RESEARCH ARTICLE

A Modified Progressive Supranuclear Palsy Rating Scale

Marie-Therese Grötsch,[1,2] Gesine Respondek, MD,[1,2,3] Carlo Colosimo, MD, FEAN,[4] Yaroslau Compta, MD,[5] Jean Christophe Corvol, MD, PhD,[6] Joaquim Ferreira, MD,[7] Meret Koroni Huber, MD,[3] Martin Klietz, MD,[3] Lea F.M. Krey, MD,[3] Johannes Levin, MD,[2,8] Milica Jecmenica-Lukic, MD,[9] Daniel Macías-García, MD,[10] Wassilios G. Meissner, MD, PhD,[11,12,13] Pablo Mir, MD,[10,14] Huw Morris, MD,[15] Christer Nilsson, MD,[16] James B. Rowe, MD, PhD,[17] Klaus Seppi, MD,[18] Maria Stamelou, MD, PhD,[19,20,21] John C. van Swieten, MD,[22] Gregor Wenning, MD, PhD,[18] Teodoro Del Ser, MD,[23] Lawrence I. Golbe, MD,[24] Günter U. Höglinger, MD,[1,2,3*] for the DescribePSP Study Group, the ProPSP Study Group, and the Movement Disorder Society–Endorsed PSP Study Group

[1]*Department of Neurology, Technische Universität München, Munich, Germany*
[2]*German Center for Neurodegenerative Diseases, Munich, Germany*
[3]*Department of Neurology, Hanover Medical School, Hanover, Germany*
[4]*Department of Neurology, Santa Maria University Hospital of Terni, Terni, Italy*
[5]*Parkinson's Disease and Movement Disorders Unit, Hospital Clínic/IDIBAPS/CIBERNED/(CB06/05/0018-ISCIII)/European Reference Network for Rare Neurological Diseases (ERN-RND)/Institut de Neurociències, Universitat de Barcelona, Catalonia, Spain*
[6]*Département des Maladies du Système Nerveux, Sorbonne Universités, UPMC Univ Paris 06; INSERM UMRS_1127, CIC_1422; CNRS UMR_7225; AP-HP; and ICM, Hôpital Pitié-Salpêtrière, Paris, France*
[7]*Faculdade de Medicina de Lisboa, Lisbon, Portugal*
[8]*Department of Neurology, Ludwig-Maximilians-Universität, Munich, Germany*
[9]*Movement Disorders Department, Clinic for Neurology, Belgrade, Serbia*
[10]*Unidad de Trastornos del Movimiento, Servicio de Neurología y Neurofisiología Clínica, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain*
[11]*University de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France*
[12]*Service de Neurologie, Hôpital Pellegrin, CHU de Bordeaux, Bordeaux, France*
[13]*Department of Medicine, University of Otago, Christchurch, and New Zealand Brain Research Institute, Christchurch, New Zealand*
[14]*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain*
[15]*Department of Clinical Neuroscience, UCL Institute of Neurology, London, United Kingdom*
[16]*Department of Clinical Sciences, Division of Neurology, Lund University, Lund, Sweden*
[17]*Department of Clinical Neurosciences and Cambridge Centre for Parkinson-Plus, Cambridge University, Cambridge, United Kingdom*
[18]*Department of Neurology, Medical University Innsbruck, Innsbruck, Austria*
[19]*Parkinson's Disease and Movement Disorders Department, HYGEIA Hospital, Athens, Greece*
[20]*Philipps University Marburg, Marburg, Germany*
[21]*School of Medicine, European University of Cyprus, Nicosia, Cyprus*
[22]*Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands*
[23]*Alzheimer's Disease Investigation Research Unit, CIEN Foundation, Carlos III Institute of Health, Noscira SA, Madrid, Spain*
[24]*Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA*

ABSTRACT: Background: The Progressive Supranuclear Palsy Rating Scale is a prospectively validated physician-rated measure of disease severity for progressive supranuclear palsy. We hypothesized that, according to experts' opinion, individual scores of items would differ in relevance for patients' quality of life, functionality in daily living, and mortality. Thus, changes in the score may not equate to clinically meaningful changes in the patient's status.

*__Correspondence to:__ Prof. Dr. Günter U. Höglinger, Department of Neurology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany; E-mail: guenter.hoeglinger@dzne.de

Marie-Therese Grötsch and Gesine Respondek contributed equally to this work.

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Members of the DescribePSP Study Group are listed as Appendix A; Members of the ProPSP Study Group are listed as Appendix B; and Members of the Movement Disorder Society-Endorsed PSP Study Group are listed as Appendix C.

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Objective: The aim of this work was to establish a condensed modified version of the scale focusing on meaningful disease milestones.
Methods: Sixteen movement disorders experts evaluated each scale item for its capacity to capture disease milestones (0 = no, 1 = moderate, 2 = severe milestone). Items not capturing severe milestones were eliminated. Remaining items were recalibrated in proportion to milestone severity by collapsing across response categories that yielded identical milestone severity grades. Items with low sensitivity to change were eliminated, based on power calculations using longitudinal 12-month follow-up data from 86 patients with possible or probable progressive supranuclear palsy.
Results: The modified scale retained 14 items (yielding 0–2 points each). The items were rated as functionally relevant to disease milestones with comparable severity. The modified scale was sensitive to change over 6 and 12 months and of similar power for clinical trials of disease-modifying therapy as the original scale (achieving 80% power for two-sample *t* test to detect a 50% slowing with n = 41 and 25% slowing with n = 159 at 12 months).
Conclusions: The modified Progressive Supranuclear Palsy Rating Scale may serve as a clinimetrically sound scale to monitor disease progression in clinical trials and routine.

Key Words: progressive supranuclear palsy; rating scale; clinical meaningfulness; sensitivity to change

Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative disease with aggregation of hyperphosphorylated 4-repeat tau isoforms in neurons, astrocytes, and oligodendrocytes.[1] Clinically, PSP presents with a spectrum of symptoms, including parkinsonism, ocular motor dysfunction, postural instability, frontal lobar dysfunction, and bulbar signs, including dysarthria and dysphagia.[2]

The Progressive Supranuclear Palsy Rating Scale (PSPRS) has been developed to quantify the presence and progression of these symptoms.[3] The PSPRS is a physician-rated measure of 28 items allocated into six categories: daily activities (by history), mentation, bulbar, ocular motor, limb motor, and gait/midline exam disturbances (by examination). Raters assign 0 to 2 or 0 to 4 points for each item, yielding a total PSPRS score range of 0 to 100 points.[3]

The scale has been used as the primary outcome measure in numerous clinical trials and observational studies, in part because it generates reproducible annual score changes across a wide range of disease severity and time, and in multiple countries, enabling multicenter trials with achievable group sizes.[4-6]

The PSPRS was developed as a tool for clinicians to monitor a patient's condition in a standard healthcare setting and not primarily as a state measure for research that would be sensitive to a progression over a short period. Moreover, some important aspects of PSP are addressed by more than one item, placing more weight on the corresponding deficits.[3] However, as an outcome measure for interventional trials, recent evaluations identified opportunities for improvement of the PSPRS; for example, (1) not all items are considered to reflect clinically meaningful aspects of the disease or clinically meaningful milestones; (2) not all items contribute the same maximum scores (range, 2–4); (3) some items may capture related and overlapping features, thus conveying multiple scores for reaching only one clinical milestone; (4) different items vary greatly in their sensitivity to change over typical trial durations (12–18 months); and (5) some items and their scores are not sensitive to change, thus conveying no score changes despite overall clinical disease progression. A previous clinimetric analysis of the motor domain of the PSPRS suggested removal of the PSPRS items limb dystonia, tremor, and dysphagia for improved internal consistency of the scale.[7]

We aimed to create a condensed and modified version of the PSPRS (mPSPRS) by retaining items that report clinically meaningful disease milestones according to experts and by eliminating those with insufficient sensitivity to change and conceptually redundant items. The retained items were recalibrated against a semiquantitative milestone severity grading. These measures aimed to ascertain that comparable mPSPRS scores would represent comparable functional impact for different patients, regardless of the items these scores had been obtained in.

Materials and Methods

The mPSPRS was established by a stepwise process that consisted of (1) semiquantitative evaluation of the PSPRS items by movement disorder experts with regard to representation of disability milestones from their point of view, (2) elimination of PSPRS items that depict only mild or moderate disability milestones, (3) calibration of the retained items against the milestone severity grading, (4) elimination of items that proved to be insensitive to detect change over a 12-month observation period, and (5) elimination of conceptually redundant items. This process is shown as a flow chart in Supporting Information Figure S1.

Ethics

Data of participants of the TAUROS trial[4] were included in our analysis. All participants of the TAUROS trial signed an informed consent for the reuse of their data within the framework of the present study. The TAUROS study protocol was approved by each local ethics committee at each of the 24 TAUROS trial site centers in the United Kingdom, Spain, Germany, and the United States.[4]

Expert Evaluation of PSPRS Items With Regard to Disease Milestones

Sixteen PSP experts from the International Parkinson and Movement Disorder Society—European Section evaluated each PSPRS item for whether, in their opinion, reaching a particular score would indicate a clinically meaningful disability milestone for the patient (not necessarily for the caregiver) as a result of impaired quality of life, reduced functionality in activities of daily living, or mortality risk, that is, how the patient feels, functions, or survives. Every expert rated every response category of each PSPRS item with 0 points (no milestone), 1 point (moderate milestone), or 2 points (severe milestone). The assessments of the experts were averaged, and a milestone grade was attributed to each response category as follows: mean value 0 to 0.5 point = no milestone (grade 0); mean value >0.5 to 1.5 points = moderate milestone (grade 1); and mean value >1.5 to 2.0 points = severe milestone (grade 2). "Clinical meaningful milestones" were defined as milestones with relevance for the patient's quality of life, functionality in daily activities, and mortality, as rated by expert physicians.

Elimination of Items Capturing No Severe Milestone

To focus the scale on clinically meaningful features according to experts, we eliminated items that did not yield a mean milestone grade of 2 in any response category.

Calibration Against Milestone Severity

To establish the same score range and proportionality with milestone severity grades for each PSPRS item, we collapsed response categories yielding the same milestone grades into joint categories, generating three response categories for all PSPRS items (grade 0 = no milestone; grade 1 = moderate milestone; grade 2 = severe milestone).

Elimination of Items Insensitive to Change at 52-Week Follow-Up

Data from participants of the TAUROS trial with a clinical diagnosis of possible or probable PSP according to the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) were available.[2,4,8] Patients in both the placebo and active treatment arms were considered, because there were no significant differences in any of the examined parameters between the groups. For the elimination of items insensitive to change, only participants with baseline and 52-week follow-up data per protocol were included in this analysis. Power calculations for the individual PSPRS items in their original and recalibrated form were performed, as described previously by Stamelou et al.,[6] to estimate their sensitivity to detect change. Standardized effect sizes were calculated from mean and standard deviation (SD) of the annual changes. For the sample size calculations, we used two-sample t tests and Mann–Whitney U tests to detect 50%, 40%, 30%, 25%, and 20% change from natural disease progression in a 52-week follow-up.[6,9,10] Bootstrapped confidence interval was calculated for mean and standardized effect sizes.[11,12] Items with insufficient sensitivity to change after 52 weeks with a standardized effect size of <0.25 were eliminated. The threshold of <0.25 was based on a pragmatic post hoc decision to generate a balance between good sensitivity to change and retention of items to cover the broad spectrum of disease aspects.

Elimination of Conceptually Redundant Items

To avoid duplicate scoring for the same clinical features, we eliminated items that capture conceptually closely related aspects of the disease, prioritizing those items yielding higher milestone grading and higher standardized effect sizes.

Comparison of the PSPRS and the mPSPRS

To compare the sensitivity to change of the original PSPRS versus the mPSPRS, we performed power calculations in the TAUROS study population described earlier. To analyze sensitivity to change at 52-week follow-up, we included data from 86 participants of the TAUROS trial, which had baseline and 52-week follow-up data per protocol.[4] To analyze sensitivity to change at 26-week follow-up, we included data from 113 participants. For correlation analysis of the PSPRS and the mPSPRS, we used the model of linear regression.

Power Calculation of mPSPRS in Confirmatory PSP Cohorts

With independent data from two German observational PSP cohorts (ProPSP and DescribePSP), we performed confirmatory power calculations.

The DescribePSP study, coordinated by the German Center for Neurodegenerative Diseases, and the ProPSP study, coordinated by the German Parkinson and

Movement Disorders Society, both use the Movement Disorder Society diagnostic criteria for PSP for inclusion of participants.[2]

To analyze effect sizes of the mPSPRS items, we included 45 patients enrolled in DescribePSP and ProPSP with a complete dataset at baseline and at a first follow-up visit between 36 and 60 weeks.

Patient Survey on the Clinical Meaningfulness of the PSPRS Items

We conducted an exploratory, anonymous survey among patients with PSP to assess the patients' perception of the clinical meaningfulness of the PSPRS. The patients were asked to rate each response category of each item of the PSPRS with regard to their perceived clinical meaningfulness (impact on quality of life, functionality in daily living, and mortality) with the same grading as described earlier for the experts. Because we conducted the survey in Germany, we used a PSPRS version translated into German lay language. Patients were also asked to provide age, sex, disease duration, and PSP phenotype, if known.

Results

Expert Milestone Ratings

In the experts' milestone ratings, seven items of the PSPRS reached a mean value of ≤1.5 points in all response categories and, therefore, were considered as not clinically meaningful, by failing to reflect severe disease milestones according to the experts (Supporting Information Table S1). Those items were eliminated from the PSPRS (Item 2: Irritability; Item 7: Sleep difficulty; Item 11: Grasping/imitative/utilizing behavior; Item 16: Voluntary left and right saccades; Item 20: Finger tapping; Item 21: Toe tapping; Item 23: Postural kinetic or rest tremor). We retained the remaining 21 items, yielding a mean milestone grade of 2 (severe milestone) for the mPSPRS.

Calibration Against Milestone Severity

The remaining 21 items were recalibrated against the milestone severity grading by collapsing categories yielding the same milestone grades, as shown in Supporting Information Table S2.

Elimination of Items Insensitive to Change at 52-Week Follow-Up

Data of 148 patients with PSP from the placebo or active arms of the TAUROS trial were available.[4] Eleven patients with different conditions at baseline interfering with the per-protocol clinical evaluation and 51 patients who terminated prematurely during the trial without a 52-week follow-up assessment were excluded. Thus, PSPRS baseline and follow-up data of 86 patients (37 females, 43%; 49 males, 57%) with unequivocal clinical diagnosis and no major protocol violation were available for the current analysis. Their age (mean ± SD) at the onset of PSP was 64.8 ± 7.1 years, their age at baseline was 67.8 ± 6.8 years, and the disease duration was 3.0 ± 2.6 years.

Results of the power calculation for the individual 21 retained and recalibrated PSPRS items (Supporting Information Table S2) demonstrated large variability in the standardized effect sizes, ranging from 0.182 (Item 22: Apraxia of hand movement) to 0.800 (Item 25: Arising from a chair). For comparison, sensitivity to change of the original PSPRS items before recalibration is shown in Supporting Information Table S1.

Based on the pragmatic threshold (<0.25), we eliminated six items because of insufficient sensitivity to change from the recalibrated PSPRS (Item 1: Withdrawal; Item 8: Disorientation; Item 9: Bradyphrenia; Item 18: Limb rigidity; Item 19: Limb dystonia; Item 22: Apraxia of hand movement).

Elimination of Conceptually Redundant Items

To avoid redundancy within the scale, Item 14 was removed (voluntary upward command movement) because it covered similar functional concepts as Item 15 (voluntary downward command movement) and had worse sensitivity to change.

In total, we removed 14 items from the PSPRS (7 items because of insufficient milestone coverage, 6 items because of insufficient sensitivity to change, and 1 because of conceptual redundancy). Fourteen items yielding 0 to 2 points each, reaching a maximum score of 28 points and distributed into five categories [daily activities (by history), mentation, bulbar, ocular motor, and gait/midline examination], were retained. The final mPSPRS, including milestone ratings and sensitivity to change for each item, is shown in Table 1.

Sensitivity to Change of mPSPRS Versus PSPRS

At 52-Week Follow-Up

At 52-week follow-up, the total PSPRS score yielded an annual change of 11.1 points (SD ± 8.5) in our sample of patients with PSP, corresponding to 11.1%, in accordance with former studies.[3,6,13] The total mPSPRS score yielded an annual change of 4.8 points (SD ± 3.8), corresponding to 17.1%. The sensitivity to change (ie, standard effect sizes and required sample sizes to detect an effect of an intervention in a 52-week follow-up therapeutic trial) of the total PSPRS score and the total mPSPRS score were similar (Table 2).

A strong positive linear correlation was evident between the mPSPRS total score and the PSPRS total score at baseline and at 52-week follow-up (Fig. 1A), as

TABLE 1. Clinical meaningfulness and sensitivity to change of mPSPRS items

Item	Clinical Meaningfulness Grading					Sensitivity to Change		
	Min	Max	Mean	SD	Median	Std. Effect Size	N, Two-Sample *t* Test[a]	N, Mann–Whitney *U* test[a]
I. History								
1. Dysphagia for solids (from patient or other informant)						0.29	774	896
0 Normal; no difficulty with full range of food textures *or* tough foods must be cut up into small pieces	0	1	0.22	0.42	0			
1 Requires soft solid diet	0	2	1.06	0.57	1			
2 Requires pureed or liquid diet *or* tube feeding required for some or all feeding	1	2	1.84	0.37	2			
2. Using knife and fork, buttoning clothes, washing hands and face (rate the worst)						0.46	297	344
0 Normal *or* somewhat slow but no help required	0	0	0.00	0.00	0			
1 Extremely slow; or occasionally help needed *or* considerable help needed; but can do some things alone	0	1	1.06	0.62	1			
2 Requires total assistance	2	2	2.00	0.00	2			
3. Falls (average frequency if patient attempted to walk unaided)						0.31	642	743
0 None in the past year	0	0	0.00	0.00	0			
1 <1 per month; gait may otherwise be normal *or* 1–4 per month	0	2	1.00	0.50	1			
2 5–30 per month *or* >30 per months (or chair-bound)	1	2	1.94	0.44	2			
4. Urinary incontinence						0.33	579	670
0 None, a few drops less than daily *or* a few drops staining clothes daily	0	1	0.13	0.34	0			
1 Large amounts, but only when asleep; no pad required during day	0	2	0.94	0.68	1			
2 Occasional large amounts in daytime, pad required *or* consistent, requiring diaper or catheter awake and asleep	1	2	1.78	0.42	2			
II. Mentation								
5. Emotional incontinence						0.33	594	687
0 Clearly absent *or* equivocal or minimal *or* clearly present, but not affecting ADLs	0	1	0.15	0.36	0			
1 Interfering mildly with ADLs	0	2	0.94	0.44	1			
2 Interfering markedly with ADLs	0	2	1.63	0.62	2			
III. Bulbar								
6. Dysarthria						0.60	174	201
0 None *or* minimal; all or nearly all words easily comprehensible	0	1	0.03	0.18	0			
1 Definite, moderate; most words comprehensible	0	2	0.88	0.50	1			
2 Severe; may be fluent but most words incomprehensible *or* mute, or a few poorly comprehensible words	1	2	1.91	0.30	2			
7. Dysphagia (for 30–50 mL of water from a cup, if safe)						0.58	189	219
0 None *or* single sips, or fluid pools in mouth or pharynx, or swallows slowly, but no choking/coughing	0	1	0.13	0.34	0			
1 Occasionally coughs to clear fluid; no frank aspiration	0	2	0.56	0.63	0.5			
2 Frequently coughs to clear fluid, may aspirate slightly; may expectorate frequently rather than swallow secretions *or* requires artificial measures (oral suctioning, tracheostomy, or feeding gastrostomy) to avoid aspiration	1	2	1.78	0.42	2			

(Continues)

TABLE 1. Continued

Item	Clinical Meaningfulness Grading					Sensitivity to Change		
	Min	Max	Mean	SD	Median	Std. Effect Size	N, Two-Sample *t* Test[a]	N, Mann–Whitney *U* test[a]
IV. Ocular Motor								
8. Voluntary downward command movement						0.65	150	173
0 Saccades not slow or hypometric; 86%–100% of normal excursion; *or* saccades slow or hypometric; 86%–100% of normal excursion; *or* 51%–85% of normal excursion	0	1	0.21	0.41	0			
1 16%–50% of normal amplitude	0	2	1.31	0.60	1			
2 15% of normal amplitude or worse	1	2	1.81	0.40	2			
9. Eyelid dysfunction						0.34	545	631
0 None *or* blink rate decreased (<15% min) but no other abnormality *or* mild inhibition of opening/closing, mild blepharospasm; no visual disability	0	1	0.10	0.31	0			
1 Moderate lid-opening inhibition or blepharospasm causing partial visual disability	0	2	1.13	0.50	1			
2 Functional blindness or near-blindness because of involuntary eyelid closure	1	2	1.88	0.34	2			
V. Gait/Midline Examination								
10. Neck rigidity or dystonia						0.52	230	266
0 Absent *or* slight or detectable only on activation *or* definitely abnormal, but full range of motion possible	0	1	0.10	0.31	0			
1 Only partial range of motion possible	0	2	0.94	0.57	1			
2 Little or no passive motion possible	0	2	1.56	0.63	2			
11. Arising from chair						0.80	100	115
0 Normal *or* slow but arises on first attempt *or* requires more than one attempt, but arises without using hands	0	1	0.19	0.39	0			
1 Requires use of hands	0	2	1.00	0.37	1			
2 Unable to arise without assistance	2	2	2.00	0.00	2			
12. Gait						0.72	123	142
0 Normal *or* slightly wide-based or irregular or slight pulsion on turns	0	1	0.13	0.34	0			
1 Must walk slowly or occasionally use walls or helper to avoid falling, especially on turns	0	2	0.94	0.44	1			
2 Must use assistance all or almost all the time *or* unable to walk, even with walker; may be able to transfer	1	2	1.94	0.25	2			
13. Postural stability (on backward pull)						0.62	165	191
0 Normal (shifts neither foot or one foot) *or* must shift each foot at least once but recovers unaided	0	1	0.13	0.34	0			
1 Shifts feet and must be caught by examiner	0	2	1.25	0.58	1			
2 Unable to shift feet; must be caught but does not require assistance to stand still *or* tends to fall without a pull; requires assistance to stand still	1	2	1.91	0.30	2			
14. Sitting down (may touch seat or back but not arms of chair)						0.60	174	201
0 Normal *or* slightly stiff or awkward	0	1	0.09	0.30	0			
1 Easily positions self before chair, but descent into chair is uncontrolled *or* has difficulty finding chair behind him/her and descent is uncontrolled	0	2	1.13	0.61	1			
2 Unable to test because of severe postural instability	1	2	1.94	0.25	2			

SD, standard deviation; Std. effect size, standardized effect size; N, total number of patients; ADLs, activities of daily living.
[a]Per group, based on a significance level of 5% and a power of 80%, sample sizes required for a two-arm, 1-year follow-up (52-week) therapeutic trial to detect 50% change.

TABLE 2. Power calculation for the PSPRS versus the mPSPRS to detect 20%, 25%, 30%, 40%, or 50% change in a two-arm, 52-week follow-up therapeutic trial

Rating Scales	Difference, Mean (SD) [95% CI][a]	Std. Effect Size [95% CI][a]	20% Change		25% Change		30% Change		40% Change		50% Change	
			Effect Size[b]	Sample Size[c]	Effect Size[b]	Sample Size[c]	Effect Size[b]	Sample Size[c]	Effect Size[b]	Sample Size[c]	Effect Size[b]	Sample Size[c]
PSPRS												
Total score	11.12 (8.49) [9.45–13.06]	1.31 [1.05–1.56]	0.26	230 (267)	0.33	148 (171)	0.39	103 (119)	0.52	59 (68)	0.66	38 (44)
Bulbar score	1.17 (1.32) [0.88–1.43]	0.89 [0.62–1.16]	0.18	498 (577)	0.22	319 (370)	0.27	222 (257)	0.36	126 (145)	0.44	81 (94)
Gait score	3.81 (3.15) [3.19–4.54]	1.21 [1.01–1.41]	0.24	270 (312)	0.30	173 (200)	0.36	121 (140)	0.48	69 (79)	0.61	44 (51)
History score	2.17 (2.70) [1.61–2.76]	0.81 [0.58–1.03]	0.16	607 (703)	0.20	389 (450)	0.24	271 (313)	0.32	153 (177)	0.40	98 (114)
Limb score	0.79 (2.26) [0.31–1.28]	0.35 [0.14–0.57]	0.07	3,208 (3,713)	0.09	2,054 (2,377)	0.11	1,427 (1,651)	0.14	803 (929)	0.18	515 (595)
Mentation score	1.15 (2.47) [0.67–1.69]	0.47 [0.25–0.64]	0.09	1,803 (2087)	0.12	1,154 (1,336)	0.14	802 (928)	0.19	452 (523)	0.23	290 (335)
Ocular score	2.01 (2.53) [1.50–2.57]	0.80 [0.60–0.98]	0.16	621 (719)	0.20	398 (461)	0.24	277 (320)	0.32	156 (181)	0.40	101 (116)
mPSPRS												
Total score	4.84 (3.83) [4.07–5.64]	1.26 [1.00–1.53]	0.25	248 (287)	0.32	159 (184)	0.38	111 (128)	0.51	63 (73)	0.63	41 (47)
Bulbar score	0.88 (1.17) [0.62–1.12]	0.75 [0.51–0.98]	0.15	692 (801)	0.19	444 (513)	0.23	308 (357)	0.30	174 (201)	0.38	112 (130)
Gait score	2.29 (2.06) [1.87–2.74]	1.11 [0.91–1.33]	0.22	320 (370)	0.28	205 (237)	0.33	143 (165)	0.44	81 (94)	0.56	52 (61)
History score	0.91 (1.53) [0.60–1.26]	0.59 [0.41–0.77]	0.12	1,120 (1,296)	0.15	717 (830)	0.18	499 (577)	0.24	281 (325)	0.30	180 (209)
Mentation score	0.12 (0.36) [0.05–0.20]	0.33 [0.22–0.45]	0.07	3,702 (4,285)	0.08	2,370 (2,743)	0.10	1,646 (1,905)	0.13	927 (1,072)	0.16	594 (687)
Ocular score	0.64 (0.93) [0.45–0.84]	0.69 [0.47–0.87]	0.14	835 (966)	0.17	535 (619)	0.21	372 (430)	0.27	210 (243)	0.34	135 (156)

PSPRS, Progressive Supranuclear Palsy Rating Scale; mPSPRS, modified Progressive Supranuclear Palsy Rating Scale; SD, standard deviation; CI, confidence interval; Std. effect size, standardized effect size.
[a]Bootstrapped 95% CI for difference mean and Std. effect size.
[b]Effect size = Std. effect size multiplied with the percentage of expected improvement considered clinically relevant.
[c]Sample size per group, for a two-sample *t* test, based on a significance level of 5% and a power of 80% (approximations of the sample size for the Mann–Whitney *U* test in parentheses). Estimated sample sizes do not account for dropouts.

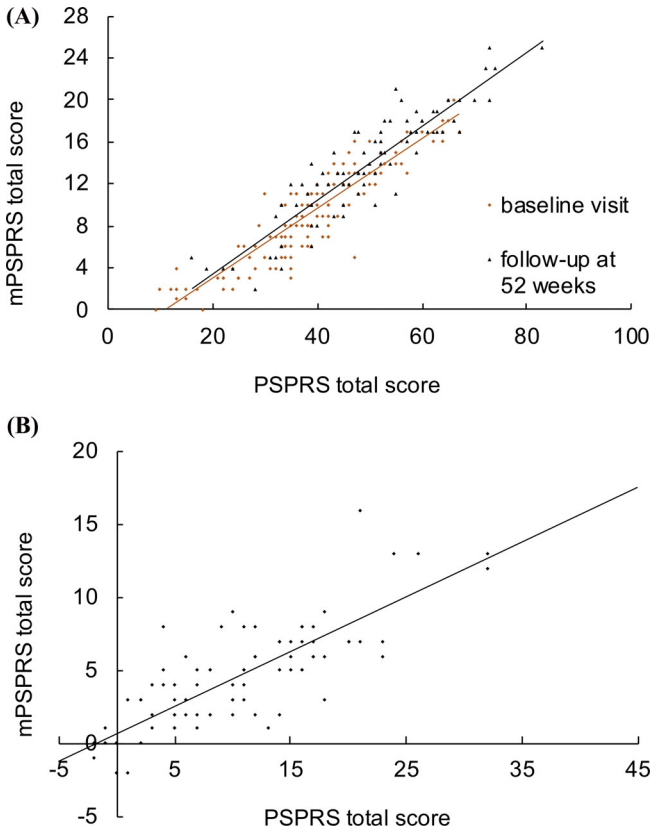

FIG. 1. Linear regression of Progressive Supranuclear Palsy Rating Scale (PSPRS) total scores against modified PSPRS (mPSPRS) total scores. (**A**) Linear regression of PSPRS total scores against mPSPRS total scores at baseline and at 52-week follow-up. Pearson's correlation at baseline: n = 137, R = 0.91, $P < 0.0001$; Pearson's correlation at 52-week follow-up: n = 86, R = 0.91, $P < 0.0001$. (**B**) Linear regression of PSPRS against mPSPRS score changes over 52 weeks. Pearson's correlation: n = 86, R = 0.83, $P < 0.0001$. [Color figure can be viewed at wileyonlinelibrary.com]

well as between the total score changes of the mPSPRS and the PSPRS over 52 weeks (Fig. 1B).

At 26-Week Follow-Up

At 26-week follow-up, the PSPRS and the mPSPRS were able to measure disease progression in our sample of patients with PSP. The total PSPRS score yielded a 6-month change of 5.6 points (SD ± 7.1) in our sample of patients with PSP, corresponding to 5.6%. The total mPSPRS score yielded a 6-month change of 2.2 points (SD ± 3.0), corresponding to 7.9%. The PSPRS required n = 103 for a two-sample *t* test per group to detect a 50% slowing in a therapeutic trial. Similarly, the mPSPRS required n = 118 to detect a 50% slowing (Table 3).

Power Calculation of mPSPRS in the Confirmatory PSP Cohort

In the power calculation with independent data from 45 patients of the observational PSP cohorts (ProPSP and DescribePSP), the mPSPRS required slightly higher sample sizes for a therapeutic trial to detect 50% change (Supporting Information Table S3). However, the standardized effect sizes of the mPSPRS correlated with the standardized effect sizes from the TAUROS trial (R = 0.54) (Supporting Information Table S4). Disease duration of DescribePSP and ProPSP participants was significantly shorter than that of the TAUROS participants (Supporting Information Table S5). Moreover, these patients presented with a broader spectrum of clinical phenotypes (Supporting Information Table S5).

Clinimetric Properties

Cronbach's alpha of 0.78 proved good internal consistency of the 14 mPSPRS items. The mPSPRS items of the subscale "gait," including "arising from chair," "gait," "postural instability," and "sitting down" correlated best with the overall score (Supporting Information Table S6).[14] A floor effect was observed in the categories "bulbar," "gait," "mentation," and "ocular" of the mPSPRS, but neither floor nor ceiling effect were observed for the mPSPRS total score (Supporting Information Table S7). The 14 items of the mPSPRS explained 56% of the scale variance in a principal component analysis using varimax rotation for discriminant validity (Supporting Information Table S8).[14]

Patient Survey on the Clinical Meaningfulness of PSPRS Items

Nine patients with PSP (56% male; mean disease duration of 3.0 ± 0.7 years; four PSP-RS, one other phenotype, four with unspecified phenotype) participated in the anonymous survey. Overall, the patients' ratings of the individual PSPRS response categories correlated well with the experts' ratings (Pearson's R = 0.8528, $P < 0.00001$; Fig. 2A). The mean patients' and experts' ratings matched in all but four PSPRS items with regard to classification of the highest response category into severe milestone (>1.5 points) or not (Fig. 2B). These four diverging items were "sleep difficulty," "emotional incontinence," "voluntary left and right saccades," and "tremor in any part." Five items of the PSPRS were not considered to report severe milestones by the patients (Fig. 2B). These were "irritability," "emotional incontinence," "grasping/imitative/utilizing behavior," "finger tapping," and "toe tapping." All items incorporated into the mPSPRS were formally considered to report severe milestones (>1.5 points) by the patients; only "emotional incontinence" scored slightly lower (1.44 ± 0.88).

Discussion

Our main objective was to create a condensed version of the PSPRS, with items that reflect the wide range of

TABLE 3. Power calculation for the PSPRS versus the mPSPRS to detect 20%, 25%, 30%, 40%, or 50% change in a two-arm, 26-week follow-up therapeutic trial

			20% Change		25% Change		30% Change		40% Change		50% Change	
Rating Scales	Difference, Mean (SD)	Std. Effect Size	Effect Size[a]	Sample Size[b]	Effect Size[a]	Sample Size[b]	Effect Size[a]	Sample Size[b]	Effect Size[a]	Sample Size[b]	Effect Size[a]	Sample Size[b]
PSPRS												
Total score	5.59 (7.12)	0.79	0.16	638 (738)	0.20	409 (473)	0.24	284 (329)	0.31	161 (186)	0.34	103 (119)
Bulbar score	1.30 (0.49)	0.37	0.08	2,815 (3,258)	0.09	1,802 (2,086)	0.11	1,252 (1,449)	0.15	705 (816)	0.19	452 (523)
Gait score	1.75 (2.44)	0.72	0.14	760 (880)	0.18	487 (564)	0.22	339 (392)	0.29	191 (221)	0.36	123 (142)
History score	1.01 (2.65)	0.38	0.08	2,718 (3,145)	0.10	1,740 (2,014)	0.11	1,209 (1,399)	0.15	681 (788)	0.19	436 (505)
Limb score	3.48 (2.80)	1.24	0.25	256 (296)	0.31	164 (190)	0.37	115 (132)	0.50	65 (75)	0.62	42 (49)
Mentation score	0.04 (2.48)	0.01	0.00	1,923,517 (2,226,292)	0.00	1,231,051 (1,424,828)	0.00	854,897 (989,464)	0.01	480,880 (556,574)	0.01	307,764 (356,208)
Ocular score	1.03 (2.28)	0.45	0.09	1,940 (2,245)	0.11	1,242 (1,437)	0.14	863 (999)	0.18	486 (562)	0.23	312 (361)
mPSPRS												
Total score	2.24 (3.05)	0.74	0.15	727 (842)	0.18	466 (539)	0.22	324 (375)	0.29	183 (212)	0.37	118 (136)
Bulbar score	0.41 (1.10)	0.37	0.07	2,862 (3,312)	0.09	1,823 (2,120)	0.11	1,273 (1,473)	0.15	717 (829)	0.19	459 (531)
Gait score	1.02 (1.67)	0.61	0.12	1,057 (1,223)	0.15	677 (783)	0.18	471 (545)	0.24	265 (307)	0.31	170 (197)
History score	0.38 (1.24)	0.31	0.06	4,179 (4,837)	0.08	2,675 (3,096)	0.09	1,858 (2,151)	0.12	1,046 (1,210)	0.15	670 (775)
Mentation score	0.10 (0.33)	0.30	0.06	4,413 (5,107)	0.08	2,825 (3,269)	0.09	1,962 (2,271)	0.12	1,104 (1,278)	0.15	707 (818)
Ocular score	0.34 (0.89)	0.38	0.08	2,766 (3,201)	0.09	1,771 (2,049)	0.11	1,230 (1,424)	0.15	693 (802)	0.19	444 (514)

mPSPRS, modified Progressive Supranuclear Palsy Rating Scale; PSPRS, Progressive Supranuclear Palsy Rating Scale; SD, standard deviation; Std. effect size, standardized effect size.
[a]Effect size = standardized effect size multiplied with the percentage of expected improvement considered clinically relevant.
[b]Sample size per group, for a two-sample *t* test, based on a significance level of 5% and a power of 80% (approximations of the sample size for the Mann–Whitney *U* test in parentheses). Estimated sample sizes do not account for dropouts.

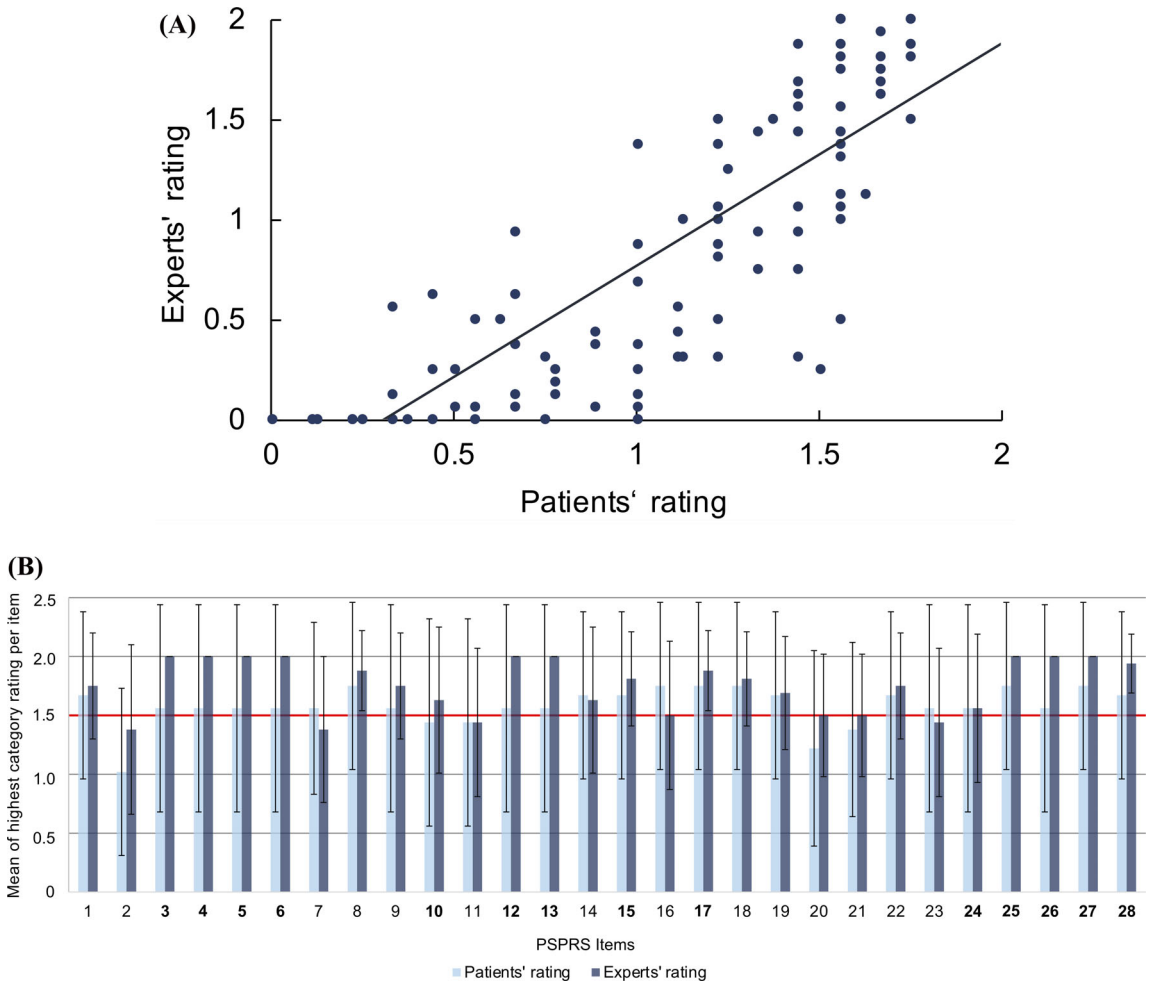

FIG. 2. Milestone ratings of Progressive Supranuclear Palsy Rating Scale (PSPRS) items by patients and experts. (**A**) Scatterplot of mean milestone ratings of the individual response categories of the 28 PSPRS items by patients versus experts with linear regression line (Pearson's R = 0.8528, $P < 0.00001$). (**B**) Bar chart of the mean (± standard deviation) milestone ratings by patients and experts for the highest response categories in the 28 PSPRS items: 1 = Withdrawal; 2 = Irritability; 3 = Dysphagia for solids; 4 = Using knife and fork, buttoning clothes, washing hands and face; 5 = Falls; 6 = Urinary incontinence; 7 = Sleep difficulty; 8 = Disorientation; 9 = Bradyphrenia; 10 = Emotional incontinence; 11 = Grasping/imitative/utilizing behavior; 12 = Dysarthria; 13 = Dysphagia; 14 = Voluntary upward saccades; 15 = Voluntary downward command movements; 16 = Voluntary left and right saccades; 17 = Eyelid dysfunction; 18 = Limb rigidity; 19 = Limb dystonia; 20 = Finger tapping; 21 = Toe tapping; 22 = Apraxia of hand movement; 23 = Tremor in any part; 24 = Neck rigidity or dystonia; 25 = Arising from chair; 26 = Gait; 27 = Postural stability; and 28 = Sitting down. Bold items are included into the mPSPRS. Items rated >1.5 points were considered as severe milestone. [Color figure can be viewed at wileyonlinelibrary.com]

functional disabilities in patients with PSP. Our stepwise process reduced the 28 PSPRS items to 14 as the "modified PSPRS." The mPSPRS reliably measures functionally relevant disease progression in PSP and captures disability milestones. The mPSPRS is suitable for both cross-sectional and longitudinal study designs.

The majority of experts who performed the milestone ratings were members of the European Movement Disorder Society. Their ratings indicated that the items of the PSPRS have different clinical relevance for patients. Ranking the items into clinically meaningful milestone grades (no, moderate, or severe) as rated by the experts was the first approach to obtain a better tool to picture disease progression and functionality with regard to quality of life, activities of daily living, or mortality for patients with PSP. Furthermore, the PSPRS contains unevenly distributed scores for response categories, ranging from 0 to 2 as well as 0 to 4 points.[3] The recalibrated mPSPRS enables three equally distributed response categories and the same score range (0–2 points) for all items. This offers the advantage of producing equal impact of each scale item on the total score, thus improving comparability of the scale items, simplifying the rating task, and consuming less time.

The sensitivity to change of the mPSPRS was only marginally lower than that of the PSPRS (Table 2), indicating that the modifications in practical terms did not reduce the metric power of the PSPRS. The calculated sample sizes required to detect a 50% change of a 1-year follow-up therapeutic trial for the mPSPRS were similar and very close to those of the PSPRS (Table 2). In power analysis, the 28 items of the PSPRS differed

significantly with regard to their standardized effect size (range, −0.047 to 0.875). The selected 14 items of the mPSPRS demonstrated more balanced standardized effect sizes (range, 0.285 to 0.800) and sample sizes.

This finding does not oppose the purpose of the PSPRS, as the authors of the PSPRS attempted to include all important areas of clinical impairment in PSP, acknowledging that some items are probably less relevant for clinical impairment in PSP.[3]

Expectedly, the PSPRS total score yielded lower effect sizes for a 26-week observation period than for a 52-week period. The same was true for all PSPRS categories (bulbar, gait, history, mentation) but the limb score category, in which the effect size was higher in the shorter observation period in this dataset, because raters had scored higher values at 26 weeks compared with 52 weeks on average. Because symptoms in PSP are progressive without remissions, this observation provides another argument not to include the limb score category items in the mPSPRS.

The selection process of the 14 items was our approach to retain items that report clinically meaningful disease milestones for patients with PSP, according to the experts. We used the judgment of physicians with longstanding experience in the care for patients with PSP to rate the clinical meaningfulness of each scale item of the PSPRS and did not take into account patients' and caregivers' opinions when designing the scale. However, a general shortcoming in designing a measure for clinically meaningful disability milestones is the difficulty of defining them, that is, which disabilities and to what extent they are meaningful to patients. This would be especially important for history and mentation aspects of the PSPRS, while taking into account that patients may lack insight into their functional deficits. This symptom ("anosognosia") is well studied in Alzheimer's disease[15] and also has been shown in PSP.[16] The perception of the patients' caregivers is also only a surrogate for the patients' perception, and there remains the challenge of defining and identifying comparable caregivers with regard to proximity to subjective experiences and perceptions and judgments of the patient. In the small exploratory patient survey on the PSPRS items, we found that all but one item incorporated into the mPSPRS were considered severe disease milestones by the patients. Only the item "emotional incontinence" scored slightly below the formal threshold of >1.5. However, further studies with higher case numbers are required to analyze the patients' and caregivers' perception of the severity and functional relevance of the PSPRS and mPSPRS items, taking into account covariables, such as disease stage, cognitive impairment, and social support.

Some items of the mPSPRS rely on recent history, including "dysphagia for solids," "using knife and fork, buttoning clothes, washing hands and face," "falls," and "urinary incontinence." For these, the caregiver should be the primary source of information for all visits to ensure consistency. The patient's opinion should also be considered, and the clinician should make the final rating based on his/her judgment when the caregiver and patient cannot come to a resolution on their own, as was also recommended for the PSPRS.[17]

Longitudinal studies with patients with PSP will have to cope with the high dropout rate caused by rapid disease progression and severe physical disability previously reported.[6] Our analyses contained only patients who completed the trial and who met prespecified per-protocol criteria of the TAUROS trial.

For planning of a trial, of course, our proposed power-calculation-based case numbers represent final numbers that need to be available for analysis. Thus, any planned trial will need to adjust the number of patients to be recruited allowing to compensate for expected dropout rates. Dropout rates within 12 months in prior trials were between 23% in the Davunetide Trial[5] and 35% in the TAUROS trial.[4]

A shorter trial duration could reduce dropout, as can be observed in the TAUROS trial: Although the dropout rate at 52-week follow-up was 41%, it was only 24% at 26-week follow-up. We demonstrated that the mPSPRS could also depict changes within shorter time ranges, such as 26 weeks (Table 3).

Although cognitive and behavioral problems play a major role in PSP,[18] the mPSPRS contains only emotional incontinence in the mentation category. We selected this item because expert milestone rating for emotional incontinence was similar to bradyphrenia and disorientation; however, the item emotional incontinence showed higher sensitivity to change after recalibration. Thus, the mPSPRS does not account for other items of mentation, including disorientation, bradyphrenia, and grasping/imitative/utilizing behavior, and this area of disability might be underrepresented for a clinical routine setting.

Further evaluation of the clinimetric properties of the mPSPRS with regard to internal consistency, reproducibility, and validity of the mPSPRS is warranted.

Our power analysis was performed in patients with PSP with a clinical diagnosis of possible or probable PSP according to the NINDS-SPSP diagnostic criteria,[8] which primarily allow for a diagnosis of PSP with Richardson's syndrome (PSP-RS) and not the variant PSP syndromes.[19] Variant PSP syndromes, as part of the new MDS-PSP criteria,[2] show different progression patterns. A recent publication demonstrated that patients with PSP-RS progressed significantly faster in the PSPRS than patients with PSP parkinsonism.[20] Thus, sensitivity to change of the mPSPRS might differ when including more patients with variant PSP syndromes. Yet, considering previous literature,[18,20] the selected items (mostly those related to dysphagia, eye

movements, and axial problems) still could be valuable in variant PSP syndromes as "turning point" clinical features that mark the change from slow to more aggressive progression at a certain disease stage.

In our confirmatory analysis with an independent cohort of patients with PSP with a broader range of PSP phenotypes, the mPSPRS required higher sample sizes to detect change, which might relate to the broader inclusion criteria for the confirmatory compared with the exploratory cohort. However, the standardized effect sizes correlated with those of the TAUROS data. Prospective studies with larger case numbers shall confirm or confute our findings.

We recommend that the mPSPRS should be preferred to measure treatment effects in disease-modifying trials, because the mPSPRS showed good sensitivity to change and is short and easy to apply. Compared with the PSPRS, the mPSPRS takes less time, and short scales to monitor disease progression play an important role in clinical care.[21,22] If a more comprehensive reporting of the spectrum of PSP-related symptoms is needed, for example, in observational natural history studies, we recommend using the full PSPRS, because it comprises symptoms more comprehensively than the mPSPRS.

With these caveats, the mPSPRS shows similar sensitivity to change compared with the PSPRS and can be completed in less time. The selected items cover the most important spectrum of symptoms for patients with PSP, and their milestone scores imply clinically meaningful changes as evaluated by experts. Thus, the mPSPRS may serve as a clinimetrically suitable scale to monitor progression of disease milestones in PSP. ■

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APPENDIX A

Members of the Movement Disorder Society–Endorsed PSP Study Group: Yaroslau Compta, Carlo Colosimo, Jean-Christophe Corvol, Joaquim Ferreira, Lawrence I. Golbe, Günter U. Höglinger, Johannes Levin, Milica Jecmenica Lukic, Wassilios G. Meissner, Pablo Mir, Huw R. Morris, Christer Nilsson, Gesine Respondek, James B. Rowe, Klaus Seppi, Maria Stamelou, John van Swieten, and Gregor K. Wenning. ■

APPENDIX B

Members of the DescribePSP Study Group: Thomas Gasser, Andreas Hermann, Günter Höglinger, Matthias

Höllerhage, Okka Kimmich, Thomas Klockgether, Andrea Kühn, Johannes Levin, Gerrit Machetanz, Antje Osterrath, Carla Palleis, Johannes Prudlo, Gesine Respondek, and Annika Spottke.

APPENDIX C

Members of the ProPSP Study Group: Daniela Berg, Katrin Bürk, Joseph Claßen, Georg Ebersbach, Carsten Eggers, Imke Galazky, Lennard Herrmann, Günter Höglinger, Matthias Höllerhage, Klaus Jahn, Wolfgang Jost, Jan Kassubek, Martin Klietz, Andrea Kühn, Franz Marxreiter, Steffen Paschen, Elmar Pinkhardt, Monika Pötter-Nerger, Gesine Respondek, Johannes Schwarz, Lars Tönges, Claudia Trenkwalder, Tobias Warnecke, Florian Wegner, and Jürgen Winkler.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution;
(2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
(3) Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.
Marie-Therese Grötsch: 1B, 1C, 2A, 2B, 3A.
Gesine Respondek: 1A, 1B, 1C, 2A, 2B, 3B.
Maria Stamelou: 1C, 3B.
Carlo Colosimo: 1C, 3B.
Yaroslau Compta: 1A, 2C, 3B.
Jean Christophe Corvol: 1A, 2C, 3B.
Joaquim Ferreira: 1A, 2C, 3B.
Meret K. Huber: 1C.
Martin Klietz: 1A, 2C, 3B.
Lea F.M. Krey: 1C.
Johannes Levin: 1A, 2C, 3B.
Milica Jecmenica Lukic: 1A, 2C, 3B.
Wassilios G. Meissner: 1A, 2C, 3B.
Pablo Mir: 1A, 2C, 3B.
Huw Morris: 1A, 2C, 3B.
Christer Nilsson: 1A, 2C, 3B.
James B. Rowe: 1A, 2C, 3B.
Klaus Seppi: 1A, 2C, 3B.
John C. van Swieten: 1A, 2C, 3B.
Gregor Wenning: 1A, 2C, 3B.
Teodoro Del Ser: 1A, 1C, 2C, 3B.
Lawrence I. Golbe: 1A, 1C, 2C, 3B.
Günter U. Höglinger: 1A, 1B, 1C, 2A, 2B, 3A.
Daniel Macías-García: 1A, 2C, 3B.

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