of those with Parkinson's disease have orthostatic hypotension[143,144]. Moreover, up to half of those with DLB and the majority of individuals with Parkinson's disease do not experience typical symptoms of orthostatic hypotension, such as dizziness, which could make the condition difficult to identify[144,145].

Bradyarrhythmia

Lastly, syncope may be caused by various heart-related conditions, collectively known as cardiac syncope. Up to 30% of syncopal events among older individuals are classified as cardiac syncope[146-148], which is mostly due to bradyarrhythmia caused by sick sinus syndrome (SSS) or high-degree atrioventricular block (HAVB) and tachyarrhythmia[149]. Cardiac syncope is associated with hospitalization, injuries and increased mortality[150,151].

Sick sinus syndrome

Sick sinus syndrome (SSS) is a clinical syndrome caused by sinus node dysfunction, which can result in profound bradycardia, sinus pauses, sinus arrest and/or chronotropic incompetence[106]. Chronotropic incompetence is defined as an inability to increase heart rate during physical activity to match physiological demands[152]. Furthermore, sinus node dysfunction might be accompanied by paroxysmal atrial tachyarrhythmia, which can result in the heart rate altering between bradycardia and tachycardia, known as tachycardia–bradycardia syndrome[152].

Epidemiological studies of SSS are scarce[153], but a frequently cited prevalence is one in 600 patients with cardiac issues over 65 years of age[152,154,155]. The incidence of SSS is estimated at 0.8 per 1,000 person-years[153] and increases exponentially with age[106]. The incidence of SSS is expected to double in the ageing population between 2014 and 2060[153], and is equally common among men and women[156].

SSS is primarily caused by intrinsic sinus node dysfunction, mostly due to idiopathic age-related conduction system fibrosis, but may also be caused by electrophysiological remodelling of the sinus node (e.g. following heart failure and atrial fibrillation)[105,106]. However, sinus node dysfunction may be exacerbated or mimicked by extrinsic factors, e.g. cardiac autonomic dysfunction and certain medications, such as digoxin, beta blockers and cholinesterase inhibitors[152,157,158].

Individuals with SSS often present with symptoms due to transient global cerebral hypoperfusion, including fatigue, dizziness and falls, with half presenting with syncope or pre-syncope[159]. Interestingly, some case reports have described instances of SSS mimicking symptoms of LBD[160-164]. Some studies have also described the presence of chronotropic incompetence among individuals with Parkinson's disease, possibly as an indicator of cardiac sympathetic denervation[165-171].

If electrophysiological cardiac abnormalities (e.g. profound sinus bradycardia, sinus pauses, sinus arrest and/or chronotropic incompetence and/or tachycardia–bradycardia syndrome) can be associated with the above-mentioned symptoms, a diagnosis of SSS is warranted[152]. As these ECG changes might fluctuate throughout the day and go undetected by standard 10-second ECG recordings, prolonged ECG monitoring (e.g. Holter monitoring) might be necessary and is considered the gold standard for SSS diagnosis[159]. In case of chronotropic incompetence, an exercise stress ECG might be useful to ascertain the diagnosis[159]. It is not possible to differentiate between intrinsic sinus node dysfunction versus extrinsic factors (e.g. cardiac autonomic dysfunction) for SSS based on ECG findings and clinical presentation[157].

In case of no apparent reversible cause (e.g. medications), the only way to manage symptomatic SSS is by implanting a permanent pacemaker[159,172]. A pacemaker stimulates the heart rate when below a set value, which normalizes the heart rate to reduce associated symptoms (e.g. syncope or lightheadedness). The risk of sudden

cardiac death is low if unmanaged and pacemaker implantation does not seem to affect survival but may increase quality of life[152,173]. It is estimated that up to half of all pacemaker implantations are due to SSS[153].

High-degree atrioventricular block

Atrioventricular block occurs when there is a disruption in the electrical conduction of the atrioventricular node. This block can vary in severity, resulting in various degrees of atrioventricular block that can be identified by ECG[174]. First-degree and Mobitz type I atrioventricular block are most often asymptomatic and rarely result in hemodynamic instability. These may be due to a physiological increase of vagal tone (seen in athletes) or ischaemic heart disease and seldom require pacemaker implantation[174]. In contrast, HAVB, including Mobitz type II and third-degree atrioventricular block, are often symptomatic and caused by an underlying disease process mostly attributed to idiopathic conduction system fibrosis[175]. Other causes include certain medication, infections or infiltrative diseases[174].

The prevalence of third-degree atrioventricular block is estimated at 0.004–0.04% in the general population, but epidemiological studies are scarce[176,177]. Similar to SSS, atrioventricular blocks may cause fatigue, dizziness, syncope and falls. If atrioventricular blocks are symptomatic without apparent reversible causes, the only effective treatment is by implanting a pacemaker. However, as HAVB might cause hemodynamic instability, pacemaker implantation is recommended even for asymptomatic individuals[174].

Cholinesterase inhibitors and bradyarrhythmia

By inhibiting the reuptake of acetylcholine in neurons, cholinesterase inhibitors may increase vagal effects on the sinus node, resulting in bradycardia[178-180]. As such, clinicians usually examine an ECG prior to initiating treatment. Initiation of cholinesterase inhibitor therapy has been associated with an increased risk of hospitalization due to bradycardia[181]. However, instances of SSS or HAVB as adverse events following administration of cholinesterase inhibitors are mostly derived from a few case reports[182-184]. In these cases, this might be due to prior underlying tendencies towards these conditions. In some individuals who experience a good effect from cholinesterase inhibitor therapy but develop bradyarrhythmia, pacemaker implantation might be necessary to continue their effective treatment[179].

In a randomized, double-blinded and placebo-controlled trial among 541 individuals with Parkinson's disease dementia, one (0.3%) developed novel SSS after 24 weeks of cholinesterase inhibitor treatment compared to none receiving placebo[185]. Interestingly, adverse events, including vascular disorders and syncope, were more common in the placebo group. In addition, in a cohort of 60 individuals with Alzheimer's disease dementia undergoing cholinesterase inhibitor therapy, Holter

monitoring revealed no cases of bradyarrhythmia and none subsequently underwent pacemaker implantation[186].

Pacemaker implantation

Irreversible symptomatic SSS and HAVB are mostly managed by implanting a permanent pacemaker to reduce associated symptoms and improve quality of life[187]. Pacemakers are usually implanted using minimally invasive techniques with local anaesthesia and the full procedure takes roughly an hour[188]. Besides ongoing infections, there are no absolute contraindications for receiving a pacemaker implant[187]. Dementia has also not been associated with an increased risk of device malfunction[189]. Several studies have shown that pacemaker therapy due to bradyarrhythmia could improve cerebral perfusion and cognitive test performance, mainly regarding executive functioning[190-193].

Rationale for the thesis

Cardiac autonomic nerves play a crucial role in maintaining an appropriate heart rate. Neurodegeneration of these structures due to α-syn pathology may disrupt its functions, potentially causing bradyarrhythmia. Bradyarrhythmia in DLB might be a prodromal feature by involving cardiac autonomic nerves early in the disease course. Symptoms associated with bradyarrhythmia (e.g. syncope) might also mimic features of DLB, making bradyarrhythmia difficult to recognize in clinical settings. Identifying and managing bradyarrhythmia in individuals with DLB (e.g. through a pacemaker implant) may help to reduce syncope and falls, ease cognitive symptoms and enhance overall quality of life.

Aims

The overarching aim of this thesis was to explore if bradyarrhythmia could represent an under-recognized and manageable feature of DLB. The specific aims of the papers were as follows:

Paper I

To explore how individuals with DLB experience daily life following a pacemaker implant to manage associated symptoms of bradyarrhythmia.

Paper II

To explore the prevalence of undetected bradyarrhythmia in individuals with DLB.

Paper III

To investigate the occurrence of SSS and HAVB in patients with DLB compared to other dementia subtypes. As secondary aims, potential associations between SSS and DLB as well as between HAVB and DLB compared to Alzheimer's disease were investigated.

Paper IV

To elucidate the prevalence of cardiac α-syn pathology in various neuropathological categories of LBD, also before clinical symptomatic disease. In addition, we aimed to confirm previous findings of α-syn being present within the sinus node.

Methodologies

Methodological overview

This doctoral thesis was mainly explorative and includes both qualitative and quantitative approaches to address the overarching aim to explore if bradyarrhythmia could represent an under-recognized and manageable feature of DLB. Furthermore, this thesis uses the research paradigms of constructivism (Paper I) and positivism (Papers II–IV) based on different ontological and epistemological assumptions. In Paper I, we used a qualitative case study design. For the quantitative studies, we used cross-sectional study designs (Paper II and IV) and a case-control study design (Paper III). As the cohorts and study designs differ for each paper, they will be presented separately in the following sections.

Selection of participants

Paper I

For inclusion in this qualitative paper, participants had to be Swedish speaking, diagnosed with DLB and newly implanted with a pacemaker to manage their concurrent bradyarrhythmia. For inclusion of family carers, they had to be Swedish speaking and living with the participant with DLB. Based on these inclusion criteria, two community-dwelling men with DLB and their wives were included for repeated in-depth interviews.

Paper II

In this paper, we consecutively enrolled participants from three memory clinics in southern Sweden between May 2021 and November 2022. For inclusion, each participant had to have been diagnosed with DLB and not have a pacemaker or implantable cardioverter-defibrillator. Based on these criteria, 30 participants were included to determine the presence of concurrent bradyarrhythmia and evaluate their cardiac autonomic functions. Two participants later declined to participate.

Paper III

In this paper, we obtained data for individuals diagnosed with various types of dementia between 1 May 2007 and 31 December 2020 from the Swedish Dementia Registry (SveDem). In total, 96,087 individuals were included. The SveDem also included data for age at dementia diagnosis, cognitive test results, date of death and dichotomous data regarding prescribed medications (e.g. 'cardiovascular medications' and 'cholinesterase inhibitors').

Furthermore, SveDem provided follow-up data indicating revisions of dementia diagnoses. After potentially revised diagnoses, those with either 'unspecified' or 'other' dementia were excluded because of their uncertainty/imprecision regarding dementia aetiology. The remaining 73,619 individuals were included for analysis. These individuals had been diagnosed with either DLB, Alzheimer's disease dementia, vascular dementia, mixed dementia, Parkinson's disease dementia or frontotemporal dementia.

Paper IV

In this paper, we consecutively included 95 individuals at clinical autopsy between January 2021 and January 2025. Of these, 82 were included as individuals suspected of having LBD based on their medical records and/or macroscopic depigmentation of the substantia nigra and locus coeruleus during autopsy. The remaining 13 individuals were not suspected of having LBD and were included as assumed non-LBD controls.

Data collection

Paper I

In Paper I, we collected qualitative data through repeated in-depth face-to-face semi-structured interviews with each husband–wife dyad within the year following pacemaker implantation due to SSS. During the interviews, we used open-ended questions and encouraged each couple to engage in free narration. Subsequent interviews were guided both by topics the couples had raised during the initial interviews and by topics based on the World Health Organization's International Classification of Functioning, Disability and Health[194]. We used the latter topics as a framework to further explore the participants' health and health-related issues.

Paper II

In Paper II, each of the included participants with DLB were referred to Holter monitoring to determine the presence of potential bradyarrhythmia. Furthermore, each participant was examined to evaluate their cardiovascular autonomic functions, including orthostatic testing and cardiac MIBG scintigraphy to determine the presence of neurogenic orthostatic hypotension and cardiac sympathetic denervation, respectively. Cardiac autonomic influence of the heart was also examined by manually calculating heart rate variability (i.e. RMSSD) based on 10-second ECG recordings provided prior to Holter monitoring[195]. We gathered data from medical records, including prescribed medications, cardiovascular comorbidities and clinical features of DLB. The primary endpoint was the diagnosis of bradyarrhythmia up until the end of December 2022, either by the Holter monitoring at inclusion or subsequent heart rate monitoring.

Paper III

For the 73,619 individuals included in this paper, we obtained data for de novo pacemaker implantation from the Swedish Pacemaker Registry between January 1997 and December 2022. This included data of pacemaker indications (e.g. SSS or HAVB), assumed bradyarrhythmia aetiology (e.g. conduction system fibrosis or ischaemic heart disease) and main arrhythmia symptoms (e.g. syncope or dizziness).

Paper IV

In this paper, we collected brain and cardiac tissue samples from all 95 included individuals. Each tissue sample were stained for haematoxylin-eosin and an α-syn antibody. Based on the extent of α-syn pathology in the brain, we categorized individuals as having either brainstem predominant, limbic or neocortical LBD[99] or multiple system atrophy. We defined controls as individuals without evident α-syn in the brain.

During autopsy, we evaluated cause of death, coronary atherosclerosis, myocardial infarction and neuropathological co-pathologies. Moreover, we gathered clinical data from medical records pertaining to clinical diagnoses (e.g. Alzheimer's disease, Parkinson's disease or DLB) as well as cardiovascular comorbidities (e.g. arrhythmia diagnoses, diabetes mellitus, acute coronary syndrome) and orthostatic hypotension.

Data analysis

Paper I

We analyzed the transcribed interview data using qualitative content analysis as described by Graneheim and Lundman[196]. Co-authors IH and EL separately read the transcripts multiple times to gain an overall understanding of the couples' daily lives. Thereafter, we independently identified meaning units, assigned codes and compared these codes in relation to the study aim. These codes were then clustered based on similarities and differences until we reached a consensus on categories and subcategories. Finally, co-author AB conducted a separate confirmatory analysis. We used NVivo software (Lumivero, Denver, CO, USA) to organize and manage the qualitative data.

Paper II–IV

For quantitative analyses, we used SPSS software (IBM SPSS, Armonk, NY, USA). To compare the continuous data between two dependent groups, we used either the non-parametric Mann–Whitney *U* test or parametric Student's *t*-test, based on the sample sizes and whether the data were normally distributed or not. To compare continuous data between more than two groups, we used either analysis of variance or Kruskal–Wallis H-test based on sample sizes and normal distribution. To compare the nominal data between two or more groups, we used chi-square test or Fisher's exact test. A p-value <0.05 was deemed statistically significant in all quantitative papers.

In Paper II, we also used simple linear regression to analyze if resting heart rate during orthostatic testing corresponded with mean heart rate during Holter monitoring. In Paper III, we used binary logistic regression to analyze the potential associations between DLB and both SSS and HAVB. We adjusted these models for age, sex, use of cardiovascular medications and use of cholinesterase inhibitors.

Ethical considerations

All papers adhered to the Declaration of Helsinki as outlined by the World Medical Association[197] and were approved by both national and regional ethics review boards. For each study, we included individuals with dementia, an especially vulnerable group[197]; therefore, it was important for us to conduct research which might directly benefit study participants with minimal risks and burden. In a broader

sense, it is important to conduct research involving individuals with dementia to decrease stigmatization and further understand these complex diseases.

In accordance with the Declaration of Helsinki, free and informed consent is integral to uphold individual autonomy[197]. For Papers I and II, each enrolled participant was informed about their right to self-determination and consented based on written and verbal information about the study. Each participant was also informed about their right to discontinue the study at any moment without providing a reason for doing so. In Paper III, the participants and their caregivers were informed verbally and in writing about their inclusion in both registries. Paper IV included participants post-mortem; as such, their enrolment was exempt from informed consent.

For Papers I and II, travelling to the interviews or examinations might have been burdensome and costly; therefore, the participants and family carers could receive compensation for their travel expenses. When conducting the examinations in Paper II, participants had an extra check-up for orthostatic hypotension and arrhythmia, which could both be beneficial. Cardiac MIBG scintigraphy could also further establish a diagnosis of DLB.

Furthermore, there is a risk of incidental findings when conducting research, which we would manage if apparent. In Paper IV, this was mainly the incidental finding of widespread α-syn pathology in some individuals, which may have caused concerns about synucleinopathies being hereditary for family members receiving the autopsy report. To address this issue, it is also important for researchers to actively engage in public education.

In our studies, we must manage sensitive personal data related to health. The study participants in Papers I, II and IV were assigned an artificial identification code, with the decoding key stored separately. For Paper III, the decoding key was never made available to us. After publication, the decoding keys were discarded, which facilitated the anonymized classification of the data in accordance with the General Data Protection Regulation[198]. When presenting the data in each paper, there was a risk that individuals with specific traits would be recognized; therefore, we carefully reported their data by intentionally keeping certain details vague.

In a broader sense, there is a risk of our findings being misinterpreted or overinterpreted by society. For example, the findings that individuals with bradyarrhythmia might have an increased risk of having DLB or that pacemakers should be used to manage all types of bradycardia in individuals with LBD may be understood adversely. Hence, we must carefully consider the conclusions we draw and how we communicate these findings to the public.

For this doctoral thesis, a generative artificial intelligence tool, ChatGPT (OpenAI, San Francisco, CA, USA), was used to improve the grammar and avoid dangling modifiers. This thesis was also proofread by an editor from a qualified, professional native-English-speaking editing service.

Summary of the results

This section highlights the most important findings from each paper. The complete results are presented in Papers I–IV, which are included at the end of this thesis.

Paper I summary

Following a qualitative content analysis, six subcategories and three main categories explored how individuals with DLB experience daily life following a pacemaker implant to manage their bradyarrhythmia. The three main categories were: gaining control, maintaining a social life and being influenced by concurrent diseases.

Considering the first category, 'gaining control', both male participants had experienced less syncope within the year after receiving a pacemaker, which increased their sense of control and predictability in their daily lives, as this meant fewer falls and injuries. With this greater sense of control of their lives, both men could engage in joyful activities, such as biking and gardening, which had been difficult prior to receiving the pacemaker. However, both couples expressed a lingering fear of syncope and subsequent falls, which still meant that they followed their daily routines cautiously. They also noted that the reduction in syncope was temporary within the year. Furthermore, remote pacemaker monitoring provided a sense of reassurance for both couples as it was understood to detect otherwise unnoticed arrhythmia and notify their heart clinic.

The second category, 'maintaining a social life', highlights how physical and cognitive barriers seemed to ease within the year after receiving the pacemaker, helping both couples to attend social activities, which were an essential aspect of their well-being. The interviews also reflected the couples' perceptions that these cognitive and physical changes were noticed by their friends, possibly reinforcing their own sense of improvement.

In the third category, both couples described how the ongoing symptoms of DLB continued to influence the men's health throughout the year after receiving the pacemaker, leading to persistent concerns in their daily lives. They also described difficulties in understanding which symptoms were due to DLB or other diseases. One couple specifically mentioned cognitive fluctuations in describing their sense of not knowing what to expect when waking up in the morning.

Paper II summary

Among the 28 participants examined, none were under current investigation for bradycardia nor had a prior bradyarrhythmia diagnosis. By the end of December 2022, three (10.7%) were diagnosed with SSS. One participant was diagnosed with SSS following the initial Holter monitoring, the second participant after follow-up Holter monitoring, while the third participant was diagnosed during in-hospital telemetry due to syncope some months after inclusion.

The main symptoms associated with bradyarrhythmia for the three participants with SSS were dizziness, fatigue and syncope, respectively. Two of the three participants subsequently received a pacemaker implant. Furthermore, a fourth participant was referred for an exercise stress ECG by an affiliated heart clinic following baseline Holter monitoring. Even though chronotropic incompetence was highly suspected, no diagnosis was set. None were diagnosed with HAVB or alarming tachyarrhythmia.

In total, 23 (82.1%) participants had visual signs of cardiac sympathetic denervation and 17 (60.7%) participants had neurogenic orthostatic hypotension. Besides RBD, there were no differences in baseline demographics, cardiovascular comorbidities or chronotropic medications between those with and without bradycardia at rest (during orthostatic testing) or an average heart rate <60 beats per minute (during Holter monitoring). Furthermore, no differences were noted regarding sympathetic denervation, neurogenic orthostatic hypotension or symptoms potentially associated with bradyarrhythmia (e.g. prior syncope). RMSSD was higher among those with bradycardia compared to those without.

Paper III summary

Among the 73,619 included individuals, 2,294 (3.1%) had DLB. The DLB cohort had the highest percentage of revised diagnoses (11.2%) from baseline to last follow-up among all dementia subtypes. In total, 3,686 (5.0%) individuals had received a pacemaker implant between January 1997 and December 2022. All-cause pacemaker implantation was more common in the DLB cohort compared to the Alzheimer's disease cohort (5.5% versus 3.9%, $p<0.001$), but not compared to the vascular dementia cohort (5.5% versus 6.3%, $p=0.122$). Overall, HAVB was the most common indication for receiving a pacemaker implant (36.0%) followed by SSS (34.3%).

SSS was more common in the DLB cohort compared to the Alzheimer's disease cohort (2.2% versus 1.5%, $p=0.008$), but not compared to the vascular dementia cohort (2.2% versus 2.1% $p=0.886$). HAVB was not more common when comparing

the DLB cohort to both the Alzheimer's disease cohort (1.5% versus 1.5%, p=0.938) and the vascular dementia cohort (1.5% versus 2.0%, p=0.083).

Those with DLB were younger at time of pacemaker implantation due to SSS compared to those with Alzheimer's disease (74.2 versus 77.2 years, p=0.011), and 80% of DLB patients had received their pacemaker due to SSS before their dementia diagnosis. There were no differences regarding prescription of cholinesterase inhibitors (66.0% versus 61.3%, p=0.647) or cardiovascular drugs (74.0% versus 78.7%, p=0.267) when comparing those DLB and those with Alzheimer's disease.

In the DLB cohort, the main symptom associated with SSS was syncope (52.0%), followed by dizziness (32.0%) and breathlessness or tiredness (16.0%). When adjusted for age, sex, use of cardiovascular drugs and use of cholinesterase inhibitors, there was a significant association between SSS and DLB (odds ratio, 1.49; 95% confidence interval: 1.11–2.01) with Alzheimer's disease as reference. With the same adjustments, HAVB was not associated with DLB (odds ratio, 0.90; 95% confidence interval: 0.63–1.29). With the same adjustments and with Alzheimer's disease as reference, there were no significant association between Parkinson's disease dementia and SSS (odds ratio, 0.59; 95% confidence interval: 0.33–1.05) or HAVB (odds ratio, 1.04; 95% confidence interval: 0.68–1.59).

Paper IV summary

In total, 77 individuals had α-syn pathology present in the brain including 72 with LBD and five with multiple system atrophy. In the LBD group, 31 had brainstem predominant, 17 limbic and 24 neocortical LBD. Eighteen individuals did not demonstrate α-syn pathology in their brain (i.e. the control group). In total, 14 (16.9%) individuals had been clinically diagnosed with Parkinson's disease, six (7.2%) with DLB and eight (9.6%) with unspecified/atypical parkinsonism. Another six of the 19 individuals diagnosed with unspecified dementia had DLB mentioned as a differential diagnosis in their medical records. Eleven patients (13.3%) had been referred for autopsy from a specialized memory clinic

Cardiac α-syn pathology was apparent in 67 of 72 individuals with LBD (93.1%), all five with multiple system atrophy, and in eight controls (44.4%). Five individuals with brainstem predominant LBD did not have any evident cardiac α-syn pathology. Moreover, the sinus node demonstrated positive α-syn immunostaining in three of four individuals with brainstem predominant LBD (one whom had SSS).

Among the 72 individuals with LBD, eight (11.1%) had SSS (four with brainstem predominant LBD and four with neocortical LBD), three (4.2%) had HAVB and 22 (30.6%) had atrial fibrillation. All individuals with LBD and concurrent SSS/HAVB

had cardiac α-syn pathology. None in the control group had SSS. Sudden cardiac death was more common among those with LBD/multiple system atrophy compared to the controls (37.7% versus 11.1%, p=0.025). Cardiovascular comorbidities (clinically and at autopsy) did not differ between those with LBD/multiple system atrophy and controls.

Discussion

The overarching aim of this thesis was to explore whether bradyarrhythmia could represent an under-recognized and manageable feature of DLB. We used a multi-method approach incorporating various methodologies to address this aim.

The main findings of the four papers were: pacemaker implants to manage concurrent bradyarrhythmia might improve the well-being of individuals living with DLB (Paper I); a notably high prevalence of SSS was observed in individuals with DLB compared to estimates in the general population (Paper II); an association between SSS and DLB and that SSS was more common in individuals with DLB compared to those with Alzheimer's disease (Paper III); and most individuals with LBD had cardiac α-syn pathology, even early in the disease process, including the sinus node (Paper IV).

Papers II and III showed a high occurrence of SSS among individuals with DLB (2.2% and 10.7%, respectively), while Paper IV found that 11.1% of individuals with LBD had SSS. As previously mentioned, these figures are higher than the prevalence regularly cited in the literature for older cardiac patients[152,154,155]. In Paper III, we also observed a relatively high occurrence of pacemaker implantation due to SSS/HAVB among those with other types of dementia (e.g. vascular or Alzheimer's disease). These observations might reflect age as a shared risk factor for both dementia and bradyarrhythmia, or inaccuracy regarding the cited SSS/HAVB prevalences in prior research. However, in Paper III, individuals with DLB who had received a pacemaker due to SSS were younger than those with Alzheimer's disease and vascular dementia. In our age-adjusted model, SSS was associated with DLB compared to Alzheimer's disease.

Besides ageing, cardiovascular comorbidity might also explain the high prevalence of SSS in DLB in our studies. However, in Paper II, there was no difference in cardiovascular comorbidity when comparing those with or without bradycardia. In Paper IV, we did not observe any differences regarding cardiovascular comorbidities (clinically or at autopsy) among individuals with LBD compared to controls. Among individuals with DLB and a pacemaker due to SSS in Paper III, the use of cardiovascular drugs did not differ compared to those with Alzheimer's disease and was lower compared to those with vascular dementia. This finding aligns with previous studies that have shown similar rates of cardiovascular comorbidities (e.g. hypertension, diabetes mellitus, heart failure and acute coronary

syndrome) when comparing individuals with DLB to those with Alzheimer's disease[57-60].

Furthermore, cholinesterase inhibitors are known to cause bradycardia as an adverse event. Importantly, if SSS or HAVB are diagnosed, reversible extrinsic factors, such as medications, are typically discontinued to observe whether the heart rate normalizes before a potential pacemaker implantation[152,174]. If the heart rate does not normalize, bradyarrhythmia is likely not primarily due to adverse events from prescribed medications. Thus, it is unlikely that the use of cholinesterase inhibitors alone would explain our observations in Paper III, as these patients had received a pacemaker. In Papers I and II, SSS was not considered to have been caused by prescribed medications.

In Paper II, individuals with DLB and bradycardia did not differ regarding features suggestive of cardiovascular autonomic dysfunction, compared to those without bradycardia. Consistent with prior research, we observed that most individuals with DLB demonstrate cardiac sympathetic denervation and neurogenic orthostatic hypotension[52,143]. These observations suggest that most participants had an underlying α-syn propagation involving cardiac autonomic nerves, including all individuals with SSS in Paper II and IV. A higher RMSSD among those with bradycardia in Paper II might suggest a predominant parasympathetic relative to sympathetic influence of the sinus node, likely due to cardiac sympathetic denervation.

During the neuropathological examination, we observed a high prevalence of epicardial α-syn pathology among individuals with LBD, including those with brainstem predominant LBD and among controls. These findings could represent instances of early body-first α-syn propagation. If SSS is caused by cardiac autonomic dysfunction, it is possible that bradyarrhythmia could represent a prodromal feature due to underlying α-syn pathology, possibly even before apparent cognitive or motor features. This finding could also explain why most individuals had received a pacemaker due to SSS prior to their DLB diagnosis in Paper III, and why four individuals with brainstem predominant LBD had SSS in Paper IV.

Furthermore, we confirmed the few prior observations showing that the sinus node may have α-syn deposits[123-125], which was observed among individuals with brainstem predominant LBD (one of whom had SSS). Thus, it remains possible that α-syn pathology of intracardiac neurons may disrupt the functioning of the sinus node, potentially contributing to bradyarrhythmia. However, as previously mentioned, the role of the intrinsic cardiac nervous system in arrhythmia is still poorly understood[107].

As observed in Paper III, HAVB was the most common indication for receiving a pacemaker among all dementia subtypes. However, HAVB was not more common in individuals with DLB compared to those with Alzheimer's disease or vascular

dementia, and there was no association between DLB and HAVB compared to Alzheimer's disease. No individuals in Paper II were diagnosed with HAVB and HAVB was less prevalent compared to SSS among individuals with LBD in Paper IV. This finding could be due to the atrioventricular node being less influenced by the autonomic nervous system compared to the sinus node[112]. Thus, this observation might further strengthen the theory that bradyarrhythmia in individuals with LBD could be a consequence of cardiac autonomic dysfunction.

We did not observe an association between SSS and Parkinson's disease dementia compared to Alzheimer's disease. This finding might be explained by the different propagation patterns of LBD, as Parkinson's disease is thought to mainly propagate in a brain-first pathway with less severe autonomic involvement compared to individuals with DLB[101]. Therefore, bradyarrhythmia might not be as common in Parkinson's disease and Parkinson's disease dementia compared to DLB.

Furthermore, the difference in prevalence of SSS among individuals with LBD when comparing Papers II and IV with Paper III might have been due to uncertainties regarding DLB diagnosis in the latter group. In Paper III, individuals with DLB had a high rate of revised dementia diagnosis, which is consistent with previous research[56].

In Paper III, we observed that most individuals diagnosed with DLB had syncope as their main symptom of SSS requiring a pacemaker implant. As noted previously, syncope is both a supportive feature of DLB (often attributed to orthostatic hypotension[137,138]) and a common symptom of bradyarrhythmia[152,174]. Because of this overlap, some individuals with LBD in Papers III and IV might have had unrecognised bradyarrhythmia, as this might not have been actively examined through heart rate monitoring antemortem.

In Paper I, both men with DLB had syncope as their main symptom of SSS. The reduction in syncope following pacemaker implantation was perceived to contribute to their improved well-being. However, both couples perceived that the reduction in syncope did not persist throughout the year following pacemaker implantation. This result may indicate that their syncope was also caused by factors other than bradyarrhythmia (e.g. neurogenic orthostatic hypotension) or that pacemaker implantation might be less effective in reducing symptoms if bradyarrhythmia is due to autonomic dysfunction.

Besides syncope, dizziness and fatigue were the second and third most common SSS symptoms among individuals with DLB in Paper III and associated symptoms of SSS of two participants in Paper II. Compared to syncope, these symptoms are likely to be even more non-specific for recognizing concurrent bradyarrhythmia in clinical settings.

Besides a reduction in syncope, both couples in Paper I perceived that pacemaker implantation improved their wakefulness and physical stamina, helping them to

maintain their social lives. In accordance with these observations, prior research has also described how individuals living with DLB and family carers often experience the need to maintain their socially active lives despite their physical and cognitive barriers[81]. Their perceived increase in wakefulness may be explained by improved cerebral perfusion due to cardiac pacing[191].

Guided by our theoretical framework, previous research and clinical experience this thesis focuses on bradyarrhythmia and the possible management of bradyarrhythmia through pacemaker implantation among individuals with DLB. However, intermittent tachyarrhythmias may also play a role in syncope among those with LBD, possibly as a consequence of cardiac α-syn pathology.

In Paper IV, sudden cardiac death was more common among individuals with LBD/multiple system atrophy compared to controls (with no difference in cardiovascular comorbidities). This finding is in accordance with prior research and might reflect an increased risk of fatal ventricular tachyarrhythmias due to cardiac α-syn pathology[130,131]. As noted earlier, the risk of sudden cardiac death in unmanaged SSS is low[173].

In Paper II, two participants with SSS also had atrial fibrillation. In Paper III, 17.0% of all pacemaker implants were due to atrial fibrillation, and in Paper IV one-third of those with LBD had atrial fibrillation. As atrial fibrillation and SSS commonly coexist and interact[105], it is possible that some individuals in Paper II– IV with LBD and atrial fibrillation also had undiagnosed concomitant SSS. However, prior studies have not shown any consistent association between atrial fibrillation and LBD[57,58,65].

Methodological considerations

Philosophy of science

Exploring lived experiences, as in Paper I, assumes that multiple realities exist (ontological relativism) and that knowledge is acquired through subjective interpretations (epistemological subjectivism). Consequently, our findings might not represent all patients, and there is no absolute 'right' or 'wrong'. Nevertheless, this type of research is valuable for gaining an in-depth understanding of a disease (e.g. DLB), a phenomenon (e.g. pacemaker implantation for individuals with bradyarrhythmia and DLB), or for generating new research questions that can be pursued in both qualitative and quantitative research.

In contrast, quantitative research, such as that in Papers II–IV, rests on ontological realism and epistemological objectivism, which are essential when investigating biological disease mechanisms or addressing epidemiological research questions.

Participant selection

Prior to Paper I, bradyarrhythmia in individuals with LBD had only been described in a few case reports, while one prior qualitative study had directly involved individuals with DLB. Because we did not know how common bradyarrhythmia requiring a pacemaker implant in individuals with DLB was (and whether qualitative interviews were possible), we limited our first study to two individuals with DLB and their family carers. Importantly, this meant that our observations lacked saturation and generalizability. However, given the novel research aim and design, the findings were considered valuable for both future qualitative DLB research and quantitative studies exploring the possible association between DLB and bradyarrhythmia.

Paper II did not include a control group (e.g. individuals with Alzheimer's disease or cognitively unimpaired controls) due to the examinations being relatively time-consuming and recruiting participants as controls was deemed to possibly cause them more harm than benefit. Had we recruited controls for Paper II, some Holter recordings might have revealed previously undiagnosed bradyarrhythmia requiring pacemaker implantation. However, this scenario was unlikely given the relatively low prevalence of SSS and HAVB.

In Paper II, the decision to end recruitment at 30 participants was guided by sample sizes reported in previous heart rate variability research and by the logistical complexity of coordinating the examinations. Recruitment spanned approximately 18 months, a duration likely attributable to the limited on-site promotion of the study at the designated memory clinics. Furthermore, there was a risk of selection bias, as neither previous bradyarrhythmia nor bradycardia was an exclusion criterion. A review of medical records after enrolment showed that none of the participants had a documented diagnosis of bradyarrhythmia or bradycardia before inclusion. However, some clinicians may have recalled the study primarily when assessing certain DLB patients, for example, those with prior bradycardia on ECG, syncope, repeated falls or multiple cardiovascular comorbidities.

When acquiring data from SveDem, we included all patients registered with a dementia diagnosis between 1 May 2007 and 31 December 2020. As such, Paper III constituted of much larger cohorts of individuals with Alzheimer's disease dementia, vascular dementia and mixed dementia compared to DLB. Although cohort sizes varied considerably, we did not consider this as a limitation for addressing our specific aims. However, the exclusion of 22,468 individuals with unspecified or other dementia prior to analysis likely excluded many misdiagnosed DLB patients.

In Paper IV, most individuals had not been referred for autopsy from a specialized memory clinic, which possibly increased the generalizability of our results, as most cases with dementia likely did not represent individuals with atypical dementia presentations. Paper IV also highlighted another aspect of LBD, that is, the

difficulties in recruiting non-α-syn controls, as several of the assumed controls had some degree of α-syn in the brain and/or heart. As it is difficult to ascertain a diagnosis of DLB antemortem, we cannot truly say that the neuropathological diagnoses of DLB in Papers I–III were accurate, nor that the underlying propagation patterns were all the same. If we had recruited a control group in Paper II, they might have had underlying prodromal LBD, as many older adults exhibit some degree of α-syn pathology in the brain or peripheral nervous system[23].

Moreover, disease heterogeneity of LBD might cause an inherent problem of replicating the results in future studies with other clinical DLB cohorts, as α-syn propagation patterns and disease presentation may differ considerably. To address this in Papers I and II, we tried to describe the clinical features of individuals with DLB and SSS as thoroughly as possible.

Data collection

Interviewing couples was a unique qualitative approach, that might have helped the couples reflect more on how the past year had been and possibly made the men with DLB feel more comfortable during the interviews. Interviewing dyads might also have decreased the risk of recall bias. We used repeated interviews, with different investigators, to increase credibility and address longitudinal experiences. Ideally, conducting an additional interview prior the pacemaker surgery might have revealed a better understanding of the couples lives in relation to after the surgery. However, this might have been difficult to coordinate.

In Paper II, some individuals diagnosed with SSS had a normal or inconclusive Holter ECG at inclusion. By December 2022, we recorded whether participants had received a bradyarrhythmia diagnosis; however, this resulted in varying follow-up durations from enrolment to study end. This approach may have missed bradyarrhythmia cases that would have been identified had all participants been followed for as long as the first enrollee. We chose this approach (recording any bradyarrhythmia diagnoses by December 2022) because SSS is not always diagnosed from a single Holter ECG and may require additional follow-up monitoring or in-hospital telemetry. Thus, future studies could benefit from repeated or prolonged monitoring to improve diagnostic ascertainment of SSS.

In Paper III, we only included individuals who had de novo pacemaker implantations and not those with reimplantations. Thus, the data might have excluded individuals with a pacemaker implanted prior to 1997. We did not request data of reimplantations as pacemaker implantations prior to 10 years before dementia was deemed unlikely to be due to underlying α-syn pathology[14]. However, this may have led to some individuals with DLB in Paper III being incorrectly coded as not having a pacemaker. Furthermore, we did not include individuals who had received an implantable cardioverter-defibrillator, which could have been valuable

if we would have also investigated potential associations between DLB and intermittent ventricular tachyarrhythmia[199].

For Paper II and IV, it was sometimes challenging to code dichotomous variables, as some data could fall into a grey area between either 'present' or 'absent'. In clarifying this issue, we kept a record of how the presence of e.g. RBD or fluctuations were coded in Paper II and showed pictures of the tissue samples that were considered 'positive' or 'negative' for α-syn pathology in Paper IV.

Moreover, we coded all diagnoses based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems for consistency. However, even though some participants in Paper IV were likely to have had SSS according to their medical records, this was coded as 'absent' if they had not received a proper diagnosis code. In Paper IV, it was challenging to retrospectively assume the absence of clinical comorbidities or symptoms when these were not explicitly documented as present (e.g. orthostatic hypotension), underscoring the inherent uncertainty of retrospective data collection. For Paper III, some dichotomous variables might not have reflected the true underlying biology, such as the assumed aetiology of SSS/HAVB.

Another important consideration was to try and make the diagnoses of DLB more accurate by using the last set dementia diagnosis. This approach likely increased the diagnostic accuracy of DLB, as many people with DLB initially receive other diagnoses (e.g. Alzheimer's disease dementia or unspecified dementia). Furthermore, DLB and PDD were not collectively categorized as 'LBD' as the presumed underlying disease propagation might differ.

In Paper IV, the presence or absence of α-syn was primarily assessed by a single experienced neuropathologist. Involving additional neuropathologists in reviewing the stainings could have improved reliability and reduced interpretation bias. To mitigate this limitation, we detailed our methodology in relation to previous studies and illustrated our interpretations with representative images.

Data analysis

In Paper I, we mostly focused on manifest content and not latent content because of the small number of participants and to avoid over-interpreting the data. Therefore, we only abstracted to the levels of categories and not themes. The confirmatory analysis conducted by our co-author (AB) was important for assessing whether the data had been over-interpreted, and for reducing interpreter bias and increasing objectivity.

Because of the small sample size in Paper II, there was a high risk of statistical uncertainties, making the results difficult to interpret. The small sample size likely increased the risk of random variabilities and type II error. It is possible that the

results of cardiac MIBG scintigraphy or neurogenic orthostatic hypotension when comparing groups were false negatives. Moreover, RMSSD and RBD might have been false positives due to multiple testing (type I error), as we did not adjust *p*-values according to Bonferroni correction, for example. However, using Bonferroni correction on a small sample size was considered to increase the risk of type II error.

Conversely, Paper III was based on a large sample with differing group sizes. These large sample sizes meant a possible risk of the data being over-powered and likely increased the risk of type I error. Although SSS was considered statistically more common in individuals with DLB compared to those with Alzheimer's disease, the accuracy and clinical relevancy of this finding is questionable.

Furthermore, in Paper III, we could not adjust our logistic regression model for specific cardiovascular comorbidities or drugs, as these data were unavailable in both registries. Instead, we used the dichotomous variable, 'cardiovascular drugs', from SveDem as a proxy of overall cardiovascular comorbidity. Adjusting for prescription of e.g. beta blockers, heart failure, acute coronary syndrome and/or atrial fibrillation in the same model might have revealed more informative results. However, this could have increased the risk of multicollinearity, and therefore our proxy of overall cardiovascular comorbidity might have been beneficial.

Conclusion

In conclusion, our findings suggest that bradyarrhythmia (i.e. SSS) represents an under-recognized feature of DLB. Furthermore, in some individuals, SSS could also be a prodromal manifestation of DLB, arising from early α-syn involvement of cardiac autonomic nerves that disrupts normal heart function. Also, SSS may mimic DLB symptoms (e.g. syncope and tiredness). If SSS is recognized, these symptoms may be improved by pacemaker implantation, thereby increasing the well-being of those affected.

For clinicians, this doctoral thesis includes the first major current research findings focused on bradyarrhythmia and DLB. Together with individual clinical expertise, our findings may be used when making decisions about the care of individuals with DLB. If reproduced, our results could have direct implications in clinical settings when assessing individuals with DLB. For example, by lowering the threshold to conduct ambulatory heart rate monitoring in outpatient care and not immediately labelling syncope and/or unexplained falls as being secondary to orthostatic hypotension in inpatient care.

Future perspectives

Our findings suggest that bradyarrhythmia represents an under-recognized and potentially manageable feature of DLB. However, additional research is needed to reproduce our findings and further understand the possible underlying mechanisms. Ideally, future studies should enrol a larger cohort of participants with LBD for prolonged ambulatory heart rate monitoring to evaluate the presence of bradyarrhythmia. This could be done by recruiting individuals with LBD who have documented syncope and/or unexplained falls. Such studies should also include age-matched control groups.

Besides traditional Holter monitoring, one might use smartwatches, extended-wear Holter monitoring or intermittent short ECG recording to assess heart rates over an extended period. These methods might be less uncomfortable compared to traditional Holter monitoring. Such studies could also evaluate the presence of intermittent tachyarrhythmia.

To further evaluate the underlying mechanisms of bradyarrhythmia in clinical LBD, future studies could use cardiac MIBG scintigraphy, orthostatic testing, heart rate variability domains, Valsalva manoeuvres and/or tilt table tests to assess cardiovascular autonomic functions. Future studies might also evaluate sinus node recovery time to determine if SSS in individuals with LBD is due to either intrinsic sinus node dysfunction or cardiac autonomic dysfunction[157,158].

Furthermore, the possible benefits of pacemaker implantation to manage SSS for individuals living with DLB should be evaluated further in quantitative and qualitative research. The latter should be used more frequently in DLB research to better understand the multi-complexity of the disease and identify what matters most for these individuals' management of their disease.

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