

# Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: a longitudinal study

Kim T.E. Olde Dubbelink<sup>a,\*</sup>, Diederick Stoffers<sup>a</sup>, Jan Berend Deijen<sup>b</sup>, Jos W.R. Twisk<sup>c</sup>,  
Cornelis J. Stam<sup>d</sup>, Henk W. Berendse<sup>a</sup>

<sup>a</sup> Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

<sup>b</sup> Department of Clinical Neuropsychology, VU University, Amsterdam, The Netherlands

<sup>c</sup> Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

<sup>d</sup> Department of Clinical Neurophysiology, VU University Medical Center, Amsterdam, The Netherlands

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## Abstract

The pathophysiological mechanisms of Parkinson's disease (PD)-related dementia (PDD) are still poorly understood. Previous studies using electroencephalography (EEG) and magnetoencephalography (MEG) have demonstrated widespread slowing of oscillatory brain activity as a neurophysiological characteristic of PD-related dementia. Here, we use MEG to longitudinally study early changes in oscillatory brain activity in initially nondemented PD patients that may be associated with cognitive decline. Using a longitudinal design, resting-state MEG recordings were performed twice at an approximate 4-year interval in 14 healthy controls and 49 PD patients. Changes in peak frequency and in relative spectral power for 10 brain regions were analyzed in relation to clinical measures of cognitive and motor function. In contrast to healthy controls, PD patients showed a slowing of the dominant peak frequency. Furthermore, analysis per frequency band revealed an increase in theta power over time, along with decreases in alpha1 and alpha2 power. In PD patients, decreasing cognitive performance was associated with increases in delta and theta power, as well as decreases in alpha1, alpha2, and gamma power, whereas increasing motor impairment was associated with a theta power increase only. The present longitudinal study revealed widespread progressive slowing of oscillatory brain activity in initially nondemented PD patients, independent of aging effects. The slowing of oscillatory brain activity strongly correlated with cognitive decline and therefore holds promise as an early marker for the development of dementia in PD.

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**Keywords:** Parkinson's disease; Cognitive decline; Dementia; Magnetoencephalography (MEG); Oscillatory brain dynamics; Longitudinal

## 1. Introduction

In addition to prominent motor features, Parkinson's disease (PD) is also characterized by the presence of nonmotor disturbances including cognitive abnormalities (Chaudhuri et al., 2006). Mild cognitive impairment (MCI) is common, even at the time of PD diagnosis (Aarsland et al., 2009; Muslimovic et al., 2005), and increases the risk of developing Parkinson's disease-related dementia (PDD)

(Janvin et al., 2006). PDD develops in up to 80% of all patients with prolonged disease duration and has a profound socioeconomic impact (Aarsland et al., 2003; Hely et al., 2008). Consequently, an understanding of the neural basis and evolution of cognitive dysfunction in PD is essential, both from a prognostic perspective as well as for the development of targeted therapeutic strategies.

The cognitive deficits in PD are often classified into 2 distinctive subtypes. Frontal executive deficits and impairments in more posterior located cognitive functions evolve differently over time (Pagonabarraga et al., 2008), with only the latter being associated with an increased risk of dementia (Williams-Gray et al., 2009). As clinicopathological

\* Corresponding author at: Department of Neurology, VU University Medical Center, PO Box 7057, 1007 MB, Amsterdam, The Netherlands. Tel.: +31 20 444 07 08; fax: +31 20 444 28 00.

E-mail address: kte.olderdubbelink@vumc.nl (K.T.E. Olde Dubbelink).

studies have demonstrated an association between cortical Lewy body pathology and the development of dementia in PD (Aarsland et al., 2003; Braak et al., 2005), these cognitive phenotypes may have different neuropathological correlates (Williams-Gray et al., 2009). In PD, Lewy body pathology is initially confined to the lower brainstem, but gradually spreads via a predictable topographical sequence over the course of the disease to ultimately affect widespread cortical areas (Braak et al., 2005).

Oscillatory brain dynamics are of great importance for adequate functioning of human brain processes in general, and local information processing in particular (Schnitzler and Gross, 2005). Disturbed oscillatory brain activity in various neurological diseases is believed to reflect cortical dysfunction associated with underlying neuropathological changes (Uhlhaas and Singer, 2006). Neurophysiologically, diffuse as well as localized slowing of oscillatory brain activity is a consistently reported feature in both advanced stage nondemented (Bosboom et al., 2006; Moazami-Goudarzi et al., 2008; Morita et al., 2009; Soikkeli et al., 1991) and early stage, drug-naïve PD patients (Stoffers et al., 2007). A correlation of oscillatory slowing with motor disease severity has only been reported incidentally (Morita et al., 2009) while comparisons between patients in a medicated and a nonmedicated state revealed no differences (Moazami-Goudarzi et al., 2008; Stoffers et al., 2007). This suggests an interference of neuropathological changes with the generation of oscillatory rhythms via the involvement of nondopaminergic neurotransmitter systems unrelated to PD motor symptomatology.

Dementia in PD is associated with further slowing and a unique spatial distribution of resting-state oscillatory brain activity, in comparison with both healthy subjects and nondemented PD patients (Bosboom et al., 2006; Neufeld et al., 1994; Tanaka et al., 2000). Although speculative, one could hypothesize that this implies the involvement of additional pathophysiological mechanisms, for example the degeneration of the cholinergic basal forebrain system, increased cortical Lewy body load, and/or concomitant tau or vascular pathology.

Based upon the results of the aforementioned cross-sectional studies, a link has been suggested between the topographical progression of Lewy body pathology and evolving changes in oscillatory brain dynamics over the course of the disease (Berendse and Stam, 2007). In addition, slowing of oscillatory brain activity has been associated with an increased dementia risk (Klassen et al., 2011). However, at this point, it is unknown how oscillatory patterns develop over time in individual PD patients and whether these changes are associated with clinical features of disease progression, in particular cognitive decline that may precede dementia.

In the present study we set out to longitudinally explore changes in oscillatory brain activity in initially nondemented PD patients relative to healthy controls. By simul-

taneously analyzing clinical measures of disease progression, we aimed to identify oscillatory slowing as an early neurophysiological marker of cognitive decline.

## 2. Methods

### 2.1. Participants

#### 2.1.1. Baseline inclusion

At baseline, a total of 70 patients (disease duration 0–13 years) with idiopathic PD and 21 healthy controls were included and selected for analysis as described previously (Stoffers et al., 2007).

#### 2.1.2. Longitudinal participation and inclusion

After an interval of  $4.3 \pm 0.8$  (mean  $\pm$  standard deviation) years, a total of 59 out of the 70 PD patients in the original study sample participated. Three patients had passed away and 8 patients were lost to follow-up. Out of the control group, 16 subjects agreed to follow-up participation, whereas 5 subjects were lost to follow-up. All patients still fulfilled UK Brain Bank clinical diagnostic criteria for PD (Hughes et al., 1992).

Ten PD patients and a single control subject were excluded from further analysis due to significant artifacts during magnetoencephalography (MEG) registration. Magnetic resonance imaging (MRI) of 1 control subject revealed extensive white matter lesions, which were already present at baseline MRI, although less pronounced. As such, this subject was excluded from further analysis, leaving baseline and follow-up measurements of 49 PD patients and 14 control subjects for further analyses.

All patients gave written informed consent to the research protocol, which was approved by the medical ethical committee of the VU University Medical Center (VUMC). Ethics review criteria conformed to the Helsinki declaration.

### 2.2. Participant characteristics

Participant characteristics are summarized in Table 1. Disease duration was calculated on the basis of the patients' subjective estimate of the time of occurrence of the first motor symptoms. Unified Parkinson's Disease Rating Scale motor ratings (UPDRS-III) (Fahn et al., 1987) were obtained in the "ON" medication state by a trained physician. Global cognitive function and presence of dementia were assessed using the Cambridge Cognitive Examination (CAMCOG) scale (Roth et al., 1986). Education level was determined using the International Standard Classification of Education (ISCED) (UNESCO, 1997). The total dose of dopaminomimetics was converted to a so-called levodopa equivalent daily dose (LEDD) using the following conversion rate: 100 mg levodopa equaling 133.33 mg levodopa sustained release, 1 mg pergolide, 1 mg pramipexol, 5 mg ropinirol, 10 mg bromocriptine or 10 mg apomorphine. Additionally, 10% was added to the total levodopa dose in case of the use of selegiline or rasagiline, while 20% was added

Table 1  
Participant characteristics

	Control (n = 14)		PD (n = 49)	
	Baseline	Follow-up	Baseline	Follow-up
Sex (M/F)	10/4	10/4	31/18	31/18
Age (y)	60.0 ± 8.55	64.7 ± 8.91	61.4 ± 6.39	65.6 ± 6.43
ISCED (0/1/2/3/4/5/6)	0/0/1/3/1/8/1		0/1/16/12/3/16/1	
Disease duration (y)	NA	NA	5.35 ± 3.51	9.59 ± 3.93
UPDRS-III	0.71 ± 1.59	2.62 ± 3.55	14.0 ± 5.92	26.5 ± 9.05
LEDD total dose	NA	NA	387 ± 430	855 ± 555
CAMCOG	100.7 ± 3.40	99.5 ± 1.56	97.6 ± 4.35	93.9 ± 7.48

Values are expressed as mean ± standard deviation unless otherwise indicated.

Key: CAMCOG, Cambridge Cognitive Examination; ISCED, International Standard Classification of Education (0, no education; 1, primary education; 2, lower secondary education; 3, upper secondary education; 4, postsecondary nontertiary education; 5, lower tertiary education; 6, upper tertiary education); LEDD, levodopa equivalent daily dose; M/F, male/female; NA, not applicable; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's disease Rating Scale motor ratings.

in case of the use of a catechol-O-methyl transferase (COMT)-inhibitor. Levodopa was always used in combination with a peripheral decarboxylase inhibitor. At time of follow-up evaluation, 4 patients were using rivastigmine.

### 2.3. Specific neuropsychological evaluation

Three tasks were used from the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized test battery (CANTAB Eclipse 2.0, Cambridge Cognition, Cambridge, UK). Tasks included were spatial span (SSP; outcome measure: SSP length, reflecting spatial working memory), spatial working memory (SWM; outcome measures: total errors and strategy, reflecting working memory and planning), and pattern recognition memory (PRM; outcome measure: correct responses, reflecting PRM). Additionally, the Vienna perseveration task (VPT) was administered (Vienna Test System, Dr. G. Shuhfried, GmbH, Mödling, Austria), measuring the amount of perseveration in the generation of random motor behavior. Verbal fluency was assessed using the 1-minute semantic fluency test (animals), which is part of the CAMCOG examination.

### 2.4. Data acquisition

MEG data were acquired using a 151-channel whole-head radial gradiometer MEG system (CTF Systems Inc., Vancouver, Canada), while subjects were seated inside a magnetically shielded room (Vacuumschmelze, GmbH, Hanau, Germany). Sensors were uniformly distributed over the helmet surface with a mean spacing of 3.1 cm.

A third order software gradient was used with a recording passband of 0.25–200 Hz and a sample rate of 312.5 (baseline) or 625 (follow-up) Hz. At the beginning and end of each condition the head position relative to the coordinate system of the helmet was recorded by leading small alternating current through 3 head position coils attached to the left and right preauricular points and the nasion on the subjects head.

MEG was recorded in an eyes-closed resting-state condition for 5 minutes, while patients were in the “ON” medication state.

### 2.5. MEG data analysis

Follow-up data were downsampled to 312.5 Hz. Subsequently, from both baseline and follow-up datasets, 4 artifact-free epochs of 4096 samples were selected by 1 of the investigators (KTEOD) blinded to diagnosis and registration time point. Of the original 151 channels, 12 channels were excluded in the analysis of all subjects because of technical problems in at least 1 of the registrations. These channels were spread randomly across the head (1 left central, 1 left frontal, 2 left occipital, 1 left temporal, 2 right central, 1 right frontal, 1 right occipital, 1 right parietal, 1 right temporal, and 1 midline channel).

For further off-line processing and spectral power analysis epochs were converted to ASCII-files and imported into the BrainWave software package (C.J. Stam, Amsterdam, the Netherlands; [home.kpn.nl/stam7883/brainwave.html](http://home.kpn.nl/stam7883/brainwave.html)). Subsequently, the MEG data were digitally filtered off-line with a band pass of 0.5–48 Hz. Filtering was based upon the aforementioned epochs of 4096 samples (sample frequency 312.5 Hz). A Fourier transform was applied to each channel. Subsequently all real and imaginary components of the Fourier transform outside the pass band were set to 0. Next, an inverse Fourier transform was used to obtain the filtered time series. In terms of filter characteristic this approach would produce a (perfect) “brickwall” filter. Dominant peak frequency value was calculated by averaging the peak frequency of a subgroup of occipital channels within the 4–13 Hz frequency range. Relative spectral power was calculated for the following 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).

Results of 4 epochs were averaged per subject. For main analyses, mean spectral power was calculated per frequency band. For exploratory post hoc analyses with respect to the

distribution of changes, MEG channels were grouped into regions of interest (ROIs) roughly corresponding to the major cortical areas (frontal, central, temporal, parietal, and occipital) areas on the left and right side of the brain, in line with previous work (Stoffers et al., 2007). As ROIs were based on the extracranial position of the MEG sensors, underlying cortical areas are to be considered as indicative.

## 2.6. Statistical analysis

### 2.6.1. Participant characteristics

Differences between patients and controls regarding sex, age, and follow-up interval were analyzed by means of  $\chi^2$  and independent sample *t* tests. Longitudinal changes in cognitive test performance were analyzed with paired-sample *t* tests.

### 2.6.2. Longitudinal changes in spectral power

Longitudinal changes in dominant peak frequency and mean spectral power per frequency band were analyzed using the General Linear Model (GLM) framework. Changes in dominant peak frequency over time were analyzed by means of a GLM analysis for repeated measures with time (2 levels) as repeated measures factor and group (control [*n* = 14] vs. PD [*n* = 49]) as between subjects factor using Greenhouse-Geisser corrected degrees of freedom. Sex, age, and baseline dominant peak frequency were added as potential confounders. When a significant group  $\times$  time interaction effect was found, post hoc analyses were performed within groups by means of a separate GLM with time as repeated measures factor. Changes in mean relative spectral power over time were analyzed by means of a single GLM analysis for repeated measures per frequency band with time (2 levels) as repeated measures factor and group as between subjects factor using Greenhouse-Geisser corrected degrees of freedom. Mean relative spectral power for each frequency band was transformed with a logarithmic function to obtain a Gaussian distribution (Gasser et al., 1982). Sex, age, and baseline relative power were added as potential confounders. When a significant time  $\times$  group interaction effect was found, post hoc analyses were performed within groups by means of a separate GLM with time as repeated measures factor. Subsequently, further exploratory analyses were performed within groups by means of a separate GLM per ROI with time as repeated measures factor to study the distribution of changes in spectral power over the different brain regions. For all analyses, partial  $\eta^2$  ( $\eta_p^2$ ) was calculated as an estimate of effect size.

### 2.6.3. Relationship between spectral power and clinical measures of disease progression

Within the group of PD patients (*n* = 49) the relationship between the longitudinal course of spectral power and measures of motor and cognitive function was investigated by means of Generalized Estimated Equations (GEE) with exchangeable working correlation matrix (Zeger et al., 1988). Analyses were performed per frequency band using either UPDRS-III or LEDD (parameters of motor disease severity);

Table 2  
Cognitive performance of PD patients (*n* = 49) over time

	Baseline	Follow-up	<i>p</i> Value
Global cognitive function			
CAMCOG	97.6 $\pm$ 4.35	93.9 $\pm$ 7.48	< 0.001
Temporal cognitive function			
PRM correct responses	21.6 $\pm$ 1.93	20.9 $\pm$ 2.77	0.029
Semantic fluency	24.7 $\pm$ 6.35	20.6 $\pm$ 6.60	< 0.001
Frontal cognitive function			
SSP span length	5.36 $\pm$ 0.90	4.72 $\pm$ 1.04	0.001
SWM between errors	31.9 $\pm$ 18.9	41.6 $\pm$ 24.5	0.001
SWM strategy	33.7 $\pm$ 5.33	34.2 $\pm$ 5.46	0.37
VPT redundancy	23.3 $\pm$ 8.19	25.0 $\pm$ 9.17	0.28

All values are expressed as mean  $\pm$  standard deviation.

Key: CAMCOG, Cambridge Cognitive Examination; PD, Parkinson's disease; PRM, Pattern Recognition Memory; SSP, Spatial Span; SWM, Spatial Working Memory; VPT, Vienna Perseveration Test.

CAMCOG (global cognitive function); PRM correct responses or semantic fluency (temporal cognitive function); SSP span length, SWM between errors, SWM strategy, or VPT redundancy (frontal cognitive function) as dependent, and mean power per frequency band as independent variable. When appropriate, dependent variables were transformed in order to comply with assumptions of normality. Sex, age, disease duration, and education level (ISCED) were added as potential confounders. To control for multiple comparisons, a Bonferroni correction was applied within the above-mentioned groups of related outcome variables. When a significant association between mean power and a measure of motor or cognitive function was found, post hoc analyses per ROI were performed to assess regional differences.

All analyses were performed using the SPSS 15.0 software package (SPSS, Inc., Chicago, IL, USA). A significance level of 0.05 (2-tailed) was applied.

## 3. Results

### 3.1. Participants

There were no significant differences in age, sex distribution, or follow-up interval between patients and controls. None of the patients fulfilled clinical diagnostic criteria for dementia at baseline. Longitudinal assessment of cognitive function revealed decreases in cognitive test performance in PD patients over time (Table 2). Moreover, 3 patients were diagnosed with PDD at the time of follow-up evaluation, according to the clinical criteria recommended by the Movement Disorder Society Task Force (Dubois et al., 2007). Excluding these patients from analysis still resulted in significant decreases in cognitive test performance over time in nondemented patients (Supplementary Table 1).

### 3.2. Longitudinal changes in spectral power

Overall changes in spectral power over time can be appreciated from 2 line charts showing global relative spectral power density averaged over all channels for controls



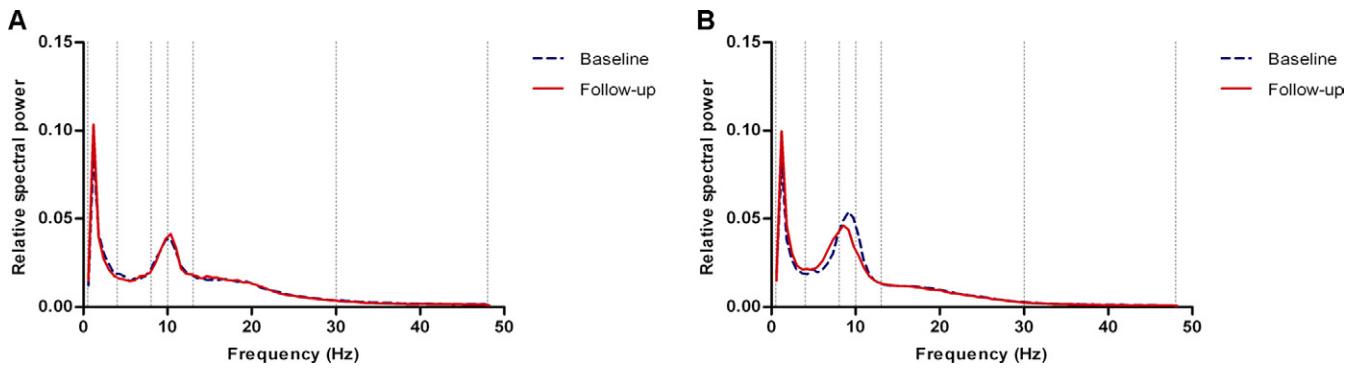


Fig. 1. Baseline and follow-up frequency spectra for controls (A) and Parkinson's disease (PD) patients (B). Grid lines mark the different frequency bands.

and PD patients respectively (Fig. 1A and B). GLM analysis for repeated measures showed a time  $\times$  group interaction effect [ $F(1,60) = 4.51$ ;  $p = 0.038$ ;  $\eta_p^2 = 0.070$ ]. Post hoc analyses revealed that control subjects demonstrated a remarkably constant frequency spectrum over time with no change of the dominant peak frequency [ $F(1,13) = 0.64$ ;  $p = 0.440$ ;  $\eta_p^2 = 0.047$ ]. In contrast, PD patients showed a slowing of the dominant peak frequency over time [ $F(1,48) = 14.6$ ;  $p < 0.001$ ;  $\eta_p^2 = 0.234$ ].

GLM analysis for repeated measures showed a time  $\times$  group interaction effect for theta [ $F(1,61) = 4.32$ ;  $p = 0.042$ ;  $\eta_p^2 = 0.066$ ], alpha1 [ $F(1,60) = 11.3$ ;  $p = 0.010$ ;  $\eta_p^2 = 0.105$ ], and alpha2 [ $F(1,60) = 5.91$ ;  $p = 0.018$ ;

$\eta_p^2 = 0.090$ ] frequency bands. Post hoc analyses within subject groups revealed no changes over time in control subjects, whereas PD patients showed an increase in mean theta power [ $F(1,48) = 8.75$ ;  $p = 0.005$ ;  $\eta_p^2 = 0.154$ ], as well as a decrease in mean alpha1 [ $F(1,47) = 24.9$ ;  $p < 0.001$ ;  $\eta_p^2 = 0.346$ ] and alpha2 [ $F(1,48) = 6.32$ ;  $p = 0.015$ ;  $\eta_p^2 = 0.116$ ] power. Exploratory analyses revealed an increase in theta power for bilateral parietal, bilateral occipital, bilateral temporal, and left central ROIs over time (Fig. 2). Alpha1 and alpha2 frequency bands displayed decreases in power over time: all ROIs for alpha1, and bilateral central, bilateral parietal, and right temporal ROIs for alpha2 (Fig. 2).

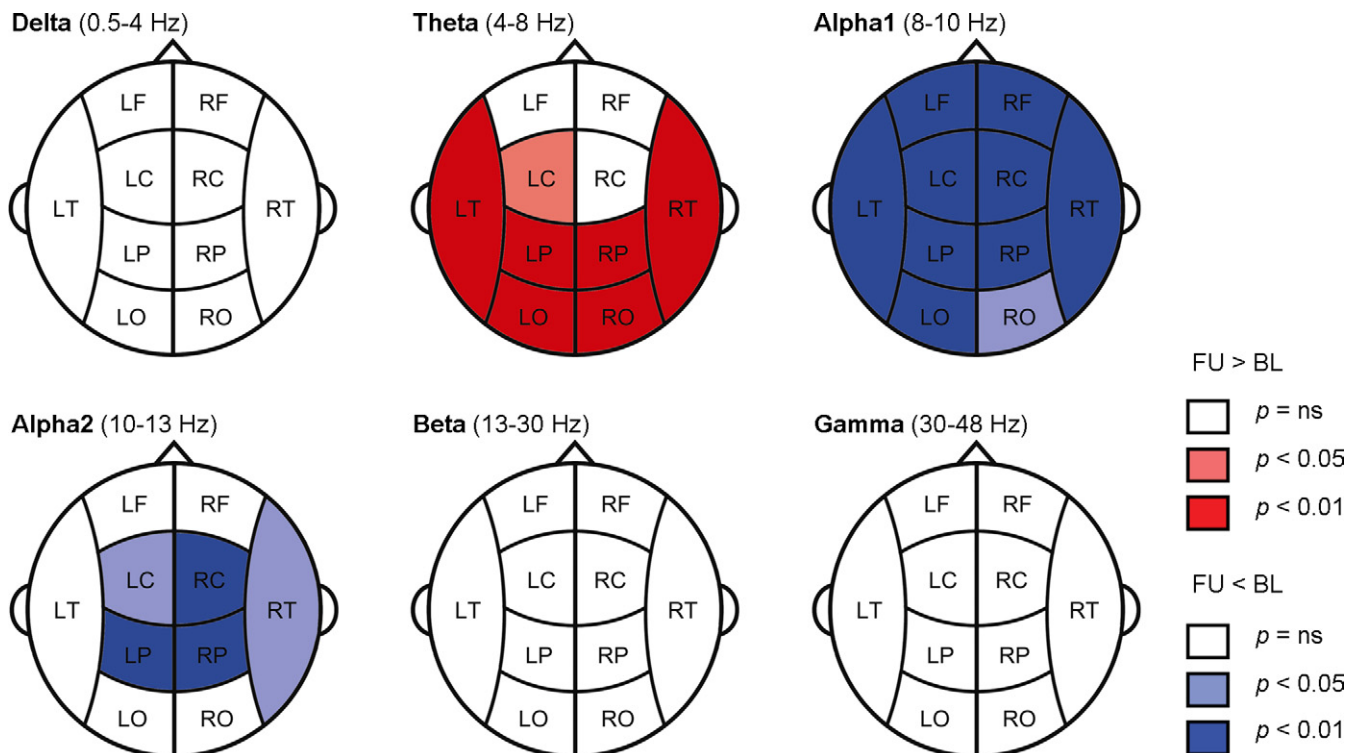


Fig. 2. Regional distribution of longitudinal power changes for Parkinson's disease (PD) patients ( $n = 49$ ) derived from post hoc analyses.

Table 3

Correlations calculated using GEE statistics between MEG spectral power and clinical measures of disease progression for each frequency band

	$\delta$	$\theta$	$\alpha 1$	$\alpha 2$	$\beta$	$\gamma$
UPDRS-III	0 (−0.145 to 0.144)	<b>0.238 *</b> <b>(0.045–0.430)</b>	−0.102 (−0.267 to 0.062)	−0.15 (−0.286 to −0.014)	−0.028 (−0.243 to 0.188)	−0.083 (−0.307 to 0.141)
LEDD	0.08 (−0.058 to 0.219)	0.042 (−0.113 to 0.197)	−0.151 (−0.301 to −0.001)	−0.033 (−0.178 to 0.112)	−0.009 (−0.183 to 0.165)	−0.039 (−0.193 to 0.114)
CAMCOG	<b>−0.267 *</b> <b>(−0.488 to −0.047)</b>	<b>−0.330 **</b> <b>(−0.485 to −0.175)</b>	<b>0.356 **</b> <b>(0.162–0.551)</b>	<b>0.269 **</b> <b>(0.110–0.428)</b>	0.226 (−0.021 to 0.472)	<b>0.220 *</b> <b>(0.015–0.425)</b>
PRM correct responses	−0.178 (−0.390 to 0.034)	<b>−0.349 **</b> <b>(−0.539 to −0.160)</b>	0.202 * (0.017–0.387)	<b>0.176 *</b> <b>(0.023–0.329)</b>	<b>0.336 **</b> <b>(0.109 to −0.563)</b>	0.191 (0.006–0.377)
Semantic fluency	−0.1 (−0.294 to 0.094)	<b>−0.297 **</b> <b>(−0.497 to −0.096)</b>	0.156 (−0.050 to 0.363)	−0.024 (−0.211 to 0.162)	0.286 (0.021–0.551)	0.1940 (0.000–0.389)
SSP span length	<b>−0.263 *</b> <b>(−0.464 to −0.062)</b>	<b>−0.215 *</b> <b>(−0.383 to −0.047)</b>	<b>0.401 **</b> <b>(0.233–0.568)</b>	0.143 (0.002–0.0285)	0.154 (−0.025 to 0.333)	0.092 (−0.129 to 0.210)
SWM between errors	0.225 (0.012–0.439)	<b>0.221 *</b> <b>(0.068–0.374)</b>	<b>−0.311 **</b> <b>(−0.501 to −0.121)</b>	−0.107 (−0.293 to 0.079)	−0.241 (−0.491 to 0.008)	−0.107 (−0.249 to 0.035)
SWM strategy	−0.02 (−0.202 to 0.162)	0.155 (−0.051 to 0.362)	−0.16 (−0.314 to −0.006)	0.05 (−0.144 to 0.244)	0.018 (−0.174 to 0.210)	0.011 (−0.099 to 0.121)
VPT redundancy	0.028 (−0.180 to 0.237)	0.137 (−0.075 to 0.349)	0 (−0.207 to 0.208)	−0.211 (−0.400 to −0.022)	−0.036 (−0.250 to 0.178)	−0.002 (−0.227 to 0.223)

Beta coefficients (with 95% confidence intervals) are standardized in order to facilitate interpretability. Significant effects are displayed in bold.

Key: CAMCOG, Cambridge Cognitive Examination; GEE, Generalized Estimated Equations; LEDD, levodopa equivalent daily dose; MEG, magnetoencephalography; PRM, Pattern Recognition Memory; SSP, Spatial Span; SWM, Spatial Working Memory; UPDRS-III, Unified Parkinson's Disease Rating Scale motor ratings; VPT, Vienna Perseveration Test.

\*  $p < 0.05$  (Bonferroni adjusted  $p$  values for groups of related outcome variables).\*\*  $p < 0.01$  (Bonferroni adjusted  $p$  values for groups of related outcome variables).

### 3.3. Relationship between spectral power and clinical measures of disease progression

#### 3.3.1. Motor function

GEE analysis showed higher UPDRS-III scores over time to be associated with higher mean theta power ( $\beta = 0.238$ ;  $p = 0.030$ ) (Table 3). Subsequent post hoc analyses revealed this effect to be present in all except frontal and right central ROIs (Fig. 3). No longitudinal relation between LEDD and relative power was found for any frequency band.

#### 3.3.2. Cognitive function

**3.3.2.1. Global cognitive function.** GEE analysis revealed a longitudinal association between mean relative power and CAMCOG scores for all except beta frequency bands: lower CAMCOG scores were associated with higher delta ( $\beta = -0.267$ ;  $p = 0.017$ ) and theta ( $\beta = -0.330$ ;  $p < 0.001$ ) power as well as lower alpha1 ( $\beta = 0.356$ ;  $p < 0.001$ ), alpha2 ( $\beta = 0.269$ ;  $p = 0.001$ ), and gamma ( $\beta = 0.220$ ;  $p = 0.035$ ) power (Table 3). Post hoc results with regard to regional distribution patterns revealed these effects to be widespread (Fig. 4): all but frontal and left temporal ROIs for delta, all ROIs for theta and alpha1, and all but frontal ROIs for alpha2 frequency band. Gamma band effects were limited to bilateral occipital and right temporal ROIs.

**3.3.2.2. Temporal cognitive function.** A longitudinal association between spectral power and PRM task performance was found for theta ( $\beta = -0.349$ ;  $p < 0.001$ ), alpha2 ( $\beta = 0.176$ ;  $p = 0.048$ ), and beta ( $\beta = 0.336$ ;  $p = 0.008$ ) frequency bands (Table 3). A worsening in test performance was associated

with higher theta as well as lower alpha2 and beta power. Impaired semantic fluency was associated with higher theta relative power ( $\beta = -0.297$ ;  $p = 0.008$ ). For both tasks, post hoc results with regard to regional patterns revealed diffuse rather than regional effects (Supplementary Figs. 1 and 2).

**3.3.2.3. Frontal cognitive function.** For the SSP task, lower span length was related to higher delta ( $\beta = -0.263$ ;  $p = 0.040$ ) and theta ( $\beta = -0.215$ ;  $p = 0.048$ ) power, as well as lower alpha1 ( $\beta = 0.401$ ;  $p < 0.001$ ) power. For SWM, task outcome was associated with changes in theta ( $\beta = 0.221$ ;  $p = 0.020$ ) and alpha1 ( $\beta = -0.311$ ;  $p = 0.005$ ) power (errors only) (Table 3). Here also, post hoc results with regard to regional patterns revealed diffuse rather than regional effects (Supplementary Figs. 3 and 4). No longitudinal association was found between performance on the VPT-task and spectral power.

## 4. Discussion

The present longitudinal MEG study demonstrates a slowing of the dominant peak frequency as well as an overall increase in low frequency and a decrease in high frequency relative spectral power over time in initially non-demented Parkinson's disease patients, but not in healthy controls. The degree of slowing is associated with clinical measures of disease progression, in particular cognitive decline. These results suggest that (changes in) spectral power could serve as an early marker of the pathophysiological mechanisms underlying cognitive decline in PD.

The present study validates and expands on a previous cross-sectional study involving the same participants. In

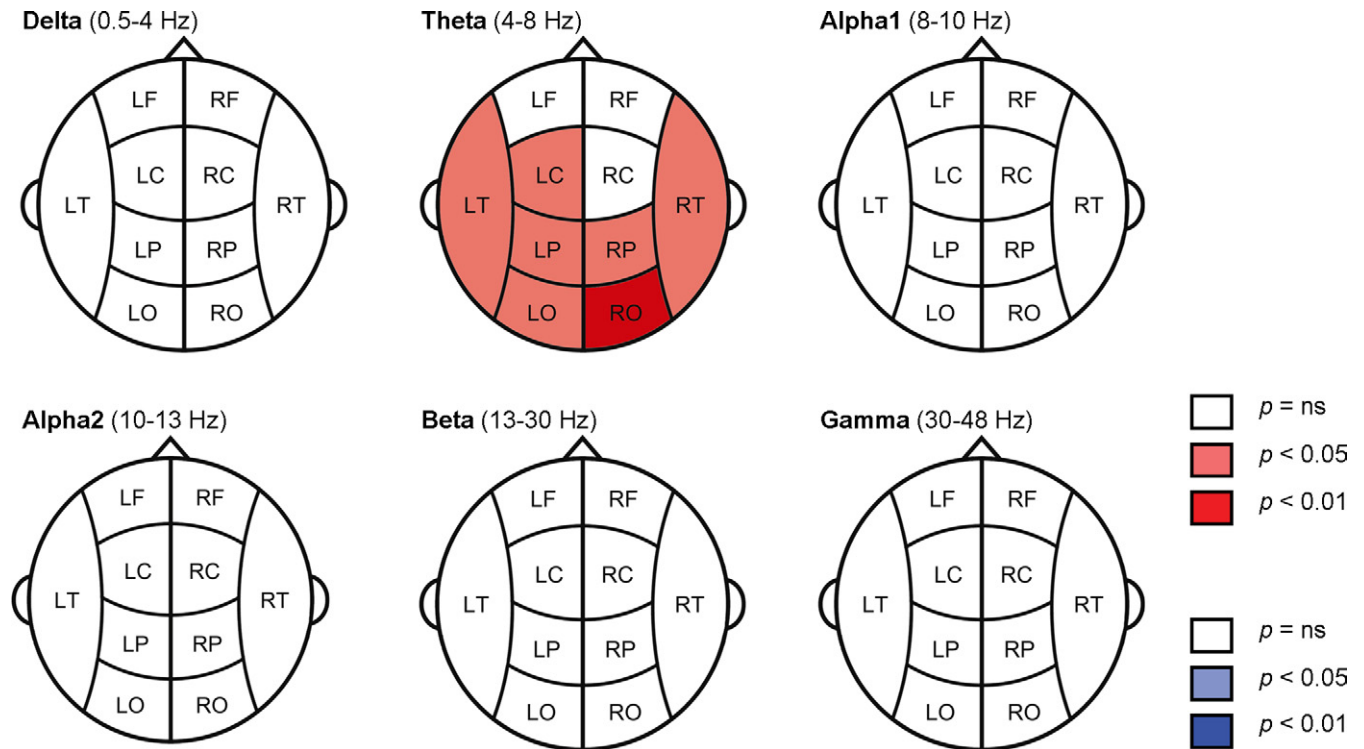


Fig. 3. Regional power distribution in longitudinal relation to Unified Parkinson's disease Rating Scale motor ratings (UPDRS-III) scores in Parkinson's disease (PD) patients ( $n = 49$ ). Positive and negative correlations are depicted in red and blue respectively. Please refer to the web version of this article to view the figure in color.

that study, we reported a widespread slowing of brain activity in de novo Parkinson patients (Stoffers et al., 2007). Our cross-sectional analyses did not show a correlation between slowing of brain activity and increasing disease duration or motor disease severity. This finding seemed to reflect a relatively stable disease effect that might even precede disease onset. This notion was strengthened by the observation that there was hardly any influence of levodopa therapy on spectral characteristics. In contrast to these cross-sectional findings, our longitudinal assessment over a 4-year period revealed that the oscillatory slowing is actually a continuous process that starts early and is gradually progressive over the course of the disease. The absence of spectral power changes in control subjects over time demonstrates that oscillatory slowing is a disease-related phenomenon and does not reflect a general aging effect. These findings underline the importance of longitudinal studies in detecting intraindividual changes in brain activity, as inter-individual variation can have a significant masking effect.

The present data reveal an association between the progression of oscillatory slowing and cognitive decline in PD patients. These findings are in line with the results of a recent study using quantitative electroencephalography (EEG) in which theta relative spectral power and background rhythm frequency were identified as predictors of PDD incidence (Klassen et al., 2011). In addition to the relation with cognitive decline, we found an association between the

progression of oscillatory slowing and motor deterioration. However, this association was limited to the theta frequency range only and far less powerful than the associations with cognitive decline. Correlations between spectral power changes and disease duration or severity have been reported previously in cross-sectional studies using EEG (Morita et al., 2009; Neufeld et al., 1994). Although the suggestion can be made that similar subcortical systems must be involved in the decline of motor and cognitive function, both phenomena could just as well result from very different mechanisms that inevitably correlate with disease progression and thus are difficult to (statistically) separate.

The associations between performance on selective cognitive tasks and changes in spectral power were spatially rather diffuse instead of limited to the specific (i.e., temporal or frontal) brain regions assumed to be involved in the cognitive function assessed. As our relative power analysis was performed using a sensor-based approach, any changes observed in specific regions of sensor space may not reflect physiological changes in the brain regions underlying the sensors but, instead, may arise from a different region. An alternative method is the use of source modeling techniques, enabling investigation of the distribution of reconstructed sources over the various cortical regions ("source space"). However, changes reported in our present study were diffusely distributed over the different ROIs and hence it is

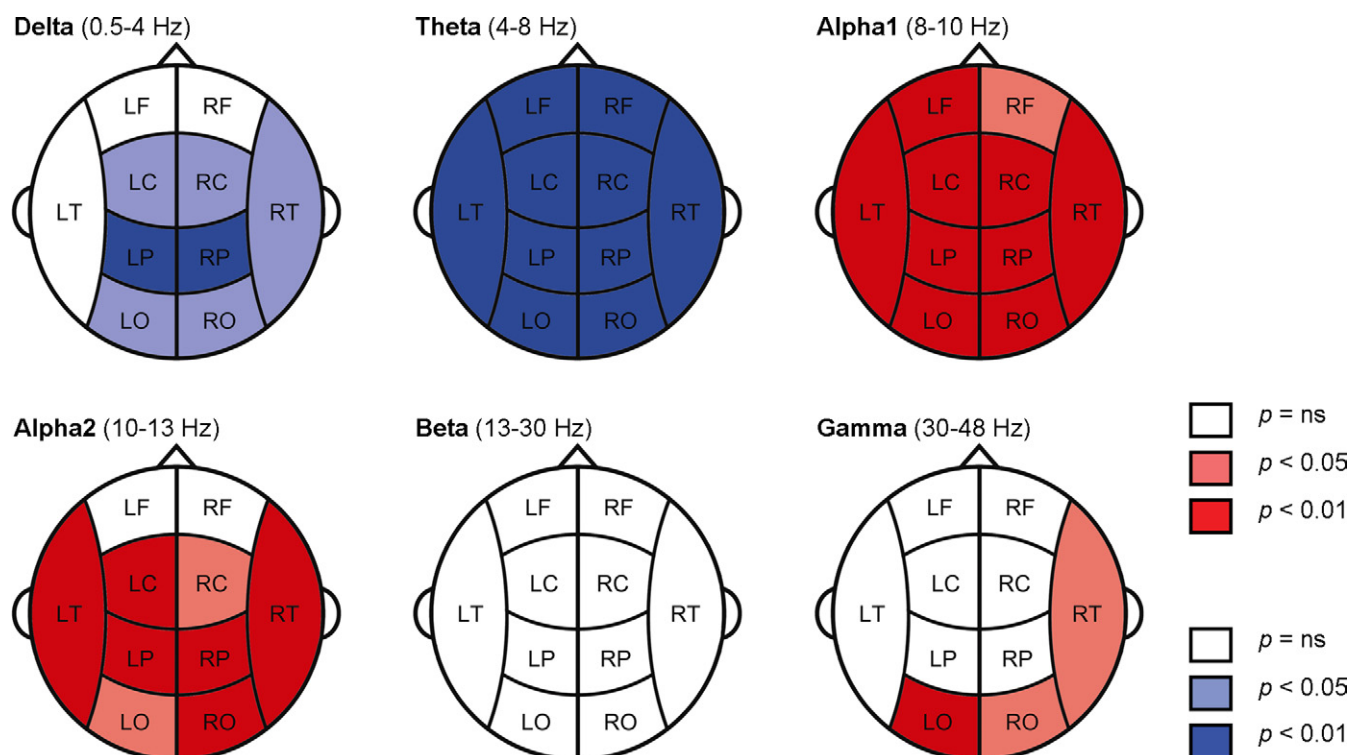


Fig. 4. Regional power distribution in longitudinal relation to Cambridge Cognitive Examination (CAMCOG) test performance in Parkinson's disease (PD) patients ( $n = 49$ ). Positive and negative correlations are depicted in red and blue respectively. Please refer to the web version of this article to view the figure in color.

unlikely that our results were significantly influenced by using sensor space rather than source space.

Although speculative in character, it is important to note that these diffuse changes also fit the pathophysiological concept of nondopaminergic ascending projection systems being affected. These ascending systems have diffuse cortical projections, in line with the widespread patterns of oscillatory changes we found. Individual contributions of noradrenergic, serotonergic, or cholinergic pathways to these effects currently remain hypothetical. An important role for a dopamine mediated pathway seems unlikely, as it was previously demonstrated that levodopa administration had little effect on spectral power distribution (Moazami-Goudarzi et al., 2008; Stoffers et al., 2007).

In the present study global cognitive task performance was associated with oscillatory changes in a broader frequency range than specific cognitive task performance. In addition, frequency bands appeared to be differentially associated with changes in frontal as opposed to temporal cognitive function. Whereas alpha power was most strongly associated with frontal cognitive performance, theta and beta power were most strongly associated with temporal cognitive performance. Although the precise circuitry defects responsible are unknown, these observations support the notion that different oscillatory rhythms may be involved in different cognitive functions (Buzsáki and Draguhn, 2004). Generated by thalamocortical circuits, al-

pha oscillations are known to play a role in a broad spectrum of cognitive functioning and attentional behavioral processes (Freunberger et al., 2011; Steriade et al., 1990). Disruption of these circuits could result in decreased relative alpha power and peak frequency slowing as found in our study, with a shift of power to the adjacent theta band. Specific involvement of beta oscillations in temporal cognitive decline is less easily explained, as the origin and function of beta oscillations are still much debated. Beta rhythmic activity may regulate both motor and cognitive performance (Engel and Fries, 2010), probably by a common (cortical) source. Interestingly, decreases in beta power have also been reported in Alzheimer's disease (AD), which might suggest involvement of the cholinergic system (de Haan et al., 2008; Fernández et al., 2006). Alternatively, disconnection of subcortical and cortical structures by local intrinsic neuropathology may explain the beta power changes in AD (Claus et al., 1998). The absence of cognition-related delta power changes in our study is most likely related to the fact that relatively few PD patients in our study population have developed dementia (yet), as delta power is closely associated with PDD (Bosboom et al., 2006; Caviness et al., 2007) but also with AD (de Haan et al., 2008; Jeong, 2004). The resemblance in neurophysiological patterns observed in these 2 types of dementia suggests that a common mechanism may underlie these changes, fitting in with a broader concept of pathological



compared with normal brain aging (Rossini et al., 2007). We postulate that disruption of (low) alpha and theta rhythmic activity is due to degeneration of ascending diffuse projection systems of attention, while beta oscillations are disturbed by intrinsic cortical pathology.

Recently, distinct cognitive phenotypes in PD were proposed to evolve differently over time (Williams-Gray et al., 2009). Frontostriatal, not more global posterior impairments, were identified as predictors of the development of dementia. Opposing this innovative concept, a study on quantitative EEG biomarkers of PDD demonstrated that frontostriatal tasks do predict dementia (Klassen et al., 2011), indicating that the literature is not conclusive on this point. Neuropathological studies have retrospectively related different amounts and progression rates of Lewy body pathology to distinct clinical subtypes of PD, suggesting that these subtypes confer different risks for the development of dementia (Halliday et al., 2011; Selikhova et al., 2009). “Old onset of disease” and “postural instability” were features associated with a high dementia risk, whereas “tremor-dominance” and “early onset of disease” were not. However, the *in vivo* relationship between specific cognitive phenotypes and the underlying neuropathological substrates remains to be established. Although highly speculative, we suggest a conceptual model in which alterations in neurophysiological parameters of brain activity, *i.e.*, dominant peak frequency and relative power distribution may reflect neuropathological changes underlying cognitive dysfunction in PD.

Although a longitudinal design as used in the present study is superior to cross-sectional designs in exploring pathophysiological concepts, some limitations need to be addressed. Firstly, several subjects were lost to follow-up, which was partly due to mortality, but also to participation withdrawal. Nevertheless, we still found medium to large effect sizes with current group sizes. As patients who withdrew from our study reported rather high subjective disease impairment (this being the reason not to participate anymore), their exclusion can only have led to an underestimation of true effects. The drop-out of more severely affected subjects could also explain our relatively low conversion rate to PDD during the current follow-up period as compared with epidemiological studies with similar time windows (Muslimović et al., 2009; Williams-Gray et al., 2007). For this reason we are presently limited in assessing the predictive value of relative power changes for the development of PDD. Secondly, in our study almost all patients had increases in dopaminergic medication dosages over time. In addition, some patients started taking cholinesterase-inhibitors during the study interval period. These alterations in medication use may have influenced oscillatory brain activity. However, our current analysis showed no association between LEDD and relative power in any frequency band. Therefore we think that the use of dopaminergic medication has not significantly influenced our findings. Moreover, in previous work no effect of an acute dopaminergic challenge

on relative power distribution was found (Moazami-Goudarzi et al., 2008; Stoffers et al., 2007). Cholinesterase inhibitors are known to affect spectral power, but were only used in a small subgroup of demented patients in our study. Moreover, effects of rivastigmine treatment in PDD as reported in literature entail increases in high frequency (*i.e.*, alpha and beta) power with simultaneous decreases in low frequency (*i.e.*, delta and theta) power, thereby partly counteracting the oscillatory slowing (Bosboom et al., 2006; Fogelson et al., 2003). We therefore believe that the use of cholinesterase inhibitors will not have distorted our main findings. Lastly, in line with our previous work, in the current study we adopted a pragmatic approach with regard to spatial locations of interest, restricting the analyses to the actually recorded signal of the MEG sensors (“sensor space”). As a consequence of this approach, the position of the subject’s head in the helmet needs to be taken into account, as differences in head position between subjects or sessions might produce different data. The absence of oscillatory changes in control subjects over time indicates there was no major confounding influence of variability in head position. In addition we registered and analyzed head coordinates during recording sessions and found no significant differences between subjects or sessions.

Our results suggest that at least a substantial subgroup of PD patients is in a transitional state between normal cognition and dementia. Further clinical follow-up of our patient cohort is necessary to identify this subgroup with concurrent assessment of possible predictors of cognitive decline and the development of PDD. Concurrent assessment of MEG functional connectivity and brain network topology would add value to the study of the pathophysiological mechanisms of cognitive decline in PD. Simultaneous use of imaging techniques with higher spatial resolution such as MRI would be of interest too, as it would allow us to combine functional and structural connectivity measures.

In summary, using a longitudinal approach we were able to demonstrate a widespread progressive slowing of brain activity in initially nondemented PD patients that was strongly related to a decline of cognitive function. As such, changes in oscillatory brain activity would seem to reflect relevant clinical phenomena and could serve as an early marker of the pathophysiological mechanisms underlying cognitive decline in PD. Further longitudinal follow-up of our PD subjects will allow us to assess whether changes in spectral power can be used as predictors of the development of dementia in PD.

### Disclosure statement

None of the authors has any biomedical financial interests or potential conflicts of interest relevant to the subject matter of this study to disclose.

Appropriate approval and procedures were used concerning human subjects by the medical ethical committee of the

VU University Medical Center (VUMC). Ethics review criteria conformed to the Helsinki declaration.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2012.02.029.

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