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ABSTRACT

Objective: To assess the ability of neurophysiologic markers in conjunction with cognitive assessment to improve prediction of progression to dementia in Parkinson disease (PD).

Methods: Baseline cognitive assessments and magnetoencephalographic recordings from 63 prospectively included PD patients without dementia were analyzed in relation to PD-related dementia (PDD) conversion over a 7-year period. We computed Cox proportional hazard models to assess the risk of converting to dementia conveyed by cognitive and neurophysiologic markers in individual as well as combined risk factor analyses.

Results: Nineteen patients (30.2%) developed dementia. Baseline cognitive performance and neurophysiologic markers each individually predicted conversion to PDD. Of the cognitive test battery, performance on a posterior (pattern recognition memory score < median; hazard ratio (HR) 6.80; $p = 0.001$) and a fronto-executive (spatial span score < median; HR 4.41; $p = 0.006$) task most strongly predicted dementia conversion. Of the neurophysiologic markers, beta power < median was the strongest PDD predictor (HR 5.21; $p = 0.004$), followed by peak frequency < median (HR 3.97; $p = 0.016$) and theta power > median (HR 2.82; $p = 0.037$). In combination, baseline cognitive performance and neurophysiologic measures had even stronger predictive value, with the combination of impaired fronto-executive task performance and low beta power being associated with the highest dementia risk (both risk factors vs none: HR 27.3; $p < 0.001$).

Conclusions: Combining neurophysiologic markers with cognitive assessment can substantially improve dementia risk profiling in PD, providing potential benefits for clinical care as well as for the future development of therapeutic strategies. *Neurology®* 2014;82:263-270

GLOSSARY

AAL = automated anatomical labeling; **AD** = Alzheimer disease; **CAMCOG** = Cambridge cognitive examination; **HR** = hazard ratio; **IED** = intra-extra dimensional set shifting; **MCI** = mild cognitive impairment; **MEG** = magnetoencephalography; **PD** = Parkinson disease; **PDD** = Parkinson disease–related dementia; **PRM** = pattern recognition memory; **RCI** = reliable change index; **SOC** = stockings of Cambridge; **SSP** = spatial span; **SWM** = spatial working memory.

Parkinson disease–related dementia (PDD) develops in up to 80% of patients with Parkinson disease (PD) and has a profound socioeconomic impact.[1,2] Early-stage identification of risk factors for PDD development is valuable from a prognostic perspective as well as for the development of targeted therapeutic strategies. Mild cognitive deficits in the early stages of PD are associated with an increased dementia risk.[3,4] Substantial heterogeneity in the range of early-stage cognitive deficits exists,[5] but whether their specific nature or rate of development improves prediction of PDD conversion is still uncertain.[6–9]

Neurophysiologic measures may be ideal biomarkers to complement cognitive testing in studying cognitive decline and dementia development in PD. Low peak frequency and oscillatory slowing (high theta power) in EEG recordings have previously been identified as independent predictors of dementia incidence in PD,[9] with a predictive ability exceeding that of cognitive testing. Pathophysiologically oriented EEG and magnetoencephalographic (MEG) studies have associated

(widespread) oscillatory slowing with cognitive impairment in both PDD and PD using cross-sectional and longitudinal designs.[10–13]

Cognitive testing is often used to assess cognitive decline and monitor the development of dementia in PD, but neurophysiologic markers derived from either EEG or MEG are generally not included in the routine clinical workup of patients. In the present study we assessed the predictive value of neurophysiologic markers combined with cognitive impairments for the future development of dementia in PD. We hypothesized that combining neurophysiologic markers with measures of cognitive function substantially improves dementia risk profiling compared to the assessment of individual predictors.

Table 1	Baseline demographic, cognitive, and neurophysiologic measures of patients with PD who converted to PDD during follow-up (n = 19) and those who did not (n = 44)	
	Nonconverters (n = 44)	**Converters (n = 19)**
Sex (male/female)	24/20	15/4
Age, y	60.9 ± 6.48	66.0 ± 5.19
ISCED (1/2/3/4/5/6)	0/17/9/2/15/1	1/6/7/1/4/0
Disease duration, y	5.05 ± 3.75	5.95 ± 3.58
UPDRS-III	13.2 ± 5.17	15.2 ± 6.93
LEDD	384 ± 448	358 ± 357
CAMCOG	96.6 ± 4.13	92.3 ± 4.15
Fluency	24.4 ± 6.11	21.6 ± 4.61
PRM	21.8 ± 2.06	20.7 ± 1.33
SSP	5.57 ± 0.97	4.53 ± 0.70
SWM	27.6 ± 16.0	49.3 ± 17.5
SOC	8.09 ± 1.61	6.58 ± 1.50
IED	45.2 ± 40.5	58.0 ± 49.6
VPT	22.7 ± 7.17	24.7 ± 8.21
Delta power, %	22.3 ± 4.03	25.4 ± 5.43
Theta power, %	18.1 ± 4.73	23.2 ± 5.43
Alpha1 power, %	15.4 ± 4.04	15.1 ± 2.85
Alpha2 power, %	12·0 ± 2.82	11.1 ± 3.42
Beta power, %	32.9 ± 6.07	26.6 ± 4.77
Gamma power, %	12.3 ± 2.61	12.6 ± 3.40
Peak frequency, Hz	9.07 ± 0.83	8.39 ± 0.91

Abbreviations: CAMCOG = Cambridge cognitive examination; IED = intra-extra dimensional set shifting; ISCED = International Standard Classification of Education; LEDD = levodopa equivalent daily dose; PD = Parkinson disease; PDD = PD-related dementia; PRM = pattern recognition memory; SOC = stockings of Cambridge; SSP = spatial span; SWM = spatial working memory; UPDRS-III = Unified Parkinson's Disease Rating Scale motor ratings; VPT = Vienna perseveration task.
Values are expressed as mean ± SD unless otherwise indicated.

METHODS **Participants.** From April 2003 to March 2006 a total of 70 patients with idiopathic PD and without dementia were prospectively included at the VU University Medical Center as described previously.[12] Exclusion criteria for patients with PD included the use of psychoactive compounds. Participants underwent longitudinal motor, neuropsychiatric, and cognitive assessments, as well as MEG and MRI recordings, at baseline and at 2 follow-up visits scheduled approximately 4 and 7 years after the baseline visit.

At each follow-up visit, we evaluated the presence of PDD according to the clinical criteria recommended by the Movement Disorder Society Task Force,[14] in which the Mini-Mental State Examination criterion was substituted with a reliable change index (RCI)[15] of the Cambridge cognitive examination (CAMCOG) score over time. The rationale for this substitution is provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org. For RCI calculation, a group of healthy controls who were also followed as part of this longitudinal project served as a reference group,[13] corresponding to an RCI of 8 points decrease in CAMCOG score over the 3 time points ($p < 0.05$). Unified Parkinson's Disease Rating Scale motor ratings[16] were obtained in the "ON" medication state by a trained physician. The total dose of dopaminomimetics was converted to a so-called levodopa equivalent daily dose using a previously described conversion rate.[13]

For the present analysis, only participants who had at least one cognitive follow-up evaluation after their baseline assessment were included (n = 63). Seven patients were lost to follow-up, 3 of whom had died. Data collection took place between April 2003 and November 2012.

Standard protocol approvals, registrations, and patient consents. All participants gave written informed consent to the research protocol, which was approved by the medical ethical committee of the VU University Medical Center. Ethics review criteria conformed to the Helsinki declaration.

Cognitive evaluation. Cognitive assessment included the 1-minute verbal fluency test (animals) from the CAMCOG and a subset of tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB Eclipse 2.0, Cambridge Cognition, Cambridge, UK): pattern recognition memory (PRM), reflecting posterior cognitive function; spatial span (SSP), spatial working memory (SWM), stockings of Cambridge (SOC), and intra-extra dimensional set shifting (IED), reflecting fronto-executive cognitive functions. Additionally, the Vienna perseveration task was administered (Vienna Test System, Dr. G. Shuhfried GmbH, Mödling, Austria). A detailed description of cognitive measures is provided in table e-1.

MEG recording and processing. At their baseline visit, all subjects underwent an MEG recording in an eyes-closed resting-state condition for 5 minutes with a sample rate of 312.5 Hz. Subjects treated with dopaminergic medication were in the "ON" medication state, as described previously.[13] All subjects also had a structural T1-weighted MRI scan (1.0 tesla, Impact, Siemens, Erlangen, Germany; follow-up: 3.0 tesla, Signa, GE Healthcare, Waukesha, Wisconsin). Vitamin E capsules were placed at the same anatomical landmarks where head position coils had been placed during MEG registration.

MEG datasets were split into epochs of 4,096 samples (13.11 seconds). Channels and epochs containing artifacts were discarded after visual inspection (K.T.E.O.D.). On average we discarded 2.3 (range: 2–7) channels and 2.2 (range: 0–11) epochs. We used an atlas-based beamformer approach to project MEG sensor signals to an anatomical framework consisting of 78 cortical regions identified

Table 2 Cox proportional hazard ratios as a function of risk group based on the independent assessment of cognitive and neurophysiologic markers

Risk factor (median cutoff category)	HR (95% CI)	p Value
Cognitive risk factors		
Fluency (<23)	1.33 (0.50–3.49)	0.568
PRM (<22)	6.80 (2.11–21.9)	0.001
SSP (<5)	4.41 (1.52–12.7)	0.006
SWM (>32)	3.22 (1.09–9.52)	0.034
SOC (<7)	2.82 (1.10–7.24)	0.031
IED (>29)	2.72 (1.01–7.30)	0.048
VPT (>21.03)	1.38 (0.52–3.64)	0.724
Neurophysiologic risk factors		
Delta power (>25.12)	1.97 (0.76–5.15)	0.165
Theta power (>22.85)	2.82 (1.06–7.52)	0.037
Alpha1 power (<14.72)	1.58 (0.58–4.27)	0.372
Alpha2 power (<11.45)	2.33 (0.87–6.24)	0.093
Beta power (<27.96)	5.21 (1.70–15.9)	0.004
Gamma power (<8.81)	0.78 (0.31–1.92)	0.582
Peak frequency (<8.21)	3.97 (1.30–12.1)	0.016

Abbreviations: CAMCOG = Cambridge cognitive examination; CI = confidence interval; HR = hazard ratio; IED = intra-extra dimensional set shifting; PRM = pattern recognition memory; SOC = stockings of Cambridge; SSP = spatial span; SWM = spatial working memory; VPT = Vienna perseveration task.

by means of automated anatomical labeling (AAL).[17] For this purpose, we coregistered MRI and MEG data for each subject through identification of the same anatomical landmarks (left and right preauricular points and nasion). Only data with an estimated coregistration error < 1.0 cm were accepted for further analysis. We then spatially normalized MRIs to a template MRI using the SEG toolbox in SPM8, after which we applied anatomical labels.

We estimated broadband time series of neuronal activation for voxels with peak activation for 6 frequency bands (delta [0.5–4 Hz], theta [4–8 Hz], alpha1 [8–10 Hz], alpha2 [10–13 Hz], beta [13–30 Hz], and gamma [30–48 Hz], using an average time window of 232 (range: 118–433) seconds as input for the beamformer computations. This resulted in a total of 6 sets (one for each frequency band) of 78 time series (one for each AAL region).

For each subject, we selected 5 artifact-free epochs per frequency band for further analysis (K.T.E.O.D.) and imported these into the BrainWave software package (version 0.9.72, available from http://home.kpn.nl/stam7883/brainwave.html). Subsequently, MEG data were digitally filtered offline with a band-pass of 0.5 to 48 Hz. A Fourier transform was applied to each channel. Subsequently all real and imaginary components of the Fourier transform outside the pass-band (using the 6 different pass-bands as defined above) were set to zero. Next, an inverse Fourier transform was used to obtain the filtered time series. In terms of filter characteristics, this approach would produce a (perfect) "brick wall" filter. We calculated dominant peak frequency value by averaging the peak frequency of occipital AAL regions (i.e., bilateral superior, middle and inferior occipital, calcarine, cuneus and lingual regions) within the 4 to 13 Hz frequency range. Relative spectral power was calculated for each frequency band.

Per subject we averaged the results of 5 epochs. For the main analyses, we calculated mean spectral power over all AAL regions per frequency band. For exploratory post hoc analyses with

respect to the spatial distribution, we assessed spectral power per AAL region.

Statistical analysis. We performed Cox proportional hazard analyses to assess the risk of converting to PDD, using dichotomized categories of cognitive and neurophysiologic (MEG) predicting variables. Each analysis included age, sex, and education level as potential confounders. Dichotomization of cognitive and neurophysiologic variables was based on the median. For patients diagnosed with PDD, we approximated time to dementia by the midpoint between cognitive evaluations.

We assessed risk factors in a univariate as well as in a multivariable way. In the multivariate analyses, we combined the strongest predictors from the univariate analyses to evaluate the predictive power of combinations of cognitive and neurophysiologic variables. In each of these multivariate analyses we combined one cognitive and one MEG risk factor, with patient stratification into 4 categories: absence of both risk factors, presence of only the cognitive risk factor, presence of only the MEG risk factor, or presence of both risk factors.

All analyses were performed using the SPSS Statistics 20.0 software package (IBM Corporation, New York). A significance level of 0.05 (2-tailed) was applied.

RESULTS Participant characteristics. Baseline demographic, clinical, and MEG characteristics are listed in table 1. Mean conversion-free follow-up time was 7.03 (SD 1.17) years. At the end of follow-up, 19 patients (30.2%) had developed PDD, with a mean time to dementia development of 4.62 (SD 1.69) years.

Independent assessment of cognitive and neurophysiologic markers. Of the cognitive test battery, a PRM score below the median value most strongly predicted dementia conversion, followed by an SSP score below the median. SWM, SOC, and IED task performance were less strongly associated with dementia development (table 2, figure e-1).

Of MEG-derived predictors for dementia conversion, mean beta power below the median value was the strongest, followed by peak frequency below the median and mean theta power above the median (table 2, figure e-2).

Figure 1 illustrates the spatial distribution of the MEG power predictors that significantly contributed to risk discrimination (post hoc analyses). For both theta and beta frequency bands, power in occipital and temporal brain regions had the strongest predictive value for dementia conversion.

Combined assessment of cognitive and neurophysiologic markers. For the combined assessment, we selected the 2 strongest individual predictors from each risk factor category. These predictors were PRM and SSP task performance for the cognitive risk factors and mean beta power and peak frequency for the MEG risk factors.

Figure 2 provides the survival curves for patient groups defined by the different combinations of risk factors. Each combination involved one cognitive and one MEG risk factor. Combining information from

Figure 1 Spatial distribution of the MEG power predictors that contributed significantly to risk discrimination
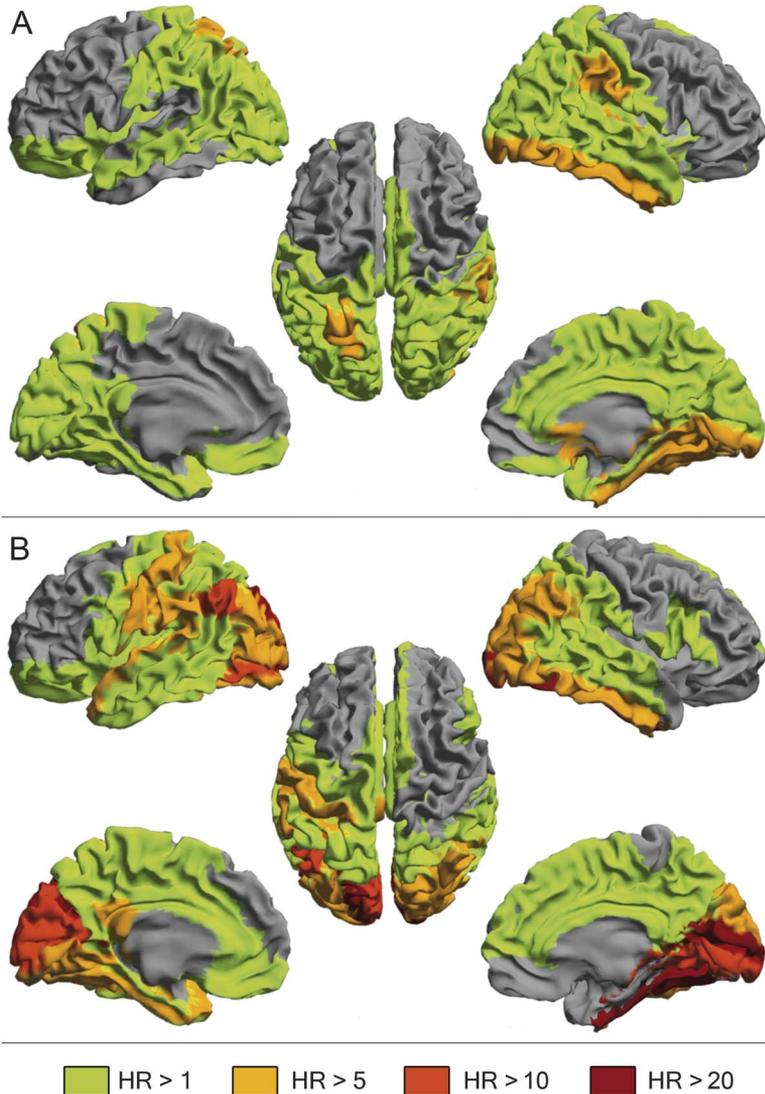
(A) Theta power, (B) beta power. HR = hazard ratio; MEG = magnetoencephalography.

the 2 risk factor categories improved prediction of conversion to dementia significantly over the assessment of individual cognitive predictors (SSP + beta power vs SSP alone: $\chi^2 = 12.99$, $p = 0.002$; PRM + beta power vs PRM alone: $\chi^2 = 8.24$, $p = 0.016$; SSP + peak frequency vs SSP alone: $\chi^2 = 11.71$, $p = 0.003$).

The combination of SSP task performance and mean beta power had the highest predictive value. The combinations of SSP task performance and peak frequency and PRM task performance and mean beta power also yielded very good predictive ability (table 3).
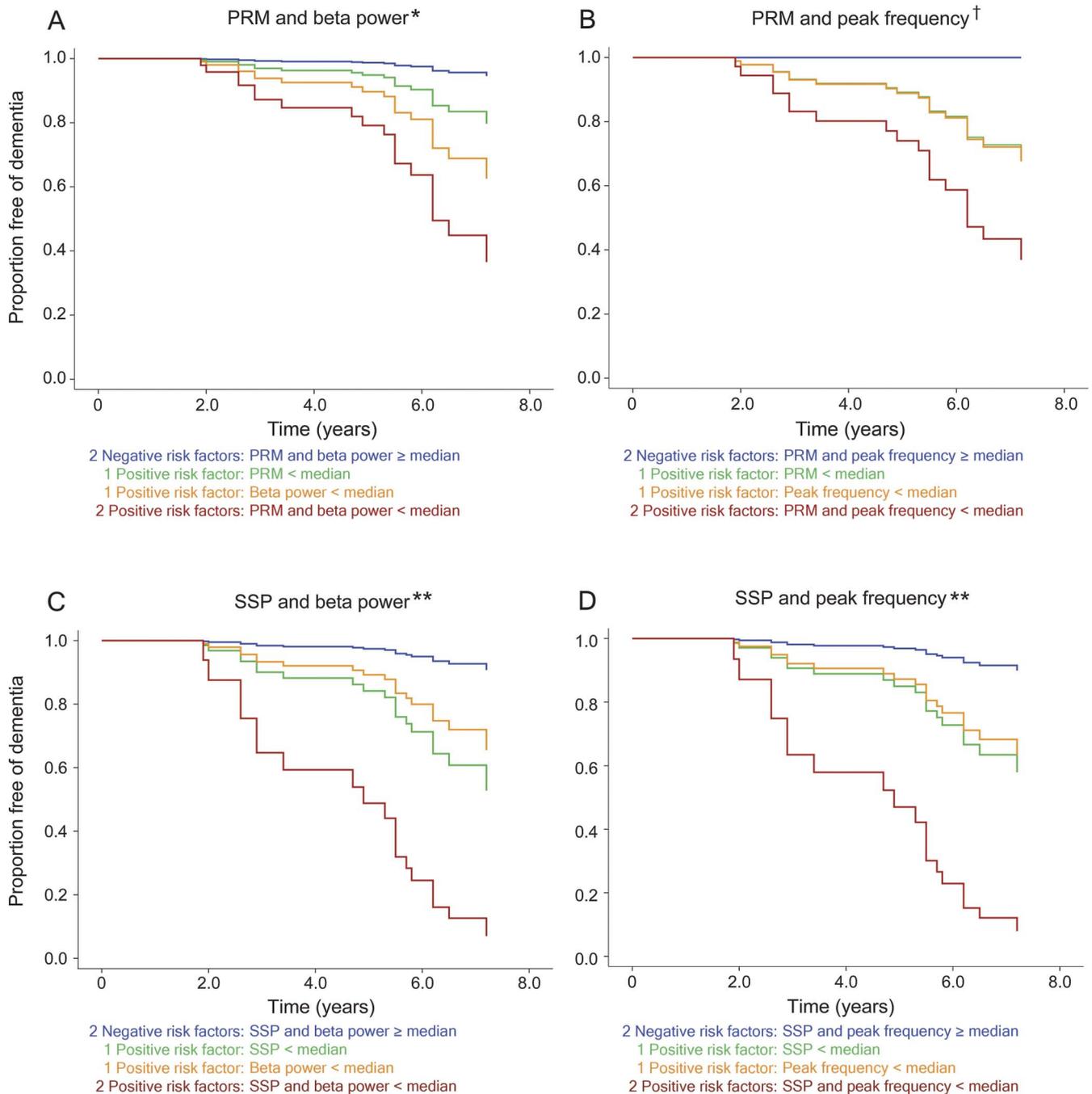
The lack of converters in the negative risk group for the combination of PRM task performance and peak frequency precluded the calculation of a hazard ratio (HR) for this combination of risk factors. Yet the survival curve for this combination of risk factors suggests high discriminatory potential (figure 2B).

DISCUSSION In this 7-year longitudinal study we demonstrated the ability of neurophysiologic markers, in conjunction with cognitive assessment, to predict progression to dementia in patients with PD. We found that impairments on multiple cognitive tasks (HRs ranging from 2.72 to 6.80) as well as oscillatory slowing in the MEG (HRs ranging from 2.82 to 5.21) predicted future conversion to PDD. In combination, baseline cognitive performance and slowing of oscillatory brain activity had even stronger predictive value, with the combination of impaired fronto-executive task performance and low beta power being associated with the highest conversion risk (HR 27.3).

In our assessment of MEG-derived neurophysiologic risk factors we found low peak frequency, low beta power, and high theta power to be associated with dementia conversion in PD. These results validate and expand on a previous longitudinal study with shorter follow-up duration in which we reported an association between these MEG-derived measures and cognitive decline in PD.[13] Moreover, in an independent EEG study others have identified both peak frequency and relative theta power as predictors of PDD incidence.[9] The similarity of the results obtained using 2 different neurophysiologic techniques in independent patient samples emphasizes the robustness of neurophysiologic measures as biological markers of cognitive decline in PD. The use of MEG instead of EEG provided us with high-density measurements of brain activity that are not confounded by the effects of a reference or passage through the skull, and thus with a reliable view of the spatial distribution of these neurophysiologic markers. Using this approach, we found that the discriminatory value of oscillatory slowing was highest in temporal and occipital regions.

From a pathophysiologic perspective, disruption of thalamocortical circuits generating alpha oscillations could result in a peak frequency slowing as found in our study, with a shift of power to the adjacent theta band.[18] In mild cognitive impairment (MCI) preceding Alzheimer disease (AD) a relative decrease of posterior low-frequency alpha sources has also been reported,[19] possibly in relation to an initial selective impairment of the cholinergic basal forebrain.[20] It is tempting to speculate that these disruptions give rise to clinical impairments in global attention and visuospatial processes and might explain the progressive decline in cognitive (attentional and visuospatial) functions across the spectrum from MCI to dementia, both in AD and PDD.[21,22] The fact that the discriminatory capacity of oscillatory slowing was highest in temporal and occipital regions supports this line of thought, as these regions have previously been implicated in visuospatial cognitive

Figure 2   Survival curves for risk groups defined by a combination of cognitive and neurophysiologic risk factors

Overall significant effects are indicated with asterisks: * = $p < 0.05$, ** = $p < 0.01$. †Since there were no converters in the negative risk group, statistics could not be computed. PRM = pattern recognition memory; SSP = spatial span.

impairment in PD.[23,24] To a lesser extent, power decreases in occipital alpha rhythms have also been reported in "normal" aging,[25] in association with changes in the cholinergic system as well.[20] However, taking into consideration the stability of spectral MEG characteristics we observed in healthy aging subjects,[13] this effect is expected to be negligible in the present analysis.

Beta activity is involved in the regulation of both motor and cognitive performance.[26] Interestingly,

decreases in beta power have been reported in AD and may imply involvement of the cholinergic system.[27,28] An alternative explanation for the changes in beta power observed in the present study could be a disconnection of subcortical and cortical structures by local intrinsic neuropathology.[29] This would imply that progressive Lewy body pathology related to the development of PDD[30] might disrupt beta oscillatory circuits as well. However, as we assessed relative power in our study, the decrease in beta power might

also reflect an increase of slow-wave activity (i.e., a shift of power into the theta band results in a relative decrease of faster activity).

Both posterior (PRM) and fronto-executive (SSP, SWM, SOC, IED) cognitive task performance were associated with a higher risk of conversion to dementia in our study. So far it remains unclear whether distinct cognitive profiles are associated with higher dementia risk than others. Some studies emphasize an association between impaired posteriorly located cognitive functions and increased dementia risk,[5,22] while ours and other studies have demonstrated a predictive role of fronto-executive deficits for dementia development too.[6,9,31] Larger studies are needed to further evaluate the role of the different cognitive profiles in PDD development.

Our results demonstrate that combining cognitive task performance with neurophysiologic markers substantially improves prediction of the risk of conversion to dementia in PD over cognitive assessment alone. The combination of impaired SSP performance and low beta power was associated with the greatest risk of developing dementia. Neurophysiologic markers could easily and effectively complement cognitive assessment in the clinical workup of patients with PD to establish the risk of conversion to PDD. For reasons previously mentioned we used MEG in the present study, but in clinical practice neurophysiologic markers reflecting slowing of brain activity can also be derived from EEG recordings. The absence of

both neurophysiologic and cognitive risk factors could offer reassurance to patients with PD that the risk of PDD conversion in the near future is low. On the other hand, the presence of both risk factors for the development of PDD would justify more careful monitoring of patients and possibly warrant early treatment with cholinesterase inhibitors.[32] Obviously, the efficacy of such an approach would first have to be assessed in an intervention study. Furthermore, patients and caregivers could be provided with better prognostic information that would help them to anticipate PDD-related problems such as psychosis, caregiver distress, and nursing home placement.[33,34] The identification of a subgroup of patients with PD at high risk for dementia is quite important for studies aimed at disease-modifying therapies to slow down cognitive decline. Conversely, the identification of a low-risk subgroup may help us to identify factors that protect against cognitive decline in PD.

The present study has a number of limitations. The use of median cutoff values in the determination of low- and high-risk categories is necessarily arbitrary. Future studies using larger independent samples should aim to define absolute cutoff values for both cognitive and neurophysiologic measures. Furthermore, our cognitive test battery focused on fronto-executive and posteriorly located cognitive functions and was chosen before the development of MCI criteria in PD.[35] Unfortunately, our choice of cognitive tests does not allow us to retrospectively diagnose MCI at baseline in the patient group. We therefore restricted ourselves in our analysis to the assessment of performance on individual tasks in relation to dementia development. Lastly, the number of patients in our combined risk factor analysis was relatively small. Studies involving larger numbers of patients are necessary to further substantiate the present observations.

Important strengths of our study include the prospective longitudinal design over a time period of 7 years, in which only 10% of patients were lost to follow-up. Moreover, patients underwent a comprehensive evaluation at each visit, covering demographics, clinical motor and nonmotor features, and functional and structural brain imaging. The use of MEG instead of EEG provided us with high-density measurements of brain activity that are not confounded by the effects of a reference or passage through the skull, and thus with a reliable view of the spatial distribution of these neurophysiologic markers. Moreover, it facilitates the application of more advanced (e.g., functional connectivity and brain network topology) analyses in the study of the pathophysiologic mechanisms underlying cognitive decline and dementia in PD.

We demonstrated that combining neurophysiologic markers (i.e., beta power, theta power, and peak frequency) with measures of cognitive function in

patients with PD substantially improved prediction of progression to dementia over the assessment of cognitive function alone. The combination of impaired fronto-executive task performance and low beta power was associated with the greatest risk of developing dementia. Improvement of dementia risk profiling by combining cognitive assessment with neurophysiologic markers could benefit routine clinical care for individual patients as well as the development of targeted therapeutic strategies.

AUTHOR CONTRIBUTIONS

H.W.B., C.J.S., D.S., J.W.R.T., and J.B.D. designed the study. D.S. and K.T.E.O.D. collected the data. K.T.E.O.D., J.W.R.T., H.W.B., C.J.S., A.H., and B.A.S. analyzed and interpreted the data. K.T.E.O.D. wrote the manuscript. All authors reviewed and edited the manuscript.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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