BIOLOC-PD:

HARMONIZATION OF BIOMARKER ASSESSMENT IN LONGITUDINAL COHORT STUDIES IN PARKINSON'S DISEASE

Report of a JPND Working Group on Longitudinal Cohorts

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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)**
  Coordinator: Professor M. Afran Ikram, Erasmus University Medical Centre, Rotterdam, Netherlands.

- **Harmonization and innovation of cognitive, behavioural and functional assessment in neurodegenerative dementias**
  Coordinator: Dr Alberto Costa, IRCCS Fondazione Santa Lucia, Rome, Italy.

- **NETCALS (Network of Cohort Assessment in ALS)**
  Coordinator: Professor Leonard van den Berg, University Medical Centre Utrecht, Utrecht, Netherlands

- **21st Century EURODEM**
  Coordinator: Professor Carol Brayne, University of Cambridge, Cambridge, UK

- **Multi-centre cohort-studies in Lewy-body dementia: Challenges in harmonizing different clinical and biomarker protocols**
  Coordinator: Professor Dag Aarsland, Stavanger University Hospital, Stavanger, Norway

- **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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JPND Website link: http://www.neurodegenerationresearch.eu/initiatives/jpnd-alignment-actions/longitdinal-cohorts/

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Summary

Aims:
- Compilation of predictive and progression markers in many European cohort studies on PD
- Delineation of assessment priorities with regard to the overall course of the disease
- Definition of assessments and standardization steps including quality control
- Setting up a minimal data set for use in longitudinal studies of prodromal and motor PD

Achievements:
- ✓ Workshop to define strategy to reach the aims in Tuebingen on Oct. 23rd/24th 2014.
- ✓ Compilation of study characteristics and assessments in each of the studies conducted by the partners of the working group.
- ✓ Submission of a manuscript on the markers and assessments used in studies of the JPND BioLoC-PD working group and lessons learned.
- ✓ Review on longitudinal studies in the prodromal phase of PD (manuscript in preparation).
- ✓ Review on markers in the clinical phase of PD (manuscript in preparation).
- ✓ Implementation of statistical harmonization methods for different assessments of same domain (manuscript in preparation).
- ✓ Compilation of a modular assessment battery for longitudinal cohort studies in PD.
- ✓ Set up of the consortium "Novel strategies for biomarker identification in longitudinal studies in Parkinson's disease" applying for the JPND research program in June 2015.

Introduction

The neurodegenerative process in Parkinson's disease (PD) starts years to decades before the onset of motor symptoms and subsequent clinical diagnosis. After the onset of motor symptoms, the disease progresses inevitably with increasingly disabling symptoms. The rate of progression of the different motor- and non-motor symptoms can differ markedly, and there are patient sub-groups with different phenotypic patterns. This heterogeneity poses a challenge for neuroprotective therapeutic strategies that aim to modulate progression. Therefore, the identification of predictive and progression markers in Parkinson's disease and its prodromal phase is essential not only for an earlier diagnosis and development of neuroprotective therapies but also for

patient stratification and the establishment of useful study endpoints. As there is no consensus regarding which symptoms/markers need to be assessed, nor on the nature of the assessment the BioLoC-PD working group set out to develop an assessment battery to help define the most useful data assessed in a comparable way.

The outcome of the BioLoC PD working group aims will set the stage for:
- a better understanding of the overall course of PD (prodromal and motor) and of the value of symptoms that may be used as predictive and progression markers
- analysis of comparable data across the studies conducted to date (with higher numbers of converters/symptom carriers)
- therapeutic studies in different stages of the disease based on novel study endpoints (defined by progression markers) and improved case stratification.

Context

A common marker and/or assessment battery is essential for the design of studies planned as well as for ongoing studies. For assessments already performed in ongoing studies, harmonization of assessment tools is necessary to allow comparability of data prospectively in larger cohorts with higher numbers of converters/symptom carriers for statistical analyses. Finally this will lead to a better understanding of the overall course of PD (prodromal and motor), the definition of study endpoints and improved case stratification.

Terminology

PD: Parkinson's Disease
JPND BioLoC PD: EU Joint Programme - Neurodegenerative Disease Research: Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson's Disease

Methods

Information about design, markers and assessments of the ongoing cohort studies represented in our working group were collected by a questionnaire and used as basis for the discussion at a workshop in Tuebingen Oct. 23rd/24th 2014. The workshop contained the following elements:

1. Overview on the design of ongoing studies
2. Discussion on predictive and progression markers
3. Consideration of suitable study endpoints
4. Suggestions and discussions on the structure of an assessment battery
5. Introduction to possibilities of marker harmonization

Based on this exchange and an adapted more detailed table with study information about longitudinal studies of the JPND working group, a manuscript providing a summary of the studies currently performed by the JPND BioLoC PD working group members, markers assessed as well as assessment methods used was composed and grouped according to systems affected (e.g. motor function, cognition etc.). This manuscript is under review.

A systematic literature search about assessments and markers in the prodromal and clinical phase of PD was conducted to determine the most useful predictive and progression markers as study end-points. Based on this literature search two manuscripts have been composed and are currently in preparation. The first will give an overview about longitudinal studies in the prodromal phase of PD, their evidence levels as well as their strengths

and limitations. The second one will give an overview about markers in the clinical phase of PD and their value as predictive or progression markers. These manuscripts will provide the current knowledge on suitable clinical study endpoints.

Moreover, outcome of the literature search as well as of current data sets of the BioloC-PD studies and PD consortia were used for the compilation of an assessment battery. According to these sources it was decided that the data set should have a modular structure with different modules of extended data sets to be added to a minimal data set. Our initial preparatory work has provided proof of concept to show that statistical harmonization is achievable. We have converted cognitive scores (MOCA to MMSE) using the equipercentile method with log-linear smoothing. Our analysis based on 2091 individuals, who had done both scales (i.e. a single group design), found only small differences between true MMSE and predicted MMSE based on MOCA (mean difference 0.06, IQR -1 to 1 RMSE 1.84).

AGREED GUIDELINES

The guidelines (modular assessment battery, see below) agreed on are based on the findings of our group:

According to the first aim - *characterization of already running longitudinal studies in different phases of PD designed to identify valid predictive and progression markers* – data of the studies included in BioLoC-PD were collected, compiled and submitted as manuscript. In brief, the two main findings are:

1. There is an interesting consensus on domains incorporated in different studies, but also an enormous variability of assessments/tests used to objectify them. Further, there are differences in the extent of the assessments, which may be explained by the complexity of a feature and its relative importance to the main study objectives. The substantial variability in the choice of the evaluation method (quantitative assessment, investigator-rated assessment, investigator interview, patient-rated questionnaire) may be explained by a number of different factors: (i) Not all scales/questionnaires are available and validated in all languages. (ii) Some of the assessments were developed, revised or expanded after some of the studies were initiated. (iii) Study designs vary with regard to outcome variables which influences the kind of assessments. (iv) Some assessments take more resources than others (more time-consuming, more costly or require trained staff members), influencing selection and composition of assessment battery. (v) Preference of assessment based on previous research experience.
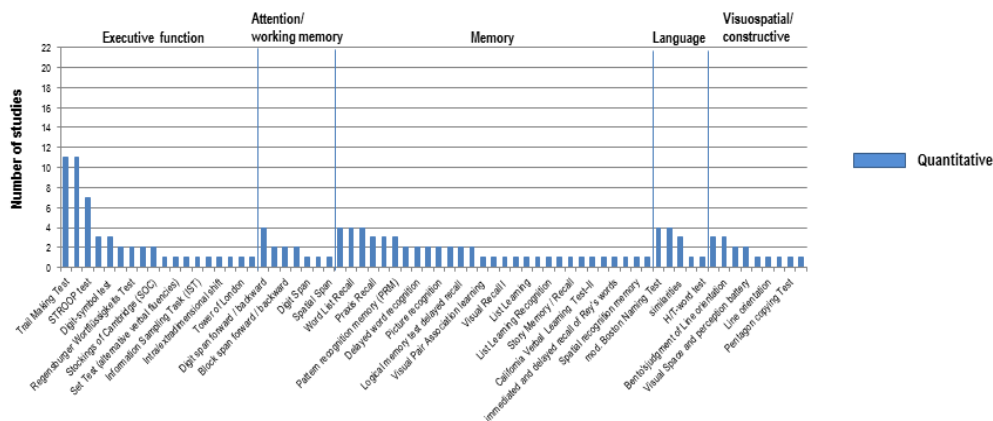

Figure 1: Example of assessment differences in the BioLoC-PD studies in the cognitive domain

2. There is a remarkable similarity in the type of markers assessed in the risk/prodromal cohorts compared to the clinical PD cohorts. The same holds true for the evaluation methods applied. Although this may partly be explained by the rather small number of longitudinal risk/prodromal and clinical PD studies, it also emphasizes the growing understanding that the current distinction between prodromal and clinical motor PD is artificial. Years before the clinical diagnosis of PD can be made according to the current diagnostic criteria, the neurodegenerative process in PD is accompanied not only by non-motor but also by subtle early motor signs. This continuum needs to be appreciated to better understand and make use of predictive and progression markers throughout the course of the disease.

Table 1: Overview of markers assessed in the different studies and number of assessments applied.

Function / Study	Demo-graphic RF	Non-demogra-phic RF	Motor	ADL	Gastrointes tinal & autonomic	Sensory	Sleep	Neuro-psychatric	Cog-nitive	Ima-ging	Number of assessed markers
ABC-PD	X	3	4	4	3	2	2	2	25	2	10
Contursi	X	3	2	1	3	1	2	4	6	2	10
DEMPARK/ Landscape	X	2	2	2	1	3	1	4	23	1	10
DeNoPa	X	6	2	1	3	5	6	6	18	3	10
Depression	X	1	4	1	2	1		2	4	2	9
EPIPARK	X	5	2	2	1	1	5	4	5	2	10
HELP-PD	X	5	6	1	2	3	2	4	13	1	10
ICD-PD	X	2	2	2	1		2	4	8	2	9
ICICLE	X	3	6	1	2		4	4	16	3	9
Melanoma-PD	X	2	2		2	2		1		2	7
MiGAP	X	1	4		3	1		2	2	1	8
MODEP	X	2	7	1	4	4	1	1	4	1	10
NASA	X	3	2	1	1	1	1	3	12	3	10
OPDC_Discovery	X	7	11	2	3	6	3	6	5	4	10
Park-West	X	3	2	2	1		3	5	6	2	9
PD-COG	X		1			1	1	4	9	2	7
PRIPS	X	5	1		1	2	1	1	1	1	9
PRoBaND_ Tracking	X	6	2	2	4	7	3	2	3		9
RBD-PD	X	5	3	1	2	4	3	1	1	4	10
TREND	X	5	6	1	4	5	3	3	12	3	10
Twin-Study	X	5	1	1	1			1	2		7

As the BioLoC PD working group comprises only a limited number of investigators and studies, we decided to expand the analyses of studies in the prodromal and clinical phase of PD and the possible predictive and progression markers in these phases to achieve a better overall view. Therefore systematic literature searches for the prodromal and clinical phase were conducted.

The literature search for the prodromal phase identified 29 publications eligible for review (Heinzel et al.; in preparation). Currently we analyze the publications for their levels of evidence according to two classification schemes. We used two approaches to classify studies; classification used by Maetzler et al. [1] to evaluate progression markers in the clinical phase of PD and on the risk of bias criteria proposed by the Cochrane Collaboration. Several lessons learned (submitted) regarding the evidence and limitations of current longitudinal studies investigating prodromal markers in PD are discussed within the manuscript. Limitations of study design are outlined to improve future study design. The observed heterogeneity of studies will be overcome by the modular minimal data-set provided by BioLoC-PD improving comparability of findings and enabling data sharing and combined analyses across studies.

A second literature search of the clinical phase of PD was conducted to update the paper of Maetzler et al, describing the progression of symptoms in the clinical phase [1]. Therefore the search was limited to papers from 2009 to April 2015. 63 papers were eligible for the review. Currently the reported studies are evaluated for their level of evidence to derive the most promising progression markers.

We have explored several different statistical approaches to data harmonization which will enable future analyses to be undertaken as a two-stage meta-analysis (within study prognostic assessment which is then pooled using a fandom effects model). We have considered internal Z-score or T-score approach where data is standardised adjusting for other patient characteristics such as age and gender. We have also used equipercentile methods to equate one scale to another (this has been successfully employed with converting MMSE to MOCA; MoCA is suggested to be used). We are currently developing the use of Item Response Theory methods to equate two different olfaction tests (UPSIT and Sniffin Sticks) that have some common shared items.

The analyses mentioned above revealed that there is a great consensus about the function/domains which should be assessed in a longitudinal PD study. Based on this work the JPND BioLoC PD working group suggests the following three-level modular assessment battery to be implemented in new and ongoing longitudinal studies for PD (figure 2). The set comprises a basic module (demographics, diagnosis, etc.), a minimum function and assessment module and optional extension modules. The basic module is meant to be applied to all participants of longitudinal studies in PD. It may also be extended to registers and patients of outpatient clinics irrespective whether they are currently recruited for a study, or whether only longitudinal documentation is warranted. The minimum module is meant to be applied to all individuals participating in at risk, prodromal and clinical longitudinal studies of PD. The optional extension module can be applied to evaluate study participants in more detail. The selection of the additional function modules depends on the main question of the study, the number of study participants and on the available stuff and finances. This may be applied to interesting sub-groups of participants if financial or pragmatic factors hinder the administration to the whole cohort.

The information, functions and their associated assessments were chosen based on a consensus of BioLoC PD members referring to their study experience, the literature reviews and to the expert knowledge of the principal investigators in their clinical practice. The functions of the minimum module are in a descending order. Functions used in all (risk, prodromal and clinical) PD studies are at the beginning of each of the lists (in the minimum and extension module). Assessments of these symptoms were suggested based on the frequency and applicability within studies (easy to apply assessments, which still provide sufficient information were preferred). Each of the assessments suggested for the minimum module (see figure) takes approximately 10 minutes depending on the cognitive capacity of the study participant. For some functions (neuropsychiatric, cognition and olfaction) one of the two suggested assessments can be chosen. This is because they are used nearly equally often and neither is obtrusive. The first suggestion, however, is slightly preferred within the BioLoC PD consortium. The assessments within the functions of the extension module were chosen based on their implementation in the BioLoC PD studies. For each subdomain (e.g. gait and balance, fine motor

movements) the most commonly used assessment is suggested in addition to the minimum module. A detailed evaluation of the functions, their assessments and usage within the BioLoC PD working group is presented in the first manuscript of the working group (Lerche et al.; Neuroepidemiology, 2015; under review).

We propose, that each study should at least collect data according to the basic module. This data is valuable also for genetic or other non-clinical analyses. Once individuals are examined, different motor and non-motor domains should be covered as suggested in the minimum module which also comprises some more data about medical history. Finally, according to the main study purpose different modules of the extension module can be chosen. In general we provide suggestions for assessment tools/scales to allow comparison across studies. For the cognition module, however, it is less important which assessments. Rather, it is important to take a minimum of two tests per domain for a sensitive and specific diagnosis of dementia and MCI level II [20]. For the analyses, a comparison of studies with different assessments will then be possible by comparing the domain Z-scores [21]. A list of neuropsychological tests suitable for the optional extension cognition module can be found in Goldman et al. 2015 and Litvan et al. 2012 [20,22].
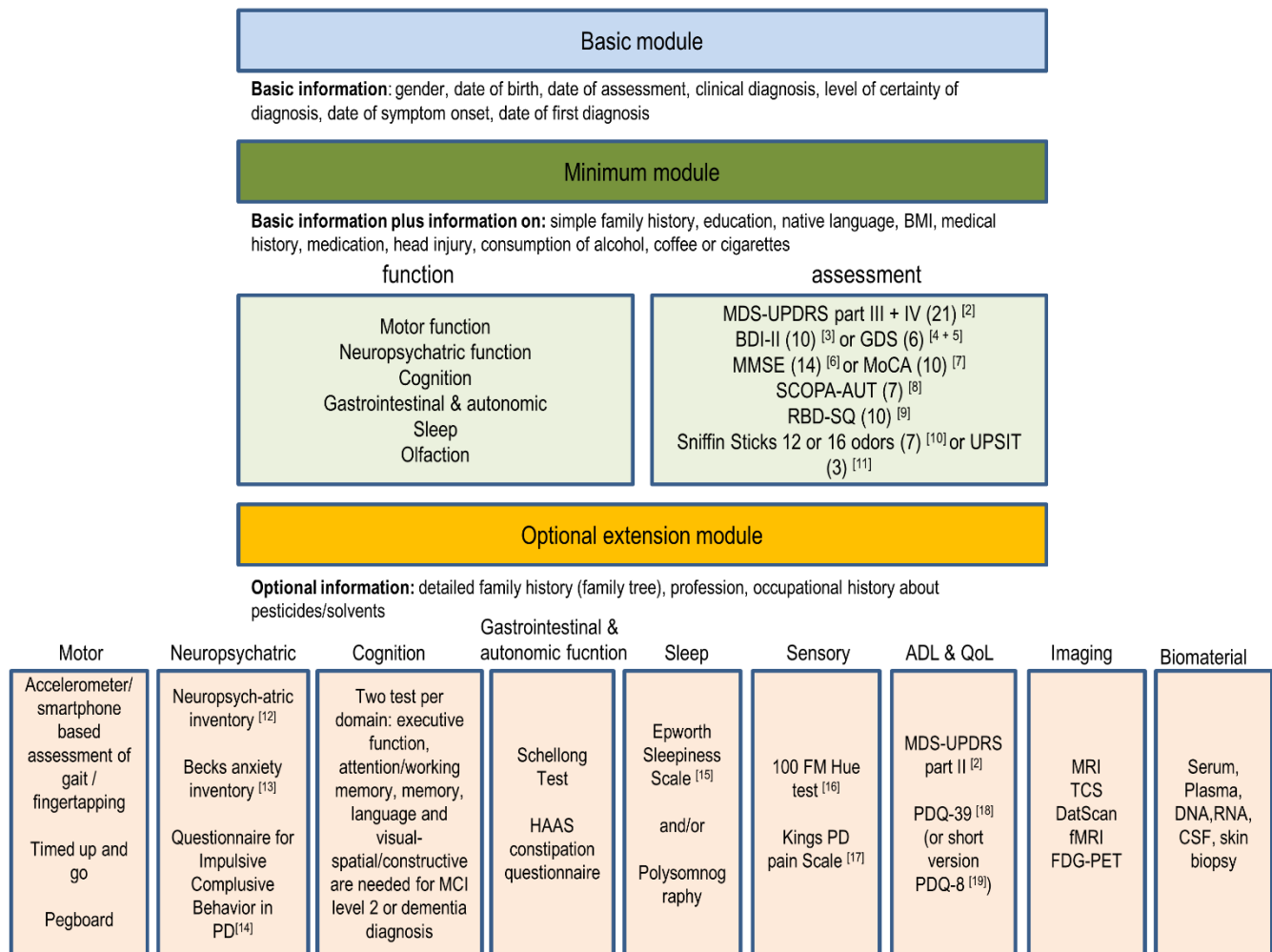
Basic module								
Basic information: gender, date of birth, date of assessment, clinical diagnosis, level of certainty of diagnosis, date of symptom onset, date of first diagnosis								

Minimum module								
Basic information plus information on: simple family history, education, native language, BMI, medical history, medication, head injury, consumption of alcohol, coffee or cigarettes								

function	assessment
Motor function Neuropsychatric function Cognition Gastrointestinal & autonomic Sleep Olfaction	MDS-UPDRS part III + IV (21) [2] BDI-II (10) [3] or GDS (6) [4 + 5] MMSE (14) [6] or MoCA (10) [7] SCOPA-AUT (7) [8] RBD-SQ (10) [9] Sniffin Sticks 12 or 16 odors (7) [10] or UPSIT (3) [11]

Optional extension module								

Optional information: detailed family history (family tree), profession, occupational history about pesticides/solvents

Motor	Neuropsychatric	Cognition	Gastrointestinal & autonomic fucntion	Sleep	Sensory	ADL & QoL	Imaging	Biomaterial
Accelerometer/ smartphone based assessment of gait / fingertapping Timed up and go Pegboard	Neuropsych-atric inventory [12] Becks anxiety inventory [13] Questionnaire for Impulsive Complusive Behavior in PD[14]	Two test per domain: executive function, attention/working memory, memory, language and visual-spatial/constructive are needed for MCI level 2 or dementia diagnosis	Schellong Test HAAS constipation questionnaire	Epworth Sleepiness Scale [15] and/or Polysomnography	100 FM Hue test [16] Kings PD pain Scale [17]	MDS-UPDRS part II [2] PDQ-39 [18] (or short version PDQ-8 [19])	MRI TCS DatScan fMRI FDG-PET	Serum, Plasma, DNA,RNA, CSF, skin biopsy

Figure 2: Suggestion for modular assessment battery for longitudinal studies in PD

In brackets number of studies using the assessment in the BioLoC-PD consortium are given. References of scales are in superscript squared brackets. ADL, Activities of daily living; BDI-II, Beck depression inventory version II; CSF, Cerebrospinal fluid; DaTSCAN, dopamine transporter scan; DNA, Deoxyribonucleic acid; FDG-PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; GDS, Geriatric depression scale; HAAS, Honolulu Asia Aging study, MDS-UPDRS, Movement Disorder Society - Unified Parkinson´s Disease Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI magnetic resonance imaging; PD, Parkinson's Disease; PDQ-39, Parkinson's Disease Questionnaire-39 items; QoL, Quality of Life; RBD-SQ, Rapid eye movement sleep behavior disorder screening questionnaire; RNA, Ribonucleic acid; SCOPA, Scales for Outcome in Parkinson's Disease; TCS, transcranial sonography

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