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Review

Intrinsic capacity in Lewy body dementia: a review

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ABSTRACT

Frailty is a clinical syndrome characterized by diminished physiological reserves and increased vulnerability to stressors. While frailty has been largely studied in Alzheimer's disease, few study focused on Lewy body dementia (LBD). Beyond frailty, the World Health Organization recently highlights the concept of intrinsic capacity (IC), offering a promising framework for the early identification and intervention to mitigate the risk of frailty and disability in older adults. IC refers to an individual's physical and mental abilities (including five dimensions: sensory, psychology, locomotion, vitality and cognition), which support the maintenance of functional capacity and promote healthy aging. In this review, we aimed to describe the prevalence of IC decline in LBD and its potential consequences. While few studies focused specifically on this question, we found evidence in the literature of a higher prevalence of IC decline in LBD, compared to cognitively unimpaired older adults and to Alzheimer's disease patients. If future studies are needed to confirm these results, we assume that IC assessment and monitoring in LBD may be a further step towards a better integrated and personalized care for patients. This may open the avenue to develop specific tailored interventions, to decrease disability and increase quality of life and "healthy ageing" of patients despite the presence of LBD.

1. Introduction

Frailty is a clinical syndrome characterized by decreased physiological reserves and increased vulnerability to stressors. The clinical manifestation of frailty is influenced by comorbidities as well as psychological, social, economic, and behavioral factors. Phenotypically, it can present as fatigue, muscle weakness, reduced gait speed, sedentary behavior, and unintentional weight loss [1]. Frailty syndrome is a recognized risk marker for mortality and adverse outcomes in older adults, including disability, falls, hospitalization, and institutionalization [2]. While age is a key determinant of frailty, it alone does not account for the complexity of the syndrome, and it is well known that chronological age is not a sufficient factor to understand complex issues in older adults [3]. Addressing the underlying factors contributing to frailty may mitigate or delay its progression. Thus, frailty represents a potentially reversible condition [4]. Several models and tools have been proposed to identify and assess frailty, both in research and clinical practice. However, they remain underutilized beyond the field of geriatric medicine, poorly understood, and relatively unknown in routine clinical settings.

The concept of intrinsic capacity (IC), introduced by the World Health Organization in 2015, offers a promising framework for the early identification and intervention to mitigate the risk of frailty [5]. IC refers to an individual's physical and mental abilities, which support the maintenance of functional capacity and promote healthy aging—enabling individuals to pursue what they value in life [6,7]. While frailty is often associated with loss and deficits, IC adopts a more positive and holistic perspective. It emphasizes optimizing the patient's preserved abilities, with the aim of maintaining functional capacity and enhancing overall well-being, and thus "healthy ageing" [8]. Moreover, although frailty was not originally intended as a criterion for excluding patients from interventions, clinicians often perceive it negatively [8], and IC

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constructs may mitigate this negative view. IC can be divided into five domains: cognition, psychology, locomotion, vitality, and sensory. Like frailty, declines in IC are associated with increased dependency and higher mortality [9]. This association allows for the prediction of a patient's clinical trajectory and the implementation of interventions aimed at modifying it. Indeed, a recent meta-analysis demonstrated an association between reduced IC and loss of autonomy; conversely, maintaining or improving IC is correlated with a decreased risk of autonomy loss, particularly in instrumental activities of daily living [9]. In this context, the Integrated Care for Older People (ICOPE) program aims to detect early declines in IC, enabling targeted interventions within the community setting [10].

In the field of neurocognitive disorders (NCD), frailty has been shown to increase the risk of developing NCD [11]. Globally, frailty is becoming a widespread model, including in neurology, beyond the perimeter of geriatric medicine [12]. This relationship has been extensively studied in Alzheimer's disease (AD), with several studies reporting that frailty affects the clinical manifestations of the disease [13,14]. Recent large-scale data from the UK Biobank confirmed this association, revealing that nearly 10 % of the risk of developing a NCD is attributable to frailty [15]. While there is extensive literature on the link between frailty and AD [8], there is surprisingly little regarding Lewy body diseases (LBD), despite it being the second most common neurodegenerative disease with cognitive manifestations [16].

LBD is a clinical construct that includes two distinct phenotypes: dementia with Lewy bodies (DLB) and Parkinson's disease dementia, which are clinically differentiated by the timing of onset between motor and cognitive symptoms [17]. These clinical syndromes are unified by a common underlying pathology: the abnormal accumulation of α-synuclein aggregates in neurons [18]. Even though neuronal α-synuclein disease Lewy body disease is a pathological entity, some authors suggest a move towards a biological definition [19], its clinical expression can be modulated by cognitive reserve or comorbidities. Today, little is known about triggers and factors of disease progression, which may be linked to clinical, lifestyle or environmental aspects [20]. LBD patients appear to be particularly vulnerable to frailty, likely due to the early onset of motor and neuropsychiatric symptoms. Several studies suggest that LBD patients are frailer than AD ones. For example, a study found a frailty prevalence of 37 % in LBD versus 19 % in AD patients [21]. It has been shown that physical frailty in the general population is associated with a modestly increased risk of developing AD but is more strongly linked to an increased risk of developing a non-AD NCD [22]. This suggests a significant association between frailty and non-AD NCD, potentially including LBD [23].

We assume that it is crucial to focus on IC in LBD, as identifying and managing these capacities could alter the natural course of the disease, potentially delaying the onset of dependency and other complications. While IC is a relatively recent construct formalized by the WHO, its conceptual underpinnings complement and align with disability theory like Nagi's disability model or the International Classification of Functioning, Disability and Health framework [24,25]. ICF framework emphasize not only impairments but also the interaction between individual capabilities and environmental demands [25]. For instance, the Late-Life Function and Disability Instrument integrates the ICF framework to operationalize function and disability through both self-reported limitations and role participation, providing a structure that parallels IC domains [26]. This supports the view that disability is not unidimensional and reinforces the need for a construct like IC that captures the interplay of multiple functional domains across the life course.

Interventions aimed at maintaining IC have been shown to be effective and could be tailored for LBD, especially given the lack of disease-modifying treatments. This review aims to describe the prevalence of IC decline in LBD and its association with clinical manifestations. Although the World Health Organization only recently formalized the IC model, previous studies have investigated nutrition, mobility, psychological health, and sensory disorders in LBD separately and outside the integrated framework of intrinsic capacity. To our knowledge, only one study assessing all IC domains simultaneously has been published, and it appeared after the submission of this manuscript [27]. The goal of this review is to synthesize these studies, focusing on all IC—excluding the cognitive domain, which is inherently impaired in LBD —such as psychological, mobility, nutrition/vitality, and sensory changes.

2. Methods

This review followed the Arksey and O'Malley's methodological framework for scoping reviews [28], consisting of 5 steps: 1) identifying the research question; 2) identifying relevant studies; 3) study selection; 4) mapping and charting the data; 5) collating, summarizing, and reporting the results. This first phase was discussed between authors and the scope and direction of this review was defined based on author's experience of dementia, LBD, frailty and IC assessment and a preliminary search (PubMed). The research questions were: what is the prevalence of IC loss in LBD, and what are the clinical consequences of IC loss in LDB. For the second and third phase (study identification and selection), bibliographic research was carried out between May and July 2024, on PubMed, MEDLINE/OVID and Embase, by FS, MS and MN. The majority of the included studies concern dementia with Lewy bodies (DLB), but in some articles there could be an overlap between DLB and Parkinson's disease dementia, so for this manuscript we have chosen the terminology Lewy body dementia (LBD).

PubMed keywords for LBD were "Lewy Body Disease", "Lewy Bodies", "lewy body", "lewy bodies". Keywords for sensory IC were "Vision", "Hearing", "Hearing loss", "Loss of smell", "Smell disorders". Keywords for vitality domain were "Activities of daily living", "Malnutrition", "Nutrition", "Mini Nutritional Assessment". Keywords for locomotion domain "Locomotion", "Gait speed", "Gait", "Tinetti Test", "SPPB (Short Physical Performance Battery)", "Sarcopenia", "Fall". Keywords for psychology domain on PubMed and Embase were: for PubMed "Depressive Disorder", "Depression", "Anxiety", "Internal-External Control", "Personal Satisfaction", "Locus of control", "Life satisfaction", "Depression", "Depressive", "Anxiety", "Anxious". The research also included assessment tools for depression and anxiety. In Embase we used the following research method: "Diffuse Lewy body disease", "dementia with Lewy bodies", "dementia with Lewy body", "DLB (dementia with Lewy bodies)", "DLBD", "LBD (Lewy body disease)", "Lewy body dementia", "Lewy body dementias", "Lewy body disease", "Lewy body diseases", "diffuse Lewy body disease" and "Depression assessment", "Depression", "Anxiety disorder", "Anxiety assessment", "Life satisfaction".

After study selection, relevant information for each paper were collected and synthetized on tables. The authors have finally written a narrative review based on these references.

3. Results

3.1. Sensory domain of intrinsic capacity

3.1.1. Olfaction

Olfactory disorders (OD) are common and increase with age, affecting 24.5 % of the general population and up to 70 % of older adults [29]. OD have a negative impact on quality of life, influencing various relational and emotional aspects, often leading to frustration, social isolation, anxiety, or depression [30,31]. They also diminish the enjoyment of food and can impair appetite [32], as odor molecules play a key role in regulating hunger and satiety through specific sensory mechanisms [33]. The olfactory system comprises the olfactory epithelium, olfactory nerves, olfactory bulbs (rich in dopaminergic neurons), and olfactory pathways, which connect to the entorhinal cortex, anterior piriform cortex, amygdala, hippocampus, and cerebral cortex, including

the orbitofrontal cortex [34].

Patients with LBD complain of having pronounced olfactory impairments, which often begin in the early stages of the disease [35]. In fact, according to Iranzo and colleagues, olfactory detection deficits are already present in patients with isolated REM sleep behavior disorder [35], and thus prodromal stages of the disease. A study reported 14 % of LBD patients had hyposmia or anosmia, compared to 2 % of AD patients [36]. Moreover, when NCD are compared, odor identification deficits are more frequent and more severe in people with DLB than in people with AD [37], vascular disorders, or mixed NCD [34]. According to Foguem and colleagues, the olfactory detection threshold and trigeminal sensitivity are more impaired in patients with LBD than in patients with Parkinson's disease [38]. Recently, it has been shown that cognitively unimpaired participants with Lewy body pathology (positive α-synuclein seeding amplification assay) had a reduced sense of smell compared to participants without Lewy body pathology [39].

In terms of pathophysiology, studies have identified the presence of Lewy bodies and α-synucleinopathy in the olfactory bulb and anterior olfactory nucleus, suggesting that the neurodegenerative process may begin in the olfactory system before spreading to other brain regions [40].

Assessing olfactory function is complex and rarely done in clinical practice [41], but several tests, such as the University of Pennsylvania Smell Identification Test (UPSIT) [42] and Sniffin' Sticks [43], are used in both clinical practice and research. These assessments aid in distinguishing patients with NCD from healthy individuals [38,44,45], or from those with psychiatric conditions [46]. They may also assist in differentiating AD from LBD, particularly in the early stages of the disease [47,48]. Moreover, screening for OD opens the door to non-pharmacological interventions, such as olfactory training, which may improve cognitive function, alleviate depressive symptoms, and enhance overall patient well-being [49].

3.1.2. Hearing

Hearing and vision are modifiable risk factors for dementia, as recently stated by the Lancet Commission on Dementia Prevention, Intervention and Care, led by Livingston and colleagues [50]. Specifically, hearing loss is independently associated with NCD from all causes [51], but the pathophysiological mechanisms between the pathologies remain uncertain [52]. The relationship between NCD and hearing impairment can be considered as a two-way relationship. On the one hand, NCD may be associated with neurosensory impairment notably due to neurodegeneration in cortical auditive areas [53], and on the other, hearing loss may lead to reduced cognitive stimulation and social interaction, as well as an increased risk of depression, all of which are NCD risk factors [51,54]. If hearing loss appears as a modifiable risk factor for cognitive decline and cognitive impairment in observational studies, interventional studies have failed to show large benefits of hearing aids on reducing NCD risk [53,55].

Few studies have specifically investigated hearing loss in LBD. Clinico-pathological studies suggest an association between LBD and hearing loss [56,57]. Moreover, hearing dysfunction is common in the spectrum of synucleinopathies (LBD and Parkinson Disease) and could be a marker of the onset, progression, and severity of the disease [58,59].

3.1.3. Vision

Vision is a complex function that depends on multiple abilities, such as visual acuity, contrast sensitivity and binocular vision, and requires the proper functioning of various structures such as the eye, the oculomotor system, the retina, the optic nerve and the primary and associative visual cortex, and other neuronal networks. Visual perception is shaped by the integration of external sensory stimuli and internal representations, modulated by various neuronal projection networks [60,61]. As part of the aging process, and especially in the context of neurodegenerative diseases, visual impairments are common and multifactorial [62]. Specifically focusing on visual acuity, patients with NCD exhibit significantly lower acuity compared to healthy control subjects [63].

Few studies evaluate peripheral visual disorders in LBD. However, various abnormalities in eye movements, including reduced saccadic speed and accuracy, as well as vertical gaze palsy, have been reported in LBD [64,65]. Akinesia and rigidity can impair visual perception and coordination, contributing to visual fatigue and discomfort. Additionally, certain ophthalmological parameters, such as retinal thickness [66], and retinal vascular density [67], are significantly altered in LBD than in AD. LBD patients also exhibit alterations in stimulus transmission and visual pathways, particularly on the right pathways, along with visual field deficit such as left homonymous hemianopsia [68,69]. Color vision disorders are highly prevalent in LBD, more frequently than in AD [70]. These disorders affect up to two-thirds of patients in the severe stages of NCD and up to 44 % in the prodromal stage, compared to less than 20 % of patients with mild to moderate AD [71,72]. Photophobia is also more common in LBD than in other NCD, with a prevalence of 47.3 %, and is notably present even in the prodromal stage, affecting 30 % of patients [73,74]. Additionally, eye dryness has been reported in 24 % of patients during the prodromal stage of LBD [73]. Visual-perceptual and visuospatial cognitive disorders are particularly pronounced in LBD, presenting as deficits in contrast sensitivity, visual identification and discrimination (e.g., length, size, angle, texture, shapes), motion and spatial perception, as well as difficulties in reproducing or drawing 2D figures, constructing 3D objects, and stereopsis [63,69,75–80]. According to Hamilton et al., the severity of visuospatial impairments in LBD may serve as an indicator of more rapid disease progression and a particularly severe clinical course [81].

In summary, while sensory functions (notably audition) were rarely specifically studied in LBD, LBD pathological inherent processes could lead to sensory disorders that can seriously affect perceived quality of life and autonomy. They can also lead to depression, by reducing participation in social and leisure activities, which are essential for maintaining good mental and physical health in old age.

3.2. Nutrition/vitality domain of intrinsic capacity

Malnutrition is defined as a state of nutritional imbalance in which the intake of nutrients is insufficient to meet the physiological needs of the body, leading to deficiencies in energy, protein, and micronutrients, with potentially serious clinical consequences for health, including impaired immune function, decreased muscle mass, and increased risk of mortality [82]. Prevalence of malnutrition in patients with severe NCD is 17 %, while the risk of malnutrition is 43 % [83]. Malnutrition in LBD appears particularly frequent. For instance, a study indicates that 18 % of patients with LBD are undernourished [84]. These patients are also at a higher risk of malnutrition [83] and exhibit lower levels of biological nutritional markers, such as serum albumin and hematocrit, compared to individuals with other NCD, including Parkinson's disease, frontotemporal lobar degeneration, and vascular NCD [85]. Weight loss and malnutrition are more prevalent in patients at more advanced stages of the disease and in older age groups. Identified risk factors for malnutrition in LBD include behavioral disorders, cognitive decline, and functional deterioration [84]. In a longitudinal study using body mass index (BMI), Borda and collaborators observed that BMI decreased significantly faster in LBD patients than in AD patients [86]. They also found a positive relationship between Mini-Mental State Examination (MMSE) score and BMI. Other authors have observed weight loss in 25 % of patients with major NCD (AD, LBD, vascular) and this is more frequent in LBD patients [87].

Weight loss result from reduced energy intake or an increase in energy expenditure. Appetite loss has been observed in 34.2 % of patients with probable LBD [74] and is more pronounced in patients with LBD than in those with AD [88]. Depending on the studies, eating disorders may affect 28 % and up to 57 % of patients with LBD [89,90].

Neuropsychiatric symptoms, such as apathy and depression, may favor a reduction in food intake [91]. Furthermore, OD and taste changes described above may favor anorexia, as may changes in the digestive system, including dysphagia [80] or constipation, bloating and vomiting after meals [74,92,93]. Eating disorders and their consequences also have an impact on the caregiver's quality of life [94].

Prior to the development of LBD, there also appears to be a link between diet style and the risk of developing LBD. In a Greek study, a Mediterranean diet which is rich in fruit, vegetables and unrefined cereals, combined with a moderate diet of poultry, dairy products and fish, and a low consumption of red meat, was associated with a lower risk of developing LBD [95]. Docosahexaenoic acids containing phospholipids (DCP) levels were found to be significantly reduced in LBD compared with controls. Several DCPs correlated negatively with soluble Aβ42 and positively with α-synuclein. In addition, DCP correlate positively with Rab3A, a protein whose levels are inversely related to Lewy body burden and cognitive decline [96]. Some authors have found a link between increased levels of low- and high-density lipoprotein cholesterol and the development of LBD [97].

It also seems possible to differentiate LBD from AD using plasma metabolites, in particular by the significant increase in glutamine in LBD patients. Glutamine plays a role in energy metabolism, synthesis of pyrimidine and purine bases, intestinal barrier function and insulin resistance [98]. Conversely, and surprisingly, sarcopenia does not appear to be more common in LBD than in AD and may not be a distinguishing factor between these two populations [99] (see next paragraph on locomotion domain).

In conclusion, LBD patients seem at greater risk of malnutrition, in relation to various symptoms of the disease that modify nutritional intake, and offer clues for future research on this field, and potential nonpharmacological interventions.

3.3. Locomotion domain of intrinsic capacity

Locomotion difficulties appear very common in LBD. Indeed, McKeith and colleagues' diagnostic criteria for LBD include among the major features the presence of parkinsonism, which comprises the triad of bradykinesia, rest tremor and rigidity [100]. This is a non-mandatory criterion, but still very common symptoms in LBD, affecting locomotor capacity. In several studies, gait disorders appear to be more frequent in LBD, with an estimated prevalence of 75 %, compared with 25 % in AD and 7 % in control subjects [101]. Gait disorders could therefore help in the etiological diagnosis as gait disorders are more frequent in 'non--Alzheimer's' diseases. One study even suggests that gait pathological signatures can be used to differentiate LBD from AD, particularly greater impairment of gait asymmetry and variability in LBD [102]. In the same vein, when comparing motor skills in patients with different types of NCD, individuals with LBD exhibit significantly slower walking speeds, shorter stride lengths, poorer balance (as measured by the Tinetti and Berg scales), and worse performance on dual-task activities compared to AD or Parkinson's disease patients [103]. Moreover, studies have demonstrated a correlation between cognition (MMSE scores) and motor tests such as the Timed Up and Go and unipedal balance in LBD patients, suggesting a link between cognitive functions and balance impairments [104]. Falls occur more frequently in LBD than in AD, and LBD patients score lower on the Tinetti scales and grip strength assessments [105]. Similarly, LBD patients experience greater difficulties with axial motor skills, gait, and balance compared to those with Parkinson's disease, likely due to coexisting parkinsonism as well as dysexecutive and visuospatial symptoms in LBD [106].

Another key factor of locomotor capacity is muscle strength and function, which may be compromised in patients with sarcopenia. Sarcopenia is defined as a 'generalized disease of skeletal muscle, characterized by low muscle strength and low muscle mass [107]. Sarcopenia is highly prevalent in patients with dementia; previous studies have linked sarcopenia and sarcopenic traits (e.g., reduced physical performance, muscular strength, and muscle quantity/quality) to cognitive impairment and AD [108,109]. Even though emerging evidence highlights potential muscle-brain crosstalk involving mitochondrial, metabolic, and inflammatory processes, as well as myokines [110], the neurobiological mechanisms underlying the sarcopenia-dementia connection remain unclear, especially in DLB. According to Dost and colleagues, sarcopenia in DLB is as prevalent as in AD (19.5 % in AD vs. 19.1 % in DLB), though its specific characteristics differ. In AD, it appears to be associated with reduced muscle mass and strength, while in DLB, it is linked to reduced muscle strength and slower gait speed [99]. In DLB, slow gait speed is unsurprising given its cognitive and motor impairments.

To conclude, decline in the locomotor domain of IC appears to be very frequent in LBD and could facilitate the development of targeted interventions to reduce fall risk and potentially modify the trajectory of functional loss. Some studies highlight the importance of early and proactive assessment, as well as the implementation of robust interventions for frailty predictors, such as locomotor impairments in LBD [111,112].

3.4. Psychological domain of intrinsic capacity

As motor symptoms, psychological assessment in LBD is particularly crucial, as psychiatric symptoms are part of the clinical features of LBD, as 'supportive clinical features' [101].

3.4.1. Anxiety

While anxiety is a common symptom in NCD, its prevalence is notably higher in LBD, affecting between 50 % and 67 % of patients [113–115]. The trajectory of anxiety symptoms in LBD remains a subject of debate. Anxiety symptoms in LBD may decrease over time as the disease progresses, a pattern that appears to be specific to LBD. In contrast, anxiety in AD often worsens as the disease advances [116]. Moreover, anxiety related to hallucinations and delusions appears to have a greater impact on LBD caregivers than hallucinations and delusions themselves [117]. Anxiety is also correlated with poorer cognitive performance, particularly in attention and visuospatial domains [118].

3.4.2. Depression

Between 34 % and 55 % of LBD patients exhibited depressive symptoms at initial assessment [119,120]. Over a six-year follow-up, 70 % of LBD patients were reported to have depressive symptoms, with 20–30 % classified as mild, 40–47 % as moderate, and 10–53 % as severe [120–122]. Symptom intensity appears to worsen over time as the disease progresses [114]. In a study by Armstrong and colleagues, 18.9 % of patients reported experiencing suicidal ideation [123]. Some studies indicate that LBD patients have more severe depressive symptoms, more major depressive disorders (19.7–24.45 % compared with 8.7–9.32 % in AD), and of longer symptoms duration than other neurodegenerative conditions [124–127]. A longitudinal study over 5 years has shown that depressive symptoms intensity and prevalence increase progressively in LBD, whereas in patients with AD these symptoms show a delayed increase [128]. Prevalence and clinical features of depression remain comparable between LBD, other synucleinopathies [125,129–133] and vascular cognitive impairment [113].

Depression in LBD presents atypical features, including a lower prevalence of sadness, a high frequency of psychotic elements (especially in women) [134–136], and a higher prevalence of apathy [137], anhedonia, sleep disorders, and low self-esteem [138]. Depressive symptoms impact sleep, leading to excessive daytime sleepiness and poor sleep quality [139]. Moreover, depression in LBD is associated with several symptoms and comorbidities, including dysautonomia [140], cardiovascular diseases [128], an abnormal ventilatory response to hypercapnia [136], as well as akinesia and rigidity [129]. According to Wright and colleagues, the prevalence and severity of affective

symptoms are not related to cognitive performance, either at baseline or during follow-up. The authors suggest that in LBD, many neuropsychiatric symptoms may not be directly linked to cognitive impairment and could arise from mechanisms distinct from those responsible for cognitive dysfunction. However, a significant correlation has been observed between neuropsychiatric symptoms (measured using the Neuropsychiatric Inventory) and deterioration in verbal fluency and reaction times. This suggests that the overall burden of neuropsychiatric symptoms may serve as an additional indicator of disease severity [141].

In conclusion, it is important to emphasize that the assessment of IC largely depends on the tools and criteria used. Furthermore, there is significant symptomatic overlap between depression and LBD, with shared features such as psychomotor slowing, attention deficits, sleep disturbances, loss of appetite, and delusion [142]. Overall, depression and anxiety are highly prevalent in LBD, more so than in normal aging and AD.

4. Discussion

LBD represents a complex and challenging disease due to the diversity of its clinical features, which go well beyond cognitive symptoms. This review highlights that LBD is associated with several alterations of IC, notably due the high prevalence of neuropsychiatric symptoms, including depression and anxiety, gait disorders, involuntary weight loss, and sensory loss.

Many manifestations of DLB are directly linked to the disease's pathological mechanisms. The question remains whether IC impairment is a core feature of DLB (due to disease characteristics and pathophysiology, Fig. 1), or whether it is due to some other additive factor beyond the DLB perimeter. Attributing IC impairment solely to the direct consequences of Lewy pathology underestimates the complexity of biological and environmental interactions influencing these dimensions. To our knowledge, no direct evidence supports the hypothesis that IC or frailty moderates the relationship between neuropathological burden and clinical phenotype in LBD. Nonetheless, one study by Buchman et al. does suggest an association of nigral neuronal loss with pathological features of LBD and frailty progression [143]. This suggests a possible indirect link between Lewy pathology and frailty via motor impairment (parkinsonism) but does not establish that frailty moderates the clinical expression of LBD. Due to the absence of widely used in vivo biomarkers of Lewy pathology or distinct molecular pathological profile [144], it is difficult to correlate Lewy body's pathology and intrinsic capacity. However, future advances, particularly with biomarkers such as RT-QuIC, may allow for more refined exploration of such interactions [145].

By contrast, in Alzheimer's disease, extensive evidence supports the role of frailty as a key modifier of the relationship between neuropathological burden and clinical outcomes or features. Frailty appears as additive factors shaping the clinical expression of dementia and lowering the threshold at which AD pathology becomes symptomatic [11,146,147]. While cognitive impairment due to neurodegeneration is a hallmark of DLB, additional factors such as cognitive reserve, educational background, and comorbidities contribute to the variability of cognitive decline. These factors are not solely related to Lewy pathology but also influence the clinical expression of symptoms, shaping the cognitive phenotype of the disease.

The recent results of Collin and collaborators (not included in the present review as published after the study selection) show that all intrinsic capacity domains are decreased in individuals with Lewy body disease compared to those with Alzheimer's disease. Moreover, they show several relationships between IC, suggesting that these domains are interconnected [27]. Several mechanisms may underlie these interconnections. A conceptual model suggests that impairments in one IC domain may trigger cascading effects in others, reinforcing a vicious cycle of decline. Mobility issues in DLB, often associated with parkinsonism and postural instability, can be further exacerbated by loss of vitality IC or other extrinsic factors such as sarcopenia, nutritional imbalances, or sensory deprivation (e.g., visual or hearing loss). These factors are modifiable and not exclusively driven by neuropathological processes. Similarly, depressive symptoms, frequently observed in LBD, may lead to reduced physical activity, social isolation, and loss of appetite, thereby contributing to nutritional decline and physical deconditioning. Sensory impairments (e.g., visual or auditory deficits) may reduce engagement in daily life, exacerbate psychological vulnerability, and hinder effective nutritional self-care. Finally, in nutrition and vitality IC, swallowing difficulties or anorexia, though potentially worsened by motor or cognitive symptoms, are also shaped by dysautonomia, comorbidities (e.g., digestive disorders), dietary choices, and social factors. On the other hand, declines across multiple domains of intrinsic capacity may arise from shared upstream biological processes. These include accelerated aging of the brain and body, chronic low-grade inflammation, who drive parallel deteriorations in psychological well-being, mobility, sensory processing, nutritional status, and dementia [148,149]. IC does not merely reflect pathological processes but may represent a distinct functional dimension of aging. From this perspective, frailty and IC complement traditional disease-centered

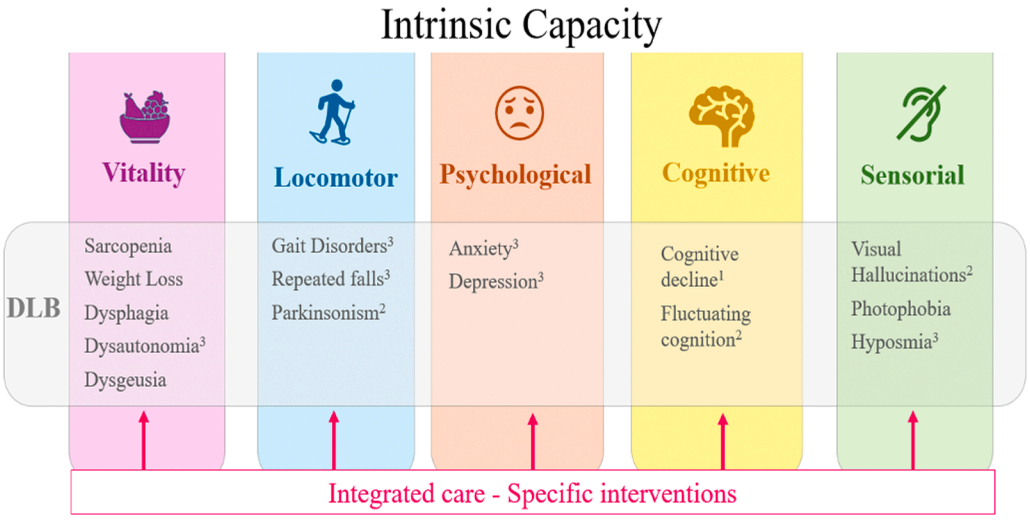

Fig. 1. Intrinsic capacity in dementia with Lewy bodies: relationships with clinical features, and opportunities for care. Some decrease in IC may be associated with features of DLB according to the McKeith criteria. [1] "essential criteria"; [2] "core clinical features"; [3] "supportive clinical features". DLB: dementia with Lewy bodies.

models, adding a functional aging layer that enhances the prediction of adverse outcomes such as cognitive impairment or dementia onset, especially in the preclinical or prodromal stages of neurodegenerative diseases [150].

The IC model, promoted by the World Health Organization highlights a "capacity-centered" approach, beyond the "disease-centered" approach and allows to understand this complexity. Indeed, the significant variability in clinical trajectories observed among DLB patients supports the need for personalized analysis for predictive and precision medicine [151,152]. Differentiating between disease-centered factors in LBD and those stemming from a decline in IC remains a major clinical and conceptual challenge. One of the core difficulties lies in the heterogeneous and poorly defined natural history of LBD [153]. In contrast to conditions like Alzheimer's disease, LBD lacks a clear pathophysiological model [154]. Familial cases are rare, and even among them, clinical trajectories often diverge, suggesting a significant influence of epigenetic, environmental, and stochastic factors [20,155,156]. Furthermore, mixed pathologies and frequent co-occurrence of Alzheimer-type lesions or cerebrovascular disease, further complicate causal attribution [157,158]. To address this complexity, several complementary strategies could be proposed. First, comparative studies across neurodegenerative disorders, such as comparing LBD to AD or PD, may help isolate disease-specific contributions to patterns of IC impairment. These conditions affect IC domains in different ways, and studying their respective trajectories may clarify the influence of underlying pathology versus systemic decline. In clinical settings, a temporal approach may also prove useful. By examining whether a symptom fits the typical progression of LBD, it may be possible to differentiate early manifestations of Lewy pathology from symptoms more likely attributable to frailty or other comorbidities. Given the limitations of purely clinical observation, the development of biomarkers is a crucial next step. While no definitive in vivo biomarker currently exists for LBD, several avenues are under investigation. These include α-synuclein assays [145] and imaging markers, particularly in populations at risk such as individuals with RBD. Importantly, this pathology-oriented biomarker development should be complemented by biomarkers of frailty and IC decline —for instance, inflammatory markers or sarcopenia indices—which may help distinguish age-related vulnerabilities from core neurodegenerative processes.

Additionally, functional stratification within LBD cohorts—based on baseline IC or frailty—may help identify subgroups with different clinical trajectories. This may clarify the extent to which symptoms are driven by underlying pathology versus loss of physiological reserve. It is also plausible that frailty itself contributes through distinct biological pathways, only partially overlapping with those involved in Lewy pathology [159].

Finally, from a pathophysiological point of view, with the rise of gerosciences, a better understanding of the biological determinants of the decline in IC could lead to a better understanding of the mechanisms of ageing and loss of independence in LBD and could open up innovative therapeutic avenues [160]. This approach would make it possible to tailor interventions more precisely to individual patient trajectories, and to better guide research into the underlying mechanisms of decline in LBD (Fig. 1).

Few studies have simultaneously assessed the five dimensions of IC. In the study from Collin and collaborators, the SPPB score (locomotion) was lower in patients with LBD compared to those with AD, the study also found that the MNA score (nutrition) was lower in LBD than in AD. Additionally, self-reported hearing ability was poorer in LBD than in AD [27]. There is considerable heterogeneity in the tools used to assess these abilities, with a variety of instruments that are often not harmonized according to the specific dimensions of IC. For instance, the work by Collin and collaborators demonstrated that different screening strategies yield different prevalence estimates for IC decline when comparing Step 1 and Step 2 of the ICOPE framework [27]. It therefore seems essential to harmonize assessment methods in order to gain a better understanding of the trajectory of patients with LBD. In addition, studies often involve small samples and are of variable methodological quality.

We believe it is crucial to structure a specific care pathway and to set up cross-disciplinary training involving neurology, geriatrics, psychiatry, clinical pharmacy, and general practitioners, in order to improve the assessment and management of IC in these patients. In LBD, curative or disease-modifying treatments remain elusive and treatment is based on symptoms. Even if interventions focused on IC may not alter the course of α-synuclein pathology, they can preserve or enhance the individual's functional reserve, allowing better compensation for deficits, and potentially delaying the onset of disability [111]. Furthermore, in other contexts, it has been shown that nonpharmacological interventions can help maintain or improve IC during ageing [161–163]. This would make it possible not only to improve assessment, but also to ensure longitudinal monitoring and earlier detection of patients at risk of frailty, and to propose interventions at an early stage. Thus, IC not as a competing framework to disease-centered models, but as a complementary and action-oriented lens, particularly suited to aging populations with neurodegenerative diseases. By preserving IC, clinicians may extend functional independence and quality of life, which are ultimately the outcomes most meaningful to patients and caregivers. These interventions need to be adapted to populations from memory clinics, and studies proving their effectiveness in patients with LBD are needed. Although the ICOPE program, which is currently being rolled out in various French regions, was primary constructed for non-dependent community-dwelling older adults, and therefore not specifically for patients with LBD, the dynamic offered by this large-scale program to identify declines in IC and the development of care pathways dedicated to the management of frailty could be beneficial to patients with LBD.

It appears important to rethink disease status and functional independence through the lens of intrinsic capacity. The limitations of a disease-centered model are particularly evident in geriatric medicine where functional independence—the ability to perform activities and maintain autonomy—emerges as a more relevant clinical outcome than disease status alone. Geriatric tools like the Comprehensive Geriatric Assessment (CGA) already reflect this functional approach and align with the ICF framework, which describes disability as the result of interactions between impairments and contextual factors [164,165]. However, unlike ICF, which provides a descriptive classification of functioning, IC focuses on physiological reserves and anticipates functional decline before disability emerges. IC thus complements ICF as an upstream determinant of health trajectories. This distinction is critical when interpreting clinical tools.

One limitation of this study is that it is a narrative review of the literature, and no meta-analysis was possible because of the heterogeneity of the studies and measures of IC, and the small number of publications for certain domains of IC. Another limitation is the lack of a consistent comparison group across studies—some lacked a control group, while others included either healthy older individuals or patients with other NCD (mainly AD). The main strength of this review lies in its comprehensive synthesis of the literature across various IC domains, without narrowing the focus to a single domain. While this study did not follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, the bibliographic research was conducted rigorously, following a well-defined algorithm and keywords as described in the Methods section.

5. Conclusion

This review shows that IC is frequently impaired in LBD in each domain, and to a greater extent than in other diseases such as AD. The question remains as to whether lower IC are an additive phenomenon associated with the risk of frailty in some LBD patients, or whether they are a core feature of LBD. In any case, whatever the precise relationship between IC decline and LBD (probably a two-way relationship), we

assume that the IC model has value and enables a shift from a disease-centered to a capacity-centered approach promoting healthy ageing, including for LBD patients. Better and earlier identification of declines in IC could enable the implementation of tailored interventions for IC and functional capacities improving. This could have a direct impact on patients, by delaying the onset of dependency and improving quality of life. However, such interventions in this population have not yet been tested and will require rigorous feasibility and impact evaluation. This holistic perspective, which goes beyond a single analysis of cognitive symptoms, could transform the way we understand and treat LBD. Future research should focus on the development of more robust IC assessment tools, especially for the longitudinal and dynamical IC monitoring, to better understand how they evolve over the course of the disease and how they influence the clinical trajectories of patients. Finally, as described above, studies evaluating the deployment and assessing the effectiveness of interventions aimed at promoting IC will be needed.

Declaration of generative AI and AI-assisted technologies in the writing process

Data acquisition, management, analysis and manuscript writing were done by authors without the use of generative artificial intelligence (AI) and AI-assisted technologies. After writing the draft, during the preparation of this manuscript the authors used occasionally DeepL (https://www.deepl.com/fr/translator) in order to help improve certain English vocabulary words. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

CRediT authorship contribution statement

Federica Sanapo: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Marie Signoret:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Mihaela Nodit:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Antoine Garnier-Crussard:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Independent of this work, Independent of this work, A.G.-C.is an unpaid sub-investigator or local principal investigator in NCT04867616 (UCB Pharma), NCT04241068 (Biogen), NCT05310071 (Biogen), NCT03446001 (TauRx Therapeutics), NCT03444870 (Roche), NCT04374253 (Roche), NCT04777396 (Novo Nordisk), NCT04777409 (Novo Nordisk), NCT04770220 (Alzheon), NCT05423522 (Medesis Pharma), NCT06079190 (GlaxoSmithKline). Other authors declare any conflict of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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