

The Cortical Basal ganglia Functional Scale (CBFS): Development and Preliminary Validation

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Abstract

Objective:To develop a patient/care-giver reported scale capable of easily and reliably assessing functional disability in 4 repeat tauopathies (4RTs).

Background:4R tauopathies including progressive supranuclear palsy, corticobasal degeneration and a subset of frontotemporal dementias manifest a range of overlapping clinical phenotypes. No available rating scale is capable of evaluating the functional impact of these complex disorders.

Methods:A multi-staged modified Delphi process was used to propose, evaluate and rank potential scale items providing content validity ratios. Staged cognitive pretesting involving input from examiners, patients and caregivers was followed by validation testing in patients participating in the 4R Tauopathy Neuroimaging Initiative or the PROgressive Supranuclear Palsy CorTico-Basal Syndrome MSA Longitudinal Study. Clinimetric properties were examined using classical test theory and item response methods, assessing data quality, reliability, construct validity, convergent validity and known-group validity.

Results:The resultant Cortical Basal ganglia Functional Scale (CBFS) included questions on Motor Experiences in Daily Living (14 items) and Non-Motor Experiences of Daily Living (17 items). Reliability was acceptable for internal consistency, test-retest stability, item discrimination, item-scaling thresholds and item-fit. Examination of construct validity revealed a parsimonious two-factor solution, and concurrent validity demonstrated significant correlations between the CBFS and other measures of disease severity and functional impairment. The CBFS significantly discriminated between all diagnostic groups and controls (all AUCs>90). The CBFS scores demonstrated sensitivity to change over a 12 follow-up in patients with probable 4RTs.

Conclusions:The CBFS is a patient/care-giver reported outcome measure with excellent clinimetric properties that captures disability correlated with motor, cognitive and psychiatric impairments.

Introduction

The 4-Repeat tauopathies (4RTs) are a related group of adult-onset neurodegenerative disorders that present clinically with several possible overlapping phenotypes including the corticobasal syndrome (CBS), behavioral variant frontotemporal dementia (bvFTD), nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA) and progressive supranuclear palsy (Richardson's) syndrome (PSP-RS) (1),(2). 4RTs demonstrate a range of neuronal and astroglial pathologies dominated by the deposition and aggregation of 4R tau primarily in straight and rare twisted filaments(3). These biochemical and pathological commonalities suggest that novel therapies designed to target tau specific gain- or loss-of-function mechanisms(4) may have similar disease modifying effects on 4RTs independent of their clinical presentation or dominant phenotype.

As these diseases progress, the patient's ability to carry out daily functions can be variably impacted by a range of motor, behavioral, cognitive and ocular motor disturbances. It is often difficult, if not impossible, to separate and rate these clinical features independently or attribute impairment or dysfunction in various daily activities to only one or a small number of clinical features. Thus, the assessment of the severity and impact of the complex clinical features in patients with 4RTs using even a composite of several available clinical evaluation tools is extremely problematic.

In preparation for clinical trials of disease modifying therapies directed at tauopathies, we developed and validated a simpler and more easily applied "functional" scale designed to evaluate the patient's "experiences in daily living" (EDL) (independent of the source of the problem), behavioral, language and cognitive impairments. The scale was also designed to be completed by the patient and caregiver, in keeping with a growing appreciation of the value of patient-reported outcomes (PROs), particularly by regulatory agencies(5, 6).

Methods

Cortical Basal ganglia Functional Scale (CBFS) Development

Supplementary Materials I provides a detailed description of the Scale Development (including references). The principal investigators (AEL, GTS, ALB) established two Delphi panels of experts in movement disorders and behavioral neurology. Panel members were provided extensive documentation for the purposes of developing initial scale criteria and content. Their input was followed by a series of Webinars and conference calls eventually resulting in a consensus-determined list of the most pertinent functional domains established using a Content Validity Ratio (CVR) approach. Given the size of the Delphi Panel, the published CVR criterion of 0.78(7) was used to classify items as potentially useful and to continue to the next stage of development. Items meeting this criterion were then linked to selected functional items evaluated in existing validated scales. When available items were deemed appropriate they were accepted either unchanged or with further editing to address concerns raised. Where a specific PRO item was not available, additional questions were created and reviewed by the panel members. The initial complete version of the scale was subsequently reviewed again by the committee members for comprehensiveness and suitability for completion by patients and caregivers.

The first draft of the scale then underwent extensive cognitive pretesting in a sample of 7 examiners unfamiliar with the scale, 15 patients and 10 caregivers (supplementary Material 1) and

based on these results the scale was further revised and selected additional cognitive pretesting was conducted to confirm that the changes made adequately addressed the concerns previously raised.

Preliminary Validation Testing

Given the frequent overlap in the clinical phenotypes of the 2 main 4RTs, CBD and PSP, and the similar rates of annual disease progression as measured by the PSP Rating Scale (8) we proposed to validate the scale for use in these disorders.

Participants

The final version of the Functional Scale was evaluated in patients participating in 2 studies, the North American 4R Tauopathy Neuroimaging Initiative (4RTNI) (8) and the UK PROgressive Supranuclear Palsy Cortico-Basal Syndrome MSA Longitudinal (PROSPECT) Study (see acknowledgements). Participants met research diagnostic criteria for each of the disorders(1),(2),(9) as operationalized for the 4RTNI and PROSPECT studies.

Measures

All participants (patients and their caregivers) completed the final version of the Functional Scale as well as measures assessing convergent validity, including the Clinical Dementia Rating Scale (CDR®) Dementia Staging Instrument plus National Alzheimer's Coordination Center Frontotemporal lobar degeneration Behavior & Language Domains (CDR® plus NACC FTLD) sum of boxes score (10) (4RTNI only), Progressive Supranuclear Palsy Rating Scale (PSPRS),(11) Schwab and England Activities of Daily Living Scale (SEADL),(12) the motor components of the Unified Parkinson's Disease Rating Scale (UPDRS) (4RTNI)(13) and the MDS-UPDRS(14) (PROSPECT) (UPDRS scores were converted to MDS-UPDRS scores as proposed in (15)), Montreal Cognitive Assessment (MoCA),(16) and Neuropsychiatric Inventory Questionnaire (NPI-Q).(17)

Statistical analyses

Subject demographics and disease-related characteristics were examined using parametric and non-parametric analyses, as appropriate. Examination of clinimetric properties of the CBFS were based on both Classical Test Theory (CTT)(18) and latent modeling approaches (Item Response Theory: IRT).(19) CTT analyses examined Data Quality for missing values and potential floor and ceiling effects defined as skewness outside of the range -2.00 to +2.00; Internal Consistency as determined by Cronbach's alpha, with a minimum alpha of 0.85 as criterion; item-to-total correlation, with a criterion of ≥ 0.40 as minimal acceptable correlation; and Construct Validity of the scale was examined using exploratory factor analyses to determine the number and types of constructs with a minimum loading of 0.40 used as a criterion for factor relevance. Item redundancy was assessed by item loading on multiple factors. Dual loading criteria was set at 0.40. IRT Analysis, using maximum likelihood parameter estimation, examined item discrimination (criterion of ≥ 1.00) item threshold and item fit statistics ($S-X^2$). Test-retest Reliability was assessed in a sample of 25 patients (4 MCI, 5 bvFTD, 3 FTD/ALS, 1 CBS, 5 PPA, 7 PSP) chosen randomly from patients enrolled in the ARTFL/4RTNI-2 study during 11/2018 – 1/2019 at UCSF Memory and Aging Center tested over a 1 week (± 2.3 days) interval using an intraclass correlation coefficients (ICC) with a criterion of ≥ 0.70 to indicate adequate stability. This sample size afforded us sufficient

power ($1-\beta = 0.80$, $\alpha=0.05$) to detect an ICC as small as 0.50, should such a level of agreement exist. Convergent Validity was assessed using Pearson product-moment correlations coefficients (r) or Spearman's rank-order correlation coefficient (ρ) for non-interval level data. Known-group Validity testing was used to discriminate among the sample diagnostic groups using a multinomial logistic regression with receiver operation characteristic curves and sensitivity/specificity determination as implemented in SAS proc logistic. Mplus 8.2 (www.statmodel.com) was used for the exploratory factor analyses, R "mirt" package for the item fit statistics and item trace lines, and the rest of the analyses were conducted in Stata MP 14.0 (StataCorp LP). The longitudinal evaluation was conducted in CBS and PSP patients with available CBFS measurements at baseline and 12-months. Cohen's d was calculated to determine the effect sizes for mean differences from baseline to 12-months, with a criterion of > 0.2 as small, > 0.5 as medium and > 0.8 as large. Correlation coefficients were estimated using the Pearson or Spearman's correlation between CBFS (total and subdomain scores) and clinical measurements (PSPRS, MDS-UPDRS and SEADL) at baseline, also between the score differences from baseline to 12-months. To examine the longitudinal changes, subjects were fitted in a mixed effect model with random intercept and slope, adjusting for age, gender and clinical diagnosis.

Results

Scale Development

The various phases of scale development and cognitive pretesting resulted in the retention of 31 items each rated on a Likert 5 point scale rating function from 0 to 4: 0 = Normal or No problems; 1 = Slight problems; 2 = Mild problems; 3 = Moderate problems and 4 = Severe problems, and was subdivided into 2 general categories: A. Motor Experiences of Daily Living (14 items); B. Non-Motor Experiences of Daily Living (17 items) (Table 1; Appendix 1). It was determined that it was preferable to emphasize scale items that evaluated "functional impact" of the disease (which includes disability and impairment) rather than exclusively emphasize "functioning" (denoting the positive aspects of the interaction between an individual [with a health condition] and that individual's contextual factors (environmental and personal factors)) (WHO 2001 International Classification of Functioning, Disability and Health (ICF) (20)). The Delphi panelists decided that the scale should be completed by both patient and care-giver together.

Validation Testing

38 healthy controls and 68 CBS, 65 PSP-RS, 15 nfvPPA, 14 unspecified Atypical Parkinsonism and 17 MSA patients (all clinically diagnosed using published criteria) from the 4RTNI or the PROSPECT studies completed the CBFS at baseline (Table 2). The sample groups were similar in age and race. Healthy controls had more females ($p = 0.04$), and nfvPPA patients had higher education compared to other disease groups ($p < 0.05$). Detailed evaluations of *Data Quality*, *Internal Consistency*, *Construct Validity*, and *RT Analysis* are provided in Supplementary Materials 1 and Supplementary Tables 1-5. One-week Test-retest Reliability was acceptable with an ICC of 0.93. Convergent Validity assessment demonstrated significant correlations between the CBFS and CDR[®] plus NACC FTLD ($r = 0.54$, $p \leq 0.001$), PSPRS ($r =$

0.69, $p \leq 0.001$), SEADL ($\rho = -0.66$, $p \leq 0.001$), MDS-UPDRS ($r = 0.52$, $p \leq 0.001$), MoCA ($r = -0.41$, $p = 0.001$) and NPI-Q ($r = 0.33$, $p = 0.02$) (Figure 1). In *Known Group* analyses, all patient groups scored significantly higher on the CBFS compared to the control group (all p 's ≤ 0.0001 ; Figure 2). ROC analyses revealed significant AUCs for all patient groups versus controls as well as sensitivity/specificity in excess of 0.80 and positive/negative predictive values in excess of 0.90 (Supplementary Figure 1). Sensitivity to severity of disability was demonstrated by increases in CBFS scores with worsening of SEADL quartiles (Supplementary Figure 2).

Longitudinal assessment

26 CBS and 16 PSP patients had complete 12 month data (Supplementary Table 6). In this combined group, the CBFS total and motor domain scores, PSPRS and MDS-UPDRS increased, and SEADL decreased from the baseline to 12-month visit ($p < 0.05$) with medium effect sizes (> 0.5). In CBS patients, results were similar except for the MDS-UPDRS which did not change ($p=0.06$). In PSP patients, CBFS motor domain score changed over time ($p = 0.05$), with a trend toward changes in the other measures (Supplemental Table 7).

In the combined CBS and PSP group, 12 month changes from baseline in CBFS total score correlated with the changes in PSPRS ($r = 0.44$, $p = 0.02$). Longitudinal mixed effects analysis demonstrated increases at the 12-month visit in CBFS total score (coefficient = 10.8, $p < 0.001$), PSPRS (coefficient = 8.0, $p < 0.001$), MDS-UPDRS (coefficient = 11.2, $p < 0.001$) and a significant decline in SEADL (coefficient = -15.0, $p < 0.001$). There were no significant differences in the rates of change between different measures ($p > 0.05$) (see Supplementary Figure 3 for the correlations and Supplementary Figure 4 for spaghetti plots of changes in individual PSP and CBS patients).

Discussion

The Cortical Basal ganglia Functional Scale (CBFS) was first developed to address the need for an evaluation tool for CBD, however, there is considerable clinical overlap between the phenotypes associated with CBD and PSP. Importantly, in terms of pathogenesis are the predominant involvement of the tau isoform containing four microtubule binding domains, the presence of prominent astroglial pathology and shared genetic risk variants in both. Thus, it is logical to consider the possibility that these two 4RTs could similarly benefit from disease-modifying therapies designed to address common pathogenic mechanisms. However, accurate and early diagnosis will be critical to the success of future clinical trials. In the past, the diagnosis of PSP has been largely based on clinical features of what is now termed the "Richardson syndrome" (PSP-RS)(4), while the diagnosis of CBD has relied on clinical features of the corticobasal syndrome (CBS)(21). However, a recent clinical-pathological exercise(22) found that a correct diagnosis of PSP was made at initial assessment in only 25.4% (31/122) while an initial diagnosis of CBD was not considered in any of the 30 patients with sufficient clinical data and CBD pathology at death. New, carefully detailed diagnostic criteria(1),(2) have since been developed to address the phenotypic variability of both of these disorders with the goal of making an earlier and more reliable diagnosis which will be required for experimental trials of putative disease modifying therapies. Of critical importance with respect to the application of a single functional scale to both disorders is the

fact that a large number of studies have demonstrated the potential for these 4RTs to initially manifest as an overlapping spectrum of clinical features including RS and CBS as well as bvFTD and nfvPPA, encouraging the . proposed umbrella term "Pick Complex" over a decade ago(23),(24).

The above issues have important implications when considering how best to evaluate the impact of future novel therapeutic agents designed to slow progression of the underlying neurodegenerative disease. In our initial plans to develop a scale for CBD, we recognized that even in cases of an isolated CBS, a clinical rating scale could not consistently and reliably score independent clinical features (e.g., dystonia, bradykinesia rigidity, apraxia). Even if this were possible, clinical rating scales developed to assay the features of isolated syndromes would be completely inadequate to assess and monitor progression of these disorders given their changing natural evolution. Furthermore, advances in our understanding of the broad spectrum of clinical phenotypes possible with these disorders requires that any rating scale designed to evaluate the impact of therapeutic interventions must assess a wide range of motor, behavioral, cognitive and other manifestations. Finally, these complex and varied clinical features impair common day-to-day functions; thus, we determined that a "functional scale" represented a more logical and reliable method of evaluating these diseases. Crucially, using patient and care-giver generated assessments addresses the importance of including the "voice of the patient" in developing outcome assessments. A scale with all of these characteristics is especially well suited for use in Basket trial designs(25) that operate on the premise that multiple syndromes may share a common underlying pathology (eg 4R tau or tau in general) but due to biological differences in the syndromes or the type of tau present (eg different tau prion strains(26)) they might respond differently to a therapeutic intervention. New endpoints that can capture clinically meaningful treatment effects are therefore needed for this new "precision medicine" approach to clinical trials.

The CBFS was constructed following standard rating scale development techniques(27) incorporating expert knowledge, respondent input and psychometric expertise. It was designed to be typically completed by both the patient and care-giver together and preliminary validation testing was conducted in this fashion. However, given the progressive impact of these diseases on cognition and behavior, at some stage the final default scoring should probably be provided by the caregiver in consultation with the patient and further validation studies will be required using this format. Obviously, for the scale to be used as an outcome measure in a clinical trial this scoring would need to be formally operationalized in the study protocol and continuity of respondent/caregiver would be mandatory.

Validation testing revealed excellent clinimetric properties including data quality, internal consistency, construct validity, test-retest reliability, concurrent validity and known-group validity. The baseline scores correlated well with other rating scales commonly used in these patient populations (i.e., the PSPRS, UPDRS, the CDR® plus NACC FTLD, the SEADL, the MoCA and the NPI-Q) to evaluate motor, cognitive, functional and neuropsychiatric status. Total scores were, not surprisingly, higher in patients with the clinical diagnoses of PSP and CBS than in those with nfvPPA. When patients were divided into quartiles of worsening SEADL impairment, increasing numbers of CBFS items were endorsed with increasing severity of functional impairment. The scale was sensitive to capture the functional decline in PSP and CBS patients - the overall and subdomain CBFS scores increased over time and the longitudinal changes of CBFS total score were consistent with the progression as measured by PSPRS, MDS-UPDRS and SEADL. In 4R tauopathies with predominantly motor disturbance, CBFS motor domain score correlated more strongly with PSPRS, MDS-UPDRS and SEADL.

This initial study of the CBFS has a number of important limitations. First, we prioritized the evaluation of the most common and disabling functional disturbances caused by the features of the different phenotypes; therefore, it is possible that in individual cases not all clinical features will be adequately assessed – e.g., emotional incontinence of pseudobulbar palsy or aggressive behavior (although this may be captured in the item on Acting Appropriately Around Others). Second, the initial validation exercise was conducted in 2 relevant research cohorts, but they did not include all possible phenotypes of interest associated with 4RTs, most notably bvFTD. Future planned studies will further investigate scale performance in this group. Our very preliminary longitudinal analysis had a limited number of PSP patients and non-significant differences in PSPRS and the SEADL between baseline and 12 months follow-up, which is clearly different from other studied cohorts. This may be due to different patient characteristics from those enrolled in previous studies including a higher percentage of non-RS phenotypes in both 4RTNI and PROSPECT, and the early termination of more severely affected patients prior to the 12-month follow-up. More data is needed to show phenotype-specific progressions in individual tauopathies.

The CBFS is a novel functional rating scale designed for use in patients with 4RTs that is based on patient/caregiver reported outcomes. Further experience with the scale will be necessary before it can be used as a primary outcome measure in clinical trials. Given the validation provided here it could be used in an exploratory fashion in combination with other more restricted clinical scales. Future studies are in progress validating the CBFS in patients presenting with bvFTD. However, given the broader pathological underpinnings of this presentation (i.e., non-tau far more common than in the PSP and amyloid-negative CBS) we believe that, apart from patients with *MAPT* mutations, more reliable diagnostic biomarkers will be required before this phenotype could be combined with the PSP and CBS presentations in a Basket-design clinical trial (28).

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Delphi panel members: Movement Disorders: A.Lang (Chair), C.Goetz, L.Golbe, G.Hoglinger, I.Litvan, H.Morris, M.Stamelou, P.Svenningsson; Behavioral Neurology: A.Boxer (Chair), B.Boeve, M.Grossman, D.Knopman, J.Kramer, B.Miller, J.Rohrer.

4RTNI (ClinicalTrials.gov NCT02966145) is a longitudinal natural history study of 4R tauopathies including CBS, PSP-RS, nfvPPA and other variant PSP syndromes in North America. Contributing 4RTNI investigators: A. Boxer (PI) , B. Boeve, Department of Neurology, Mayo Clinic, Rochester, MN; B. Dickerson, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston,, MA; M. Grossman, Department of Neurology, University of Pennsylvania, Philadelphia, PA; I. Litvan, Department of Neurology, University of California, San Diego, CA; P. Ljubenkov, Department of Neurology, University of California, San Francisco, CA; A. Pantelyat, Department of Neurology, Johns Hopkins University, Baltimore, MD; J. Rojas-Martinez, Department of Neurology, University of California, San Francisco, CA; M-C. Tartaglia, Department of Medicine (Neurology), University of Toronto, Toronto, ON; A-M. Wills, Department of Neurology, Massachusetts General Hospital, Boston, MA.

PROSPECT (ClinicalTrials.gov Identifier: NCT02778607) is a longitudinal natural history study that evaluates CBS, PSP and MSA patients in the UK. Contributing PROSPECT investigators: H. Morris (PI), K. Amar, Royal Bournemouth and Christchurch NHS FT, Dorset,UK; E. Capps, Shrewsbury and Telford Hospital NHS Trust, UK; G. Carey, Department of Neurology, Ashford and St Peter's Hospital NHS Foundation Trust, Ashford, UK; A. Church, Department of Neurology, Royal Gwent Hospital, UK; P. Critchley, Department of Neurology, University Hospitals Leicesters NHS Trust, Leicester, UK; B. Ghosh, Wessex Neurological Centre, University Hospital Southampton, UK; H.Houlden, Oxford Parkinson's Disease Centre (OPDC) and Nuffield Department of Clinical Neurosciences, University of Oxford, UK; M. Hu, Oxford Parkinson's Disease Centre (OPDC) and Nuffield Department of Clinical Neurosciences, University of Oxford, UK; Edwin Jabbari, Department of Clinical and Movement Neurosciences, Institute of Neurology, UCL, UK; C. Kobylecki, Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, UK; L. Massey, Department of Neurology, Poole Hospital NHS Foundation Trust, Poole, UK; S. Molloy, London North West University Healthcare NHS Trust, UK; U. Nath, Sunderland Royal Hospital, UK; N. Pavese, Clinical Ageing Research Unit, Newcastle University, UK; J. B. Rowe, Department of Clinical Neurosciences, Cambridge University, UK.

These studies were reviewed and approved by the relevant institutions' ethics review boards and all patients signed written informed consent to participate in either the 4RTNI or PROSPECT studies.

Table and Figure Legends:

Table 1. Items of the Cortical Basal ganglia Functional Scale (CBFS).

Table 2. Subject Demographics and Clinical Features.

Figure 1. Correlations between CBFS total score and clinical measurements.

Note: CBS, Corticobasal Syndrome; PSP, Progressive Supranuclear Palsy; nfvPPA, non-fluent variant Primary Progressive Aphasia; CDR[®] plus NACC FTL, Clinical Dementia Rating Scale[®] plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration Module; PSPRS, Progressive Supranuclear Palsy Rating Scale; SEADL, Schwab and England Activity and Daily Living Scale; UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory Questionnaire. MDS-UPDRS, Movement Disorder Society- Unified Parkinson's Disease Rating Scale.

Figure 2. Box plots of Cortical Basal ganglia Function Scale total score in normal controls (n=38), patients with Corticobasal Syndrome (n=68), Progressive Supranuclear Palsy Richardson Syndrome (n=65), non-fluent variant Primary Progressive Aphasia (n=15), Atypical Parkinsonian Syndromes (n=14), and Multiple System Atrophy (n=17).

Supplementary material:

Supplementary Material 1: Details of Scale Development, Validation Testing and Longitudinal Analysis.

Supplementary Table 1. Clinimetric Properties of CBFS Scale Items.

Supplementary Table 2. Internal Consistency of Cortical Basal ganglia Functional Scale (CBFS).

Supplementary Table 3. Exploratory Factor Analysis.

Supplementary Table 4. Item discrimination and location parameter estimates using the graded response model (GRM).

Supplementary Table 5. Item Fit Statistics Using the Graded Response Model.

Supplementary Table 6. Baseline correlations between CBFS scores and clinical measurements in longitudinal PSP and CBS subjects.

Supplementary Table 7. Clinical Features for longitudinal PSP and CBS subjects at baseline and 12 month visit.

Supplementary Figure 1: Receiver Operator Characteristic curves to the CBFS across different diagnostic groups.

Note: CBS, Corticobasal Syndrome; PSP, Progressive Supranuclear Palsy Richardson Syndrome; nfvPPA, non-fluent variant Primary Progressive Aphasia; APS Atypical Parkinsonian Syndrome; MSA Multiple System Atrophy

Supplementary Figure 2: Item distributions of CBFS total scores in Schwab and England Activity and Daily Living (SEADL) Scale quartiles.

To assess the qualitative changes in responses with worsening CBFS scores, all patients were grouped by SEADL score into quartiles (Supplementary Figure 2). Diagnosis distributions were similar across SEADL quartiles (Fisher's exact test, $p = 0.20$). In a regression model examining the change of CBFS as a function of SEADL quartiles, CBFS increased with worsening SEADL ($p < 0.05$), but the SEADL quartile-by-diagnosis interactions were not significant ($p > 0.05$) indicating that the severity dependent differences were not driven by any one particular diagnostic group. In the mildest quartile (SEADL 80-100%), the most commonly endorsed difficulties rated as severe were writing, completing finances, anxiety, fatigue and urinary control. In participants who were more impaired (SEADL 60-80%), difficulties with speaking, walking, dressing, hobbies, getting in or out of car, eating, sleeping, multi-tasking, staying awake, mood, remembering, turning in bed and saliva and drooling emerged. In moderately impaired participants (SEADL 40-60%), additional or worse difficulties with feeling motivated, navigation, dressing, turning in bed, walking, understanding, remembering and other visual problems emerged. In the most severely impaired patients (SEADL $\leq 40\%$), mild or worse CBFS impairments were reported in $>50\%$ respondents in writing, hobbies, dressing, finances, walking, multi-tasking, hygiene, getting in or out of a car, eating, speaking and spontaneous involuntary movements.

Supplementary Figure 3. Correlations between 12- month change of CBFS score and change of clinical measures.

Supplementary Figure 4. Spaghetti plots for individual changes in clinical measures from baseline to 12-month.

Appendix 1: Full Cortical Basal ganglia Functional Scale (CBFS)

Author Roles:

1. Research Project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing the First Draft, B. Review and Critique.

AEL: 1ABC, 2C, 3A

GTS: 1ABC, 2AB, 3B

PW: 1C, 2AB, 3B

HM: 1C, 2C, 3B

EJ: 1C, 2C, 3B

RL: 1C, 2C, 3B

ALB: 1ABC, 2C, 3B

FULL FINANCIAL DISCLOSURE FOR THE PREVIOUS 12 MONTHS

AEL: Consultancies: Abbvie, Acorda, AFFiRis, Biogen, Bristol Myers Squibb, Intracellular, Janssen, Jazz, Lilly, Lundbeck, Merck, Ono, Paladin, Roche, Seelos, Syneos, Sun Pharma, Theravance, and Corticobasal Degeneration Solutions; Advisory Boards: Jazz Pharma, PhotoPharmics, Sunovion; Honoraria: Sun Pharma, AbbVie and Sunovion; Grants: Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, Parkinson Foundation, Parkinson Canada, and W. Garfield Weston Foundation; Royalties: Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press.

PW: No conflicts

GTS: Consulting and Advisory Board Membership with honoraria: Acadia, Pharmaceuticals, Adamas Pharmaceuticals, Inc., Biogen, Inc., Ceregene, Inc., CHDI Management, Inc., Cleveland Clinic Foundation, Ingenix Pharmaceutical Services (i3 Research), MedGenesis Therapeutix, Inc., Neurocrine Biosciences, Inc., Pfizer, Inc., Tools-4-Patients, Ultragenyx, Inc., Sunshine Care Foundation. Grants and Research: National Institutes of Health, Department of Defense, Michael J. Fox Foundation for Parkinson's Research, Dystonia Coalition, CHDI, Cleveland Clinic Foundation, International Parkinson and Movement Disorder Society, CBD Solutions. Honoraria: International Parkinson and Movement Disorder Society, American Academy of Neurology, Michael J. Fox Foundation for Parkinson's Research, Food and Drug Administration, National Institutes of Health, Alzheimer's Association. Intellectual Property Rights: none.

EJ: Grants: Medical Research Council UK, PSP Association.

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HRM: Employment: UCL; Consultancies: Biogen, UCB, Abbvie, Denali, Biohaven; Lecture fees/honoraria: Biogen, UCB, C4X Discovery, GE-Healthcare, Wellcome Trust, Movement Disorders Society; Grants: Parkinson's UK, Cure Parkinson's Trust, PSP Association, CBD Solutions, Drake Foundation, Medical Research Council. Patents : HRM is a co-applicant on a patent application related to C9ORF72 - Method for diagnosing a neurodegenerative disease (PCT/GB2012/052140)

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