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Methods in Neuroepidemiology Characterization of European Longitudinal Cohort Studies in Parkinson's Disease – Report of the JPND Working Group BioLoC-PD

Stefanie Lerche[a, b] Inga Liepelt-Scarfone[a, b] Guido Alves[h] Paolo Barone[i] Stefanie Behnke[c] Yoav Ben-Shlomo[k] Henk Berendse[j] David Burn[l] Richard Dodel[d] Donald Grosset[m] Sebastian Heinzel[a, b] Michele Hu[n] Meike Kasten[e] Rejko Krüger[o] Walter Maetzler[a, b] Marcello Moccia[i] Brit Mollenhauer[f] Wolfgang Oertel[d] Benjamin Roeben[a, b] Ulrike Sünkel[a, b] Uwe Walter[g] Karin Wirdefeldt[p] Daniela Berg[a, b]

[a]Center of Neurology, Department of Neurodegeneration and Hertie-Institute for Clinical Brain Research, [b]German Center for Neurodegenerative Diseases, University of Tuebingen, Tuebingen, [c]Department of Neurology, University of Homburg, Homburg, [d]Department of Neurology, Philipps-Universität Marburg, Marburg, [e]Institute of Neurogenetics, University of Lübeck, Lübeck, [f]Paracelsus-Elena-Klinik, Kassel & University Medical Center, Göttingen, and [g]Department of Neurology, University of Rostock, Rostock, Germany; [h]Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway; [i]Center for Neurodegenerative Diseases (CEMAND), Neuroscience Section, Department of Medicine, University of Salerno, Salerno, Italy; [j]Department of Neurology and Neuroscience Campus Amsterdam, VU University Hospital, Amsterdam, Netherlands; [k]Department of Social Medicine, Bristol, [l]Clinical Ageing Research Unit, Newcastle, [m]Department of Neurology, Southern General Hospital, Glasgow, and [n]Department of Physiology, Anatomy and Genetics, Oxford Parkinson's Disease Centre, Oxford, UK; [o]Head of Clinical and Experimental Neuroscience, Belva, Luxembourg; [p]Department of Neurology, Karolinska University, Stockholm, Sweden

Key Words
Longitudinal · Parkinson's disease · Marker · Cohort studies

Abstract
Background: Enormous effort is being put into the identification and characterization of symptoms that may be used as predictive and progression markers in Parkinson's disease (PD). An impressive number of PD patients and individuals at risk for or in the prodromal stage of PD are currently followed in longitudinal studies; however, there does not exist an overview on the kind of markers evaluated and the assessments used. ***Methods:*** Information on the design, sample size, evaluated markers and assessments of 21 studies of the Joint Programme – Neurodegenerative Disease Research BioLoC-PD working group were collected by questionnaire. The studies were classified into at risk/prodromal or clinical PD cohorts. The assessments were grouped into quantitative assessments, investigator-rated assessments, investigator inter-

S.L. and I.L.-S. contributed equally to this work.

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E-Mail karger@karger.com
www.karger.com/ned

Stefanie Lerche, PhD
Department of Neurodegeneration
Hertie Institute for Clinical Brain Research, University of Tuebingen
Hoppe Seyler-Strasse 3, DE–72076 Tuebingen (Germany)
E-Mail Stefanie.lerche@uni-tuebingen.de

views, patient-rated questionnaires and caregiver-rated questionnaires. ***Results:*** Compilation of these data revealed an interesting consensus on evaluated markers, but there was an enormous variability of assessments. Furthermore, there is a remarkable similarity in the markers assessed and evaluation methods applied in the risk/prodromal and clinical PD cohorts. ***Conclusions:*** The inventory of the longitudinal cohorts that are part of the BioLoC-PD consortium reveals that there is a growing consensus on the markers that should be assessed in longitudinal cohort studies in PD. However, controversy still exists on the specific type of assessment. To allow comparison of data and common analyses it will be essential to harmonize scales and assessment outcomes.

Introduction

The identification of validated predictive and progression markers in Parkinson's disease (PD) is essential for an earlier diagnosis, patient stratification, implementation of neuroprotective therapies and definition of useful study end points.

Currently, a considerable number of ongoing longitudinal cohort studies in patients and subjects-at-risk attempt to identify and characterize risk factors (RFs), clinical signs or symptoms, biomaterial-associated changes or neuroimaging abnormalities that may be used as predictive and/or progression markers in PD. Although extensive effort is being put into each of the existing cohort studies, many important conclusions cannot be drawn because of a lack of sufficient sample size in individual studies (e.g. conversion to PD in at risk studies) or an inability to accurately determine specific signs or symptoms (e.g. occurrence of slight motor symptoms in population based studies). Therefore, combining data across studies is needed to provide more precise estimates and validate predictive and prognostic models. However, merging data sets is difficult for several reasons:

(1) The design of longitudinal cohort studies vary widely, ranging from retrospective compilation of data to prospective population-based studies, enriched risk cohorts and detailed follow-ups of strictly defined sub-cohorts.

(2) Longitudinal cohort studies assess different phases of the disease course. In the motor phase, studies may either cover the very early phases or focus on later phases to understand the course and development of specific complications. With regard to earlier phases, a distinction between 'motor' and 'premotor' or 'prodromal' PD is mostly kept, which seems increasingly artificial with our growing understanding of the pathologic process and presence of subtle motor symptoms that may occur years before a clinical diagnosis.

(3) There is neither consensus regarding the symptoms that need to be assessed nor regarding the nature of the assessment.

Thus, harmonization of assessment of PD-associated markers in longitudinal cohort studies is urgently needed. The Joint Programme – Neurodegenerative Disease Research (JPND) has set up a program for 'Working Groups to Inform Cohort Studies in Neurodegenerative Disease Research'. Within this program, the working group 'Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson's Disease' (BioLoC-PD) is working on (1) a minimal data set of markers that should be assessed in all longitudinal cohort studies to allow a comparison of data from different centers and (2) a consensus on all kind of markers as well as assessments to be used for specific features.

A first step in this process is the characterization of already ongoing longitudinal studies investigating predictive and progression markers in PD to get an overview of the markers and assessments performed. For practicality reasons, such an effort must be restricted to a limited number of studies. We present an inventory of the markers and assessments being used in studies performed by the BioLoC-PD members, which will serve as a basis to define a modular common data protocol for the longitudinal follow-up of PD patients.

Methods

Studies Included

Principal investigators (PIs) of longitudinal cohort studies, including either a PD risk, prodromal or motor group, who were eligible to participate in the JPND program were asked to join the BioLoC-PD working group between April and June 2014. PIs from Germany, Italy, Luxembourg, the Netherlands, Norway, Sweden and the United Kingdom were eligible and willing to join the group. In total, 18 PIs (or their representatives) and one clinical neuroepidemiologist representing 22 European studies formed the BioLoC-PD working group.

Because of missing details on the final study design, recruitment and assessment strategies of one study was excluded from data analyses.

Thus, 21 studies were considered for further analyses (table 1). These studies were classified according to their participants in (i) at risk, (ii) prodromal and (iii) clinical PD cohorts. Some studies (n = 5) follow more than one cohort of participants. A detailed overview of the studies is given in table 1 (fig. 1).

Table 1. Overview of study characteristics listed in alphabetical order

Study	Scope of interest	Recruitment strategy	Classification of study	Individuals included	Planned follow-ups	Inclusion criteria	Exclusion criteria
ABC-PD	Identification at risk for PD	Clinical based	Clinical PD	47 (intended 100)	2 (yearly)	Patients were selected according to Amyloid beta CSF values	PD, age <50 years
Contursi	Identification of markers of PD motor onset in a cohort of subjects with alpha-synuclein and LRRK2 mutations	Population based	Risk PD	Ongoing recruitment	Conversion to PD	LRRK2 or SNCA mutation in pre-symptomatic subjects	
DEMPARK/ Landscape	Worsening of cognitive function, conversion to PDD	Clinical based	Clinical PD	260 PD, 250 PD-MCI, 150 PDD, 44 DLB (ongoing recruitment)		Criteria for PD, PD-MCI and PDD	Atypical PD
DeNoPa	Non-motor symptoms and biomarker for diagnosis, progression and as prognostic markers	Clinical based	Prodromal PD and clinical PD	159 PD, 110 healthy controls, 25 RBD (ongoing recruitment)	Biannual for 10 years	UK brain bank; PD drug naïve at baseline, controls matched to age, gender and education; idiopathic RBD diagnosed by video supported PSG	HC: neurological disorder/ positive family history PD: fulfilled criteria for atypical PD at BL
Depression-PD	Risk factors for subsequent parkinsonism/PD	Clinical based	Prodromal PD	57	Completed	Severe episode of major depressive disorder	Psychiatric diseases other than depression
EPIPARK	Identification of risk factors for subsequent PD and risk factors for thedevelopment of non-motor symptoms in PD	Population based	Prodromal PD and clinical PD	10,000 screened, 721 examined		Selected from population based screening or PD patient from outpatient clinic	Age <50/>80 years at screening
HELP-PD	Comprehensive assessment of parkinsonism in Luxembourg	Population based	Clinical PD	4 PD (intended 1,600)		Parkinsonism affected (PD, atypical PD) and healthy individuals	
ICD-PD	Risk factors for the development of impulse control disorders in PD	Clinical based	Clinical PD	60 (ongoing recruitment)		drug naive at baseline	

Table 1. (continued)

Study	Scope of interest	Recruitment strategy	Classification of study	Individuals included	Planned follow-ups	Inclusion criteria	Exclusion criteria
ICICLE-PD	Identification of risk factors for cognitive worsening and dementia in PD	Clinical based	Clinical PD	219		UK BB criteria	Prevalent PD, dementia, atypical parkinsonian syndromes, insufficient English
Melanoma-PD	Risk factors for subsequent parkinsonism/PD	Clinical based	Risk PD	65 melanoma, 35 healthy controls	2 (after 3 and 5 years)	History of treated high-risk cutaneous or uveal melanoma	Melanoma: parkinsonism/PD, HC: neurological disorder
MiGAP	Identification of markers for early detection, progression, of PD and disease mechanisms	Prodromal PD	Risk PD	35 (intended 300)	After 1 year	Healthy carriers and non-carriers of GBA mutations	Age <40/>90 years; dementia; cerebral bleedings
MODEP	Identification of progression markers in PD	Clinical based	Clinical PD	74	Biannually	Age >50 years;disease duration 0–8 years at inclusion	Dementia; atypical PD syndrome; HC: neurological disorder/ positive family history
NASA	Identification of markers for PD progression	Clinical based	Clinical PD	140 early PD	After 2 and 4 years	drug naive at baseline	
OPDC_ Discovery	Identify targets for new and better treatments for PD; develop simple ways to diagnose and monitor PD much more accurately	Clinical based	Risk PD and prodromal PD and clinical PD	1,370			
Park-West	Incidence, neurobiology and prognosis of PD	Population based	Clinical PD	212 incident PD; 207 healthy controls	Lifelong	Early PD; drug naive at baseline	Atypical, drug-induced, or vascular parkinsonism
PD-COG	Identification of variations in clinical features (including progression rates) in PD	Clinical based	Clinical PD	78			Dementia at baseline
PRIPS	Incidence of PD	Population based	Prodromal PD	1,847	After 3 and 5 years	Age >50 years; no neurodegenerative disease	

Table 1. (continued)

Study	Scope of interest	Recruitment strategy	Classification of study	Individuals included	Planned follow-ups	Inclusion criteria	Exclusion criteria
PRoBaND_ Tracking	Identification of variations in clinical features (including progression rates) in PD	Clinical based	Risk PD and clinical PD	240 young onset PD; 2,000 early PD; 850 siblings		Age <50 years at diagnosis (young onset); diagnosis <3 years (early PD); unaffected (siblings)	Drug-induced, vascular
RBD-PD	Conversion to PD	Clinical based	Prodromal PD	30 (ongoing recruitment)		Video-polysomnography according to consensus criteria of the international RBD study group (Schenck et al. 2013, Sleep Medicine), 35 years and older	Drug- or lesion-induced RBD, all other secondary causes for RBD, RBD in narcolepsy, clinical signs for PD, DLB, MSA, PSP or any other akinetic rigid tremor syndrome
TREND	Identification of markers for subsequent PD	Clinical based	Prodromal PD	715 (intended 1,200)	Until death/ autopsy	Age >50 years; no neurodegenerative disease	Psychiatric diseases other than depression
Twin-Study	Study heritability of PD by following a twin cohort from the 1960's onward	Population based	Risk PD and clinical PD	36,030 (ongoing recruitment)	Until death by national health registers	Selected from population-based twin registry	None

Process of Study Inventory

A questionnaire was sent to all PIs to collect information on the design, sample size, functions and assessments of each study in a first step. Detailed information on assessments was asked for the following functions: motor, activity of daily living (ADL), gastrointestinal and autonomic, sensory, sleep, neuropsychiatric, cognitive function as well as health-related quality of life. Furthermore, information on demographic and non-demographic RFs was recorded. Information on subjects' age and gender were coded as demographic RFs and information on smoking or dietary habits, coffee/tea consumption, exposure to solvents or pesticides, head injuries, frequency of sports and the body mass index were coded as non-demographic RFs. In addition, application of the following brain imaging methods was listed: MRI, single-photon emission computed tomography, transcranial ultrasound (TCS), magnetoencephalography and near-infrared spectroscopy. We included information about the collection of biomaterial (blood, cerebrospinal fluid, urine, saliva, nasal fluid, skin or colon biopsies and consent to brain donation). Additional information about non-specified assessments was also possible.

The assessments were grouped according to the evaluation method applied, as one of the following: quantitative assessments (e.g. Timed Up and Go Test), investigator-rated assessments (e.g. Unified Parkinson Disease Rating Scale motor part, UPDRS part III), investigator interviews (e.g. NeuroPsychiatric Inventory), patient-rated questionnaires (e.g. Non-Motor Symptom Questionnaire) and caregiver-rated questionnaires (e.g. Mayo Sleep Questionnaire). Three studies used consensus criteria to assess gastrointestinal symptoms and impotence (e.g. Rome III Criteria for gastrointestinal diseases), which were defined as investigator-rated interviews.

Measurements of symptoms were classified as either the assessment of several PD features/functions (global PD) or different aspects of a single feature/function (global function) or one aspect of a single feature/function (SF). Motor-SFs assessments were subdivided into 'gait and balance', 'fine motor' or 'other' tasks. ADL-SFs were classified as basic, instrumental function or others. For gastrointestinal and autonomic symptoms, the following SFs were defined: gastrointestinal, cardiovascular symptoms and others. The most common sensory SFs were olfaction, color vision and pain, which are presented as distinct categories. Tools assessing other sensory modalities were added to the category of 'others'. The REM sleep behavior disorder (RBD) assessments were coded as SF for sleep. Depression, anxiety, apathy and emotion were the most commonly reported neurobehavioral SFs. All other specific neu-

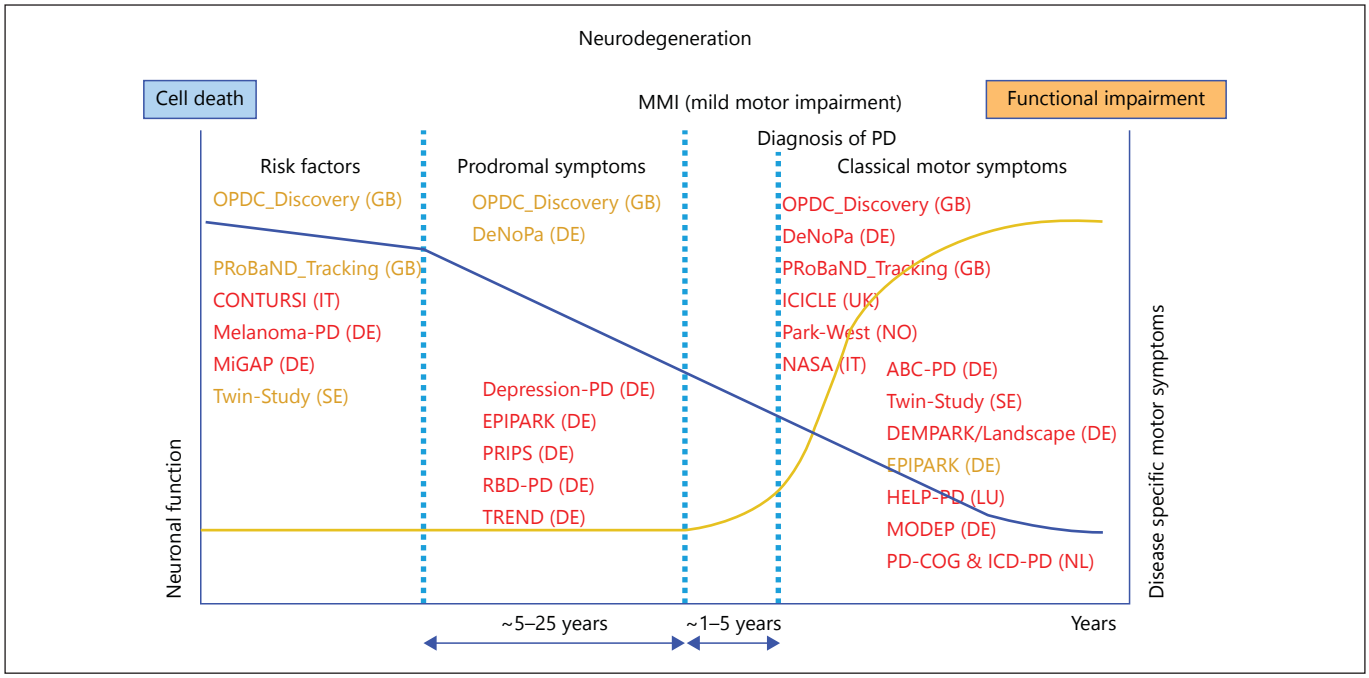

Fig. 1. Simplified draft of the overall course of PD, arranged into the currently advocated phases, that is, phase of RFs, prodromal symptoms and of classical motor symptoms. Mild motor symptoms characterize a phase of so far unknown duration between the occurrence of prodromal and classical motor symptoms. During these phases, neuronal function declines until disease specific motor symptoms occur, which worsen with increasing neuronal dysfunction. Within the phases, the European Longitudinal Cohort Studies of Members of the JPND Working Group are mentioned (abbreviation of conducting country in brackets). For studies covering different phases (motor, prodromal, at risk), the major study arm with the largest number of participants is presented in red. The second/(third) study arm with lower subjects numbers is shown in yellow. Importantly, it turned out that most of the longitudinal studies targeting the 'risk or prodromal' phase are extended to the motor phase, which is not depicted in the figure. ABC-PD, Amyloid-beta in CSF as RF for cognitive dysfunction in PD; CONTURSI, CONTURSI kindred (PARK1) genetic project; Depression-PD; DEMPARK, Demenz bei Parkinson; DeNoPa, De Novo PD; EPIPARK, Epidemiology of non-motor symptoms in PD: frequency, specificity, and course; HELP-PD, Health of the Elderly Luxembourgish Population with a focus on PD; ICD-PD, Impulse control disorders in PD, ICICLE-PD, Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – PD; Melanoma-PD; MiGAP, Markers in GBA-associated PD; MODEP, Modeling epidemiological data to study PD progression; NASA, NAples and SAlerno cohort of early PD; OPDC_Discovery, Oxford Parkinson's Disease Centre_discovery cohort; Park-West, The Norwegian ParkWest study; PD-COG, PD-related cognitive dysfunction; PRIPS, Prospective validation of RFs for the development of PD; PRoBaND_Tracking, Parkinson's Repository of Biosamples and Networked Datasets; RBD-study group, Rapid eye movement sleep behavior disorder study group; TREND, Tuebinger Evaluation of RFs for early detection of neurodegeneration.

ropsychiatric symptom assessments were summarized as 'others'. Measurements assessing cognition were differentiated between scales (either investigator rated, patients' or caregivers' complaints), screening tools or standardized tests covering a specific cognitive domain. Tests were assigned to one of the following cognitive domains: executive, attention and working memory, memory, language, visuospatial/visuo-construction (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000439221).

In a second step, the compilation of the collected study information, functions and assessments were discussed in person at the BioLoC-PD meeting October 22–24, 2014. Each PI was requested to check, modify and confirm validity of data entry. Further a consensus decision on the strategy of final data analysis was made by the consortium.

Data Analysis and Statistics

A total number of 21 studies was sampled, including data from 6 cohorts following at risk, 7 cohorts investigating prodromal and 14 cohorts including clinical PD participants (table 1 for study/cohort classification).

Descriptive data are reported as absolute frequency and percentages. For statistics comprising all studies, studies including different cohorts (study arms) according to the different disease phases (risk and/or prodromal and/or clinical PD) were counted only once to avoid overrepresentation of assessments and markers. However, for reports focusing on marker frequency of either risk/prodromal or clinical PD, each study (sub)cohort was counted separately. Five studies are following more than one study arm.

Categorical statistical comparison of risk/prodromal versus clinical PD samples was compared by use of the Fisher's exact test.

Table 2. Overview of markers assessed in the different studies and number of assessments applied

Study	Function										
	demographic RF	non-demographic RF	motor	ADL	gastro-intestinal and autonomic	sensory	sleep	neuro-psychiatric	cognitive	imaging	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

For the analysis of non-categorical data a 2-sided t test was used. A p value <0.05 was considered as significant difference between groups.

Results

We analyzed data from 21 studies, 16 (76%) studies consisting of one study arm, 4 (19%) studies following cohorts in 2 different phases/arms (n = 2 risk and clinical PD, n = 2 prodromal and clinical PD) and one study (5%) following a risk, prodromal and a clinical PD cohort (table 1). In 11 (52%) of the 21 studies recruitment is still ongoing.

The analysis reveals an interesting consensus on the domains included in different studies (table 2). Demographic RFs, motor function and neurobehavioral functions are assessed in all studies of the BioLoC-PD working group focusing on risk, prodromal and clinical PD. In addition to demographic RFs non-demographic RFs are assessed in 20 studies. Among those coffee/tea consumption (n = 18; 86%) is the most commonly assessed non-demographic RF. All studies included assessments of at least 7 of the 10 domains requested in our inventory, most studies assess more than 9 domains (81% of the studies).

Specification of Assessments per Function (see fig. 2 and 3)

Motor Function

Global motor function is assessed exclusively using investigator rated scales (100%). The UPDRS part III is included in all studies irrespective of the phase assessed, however, 10 studies (48%) use the original UPDRS scale [1], 9 (43%) studies apply the MDS-UPDRS scale [2] and 2 (10%) studies assess both scales.

In contrast, fine motor (100% of n = 4 assessments) and gait abnormalities (71% of n = 7 assessments) are primarily assessed using quantitative methods. Tests for gait and balance are included in 38% (n = 5) of risk/prodromal studies and 36% (n = 5) of clinical PD trials (p = 0.89). Both functions are primarily evaluated by quantitative methods (85% risk/prodromal and 71% clinical PD of all tests used). In contrast, fine motor movements are recorded in 46% of risk/prodromal cohorts (n = 6) and 36% of clinical PD cohorts (n = 5; p = 0.70).

ADL Function

ADL function is primarily verified by investigator interviews (50% of n = 6 assessments) followed by the application of investigator rated (33%) or caregiver-rated

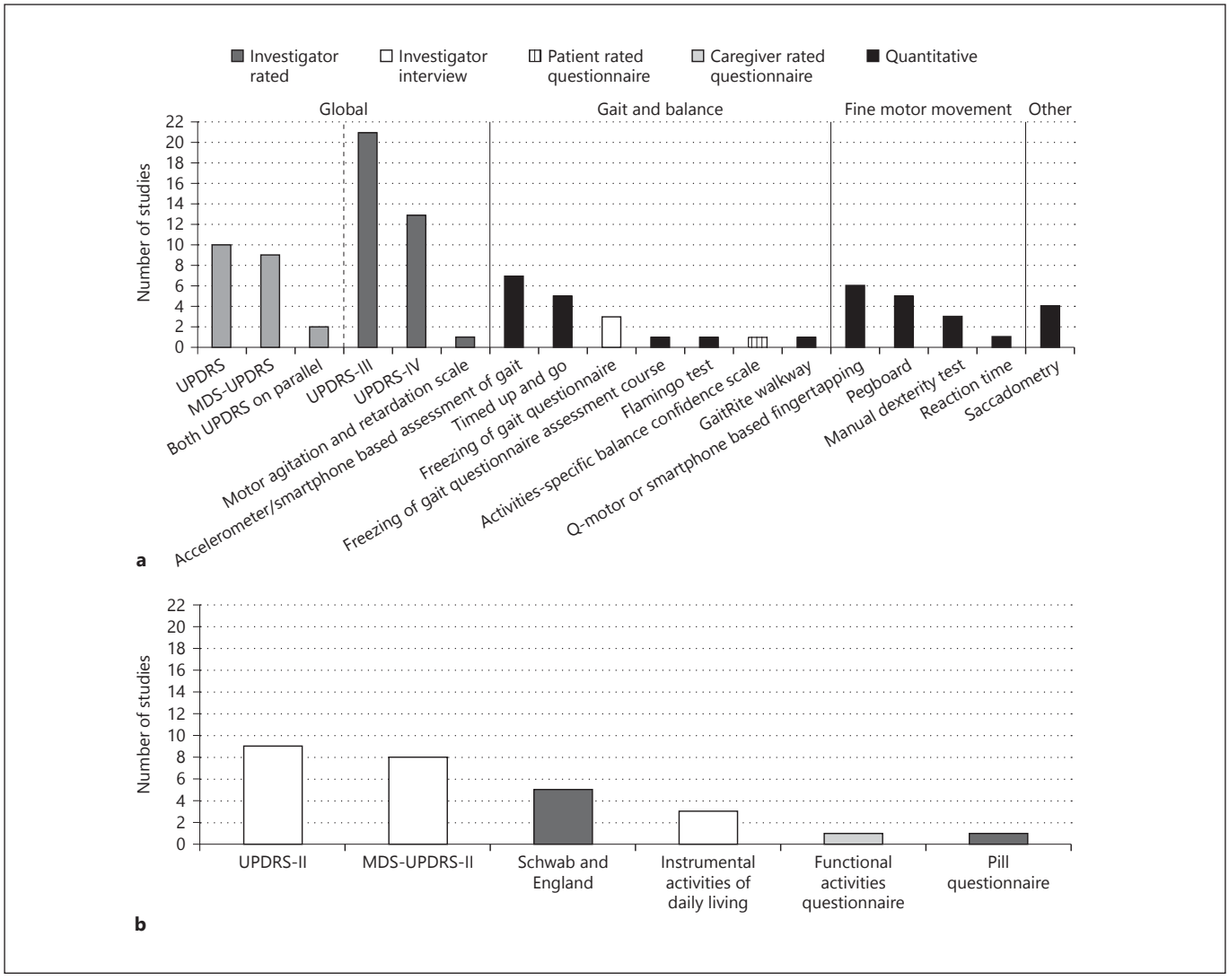

Fig. 2. Overview of assessments and markers part 1: **a** motor function, **b** ADL function. MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; RLS = restless leg syndrome; UMSARS = Unified Multiple System Atrophy Rating Scale.

(17%) scales. Assessments for ADL function are applied in 77% (n = 10) of risk/prodromal cohorts and 93% (n = 13) of clinical PD samples (p = 0.33). ADL is mainly assessed by investigator rated interviews (71% risk/prodromal and 71% clinical PD).

Gastrointestinal and Autonomic Functions

Global gastrointestinal and autonomic functions are mainly assessed by patient rated questionnaires (66% of n = 3 global assessments). Detailed assessment of gastrointestinal SF is equally done with either investigator interviews or patient rated questionnaires whereas cardiovascular SF is solely assessed by quantitative tests.

Measurement of global gastrointestinal and autonomic functions are performed in 52% (n = 11) of the studies (46% risk/prodromal samples and 43% of clinical PD samples, p = 1.0). Gastrointestinal SF are assessed in 38% (n = 5) of all risk/prodromal cohorts and in 14% (n = 2) of all clinical PD cohorts (p = 0.21). Fifty percent of the risk/prodromal cohorts use patient rated questionnaires compared to 100% of clinical PD cohorts. Cardiovascular SF are assessed in 77% (n = 10) of risk/prodromal samples and in 86% (n = 12) of clinical PD samples (p = 0.65).

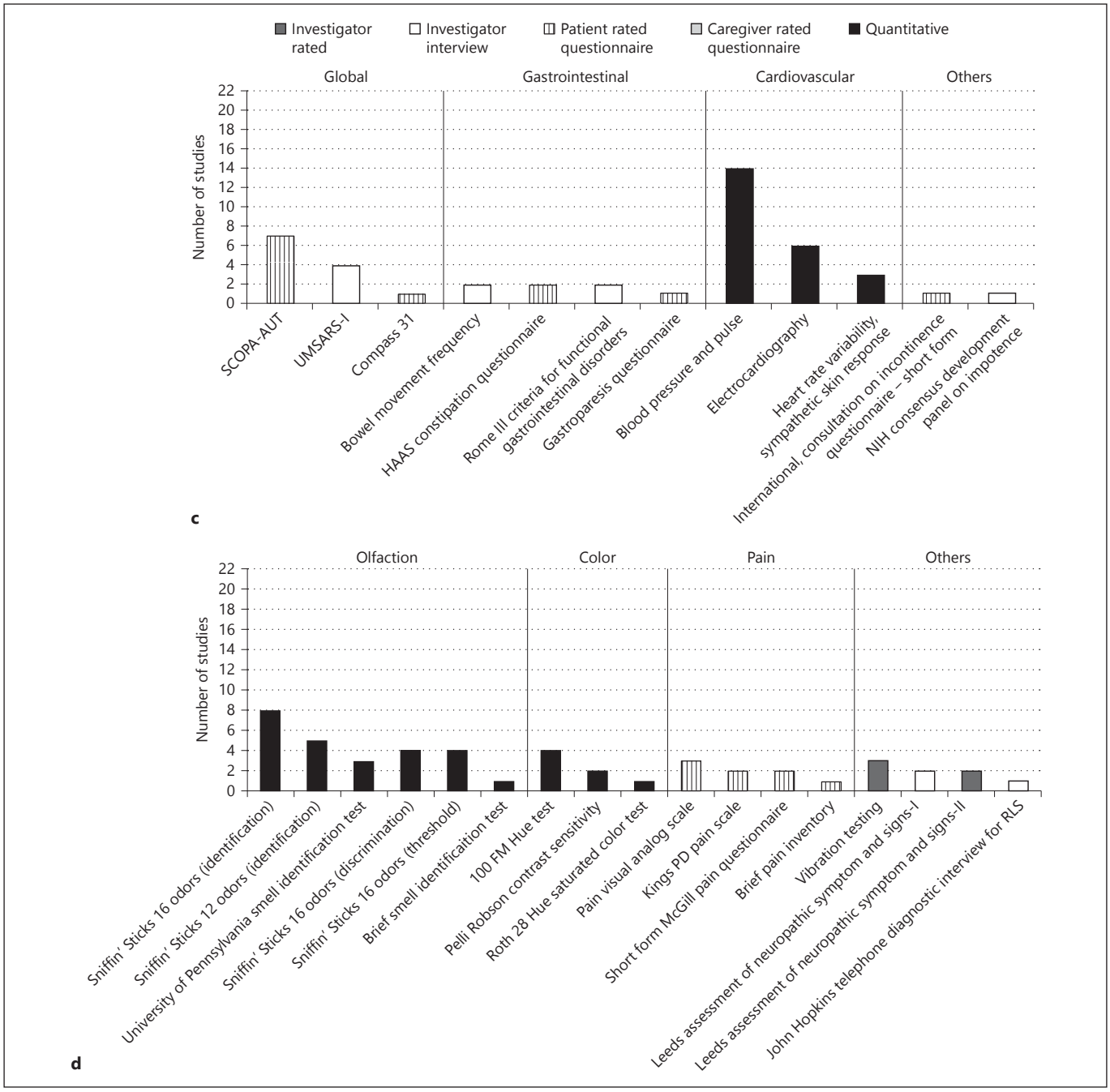

Fig. 2. Overview of assessments and markers part 1: **c** gastrointestinal and autonomic markers, **d** sensory markers. MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; RLS = restless leg syndrome; UMSARS = Unified Multiple System Atrophy Rating Scale.

Sensory Functions

Assessment methods (e.g. quantitative vs. patient-rated) are very homogenous in the evaluation of sensory functions in the BioLoC-PD cohorts. However, features and kind of assessment (different quantitative analyses, different scales) vary largely. Olfaction and color vision are solely assessed by quantitative measurements, whereas patient-rated questionnaires are used for the assessment of pain.

Olfactory SF is assessed in 92% (n = 12) of risk/prodromal cohorts and in 64% (n = 9) of clinical PD cohorts (p =

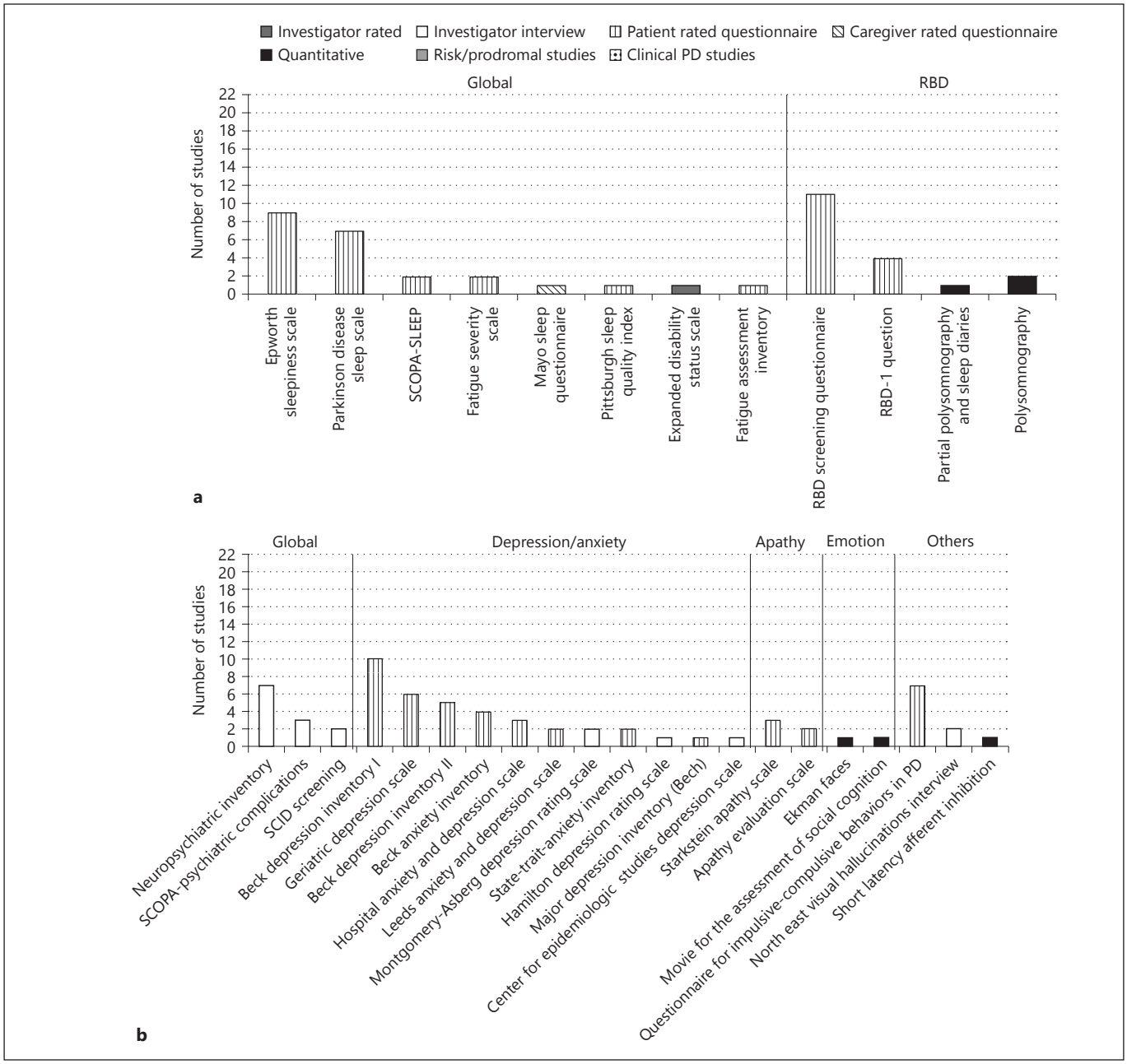

Fig. 3. Overview of assessments and markers part 2: **a** sleep, **b** neuropsychiatric markers. DaTSCAN = Dopamine transportscintigraphy; FDG-PET = fluorodeoxyglucose positron emission tomography; fMRI = functional MRI; MEG = magnetoencephalography; NIRS = near-infrared spectroscopy; SCID = structured clinical interview for DSM disorders; SPECT = single-photon emission computed tomography.

0.16). The most commonly used assessment for this SF is the Sniffin' Sticks test (62% n = 13 of 21 studies). Color vision is assessed in 23% (n = 3) of risk/prodromal samples compared to 14% (n = 2) of clinical PD samples (p = 0.65). Pain is assessed in 31% (n = 4) of risk/prodromal samples versus 29% (n = 4) of clinical PD samples (p = 1.0).

Sleep

For the evaluation of global sleep alterations patient-rated questionnaires seem to be preferred (75% of n = 8 assessments) in the cohorts represented in our working group. For the evaluation of RBD, there are only 2 kinds of assessments (patient-rated questionnaire or quantitative).

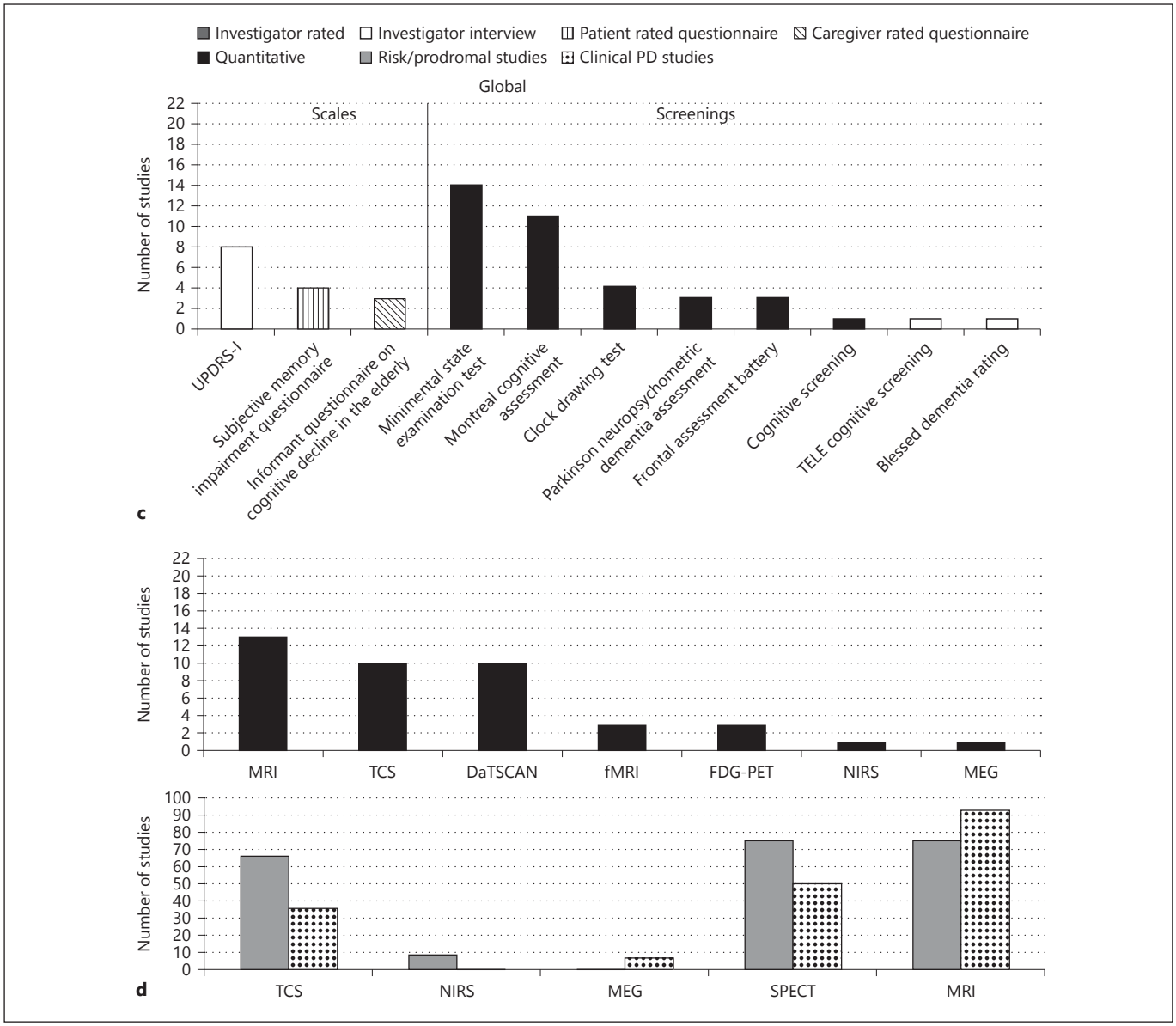

Fig. 3. Overview of assessments and markers part 2: **c** cognitive functions, **d** imaging techniques. DaTSCAN = Dopamine transportscintigraphy; FDG-PET = fluorodeoxyglucose positron emission tomography; fMRI = functional MRI; MEG = magnetoencephalography; NIRS = near-infrared spectroscopy; SCID = structured clinical interview for DSM disorders; SPECT = single-photon emission computed tomography.

Global sleep alteration is assessed in 54% (n = 7) of risk/prodromal samples compared to 79% (n = 11) of clinical PD samples (p = 0.24). Most times, it is assessed with patient-rated questionnaires (risk/prodromal: 92%, n = 11 and clinical PD: 90%, n = 19 of total used tests). RBD is assessed in 62% (n = 8) of risk/prodromal samples and in 64% (n = 9) of clinical PD samples (p = 1.0). Like global sleep alteration, RBD is mainly assessed with patient-rated questionnaires (risk/prodromal: 73% n = 11; clinical PD: 75% n = 9).

Neuropsychiatric Functions

In contrast to the preference of investigator interviews for the assessment of global neurobehavioral function (100% of n = 3 assessments), depression/anxiety (73% of n = 11 assessments) and apathy (100% of n = 2 assessments) are primarily assessed by patient-rated questionnaires. Emotion is the only SF assessed by a quantitative method in our cohorts.

Measurement of global neurobehavioral functions are performed in 52% (n = 11) of the studies (46% risk/prodromal samples and 71% of clinical PD samples, p = 0.25). Depression/anxiety is assessed in 92% (n = 12) of risk/prodromal samples and 93% (n = 13) of clinical PD samples (p = 1.0). In 92% of the risk/prodromal cohorts and clinical PD cohorts, respectively, patient-rated questionnaires are used. Apathy is assessed in 8% (n = 1) of risk/prodromal samples and in 29% (n = 4) of clinical PD samples (p = 0.33). Emotion is assessed in 8% (n = 1) of risk/prodromal samples and in 14% of clinical PD samples (n = 2).

Cognitive Function

For screening of global cognitive functions, mainly, quantitative neuropsychological tests are used (55% of n = 11 assessments), followed by investigator interview (27%), patient-rated questionnaire (9%) and caregiver-rated questionnaire (9%). Global cognition is assessed in nearly all study samples (risk/prodromal: 92%, n = 12; clinical PD: 100%, n = 14; p = 0.48). In general, the Mini Mental State Examination Test (MMSE) is the most common global cognitive screening instrument (70%, n = 14 studies) followed by the Montreal Cognitive Assessment (MoCA; 52%, n = 11 studies) and the clock drawing test (19%, n = 4). Risk/prodromal study samples use MMSE and MoCA equally (each 58%, n = 7), partly in parallel (n = 4 studies), whereas clinical PD samples showed a tendency to prefer the MMSE (n = 11) over MoCA (n = 8).

More detailed neuropsychological testing is applied in 19 of 21 studies (risk/prodromal: 85%; clinical PD: 100%; p = 0.46). But only 3 studies, all focusing on clinical PD (DeNoPa, ABC-PD and DEMPARK/Landscape), investigate all 5 cognitive domains. However, many different tests are used for the same cognitive domains (table 3). Executive function is the most commonly assessed domain (86%, n = 18 of 21 studies) followed by the assessment of memory (52%, n = 11), visuospatial/constructive (48%, n = 10), attention and working memory (48%, n = 10) and language (43%, n = 9) abilities.

Executive function is assessed in 69% of risk/prodromal study samples and 86% of clinical PD samples (p = 0.38), and 15% of risk/prodromal samples and 50% of clinical PD samples record attention and working memory (p = 0.10). Memory testing is considered in 31% of risk/prodromal samples and in 57% of clinical PD samples (p = 0.21). Language performance is evaluated in 46% of risk/prodromal samples and in 43% of clinical PD samples (p = 1.0). Visuospatial/constructive function is tested in 38% of risk/prodromal cohorts and in 50% of clinical PD cohorts (p = 0.70). In total, mean number of domains assessed in risk/prodromal samples is 2.0 ± 1.6, and 2.9 ± 1.7 in clinical PD samples (p = 0.20).

Imaging

The most commonly used imaging technique is MRI (62% n = 13) followed by TCS and DaTScan (both 48% n = 10). Risk/prodromal study samples prefer TCS (69%) in our cohorts compared to 36% of clinical PD samples (p = 0.13). In contrast, clinical PD samples primarily use MRI techniques (MRI/fMRI) (93%) compared to 75% of risk/prodromal samples (p = 0.26).

Discussion

One aim of the BioLoC-PD working group is the characterization of already running longitudinal studies in different phases of PD designed to identify valid predictive and progression markers. This knowledge will allow the identification, harmonization and subsequent analysis of comparable data across studies, and thus enhance our understanding of the overall course of PD (in prodromal and motor phases). This will set the stage for improvement of clinical trials based on novel study end points (defined by progression markers) and improve case stratification. Finally, the increased understanding of the overall course of PD and the development of predictive and progression markers will encourage a common modular assessment battery for longitudinal cohort studies in PD, supporting the design of new studies and the comparability of study data.

Two main findings can be derived from this characterization of longitudinal cohort studies in PD.

(1) The compilation presented in this paper reveals an interesting consensus on domains incorporated in different studies, but also an enormous variability of assessments/tests used to objectify them. Demographic RFs, motor function and neuropsychiatric functions are assessed in all studies reflecting the high value of these markers in risk/prodromal and clinical PD. The substantial variability in the choice of the evaluation method (quantitative assessment, investigator-rated assessment, investigator interview and patient-rated questionnaire) may be explained by a number of different factors as follows: (i) not all scales/questionnaires are available and validated in all languages. (ii) Study designs vary with regard to outcome variables, which influences the kind of assessments. (iii) Some assessments take more resources

Table 3. Overview of specific cognitive domains considered in longitudinal studies by detailed neuropsychological testing

	Cognitive domain					
	executive function	attention/working memory	memory	language	visuospatial/ constructive	number of domains assessed
Risk/prodromal						
Number of assessment	16	7	28	5	9	
Contursi	x		x		x	3
MiGAP	x					1
Melanoma-PD						0
OPDC_Discovery	x			x		2
PRoBaND_Tracking		x			x	2
Twin-Study						0
Depression-PD	x			x		2
PRIPS	x		x	x	x	4
RBD-PD						0
TREND	x		x	x	x	4
DeNoPa	x	x	x	x	x	5
OPDC_Discovery	x			x		2
EPIPARK	x					1
Number of risk/prodromal cohorts	9	2	4	6	5	
Clinical PD						
DeNoPa	x	x	x	x	x	5
EPIPARK	x					1
OPDC_Discovery	x			x		2
ABC-PD	x	x	x	x	x	5
HELP-PD	x	x	x		x	4
ICD-PD	x			x		2
ICICLE	x	x	x	x		4
MODEP	x					1
NASA	x		x		x	3
Park-West	x	x	x		x	4
PD-COG	x	x	x	x		4
PRoBaND_Tracking		x			x	2
Twin-Study						0
DEMPARK/Landscape	x	x	x	x	x	5
Number of clinical PD cohorts	12	7	8	7	7	

than others (more time-consuming, more costly or require trained staff members), influencing selection and composition of assessment battery. (iv) Preference of assessment based on previous research experience.

(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 by not only non-motor signs but also 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. Current knowledge suggests that individual markers may follow different prevalence as well as severity curves throughout the disease course. Some curves may be linear, others may be indicative of an exponential decline or an increase, while yet others have a U-shaped form over the neurodegenerative course [3–5]. A better understanding of these curves will markedly influence the end points of clinical trials. In the following, we will discuss specific markers and assessments in more detail.

Unsurprisingly, all studies included testing of motor function as this is the hallmark of PD. Half of the studies analyzed here use the original version, and the other half uses the modified MDS-UPDRS motor scale. One reason might be that the modified MDS-UPDRS scale is available only since 2009 [2] and therefore could not be applied beforehand. Furthermore, there are no validated versions of the modified MDS-UPDRS scale except in English, and it is licensed for research purposes, which hinders application in less well-funded studies. Fortunately, a good correspondence between both scales has been reported allowing the harmonization of outcomes [6]. Besides motor assessment by the UPDRS, there seems to be a growing interest in quantitative motor assessment, especially of gait (70% of assessments) and fine motor movements (100% of assessments). The need for objective unbiased measurements of PD is increasingly recognized [7]. However, at this point in time, there is neither a consensus on which device to use nor on which outcome variable to prefer. A large number of devices offering continuous, unobtrusive and objective data collection in the clinical setting as well as at home are being tested. One of the major challenges of the future will be to derive the best outcomes for prediction of PD as well as for monitoring disease progression and response to therapeutic interventions.

Also, neuropsychiatric function is being assessed in all studies reflecting the realization of the importance of symptoms occurring in this domain. This may seem surprising as psychiatric symptoms such as depression increase the risk of PD by only 2–3 times [8]. However, anxiety, depression and apathy, are the most common non-motor symptoms in early untreated PD patients [9, 10]. In accordance with these findings, mainly, depression/anxiety and apathy scales are used in the longitudinal studies presented here. To account for the complexity of these symptoms, several assessment tools are often used. For example, 55% of the studies use more than one assessment to test for prevalence and severity of depression and anxiety. As not only the number but also the kind of assessment vary largely between different studies, harmonization of the assessment tools is essential to compare data.

Besides, neuropsychiatric assessment screening for global cognitive function is performed in all clinical and in 92% of the risk/prodromal studies mainly by applying the MMSE (70%) and/or the MoCA (52%). Both tests are available in more than 30 different languages (http://www.mocatest.org), and conversion scores between both scales have already been published [11] allowing comparison of data. Our own preliminary analyses provide more robust data validating the use of conversion scales to interchange between these scales (Michael Lawton – personal communication). In general, the MMSE may be more sensitive to change [12] but the MoCA seems to be superior and more sensitive for the detection of mild cognitive decline in PD [13, 14], thus avoiding ceiling effects.

The kind of neuropsychological tests applied is extremely heterogeneous between studies. With regard to domains, most studies focus on executive function and memory performance. All 5 cognitive domains, required for example for the classification of Level II diagnosis of mild cognitive impairment and PDD [15, 16], are tested only in a minority (n = 3) of studies.

Sensory function is assessed in a more homogeneous way. The most frequently assessed sensory feature is olfaction, which is highly prevalent in motor and non-motor PD [17, 18] and thus assessed in 76% (n = 16) of the studies. Other sensory symptoms like pain or color vision are evaluated less frequently by more heterogenic methods.

Impairment in gastrointestinal and other autonomic functions is mainly addressed using global non-motor symptom scales such as the NMS-Q or the Scales for Outcome in Parkinson's Disease-Autonomic (SCOPA-AUT; NMS-Q n = 11, SCOPA-AUT n = 7, both n = 5 studies). For the specific assessment of bowel function, there is no preference for any specific methods indicating the need for a methodological consensus decision. Blood pressure and pulse are registered in 67% (n = 14) of studies reported here. However, a more detailed evaluation of cardiovascular symptoms is done in only 29% (n = 6) of studies.

Sleep assessment in our summary is mainly based on global sleep quality scales or the assessment of RBD. Among global sleep scales, the Epworth Sleepiness Scale [19] is preferred, especially in the UK. The Epworth Sleepiness Scale is translated in many different languages offering an excellent choice for international cooperation [20–22]. Clinical PD studies presented in this paper focus on alteration in other sleep quality aspects in addition to RBD, while risk/prodromal studies concentrate more on RBD assessment.

The importance of RBD as a predictive marker for future onset of PD is widely accepted [23], and its predictive value for PD dementia is increasingly discussed [24, 25]. In mid/late stages of PD, the risk for other sleep abnormalities increases [26], requiring a more comprehensive sleep assessment. In our summary, RBD is assessed mainly by the use of patient-rated questionnaires in accor-

dance with the assessment of other sleep qualities, although polysomnography is still regarded as the gold standard for RBD diagnosis. This exemplifies an important issue in the design of longitudinal studies: assessments need to be as little time consuming and unobtrusive as possible. Diagnostic accuracy of the RBD screening questionnaire have shown moderate to good sensitivity and specificity for the condition [27], even though completion of this questionnaire is depending on the clinical setting and may be influenced by the individual's awareness of RBD [28].

The decision to apply imaging techniques in longitudinal studies depends not only on the specific aim of the study, but also on time constraints, burden to patients and financial resources. In our compilation, TCS is more frequently applied in risk/prodromal cohorts, whereas clinical PD cohorts primarily use MRI techniques (MRI/fMRI). This discrepancy may be due to the fact that an enlarged hyperechogenic substantia nigra has a high predictive value for PD, yet is stable throughout the disease course [29]. On the other hand, preference and experience of the respective sites with this tool may also play a role. Still, as TCS is quick to apply, easy to administer and cheap, application in large at-risk or prodromal cohorts seems feasible.

Limitations

The main limitation of this summary is that we only analyzed studies that were included in the initial JPND working group 'Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson's Disease'. To address this issue, we plan to set up a web-based platform in which further studies will have the possibility to add their study information. With this tool, it will be possible to perform an even more detailed analysis and develop a better minimal data set. Moreover, cooperation between the different studies may be further fostered.

Conclusion

The inventory of the longitudinal cohorts that are part of the BioLoC-PD consortium reveals that there is a growing consensus on the domains to be assessed in longitudinal cohort studies in PD. However, controversy still exists on the specific type of assessment. This may be due to differences in the availability of assessments in different countries, variation in study designs and/or differences in the choice of study end points. Another aspect is the historical nature of some studies. Some of the assessments were developed, revised or expanded after some of the studies were initiated. To allow comparison of data and common analyses, it will be essential to harmonize scales and assessment outcomes. Future studies are needed to resolve an obvious tension between collecting popular assessments that are present in existing studies, hence facilitating shared analyses or using a new and potentially better assessment. In such a scenario, it is sensible to collect data on both the old and new measure in a sub-group of participants; so cross-calibration methods can be used to facilitate harmonized analyses [30]. Moreover, a common modular data set would be of great help, which may allow the collection of data according to a common minimal data set that may then be supplemented by different assessment modules according to study design and study end point.

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Disclosure Statement

There are no conflicts of interest for any of the authors.

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Erratum

In the article by de Pedro Cuesta et al., entitled 'Sensitivity to biases of case-control studies on medical procedures, particularly surgery and blood transfusion, and risk of Creutzfeldt-Jakob disease' [Neuroepidemiology 2012;39:1–18, DOI: 10.1159/000339318], the authors noticed to their dismay that line 4 of the Introduction contains an error which could very easily mislead the reader.

As published, the phrase in question reads 'CJD exists in three forms: sporadic (sCJD), which is acquired, either variant (vCJD) or iatrogenic (iCJD) CJD, and cases caused by mutations in the gene-encoding PrP^{C}, here denoted for purposes of simplicity as genetic CJD (gCJD) [1]'. The words 'which is' are clearly erroneous and should be deleted. The sentence correctly reads 'CJD exists in three forms: sporadic (sCJD), acquired, either variant (vCJD) or iatrogenic (iCJD) CJD, and cases caused by mutations in the gene-encoding PrP^{C}, here denoted for purposes of simplicity as genetic CJD (gCJD) [1]'.