MULTI-CENTRE COHORT-STUDIES IN LEWY-BODY DEMENTIA:

CHALLENGES IN HARMONIZING DIFFERENT CLINICAL AND BIOMARKER PROTOCOLS

Report of a JPND Working Group on Longitudinal Cohorts

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JPND research

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This document is the final report from one of ten working groups commissioned by the EU Joint programme – Neurodegenerative Disease Research (JPND) in 2014 through a peer-reviewed call for proposals. The working groups were established to address methodological challenges preventing current population- and disease-based cohorts being further exploited for ND research. All ten reports are listed below and are available to download on the JPND website by clicking on the website link at the bottom of this page:

- **HD-READy (High-Dimensional Research in Alzheimer's Disease)**
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- **Harmonization and innovation of cognitive, behavioural and functional assessment in neurodegenerative dementias**
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- **NETCALS (Network of Cohort Assessment in ALS)**
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- **21st Century EURODEM**
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- **Multi-centre cohort-studies in Lewy-body dementia: Challenges in harmonizing different clinical and biomarker protocols**
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- **Developing a methodological framework for trials in presymptomatic neurodegenerative disease – the Presymtomatic Neurodegeneration Initiative (PreNI)**
  Coordinator: Dr Jonathan Rohrer, University College London, London, UK

- **BioLoC-PD: Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson's disease**
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- **Dementia Outcome Measures: charting new territory**
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- **Body fluid biobanking of longitudinal cohorts in neurodegenerative diseases**
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- **Realising the potential of cohort studies to determine the vascular contribution to neurodegeneration**
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Summary

The overall aims of this project were to:

a) Identify available longitudinal DLB cohorts and develop methods for data pooling;
b) Provide overall guidelines and detailed protocol recommendations for future prospective cohort studies in DLB, including biomarker procedures and clinical scales with sound psychometric properties and sensitive to change;
c) Develop strategies for defining and identifying prodromal DLB

a) We have now gathered clinical information on more than 1100 DLB patients, summarized at international PD and AD conferences and in several manuscripts which will be submitted during 2015. In one of the manuscripts we outline how the two most commonly used cognitive screening scales, the Mini-Mental State Examination and the Montreal Cognitive Assessment scale have a very similar sensitivity to change in DLB and thus can be combined in multi-centre studies.

b) We have completed guidelines and detailed protocol recommendations for future prospective cohort studies in DLB, including clinical scales (cognition, psychiatric, motor, and autonomous symptoms) and biomarker procedures (MRI, dopamine transporter scan and other functional imaging techniques, cerebrospinal fluid, blood). The recommendations are based on empirical evidence when available, and on expert opinion when evidence is unavailable or incomplete/preliminary.

c) A document outlining strategies for defining and identifying prodromal DLB has been prepared.

Introduction

Dementia with Lewy bodies (DLB) is common, representing 10-20% of the dementia population. There is evidence that the prognosis is even more severe than other dementia disorders including Alzheimer's disease (AD). Despite this, very few longitudinal studies have been reported in DLB, and no longitudinal multicentre studies. Barriers to such research include the challenges in recruiting a sufficiently large and unbiased cohort, and lack of knowledge about which rating instruments are sensitive to change in DLB. Most previous or ongoing cohorts are small with less than 100 DLB patients included, and there is little information regarding how clinical

and biomarker data from available single-centre cohorts can be combined. Accordingly, there is a need for multi-centre cohort studies, with cross-centre harmonization of the procedures. Pooling data from different centres that have been collected using different protocols is another, less ideal, way to learn about the longitudinal course of DLB, and requires strategies for how to combine the various clinical and biomarker data.

Unlike the situation in AD, little is known about the pre-dementia, prodromal stages of DLB. Given the importance of early diagnosis both for clinical management and research, knowledge about prodromal DLB is crucial, including clinical and biomarker criteria.

Context

The guidelines are intended to inform clinical research, in particular longitudinal cohort studies. For most biomarkers, we have included suggestions for a basic Level 1, which we believe can be implemented on nearly all centres aiming to run longitudinal cohort studies. In addition, we have proposed a Level 2, to be performed in more specialized centres with more resources.

Given the scarcity of cohort studies in DLB, it is important to facilitate longitudinal studies which can be conducted even at centres with small resources and small budgets. Thus, our aim is to provide recommendations which can be implemented at most specialist centres across Europe, i.e. not requiring extensive external resources. We also provide recommendations how to combine data from different cohorts with different protocols, discussing the many methodological challenges associated with this.

Terminology

Lewy body disease:	A group of diseases characterized by intraneuronal aggregates consisting of alpha-synuclein and other proteins, i.e. the Lewy bodies
DaT scan:	Dopamine transporter (DAT) imaging is a functional imaging technique based on single photon emission computer tomography (SPECT) and a ligand binding tot he dopamine transporter. This technique has shown high sensitivity and specificity to distinguish between DLB and AD.
CSF:	Cerebrospinal fluid; established biomarker for AD
NPI:	Neuropsychiatric Inventory; standardized carer-based structured interview rating 12 psychiatric symptoms.
RBD:	REM-sleep behavioural disorder; a parasomnia typically occurring in people with DLB or PD

Methods

The work-plan included convening an expert workgroup, and organising workshops. The Working group has convened four times: a first preliminary meeting was held in Stockholm 10.6.2014, (back-to-back with the Annual Movement Disorders Society meeting), the first official meeting was held at Karolinska Institute in Stockholm on September 22, followed by a smaller meeting of the working group was held during the 10th Non-motor dysfunction in Parkinson's disease on November 4th in Nice. The final and full meeting was held at Hafjell, Lillehammer, 25-27 February 2015.

Several subgroups were established, and the main work was based on email contacts and a few telephone/Skype meeting. The workgroup discussed strategies for how to address the aims. In order to meet

Aim A (Collecting database of existing patients) a number of colleagues were contacted, in addition to the initial Working group members. The subgroups have produced reports which have been circulated several times to the full group, and the current report and guidelines is the final condensed result of these efforts.

AGREED GUIDELINES

Objective A: Available longitudinal cohort studies

Clinical and research records of more than 1100 DLB patients from > 20 European centres have been collected and systematized. Several manuscripts are currently under preparation based on this cohort, which represents the largest DLB cohort in the world. Key data of the 653 DLB cases with longitudinal data are summarized in Table 1a (Kramberger et al. Work in preparation).

Table 1. Characteristics of the multicentre DLB cohort

	DLB	*PDD*	*AD*
N total	1086	465	300
Sex, % male	52.3	68.6	37.5
Age, years	76.0 (7.5)	75.9 (7.3)	75.7 (7.1)
UPDRS III	21.8 (12.6)	43.2 (15.1)	3.8 (4.7)
Duration of dementia, years	2.8 (2.0)	3.4 (4.4)	2.2 (1.9)
N with 1-year follow-up	653	186	257
MMSE at year 1	19.2 (6.1)	18.8 (6.4)	19.8 (5.3)
N with 2-yearr follow-up	378	125	125
MMSE at year 2	16.9 (6.5)	18.6 (6.6)	17.8 (5.4)

Objective B: Guidelines for longitudinal cohort studies

A: Clinical aspects

Sources of case selection

Due to the variety of clinical symptoms, DLB patients can present to different medical specialities, including *movement disorders specialists, memory clinic, psychiatry, neurology, sleep clinics, geriatrics and internal medicine*. Accordingly, in order to recruit a sufficiently large number of patients, and a reasonably unselected cohort, patients should be recruited from several sources. In addition, recruitment should be *consecutive,* i.e. each potentially relevant patient should be screened for inclusion and invited to participate if criteria are fulfilled. We recommend an *inclusive approach*, i.e. all cases with a diagnosis of probable DLB and the majority with possible DLB, should be included with only a few exclusion criteria (see below). Recruitment to brain donation is recommended to ascertain the diagnosis of DLB. Drugs potentially influencing the clinical evaluations must be recorded, i.e. detailed recording of dose and duration of CNS-active drugs. Specifically, for those taking LDOPA or dopamine agonists, drug-related fluctuation (”on-off”) should be recorded, and recorded whether tested in on or off-stage (preferentially off-stage).

Inclusion criteria:

- Mild dementia (i.e. Clinical Dementia Rating (CDR) $\geq$ 0.5, and/or MMSE $\geq$ 20)

- Fulfilling criteria for possible or probable DLB (consensus criteria, (McKeith et al 2005)

Exclusion criteria

- Severe physical or life-threatening conditions
- Post-stroke dementia
- Possible DLB with negative dopamine transporter scan (DaT scan)
- Long-term previous use of antipsychotic drugs

Justification

A broad and inclusive approach for patient selection will reduce specificity, i.e. risk of including cases with diseases other than DLB. However, it increases sensitivity and thus increases the proportion of DLB patients to be included, in particular patients with unusual, early, or less characteristic clinical presentation. With a comprehensive and detailed clinical and biomarker assessment program, including dopamine transporter SPECT and recruitment to autopsy, and a longitudinal design, the risk for false positive diagnosis is likely small. Therefore, we recommend inclusion also of patients with *possible* DLB. Little is known regarding the diagnostic status of this group, and longitudinal cohort studies are needed to fully understand the diagnostic status of these patients, i.e. who will develop probable DLB compared to non-DLB. Most cases with a negative DAT scan and clinical possible DLB have non-DLB disease and thus should not be included (O'Brien et al 2009).

In order to follow the full disease course, attempts should be made to recruit patients at the stage of *mild* dementia, for example defined as Clinical Dementia Rating (CDR) stage 1 or a minimum MMSE score of 20. Distinguishing between dementia and not dementia can be difficult, and to be inclusive, we recommend that also patients with CDR=0.5, which is usually considered mild cognitive impairment, who otherwise fulfil the DLB criteria, are included.

Most elderly patients with dementia will have at least some *cerebrovascular* changes. Previous clinico-pathologic studies suggest that this should *not* be an exclusion criterion, since they still have a very high likelihood of having DLB if the clinical criteria are fulfilled (McKeith et al 2000). Hence, we recommend to exclude only patients with severe physical or life-threatening conditions, and with dementia immediately following a stroke (post-stroke dementia) and with large basal ganglia infarcts (to exclude false-positive DaT scans). Patients with a history of chronic psychotic disease should be excluded only if they have received long-term antipsychotic treatment. It is known that depression and anxiety disorders increase the risk for subsequent AD and PD, and thus possibly also DLB. Thus, a history of these disorders is not an exclusion criterion.

Diagnostic procedures

Clinical examination, detailed history, brain imaging to screen for structural lesions, routine blood; CSF routine evaluation. To ascertain the diagnostic criteria, we strongly recommend the use of standardized scales and instruments for the central, core and suggestive features. In addition, these criteria should be operationally defined. Using the findings from Rongve et al. (2010) (Rongve et al 2010) as a guide, we recommend the following definitions (please see the description of scales below):

- Central feature:
    - Dementia, defined as CDR 1 or higher
- Core features:
    - Repetitive Visual hallucinations: clear clinical history supporting this and a NPI item 2 score of 1 or higher
    - Parkinsonism: 2 of 4 cardinal features; UPDRS Motor score > 9
    - Fluctuating cognition: clear clinical history, positive scale score
- Suggestive features:

- RBD: Mayo RBD screening question positive
- Brain SPECT with dopamine transporter radiopharmaceuticals: visually or quantitatively rated as pathological
- Neuroleptic hypersensitivity: combined motor and mental symptoms shortly after onset of antipsychotic treatment, or severe worsening of either (Aarsland et al 2005)

Standardized clinical rating scales

General comments

Choosing tests for DLB is challenging since clinicometric data are usually not available in DLB. Therefore most recommendations are based on evidence from related diseases such as AD and PD, and on expert consensus, rather than formal evaluation. For assessment of several domains, including cognitive and psychiatric symptoms, we have provided a basic Level 1, and a more advanced Level 2. The recommendations are summarized in Table 1. It is preferable to have a similar clinical and biomarker assessment programme at baseline and at follow-up evaluations. However, due to the rapid decline in many DLB patients, scales that can be performed at the time of diagnosis, i.e. at the mild dementia stage, may not be performed at more severe stages. This will influence the choice of instruments. Therefore, we recommend instruments that can track disease change across most of the course without floor or ceiling effects.

<u>Global measures of cognitive functioning:</u>

Clinical Dementia Rating (CDR) sum of boxes and Clinical Global Impression (of Severity and Change) (CGI-S and CGIC)

General comments:

We suggest to modify the CGIC for use in DLB, by specifically addressing all relevant clinical domains, such as cognition, attention and wakefulness, psychiatric symptoms, motor symptoms, and daily functioning, when scoring the CGIC. The CDR and CGIC ratings should preferably be performed by a team member who is not involved in other test procedures, or the global ratings can be performed prior to administration of the scales. CDR and CGIC are not disease specific, and thus scores from DLB can be directly compared with those of cohorts with PD and AD. Both scales are based on clinical judgement and thus reliability needs to be considered, and procedures to harmonize administration and scoring should be implemented.

Justification:

The CDR is a global rating system for cognitive functioning. It provides a global scoring (ranging from 0 to 3-severe dementia), and in addition this 0-3 scoring system is applied to 6 different domains, enabling for a sum-score to be calculated (0-18). There are guidelines and instructions for the use of CDR (Lowe et al 2012, Nyunt et al 2013); this is recommended in order to increase inter- and intra-rater reliability.

The CGI is a seven-point categorical scale and is rated after a clinical interview with the patient and a caregiver. There are different versions with recommended guidelines available (Olin et al 1996, Schneider et al 1997). The CGI-S provides rating of *severity* from 1 (very mild) to 7 (very severe). The CGI-C gives a global rating of *change* in symptoms from baseline: a score of 1 indicates substantial improvement, a score of 2 indicates a moderate improvement, a score of 3 indicates a minimum improvement, a score of 4 indicates no change, a score of 5 indicates minimum worsening, a score of 6 indicates moderate worsening, and a score of 7 indicates substantial worsening.

<u>Cognitive screening tests:</u>

MMSE and/or MoCA

Justification for choice of cognitive screening tests

The MMSE and MOCA are cognitive screening scales which can be completed in around 10 minutes. Both scales can be used for diagnostic and prognostic purposes in DLB. There is evidence from several studies that MOCA is more sensitive to the early changes in PD (Dalrymple-Alford et al 2010, Hoops et al 2009, Nazem et al 2009, Zadikoff et al 2008), whereas there are no studies reporting change of MOCA in DLB. Recent data from our group provide an opportunity to transform between scores of the two scales (van Steenoven et al 2014). In contrast, in PD, sensitivity to change was reported to be higher in MMSE than MOCA (Lessig et al 2012), although this needs to be replicated. Preliminary evidence from our Working Group suggest that in PD and DLB, MOCA is more sensitive to detect the earliest stage, whereas MMSE is more sensitive in the more advanced stage (Biundo et al. Work in progress). We therefore recommend both scales to be used.

Cognitive domains:

Overall Comments and justifications

Similar to the recommendations of the PD-MCI Task Force, we discuss five cognitive domains: memory, visuospatial, language, attention/working memory, and executive functions. We recommend one test per domain for Level 1 and two tests per domain for Level 2, i.e. at Level 2 the test recommended for that domain at Level 2 should be added to the Level 1 test (Table 1).

In DLB, memory is often relatively preserved, whereas visuospatial and executive functioning are more impaired. In most patients, the profile of cognitive impairment represents a mixture of features seen in AD and in PD, reflecting the combination of Lewy body and Alzheimer type pathologies. The cognitive profile varies however, likely reflecting the variation in underlying pathologies. Both domains which are often impaired as well as those that are relatively unimpaired in DLB should be measured, in order to facilitate comparison with other diseases such as AD.

A variety of neuropsychological tests have been used in DLB and PDD, but psychometric properties are rarely available in DLB. Tests should be relevant to the diagnostic process, usually at the mild dementia stage, but also be able to track the cognitive decline across the disease course. Whereas MMSE and MOCA can be applied across the full spectrum of dementia severity, although with a potential risk of ceiling and floor effects, many neuropsychological tests are more challenging to perform for patients with moderate or severe dementia. Choosing tests that are relatively simple to perform for people with mild and moderately severe dementia is important for reducing the number of missing data. In addition, tests should be acceptable and not frustrating in order to avoid subsequent dropout from the study. The choice of tests is thus partly based on data from our group about which tests can be performed by people with Lewy body dementia (Biundo et al. Work in progress). Tests should also be free of motor components, since most DLB patients have motor impairment. We also focused on tests which are commonly use at many centres, or at least similar to frequently used scales, and we tried to align the procedures to those of ADNI, CERAD, and PPMI, in order to facilitate comparison with these studies.

In multi-centre studies without fully harmonized procedures, scores from different tests within one domain can be combined using standardized scores, such as z or T scores. These can be computed from a healthy control group, or preferably based on age- and education-based norms. Published norms should be available, preferentially from the relevant cultural and language settings. If control subjects are used, these should be recruited from all participating centres, to enable calculation of standardized scores based on comparable control groups.

Psychiatric symptoms

Overall comments

Psychiatric symptoms are very common in DLB. Although few scales are validated and tested in DLB, several have been extensively used and validated in PD and AD and thus can be recommended also in DLB. Psychiatric symptoms can be measured using a clinical interview, which can be more or less structured. The benefit of highly structured interviews is their high reliability. Questionnaires are user-friendly and time-efficient. The source can be the patient themselves, or carers. In people with dementia, patient-based scales can be unreliable, due to reduced memory, awareness, and abstract thinking, and thus carer-based interviews are preferred in order to track changes across the full range of the disease course.

Combining data from studies using different rating scales is difficult. One strategy is to use the available cut-offs for clinically relevant psychiatric symptoms or psychiatric diagnosis, for example "clinical significant depression", and then combine the proportions with and without the disorders across centres.

Some scales screen the spectrum of psychiatric symptoms, for example Neuropsychiatric Inventory (NPI), which covers 12 common neuropsychiatric symptoms, based on a clinical structured interview of a family-member. NPI also has a nursing home (formal carer) and a shorter questionnaire (NPI-Q) version. The spectrum of psychiatric symptoms can be useful for diagnosis, for example hallucinations being common in DLB but not in frontotemporal dementia, as well as for tracking clinical course, i.e. describing the emergence of psychotic symptoms. For most specific symptoms, we recommend the relevant item of the NPI at Level 1, and a more detailed specific symptom scale at Level 2 (Table 1).

Table 2. Clinical symptoms: Recommendation of standardized scales

	Level 1	Level 2
Cognition		
Staging	CDR	CGI-S, CGI-C
Global screening test	MMSE, MOCA	
Memory	CERAD Word list	Benton visual retention test
Visuospatial	Degraded letter test (VOSP)	Benton Line orientation
Executive	Similarities (WAIS)	Stroop test
Attention	Adaptive Digit Ordering	Trail making test
Language	Fluency, animals	Boston naming test-15 item
Psychiatric symptoms		
Profile	NPI Questionnaire	NPI
Depression	NPI item 4, GDS-15	Cornell scale
Apathy	NPI item 7	Apathy evaluation scale
Psychosis	NPI items 1 +2	CUSPAD misidentification, NEVI
Other		
Quality of life	Quality of life-Alzheimer's disease	
Carer burden	Zarit burden of care	
Autonomous	Orthostatic blood pressure, items from NMSS*	ECG (heart rate variability, frequency)

Sleep	Sleep items, NMSS	Mayo sleep scale
Motor	UPDRS III, timed up-and-go	Finger tapping, Hoehn &Yahr
Cognitive fluctuations	Mayo fluctuation scale	Fluctuation assessment scale
Falls	Semiquantitative question	Tinetti scale
Activities of daily living	Functional Activities Questionnaire	
Milestones	CDR=3, admission, death	

*Orthostatic blood pressure and pulse measurements in supine position after 5 min´s rest, immediately after standing, after 1 and 3 minutes. Selected items from NMSS: Constipation (#21) and urinary symptoms (# 22-23).

Abbreviations:
CDR: Clinical Dementia Rating; CGI-S/C: Clinical Global Impression of Severity (S)/Change (C); MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment Scale; CERAD: Consortium to Establish a Registry for Alzheimer's *Disease; VOSP: Visual Object and Space Perception Battery; WAIS: Wechsler Adult Intelligence Scale; NPI: Neuropsychiatric Inventory; CUSPAD: Columbia University Scale for Psychopathology in Alzheimer's Disease; GDS: Geriatric Depression Scale; NEVI: North-East Visual hallucinations Inventory; NMSS: Non-Motor Symptom Scale; ECG: Electrocardiogram; UPDRS-III: Unified Parkinson's Disease Rating Scale, subscale III*

B: Biomarkers

The work group has discussed biomarker techniques including imaging, cerebrospinal fluid (CSF), EEG and blood. We focused on standardization of acquisition, which is crucial for reliable analyses, and included both diagnostic and potentially prognostic markers. In multicentre studies, central analysis is preferred. Again we have provided recommendations for a more simple clinical level (Level 1) and a more detailed and advanced research level (Level 2). The recommendations are summarized in Table 2 (see below).

Table 3: Recommendations for biomarker acquisition in multi-centre longitudinal DLB studies

	Level 1	Level 2
Imaging:		
MRI	T1, FLAIR, SWI, fMRI, T2 spin echo	DTI, spectroscopy, ASL, DKI, relaxometry
Functional	DAT SPECT	MIBG, FDG-PET, amyloid PET
CSF	Storage of 18 ml for central analysis	
Blood	Serum 18 ml	
	Plasma 18 ml	
	18 ml full blood	Full blood for gene expression
EEG	Standard 21 scalp EEG	

Abbreviations:
FLAIR: Fluid attenuation inversion recovery; SWI: Susceptibility-weighted imaging; DTI: Diffusion tensor imaging; FDG: fluorodeoxyglucose; ASL: arterial spin labelling; DKI: Diffusional kurtosis imaging; PET: Positron emission tomography; DAT: Dopamine transporter; SPECT: Single-photon emission computed tomography; EEG: Electroencephalography

Objective C: Prodromal DLB JPND Working Paper for the development of clinical criteria

Consensus clinical diagnostic criteria for DLB have been in widespread use for almost two decades (McKeith et al 2005, McKeith et al 1996). They have recently been assimilated into DSMV and are anticipated to be similarly incorporated into ICD11. Such criteria identify probable and possible DLB cases, depending upon the number of core and suggestive features present, both levels requiring the presence of "**dementia** defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function". By definition therefore these criteria exclude individuals presenting with early symptoms and signs indicative of incipient DLB. In recent years there has been a concerted effort to establish the phenotype of pre-dementia (prodromal) AD (Dubois et al 2010) and to a lesser extent, prodromal PD (Gaenslen et al 2011).The main justification for this shift to earlier diagnosis is that preventative treatment will only be effective if given before extensive neurochemical and anatomic pathological changes have occurred in the brain, i.e. at a prodromal stage. It follows that trials of potential preventative agents will only be possible once reliable methods of prodromal diagnosis have been established. In AD, prevention trials are presently being addressed using genetically at risk trial populations e.g. DIAN and prodromal cases e.g. A4 study. Studies of this type are lengthy and expensive requiring partnership funding by government, pharma, academic and voluntary sector sources.

Evidence for the early (Auning et al 2011) and prodromal (Chiba et al 2012, Fujishiro et al 2013) presentation of DLB is also emerging and this paper briefly sets out what will be required to establish criteria for the clinical diagnosis of pre-dementia (prodromal) DLB using a combination of clinical and biomarker variables.

The presenting features of DLB can be broadly placed in three categories: **cognitive impairment** (particularly non-amnestic cognitive impairments), **behavioural/psychiatric phenomena** (for example, hallucinations, rapid eye movement sleep behaviour disorder (RBD)) and **physical symptoms** (for example, parkinsonism, hyposmia and autonomic dysfunction). Any of these may occur as the first presenting symptom of DLB with hyposmia, autonomic dysfunction and RBD sometimes present for one or two decades before cognitive decline is seen. This is consistent with pathological studies finding that the earliest sites of α-synuclein pathology are the olfactory bulb, the dorsal motor nucleus of the vagal nerve and the peripheral autonomic nervous system, including the enteric nervous system, and the brainstem. Although this long prodromal phase offers a substantial window for early detection, very early prodromal symptoms are not specific for DLB but are instead predictive of the broader spectrum of Lewy body disease. RBD, for example, which is the best current prodromal indicator of Lewy body disease is predictive not just of DLB but also PD and multi-system atrophy (MSA). Since we do not yet know why some cases of Lewy body disease progress to PD and others to DLB, making very early prodromal diagnosis will only identify individuals at risk of Lewy body disease of uncertain future clinical course and progression. Although this may in time become an appropriate diagnostic and treatment target, our current aim is to identify with a high level of certainty, those individuals who will progress to a dementia syndrome of the DLB type.

Prodromal DLB criteria for the identification of cases at high risk of progression to a dementia syndrome of the DLB type and suitable for recruitment into prevention studies, will require a person to have *at least one clinical feature suggestive of prodromal DLB* and *at least one biomarker supportive of Lewy body disease*. Given the large number of potential prodromal symptoms and existence of several biomarker candidates, it is likely it will be relative weighting of these items, alone and in combination, which is the key issue in generating robust criteria for prodromal DLB. This will include the temporal order of appearance of symptoms and biomarker abnormalities. We propose a two stage process to develop these, both requiring the use of longitudinal cohort studies. The **first phase** will be retrospective analysis of data from previous and existing cohorts which contain relevant data from longitudinal follow up of subjects from first presentation to clinical conversion to DLB,

preferably with autopsy confirmation. These will then be used to generate provisional prodromal DLB criteria which will subsequently need to be tested in a utilizing a new cohort, established for the purpose.

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