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MEG resting state functional connectivity in Parkinson's disease related dementia

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Abstract Parkinson's disease (PD) related dementia (PDD) develops in up to 60% of patients, but the pathophysiology is far from being elucidated. Abnormalities of resting state functional connectivity have been reported in Alzheimer's disease (AD). The present study was performed to determine whether PDD is likewise characterized by changes in resting state functional connectivity. MEG recordings were obtained in 13 demented and 13 non-demented PD patients. The synchronization likelihood (SL) was calculated within and between cortical areas in six frequency bands. Compared to non-demented PD, PDD was characterized by lower fronto-temporal SL in the alpha range, lower intertemporal SL in delta, theta and alpha1 bands as well as decreased centro-parietal gamma band synchronization. In addition, higher parieto-occipital synchronization in the alpha2 and beta bands was found in PDD. The observed changes in functional connectivity are reminiscent of changes in AD, and may reflect reduced cholinergic activity and/or loss of cortico-cortical anatomical connections in PDD.

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Introduction

Dementia develops in up to 60% of patients suffering from Parkinson's disease (PD) (Buter et al. 2008), and importantly contributes to the impairment of the quality of life and to caregiver distress. The mechanisms of PD related dementia (PDD) are still poorly understood. Although the loss of nigrostriatal and corticopetal dopaminergic (and serotonergic and noradrenergic) projection systems may contribute to the development of dementia in PD, it is generally believed that additional mechanisms must be involved, most notably degeneration of cholinergic cortical projections and/or local cortical Lewy body- and tau-pathology.

Most normal cognitive processes require dynamic coordination of activity within and between specialized brain areas (Varela et al. 2001). The way the brain accomplishes such functional coupling has received growing attention in recent years. Synchronization of oscillatory neuronal activity within as well as between brain regions is thought to be a possible mechanism, which can be studied by measuring statistical interdependencies between oscillating neurophysiological signals (Pereda et al. 2005). Using this approach, non invasive neurophysiological studies have demonstrated that synchronization of neuronal activity is associated with a variety of cognitive processes, for example, working memory and processing of stimuli (For reviews see (Uhlhaas and Singer 2006; Schnitzler and Gross 2005; Fries 2005; Stam et al. 2005)).

Patterns of functional connectivity can also be studied in the resting state and may be relevant to our understanding of neurodegenerative disorders (Buckner and Vincent 2007). Changes in resting state functional connectivity have been demonstrated using EEG and MEG in several brain disorders, including multiple sclerosis (Cover et al. 2006), brain duct tumors (Bartolomei et al. 2006), Mild Cognitive Impairment (MCI) (Babiloni et al. 2006; Pijnenburg et al. 2004; Stam et al. 2003) and Alzheimer's disease (AD) (Stam et al. 2002, 2006; Koenig et al. 2005; Pijnenburg et al. 2004; Babiloni et al. 2004; Berendse et al. 2000; Locatelli et al. 1998; Besthorn et al. 1994; Leuchter et al. 1992).

Changes in functional connectivity have also been reported in non-demented PD patients at several different stages of disease. Using MEG and a general measure of synchronization, the synchronization likelihood (SL) (Stam and van Dijk 2002), in early stage, untreated PD patients, we recently demonstrated increased synchronization for both local and long distance connections in the alpha1 frequency range compared to healthy controls (Stoffers et al. 2008). In advanced, but non-demented PD patients, higher levels of cortico-cortical synchronization in the 10–35 Hz frequency range were correlated with more severe parkinsonism and could be attenuated by treatment with levodopa or deep brain stimulation of the subthalamic nucleus, in parallel with clinical motor improvement, suggesting an association between increased synchronization and impaired motor function (Silberstein et al. 2005). Several other studies also suggest that increased (mainly beta) synchronization in basal ganglia-thalamo-cortical circuits may play an essential pathophysiological role in the development of motor symptoms in PD (For review see (Hammond et al. 2007)).

To date, studies of functional coupling in patients with PD related dementia are not available, and it is therefore fully unknown whether dementia in PD is also characterized by changes in synchronization and if so, whether these changes consist of a progression of changes already present in early stage PD (without dementia) or whether the pattern is more like the changes described in AD.

Recently, using power spectral analysis of MEG data, we found a qualitatively different pattern of slowing of background activity in demented compared to non-demented patients (Bosboom et al. 2006). Whereas in PD without dementia an increase in theta and a decrease of beta power were found compared to healthy controls, in PDD an additional increase of delta relative power and a decrease of alpha band power could be demonstrated relative to the non-demented patients. This raises the question whether changes in resting state functional connectivity in demented PD patients, if present, likewise exhibit a qualitatively different pattern from that observed in non-demented patients, suggesting the involvement of different or at least additional pathophysiological mechanisms.

The aim of this study was to analyze resting state cortico-cortical functional connectivity in non-demented and demented PD patients using the SL as a general measure of synchronization.

Our research questions were:

1. Is PD related dementia characterized by changes in resting state functional connectivity compared to PD without dementia?
2. Do the changes in functional connectivity in PDD, if present, reflect a progression of the changes observed in non-demented PD patients or is the pattern similar to the changes recently reported for AD?

Materials and methods

Subjects

Two groups of subjects were studied: PD patients with dementia (PDD; $N = 13$; 8♂/5♀) and PD patients without dementia (PD; $N = 13$; 6♂/7♀). All PD patients underwent a full physical and neurological examination, and fulfilled the UK Parkinson's Disease Society Brain Bank (UK-PDSBB) clinical diagnostic criteria for probable Parkinson's disease (Gibb 1988). Demented PD patients additionally fulfilled DSM-IV-criteria (American Psychiatric Association 1994) for dementia and had a Mini Mental State Examination (MMSE) score (Folstein et al. 1975) of 24 or lower out of a maximum of 30 points, with lower scores indicating worse cognition. Blood examination and MR-imaging were performed to exclude other potential causes of dementia. Non-demented PD patients did not experience difficulties with cognitive functioning in daily life and did not display any signs of dementia on clinical as well as neuropsychological examination. Disease stage and severity were assessed using the (modified) Hoehn and Yahr scale (H&Y; range 0–5 with higher scores indicating more advanced disease stage) (Jankovic et al. 1990), and the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS; range 0–108 with higher scores indicating worse motor functioning) (Fahn et al. 1987), respectively. Exclusion criteria for PD patients consisted of stereotactic surgery in the past and the use of anticholinergics, neuroleptics or cholinesterase inhibitors.

All patients were treated with a combination of levodopa and a decarboxylase inhibitor. Eight demented patients and nine non-demented patients were also treated with a dopamine agonist.

The study protocol was approved by the medical ethical committee of the VU University Medical Center. After

careful explanation of the procedures, all subjects gave written informed consent prior to participating.

MEG-procedures

MEG data were acquired using a 151-channel whole-head MEG system (CTF Systems Inc., Port Coquitlam, BC, Canada), with patients seated in a magnetically shielded room (Vacuum-schmelze GmbH, Hanau, Germany). All MEG recordings were acquired in the morning. Patients were asked to come to the hospital without taking their first morning dose of dopaminergic medication (practically defined "OFF"). MEG registration took place in this OFF-state in a no task, eyes closed, resting state condition. At the beginning and end of the measurement, head position was recorded by leading small currents through three position coils situated at the left and right pre-auricular points and the nasion.

The recording pass band was 0–125 Hz with a sample rate of 312.5 Hz. A third-order software gradient was applied. Two approximately 13-s-long artifact free epochs (sample rate 312.5 Hz; 4,096 samples) were selected for further analysis. Epoch selection was always done by the same investigator (J.L.W.B.), who was blinded for group membership. MEG recordings were filtered offline with a band pass of 0.5–48 Hz.

Synchronization likelihood

A technical description of SL can be found elsewhere (Montez et al. 2006; Stam and van Dijk 2002) and is summarized briefly here. We assume two dynamic systems, for instance, neural networks designated X and Y. From both systems, time series x_i and y_i, for instance, using EEG or MEG signals, are recorded. The general problem is to infer functional interactions between X and Y from x_i and y_i. Usually it is assumed that the more x_i and y_i "resemble" each other, the stronger X and Y interact. This "resemblance" can be quantified, for instance, by the cross-correlation. When this is done as a function of frequency, the coherence is determined, which is the most commonly used tool for this purpose. However, it has been shown that X and Y can interact even when x_i and y_i do not "resemble" each other in a simple way. This more general concept, called *generalized synchronization,* implies that the state of Y is a function of the state of X. The SL is a way to quantify this "generalized synchronization". Recently it has been shown that the parameters lag (L) and embedding dimension (m) should take into account the low and high frequency filter settings rather than using fixed values of these parameters (Montez et al. 2006). Therefore, in the present study the choice of L and m was based explicitly on the frequency content of the data, which resulted in the following L and m: delta: $L = 20$, $m = 20$; theta: $L = 10$, $m = 9$; alpha1: $L = 8$, $m = 6$; alpha2: $L = 6$, $m = 6$; beta: $L = 3$, $m = 9$; gamma: $L = 2$, $m = 6$; P_{ref} was set at 0.01 for all frequency bands.

The SL was computed for the two 13-s-epochs in the following frequency bands: 0.5–4 Hz (delta), 4–8 Hz (theta), 8–10 Hz (alpha1), 10–13 Hz (alpha2), 13–30 Hz (beta) and 30–48 Hz (gamma; cut off at 48 Hz to exclude the line artifact of 50 Hz). For each frequency band, average SL was calculated within and between a number of regions of interest (ROI) corresponding to the major cortical areas (frontal, central, temporal, parietal and occipital) on the left and right side. The midline channels (Z; $N = 9$) were left out of this clustering and one channel was not available for analysis due to technical problems, leaving a total of 141 MEG channels to be analyzed. A schematic distribution of these ROIs and SL measures is shown in Fig. 1. Short distance (local) functional connectivity was calculated by averaging the SL values of all possible sensor pairs within each ROI. Long distance connectivity was calculated by averaging the SL values of all possible sensor combinations between two ROIs. Long distance functional connectivity measures included eight intrahemispheric SL parameters (four for each hemisphere, Fig. 1c) and five interhemispheric SL parameters (Fig. 1d).

Finally, for each of the SL measures, the results of the two epochs were averaged for each subject.

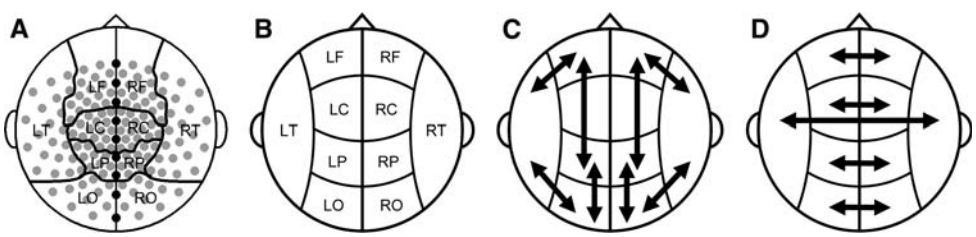

Fig. 1 **a** Schematic representation of the distribution of individual MEG sensors. **b** Schematic representation of the major cortical areas after clustering of MEG sensors. **c** Interhemispheric connections studied with SL: interfrontal, intercentral, intertemporal, interparietal and interoccipital. **d** Intrahemispheric connections studied with SL: frontotemporal, frontoparietal, temporo-occipital and parieto-occipital, in both hemispheres

Statistical analysis

Demographics

Differences between groups in the distribution of gender and (modified) Hoehn and Yahr scores were analyzed by means of Chi-square tests. Student's *t* tests were used to analyze differences between the groups in age, disease duration and UPDRS motor scores.

Synchronization likelihood

To increase statistical power, we attempted to normalize SL parameters by means of a transformation that is commonly used when trying to normalize relative spectral power (Gasser et al. 1982), a neurophysiological variable that also varies between 0 and 1; log10[x/(1 − x)]. Unfortunately, several parameters could not be sufficiently normalized by means of this transformation to pass Kolmogorov–Smirnov tests of normality. However, the linear regression technique we used for post hoc analyses of SL in the current study is rather robust when it comes to violations of the assumption of normality as long as there are (roughly) more than ten observations and no substantial non-normality that leads to outliers in the X–Y data. In that case, skewed distributions, light-tailedness as well as heavy-tailedness have little effect on linear regression statistics. As our smallest group still contains 13 observations per parameter, and SL does not result in extreme outliers, we chose, in the interest of uniformity, to report parametric analyses of log-transformed SL values only.

For each frequency band, three separate ANOVA's with repeated-measures were performed, using Greenhouse–Geisser corrected *P*-values when appropriate. For short distance synchronization, the repeated-measures factor had ten levels (left and right frontal, central, temporal, parietal and occipital SL); for long distance intrahemispheric synchronization, the repeated-measures factor had eight levels (left and right fronto-temporal, fronto-parietal, parieto-occipital and temporo-occipital SL); for long distance interhemispheric synchronization, the repeated-measures factor had five levels (interfrontal, intercentral, intertemporal, interparietal and interoccipital SL). The between-subjects factor had two levels (non-demented PD and demented PD).

In case of a significant main effect of group or an interaction effect of group with the repeated measure, subsequent post hoc analyses with regard to differences in SL between non-demented PD patients and demented PD patients were performed by means of linear regression using each of the SL measures as dependent and group membership (effect of dementia) as determinant.

Correlation with clinical parameters

To study the correlation of SL values with clinical parameters of motor (UPDRS) and cognitive (MMSE) function, three separate univariate analyses of variance with repeated-measures were performed: one with the UPDRS OFF in the PD group, one with the UPDRS OFF in the PDD group, and finally, one with the MMSE in the PDD group as independent variable, all three analyses with SL as dependent variable. In case of a significant main effect of the UPDRS or MMSE or an interaction effect with SL, post hoc linear regression analyses were conducted.

Partial eta squared (η^2) was calculated when performing ANOVA with repeated-measures. Coefficients for relevant determinants when performing regression analysis were standardized and subsequently squared (β^2). Both η^2 as well as β^2 represent the proportion of the total variability in the dependent variable (SL) that is accounted for by the relevant determinant and, throughout the paper, are expressed as a percentage of the total variance.

All analyses were performed at a significance level of 5% (two-tailed) using the SPSS 15.0.0 software package (SPSS inc., Chicago, IL, USA).

Results

Subject characteristics

In Table 1, the general characteristics of the study groups are listed. Demented patients had a mean MMSE score of 20.9 ± 3.3. Age was not significantly different between demented and non-demented patients (74.4 ± 4.9 and 71.7 ± 5.1 years, respectively; $P = 0.180$). Demented patients had significantly higher UPDRS OFF-motor scores

Table 1 Patient characteristics

	PDD (SD)	PD (SD)	Statistic	*P*
Sex (♂/♀)	8/5	6/7	$\chi^2 = 0.619$	0.431
Age (years)	74.4 (4.9)	71.7 (5.1)	$t = -1.380$	0.180
Disease duration (years)	11.2 (4.0)	9.7 (4.5)	$t = -0.923$	0.365
MMSE (0–30)	20.9 (3.3)			
UPDRS III OFF (0–108)	23.9 (5.6)	16.2 (3.4)	$t = -4.266$	0.000
H&Y stage OFF (2/2.5/3/4)	0/5/7/1	4/6/3/0	$\chi^2 = 6.691$	0.082

PDD Parkinson's disease patients with disease related dementia, *PD* Parkinson's disease patients without disease related dementia, *H&Y* Hoehn and Yahr, *UPDRS* Unified Parkinson's Disease Rating Scale, *MMSE* Mini Mental State Examination

compared to non-demented PD patients (23.9 ± 6 and 16.2 ± 3, respectively; $P < 0.001$).

Synchronization likelihood

Mean SL values as well as the values after logarithmic transformation are displayed in Table 2. Significant differences between the study groups are graphically represented in Fig. 2 and are discussed below.

In the delta band, a significant result for the interaction between group and long distance, interhemispheric SL was found ($P = 0.021$; $\eta^2 = 13\%$). Post hoc linear regression showed that demented patients had significantly lower intertemporal synchronization compared to the non-demented group ($P < 0.001$; $\beta^2 = 43\%$; Fig. 2). There were no significant main or interaction effects for long distance intrahemispheric or short distance regional synchronization.

Likewise, in the theta band, a significant interaction effect was found between group and interhemispheric SL ($P = 0.044$; $\eta^2 = 11\%$). As for the delta band, linear regression demonstrated lower synchronization between temporal regions in PDD compared to PD ($P < 0.001$; $\beta^2 = 42\%$; Fig. 2). For intrahemispheric and regional SL, no significant main group or interaction effects were found.

In the alpha1 band, a significant main group effect was found for long distance intrahemispheric synchronization ($P = 0.041$; $\eta^2 = 16\%$). Post hoc linear regression showed lower fronto-temporal SL values in demented patients in both hemispheres ($P = 0.001$; $\beta^2 = 37\%$ and $P = 0.016$; $\beta^2 = 22\%$) as well as lower fronto-parietal SL values on the left side ($P = 0.046$; $\beta^2 = 16\%$; Fig. 2).

Furthermore, the interaction effect between group and long distance interhemispheric synchronization also reached significance ($P = 0.005$; $\eta^2 = 16\%$). Comparable to the delta and theta bands, post hoc regression analysis showed lower intertemporal SL in demented patients ($P < 0.001$; $\beta^2 = 41\%$; Fig. 2).

A significant interaction effect between group and intrahemispheric SL was found in the alpha2 frequency band ($P = 0.002$; $\eta^2 = 18\%$). In the post hoc analysis, significantly lower right and left fronto-temporal SL was found in demented patients ($P = 0.004$; $\beta^2 = 29\%$ and $P = 0.012$; $\beta^2 = 23\%$, respectively), as well as higher left parieto-occipital SL ($P = 0.046$; $\beta^2 = 16\%$; Fig. 2). For interhemispheric and regional synchronization, no significant results were found.

In the beta band, a significant interaction effect was found between group and both intrahemispheric ($P = 0.006$; $\eta^2 = 16\%$) and interhemispheric synchronization ($P = 0.023$; $\eta^2 = 12\%$). In the post hoc analysis of intrahemispheric SL, demented patients displayed lower right fronto-temporal synchronization ($P = 0.031$; $\beta^2 = 18\%$) together with higher left temporo-occipital ($P = 0.040$; $\beta^2 = 16\%$) as well as parieto-occipital synchronization ($P = 0.021$; $\beta^2 = 20\%$). Post hoc analysis did not show any differences for individual interhemispheric measures. Short distance effects could not be demonstrated (Fig. 2).

Lastly, in the gamma band, a significant interaction effect between group and interhemispheric as well as regional SL was found ($P = 0.036$; $\eta^2 = 12\%$ and $P = 0.024$; $\eta^2 = 12\%$, respectively). Post hoc regression analysis revealed lower interparietal SL in demented patients ($P = 0.005$; $\beta^2 = 28\%$) together with lower SL in left ($P = 0.006$; $\beta^2 = 28\%$) and right parietal ($P = 0.001$; $\beta^2 = 37\%$) as well as left central ($P = 0.018$; $\beta^2 = 21\%$) local synchronization (Fig. 2).

Correlations with clinical parameters

MMSE

In demented patients, the only significant result in the ANOVA with repeated-measures was found for the main effect of MMSE for intrahemispheric SL in the delta band ($P = 0.040$; $\eta^2 = 33\%$). Post hoc linear regression showed that for right parieto-occipital and temporo-occipital SL, lower MMSE scores (meaning worse cognition) correlated with higher synchronization ($P = 0.018$; $\beta^2 = 41\%$ and $P = 0.042$; $\beta^2 = 32\%$, respectively).

UPDRS

No significant correlations were found in any of the frequency bands between UPDRS OFF-motor scores and SL parameters in demented or non-demented PD patients in the ANOVA with repeated-measures.

Discussion

To our knowledge, this is the first MEG study comparing resting state functional connectivity between demented and non-demented PD patients. Our main findings are a reduction in long distance intrahemispheric, predominantly bilateral fronto-temporal synchronization in the alpha1 and alpha2 bands in demented patients together with a reduction in intertemporal synchronization in the 0.5–10 Hz frequency range. In addition, local and interhemispheric gamma band synchronization in centro-parietal regions is lower in demented PD patients, whereas left sided parieto-occipital synchronization in the alpha2 and beta band is higher in the demented patients.

Changes in functional connectivity have been reported in non-demented PD patients in several stages of disease.

Table 2 Group SL-values before and after logarithmic transformation

DELTA

Regional SL

	F	p
Main group effect	3.667	0.067
Interaction effect	2.046	0.083

		PDD		PD		
		SL	log	SL	log	p
left	**C**	0.189	-0.64	0.179	-0.67	
	F	0.202	-0.61	0.175	-0.68	
	O	0.181	-0.66	0.173	-0.69	
	P	0.277	-0.42	0.247	-0.49	
	T	0.114	-0.89	0.122	-0.86	
right	**C**	0.184	-0.66	0.161	-0.72	
	F	0.188	-0.64	0.163	-0.71	
	O	0.197	-0.62	0.190	-0.64	
	P	0.280	-0.42	0.233	-0.52	
	T	0.111	-0.91	0.119	-0.87	

Intrahemispheric SL

	F	p
Main group effect	0.988	0.330
Interaction effect	2.169	0.068

		PDD		PD		
		SL	log	SL	log	p
left	**FP**	0.025	-1.60	0.027	-1.57	
	FT	0.048	-1.31	0.045	-1.34	
	PO	0.053	-1.28	0.040	-1.39	
	TO	0.043	-1.35	0.041	-1.39	
right	**FP**	0.027	-1.57	0.029	-1.55	
	FT	0.042	-1.37	0.040	-1.39	
	PO	0.052	-1.30	0.035	-1.45	
	TO	0.043	-1.37	0.045	-1.35	

Interhemispheric SL

	F	p
Main group effect	0.821	0.374
Interaction effect	3.444	***0.021***

	PDD		PD		
	SL	log	SL	log	p
inter C	0.061	-1.22	0.052	-1.28	
inter F	0.078	-1.10	0.082	-1.07	
inter O	0.076	-1.13	0.079	-1.10	
inter P	0.063	-1.23	0.050	-1.30	
inter T	**0.039**	**-1.41**	**0.064**	**-1.18**	**0.000**

THETA

Regional SL

	F	p
Main group effect	1.005	0.326
Interaction effect	1.691	0.148

		PDD		PD		
		SL	log	SL	log	p
left	**C**	0.147	-0.77	0.142	-0.79	
	F	0.156	-0.74	0.148	-0.77	
	O	0.162	-0.72	0.151	-0.75	
	P	0.237	-0.52	0.221	-0.55	
	T	0.087	-1.02	0.098	-0.97	
right	**C**	0.144	-0.78	0.131	-0.82	
	F	0.153	-0.75	0.140	-0.79	
	O	0.177	-0.67	0.165	-0.71	
	P	0.241	-0.51	0.219	-0.55	
	T	0.090	-1.01	0.098	-0.97	

Intrahemispheric SL

	F	p
Main group effect	0.237	0.631
Interaction effect	0.776	0.518

		PDD		PD		
		SL	log	SL	log	p
left	**FP**	0.015	-1.83	0.016	-1.79	
	FT	0.023	-1.63	0.027	-1.57	
	PO	0.032	-1.52	0.031	-1.52	
	TO	0.025	-1.61	0.023	-1.62	
right	**FP**	0.016	-1.78	0.016	-1.78	
	FT	0.024	-1.64	0.026	-1.57	
	PO	0.035	-1.48	0.031	-1.50	
	TO	0.027	-1.57	0.026	-1.58	

Interhemispheric SL

	F	p
Main group effect	0.371	0.548
Interaction effect	2.964	***0.044***

	PDD		PD		
	SL	log	SL	log	p
inter C	0.041	-1.39	0.034	-1.47	
inter F	0.054	-1.28	0.048	-1.31	
inter O	0.062	-1.21	0.053	-1.29	
inter P	0.040	-1.42	0.033	-1.50	
inter T	**0.019**	**-1.73**	**0.026**	**-1.58**	**0.000**

ALPHA1

Regional SL

	F	p
Main group effect	1.566	0.223
Interaction effect	2.181	0.063

		PDD		PD		
		SL	log	SL	log	p
left	**C**	0.131	-0.82	0.147	-0.79	
	F	0.146	-0.77	0.156	-0.76	
	O	0.159	-0.72	0.162	-0.75	
	P	0.220	-0.55	0.237	-0.58	
	T	0.088	-1.01	0.087	-0.94	
right	**C**	0.130	-0.83	0.144	-0.81	
	F	0.137	-0.80	0.153	-0.79	
	O	0.169	-0.69	0.177	-0.71	
	P	0.217	-0.56	0.241	-0.54	
	T	0.089	-1.01	0.090	-0.94	

Intrahemispheric SL

	F	p
Main group effect	4.673	***0.041***
Interaction effect	1.571	0.179

		PDD		PD		
		SL	log	SL	log	p
left	**FP**	**0.022**	**-1.65**	**0.015**	**-1.58**	**0.046**
	FT	**0.029**	**-1.53**	**0.023**	**-1.43**	**0.016**
	PO	0.038	-1.43	0.032	-1.42	
	TO	0.031	-1.50	0.025	-1.47	
right	**FP**	0.024	-1.62	0.016	-1.58	
	FT	**0.029**	**-1.54**	**0.024**	**-1.42**	**0.001**
	PO	0.041	-1.39	0.035	-1.39	
	TO	0.032	-1.49	0.027	-1.44	

Interhemispheric SL

	F	p
Main group effect	4.662	***0.005***
Interaction effect	0.114	0.739

	PDD		PD		
	SL	log	SL	log	p
inter C	0.041	-1.38	0.041	-1.38	
inter F	0.047	-1.32	0.054	-1.33	
inter O	0.058	-1.23	0.062	-1.32	
inter P	0.045	-1.36	0.040	-1.44	
inter T	**0.025**	**-1.59**	**0.019**	**-1.47**	**0.000**

ALPHA2

Regional SL

	F	p
Main group effect	0.360	0.554
Interaction effect	2.001	***0.084***

		PDD		PD		
		SL	log	SL	log	p
left	**C**	0.121	-0.86	0.124	-0.85	
	F	0.128	-0.83	0.135	-0.81	
	O	0.155	-0.74	0.140	-0.79	
	P	0.206	-0.59	0.194	-0.62	
	T	0.085	-1.03	0.087	-1.02	
right	**C**	0.121	-0.86	0.118	-0.87	
	F	0.128	-0.84	0.130	-0.82	
	O	0.162	-0.72	0.151	-0.76	
	P	0.199	-0.61	0.188	-0.64	
	T	0.083	-1.05	0.087	-1.02	

Intrahemispheric SL

	F	p
Main group effect	0.230	0.636
Interaction effect	5.122	***0.002***

		PDD		PD		
		SL	log	SL	log	p
left	**FP**	0.019	-1.72	0.020	-1.70	
	FT	**0.023**	**-1.63**	**0.027**	**-1.56**	**0.012**
	PO	**0.037**	**-1.44**	**0.029**	**-1.54**	**0.046**
	TO	0.029	-1.54	0.025	-1.60	
right	**FP**	0.018	-1.74	0.019	-1.71	
	FT	**0.022**	**-1.65**	**0.026**	**-1.57**	**0.004**
	PO	0.036	-1.45	0.029	-1.54	
	TO	0.027	-1.56	0.026	-1.58	

Interhemispheric SL

	F	p
Main group effect	3.203	***0.034***
Interaction effect	0.628	0.436

	PDD		PD		
	SL	log	SL	log	p
inter C	0.039	-1.40	0.033	-1.47	
inter F	0.039	-1.40	0.044	-1.35	
inter O	0.053	-1.27	0.046	-1.33	
inter P	0.041	-1.39	0.033	-1.48	
inter T	0.022	-1.66	0.025	-1.60	

BETA

Regional SL

	F	p
Main group effect	0.138	0.713
Interaction effect	1.515	0.193

		PDD		PD		
		SL	log	SL	log	p
left	**C**	0.117	-0.88	0.120	-0.87	
	F	0.126	-0.85	0.131	-0.83	
	O	0.155	-0.74	0.143	-0.78	
	P	0.207	-0.59	0.199	-0.61	
	T	0.084	-1.04	0.086	-1.03	
right	**C**	0.121	-0.86	0.120	-0.87	
	F	0.130	-0.83	0.128	-0.83	
	O	0.165	-0.71	0.155	-0.74	
	P	0.199	-0.61	0.195	-0.62	
	T	0.085	-1.03	0.088	-1.02	

Intrahemispheric SL

	F	p
Main group effect	2.380	0.136
Interaction effect	4.507	***0.006***

		PDD		PD		
		SL	log	SL	log	p
left	**FP**	0.017	-1.77	0.016	-1.78	
	FT	0.020	-1.70	0.021	-1.67	
	PO	**0.036**	**-1.45**	**0.027**	**-1.56**	**0.021**
	TO	**0.028**	**-1.56**	**0.022**	**-1.65**	**0.040**
right	**FP**	0.016	-1.80	0.016	-1.79	
	FT	**0.019**	**-1.72**	**0.022**	**-1.66**	**0.031**
	PO	0.035	-1.46	0.028	-1.56	
	TO	0.027	-1.57	0.023	-1.63	

Interhemispheric SL

	F	p
Main group effect	3.339	***0.023***
Interaction effect	0.317	0.578

	PDD		PD		
	SL	log	SL	log	p
inter C	0.040	-1.39	0.038	-1.42	
inter F	0.038	-1.41	0.043	-1.36	
inter O	0.059	-1.22	0.049	-1.31	
inter P	0.041	-1.37	0.036	-1.45	
inter T	0.019	-1.72	0.021	-1.68	

GAMMA

Regional SL

	F	p
Main group effect	0.643	0.431
Interaction effect	3.353	***0.024***

		PDD		PD		
		SL	log	SL	log	p
left	**C**	**0.088**	**-1.01**	**0.093**	**-0.99**	**0.018**
	F	0.088	-1.02	0.089	-1.01	
	O	0.128	-0.83	0.125	-0.84	
	P	**0.138**	**-0.80**	**0.146**	**-0.77**	**0.006**
	T	0.069	-1.13	0.070	-1.13	
right	**C**	0.090	-1.01	0.093	-0.99	
	F	0.092	-1.00	0.090	-1.01	
	O	0.129	-0.83	0.127	-0.84	
	P	**0.135**	**-0.81**	**0.142**	**-0.78**	**0.001**
	T	0.071	-1.12	0.070	-1.13	

Intrahemispheric SL

	F	p
Main group effect	0.744	0.397
Interaction effect	0.570	0.600

		PDD		PD		
		SL	log	SL	log	p
left	**FP**	0.015	-1.83	0.015	-1.83	
	FT	0.016	-1.79	0.016	-1.80	
	PO	0.019	-1.70	0.019	-1.71	
	TO	0.019	-1.72	0.018	-1.74	
right	**FP**	0.015	-1.82	0.015	-1.83	
	FT	0.017	-1.78	0.016	-1.80	
	PO	0.018	-1.74	0.018	-1.74	
	TO	0.018	-1.74	0.017	-1.77	

Interhemispheric SL

	F	p
Main group effect	3.249	***0.036***
Interaction effect	0.697	0.412

	PDD		PD		
	SL	log	SL	log	p
inter C	0.020	-1.69	0.023	-1.64	
inter F	0.021	-1.68	0.021	-1.67	
inter O	0.027	-1.57	0.024	-1.62	
inter P	**0.018**	**-1.73**	**0.021**	**-1.67**	**0.005**
inter T	0.015	-1.83	0.015	-1.82	

Significant differences in SL between the groups are in bold*FP* fronto-parietal, *FT* fronto-temporal, *PO* parieto-occipital, *TO* temporo-occipital, *PDD* Parkinson's disease with dementia, *PD* Parkinson's disease without dementia, *C* central, *F* frontal, *O* occipital, *P* parietal, *T* temporal

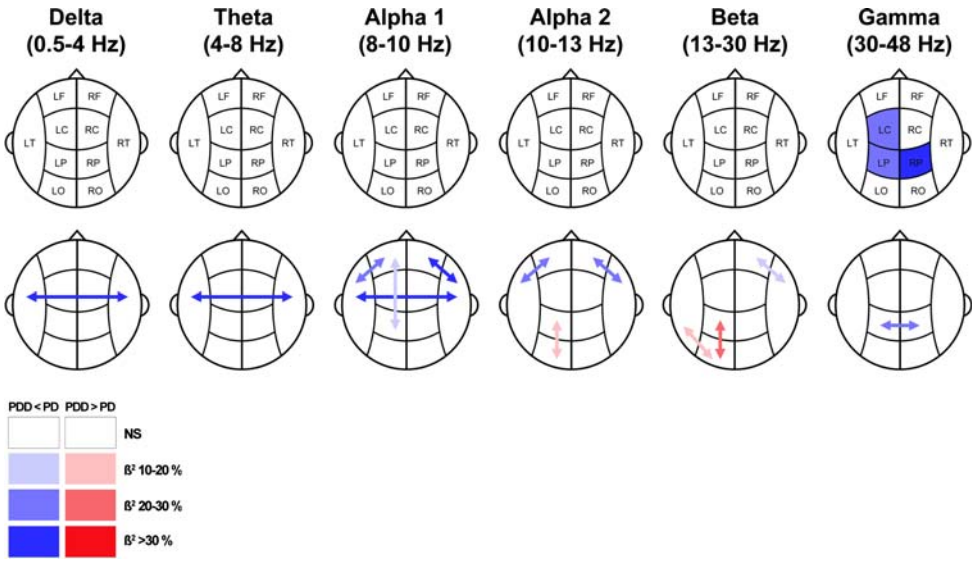

Fig. 2 Schematic representation of the differences in resting state synchronization between demented and non-demented patients. Statistically significant higher SL values in demented patients compared to non demented patients are coloured *red*, lower values *blue*. The intensity of the colours indicates the magnitude of the β squared in the post hoc linear regression (light = 10–20%; middle = 20–30%; dark $\geq$30%). Decreased fronto-temporal SL as well as increased left sided posterior synchronization is seen in the alpha and beta bands in demented patients. Intertemporal decrease of SL in demented patients is found in the 0, 5–10 Hz range. Lastly, decreased gamma band SL is demonstrated in demented patients in local and interhemispheric centro-parietal areas. *PDD* demented Parkinson's disease patients, *PD* non demented Parkinson's disease patients, *LF* left frontal, *LC* left central, *LT* left temporal, *LP* left parietal, *LO* left occipital, *RF* right frontal, *RC* right central, *RT* right temporal, *RP* right parietal, *RO* right occipital

In very early stage, untreated, non-demented patients, we recently found increased alpha1 synchronization (Stoffers et al. 2008). In moderately advanced patients, the increase in functional connectivity involved a more extended frequency range, also including the theta, alpha2 and beta bands (Stoffers et al. 2008). In advanced stage non-demented PD patients receiving deep brain stimulation, Silberstein et al. found a correlation between higher cortico-cortical coupling in the beta band and more impaired motor function (Silberstein et al. 2005).

In the present study, we report a completely different pattern of changes in demented PD patients in comparison to non-demented patients, mainly consisting of reductions in long-distance fronto-temporal and intertemporal functional connectivity as well as in short distance functional connectivity in several frequency bands.

Combining the results of the present and previous studies, there appear to be differential patterns of change in functional connectivity when comparing between groups of PD patients in different stages of disease and between PD patients and controls. It is therefore tempting to speculate that there are stage-specific patterns of change in synchronization in PD. According to the neuropathological staging system for PD (Braak et al. 2003), the earlier stages of PD are mainly characterized by degeneration of dopaminergic (and serotonergic and noradrenergic) ascending pathways. This would suggest that changes in these neurotransmitter systems might be involved in the increases of functional connectivity observed in early stage non-demented patients. Indeed, the results of the study by Silberstein seem to point to a modulatory role of dopaminomimetic treatment on cortico-cortical synchronization (Silberstein et al. 2005). The qualitatively completely different pattern of changes in dementia in PD we report in this study, however, suggests that these changes are not just related to progression of the above mentioned degeneration of neurotransmitter systems already involved in non-demented PD, but that additional mechanisms are involved.

In AD, using coherence and more recently, the SL, reductions of general synchronization as well as loss of functional connectivity in the alpha and gamma bands have been demonstrated in patients compared to healthy controls in EEG as well as MEG studies (Koenig et al. 2005; Pijnenburg et al. 2004; Stam et al. 2003, 2002, 2006; Berendse et al. 2000; Besthorn et al. 1994). In several studies, the decrease of synchronous activity was correlated with worse cognition (lower MMSE scores) (Stam et al. 2006, 2003; Locatelli et al. 1998). Interestingly, this pattern of changes reported in AD is very similar to the loss of long-distance fronto-temporal and intertemporal resting state functional connectivity we demonstrate in the present study in demented PD patients. Recently, in dementia with Lewy bodies (DLB), a disease considered to be part of the same disease spectrum as PDD, a reduction of long distance intrahemispheric functional coupling in the alpha

frequency range, as measured with coherence, has been reported in an MEG study (Franciotti et al. 2006).

Given the similarities in the pattern of reduction of synchronization in AD, DLB and PDD, common pathophysiological mechanisms may be underlying changes in these conditions. A possible common candidate accounting for the loss of synchronization could be the profound loss of cortical cholinergic projections from the basal nucleus of Meynert, since this is a characteristic of AD, DLB and PDD (Braak et al. 2003; Londos et al. 2002; Lippa et al. 1999; Cullen and Halliday 1998; Lehericy et al. 1993; Vogels et al. 1990; Candy et al. 1983). Involvement of the cholinergic system is supported by an animal study, in which lesioning of the cholinergic system resulted in a reduction of long distance intrahemispheric as well as interhemispheric coherence (Holschneider et al. 1999). Furthermore, even in young and elderly healthy subjects, a reduction in interhemispheric EEG and MEG coherence can be demonstrated after the administration of the anticholinergic drug scopolamine (Osipova et al. 2003; Kikuchi et al. 2000), which has been shown to be able to cause temporary cognitive deficits in healthy subjects (Broks et al. 1988; Sunderland et al. 1986).

In addition to a decrease of long distance intrahemispheric and interhemispheric SL, we found a loss of short range gamma synchronization in centro-parietal regions in PDD. Interestingly, in AD, loss of gamma band synchronization has also been demonstrated using MEG (Stam et al. 2002). Since cholinergic activity is often associated with a shift of the power spectrum to faster frequencies as well as with induction of coherence in the high frequency range (Varela et al. 2001), it could well be that the decrease of gamma synchronization in central and parietal areas also reflects loss of cholinergic activity.

Given the suspected pathophysiological significance of degeneration of the cholinergic system in PD related dementia, it would be extremely interesting to see whether cholinesterase inhibitors are able to (partly) reverse the changes in functional connectivity.

In addition to the cholinergic deficit, especially in relation to the decrease of long distance synchronization, other pathophysiological mechanisms may be involved. It seems obvious that loss of anatomical connections between brain areas may lead to a reduction of functional coupling. In AD, atrophy of the corpus callosum has been shown to be associated with loss of lower interhemispheric coherence (Pogarell et al. 2005). Furthermore, in multiple sclerosis, associated with widespread degeneration of the white matter, and therefore, loss of anatomical connections, a strong reduction in interhemispheric connectivity has been reported (Cover et al. 2006). Especially in demented PD patients cortical atrophy can be found, including atrophy of the temporal lobes (Tam et al. 2005; Junque et al. 2005; Camicioli et al. 2003; Burton et al. 2002). Therefore, cortical atrophy as well as pathological changes in the surviving cortex, such as Lewy body- and/or tau-pathology, may be associated with the loss of functional coupling we report in the present study.

The last observation in the present study is an increase in left posterior synchronization in demented patients in the alpha2 and beta frequency range. Interestingly, a similar posterior increase of synchronization levels has recently also been demonstrated in mildly affected AD patients (Stam et al. 2006). The similarity in these observations might suggest that these changes in functional connectivity might be associated with cognitive impairment. An alternative, but speculative explanation might be that increased synchronization constitutes a compensatory mechanism in relatively healthy networks for the loss of functional connectivity in other more damaged networks.

In the present study, we found hardly any correlation between cognition, as measured with the MMSE, and SL parameters. Several factors might explain the absence of significant correlations. First, the MMSE is a global screening tool for cognitive dysfunction. Impairments in specific cognitive domains that might possibly be related to changes in synchronization are not specifically assessed with this measure. Second, the variance of MMSE scores in our demented PD group was relatively small. Last, our study sample was relatively small, and therefore, correlations might not have reached significance because of a lack of power.

In the future, studies using more specific measures of different cognitive domains, for instance, executive dysfunction, in a larger group of PD patients are needed to further address the relationship between cognitive dysfunction and changes in functional connectivity.

Some possible limitations of our study have to be considered. First, demented patients had significantly higher UPDRS motor scores compared to the non-demented patients. Therefore, it might be argued that our results are partly related to differences in motor function between patient groups. However, for the UPDRS OFF scores, there were no significant results nor even a trend towards significance for any of the SL parameters in the ANOVA with repeated-measures in both the demented and non-demented PD group. Furthermore, previous studies have shown that impaired motor function in early as well as more advanced stage, non-demented PD patients is associated with increases in synchronization (Silberstein et al. 2005; Stoffers et al. 2008)). Since, in the present study, we mainly report significant reductions in the demented patients, it seems highly unlikely that our results can be explained by worse motor function in our demented patients. To the contrary, worse motor function in the demented PD patients might have even partly masked reductions in SL.

Second, MEG correlations between signals from nearby sensors could be due to common sources rather than true interactions. This is the well-known problem of volume conduction that may give rise to spurious correlations in sensor space. One possible solution is to estimate correlations between signals from reconstructed sources (source space) rather than the actually recorded signal (signal space) (Hadjipapas et al. 2005; David et al. 2002; Gross et al. 2001). However, no unique way exists to reconstruct the sources, and the source reconstruction algorithm used could influence the interdependencies between the sources (Hadjipapas et al. 2005). Therefore, in the present study, we used a pragmatic approach, restricting the analysis to signal space. Although volume conduction may influence SL values in this way, it seems unlikely that this can explain major group differences in SL between PDD and PD. Furthermore, the majority of our main results involve changes in long distance interactions which are less likely to be affected by volume conduction.

Conclusion

In conclusion, dementia in PD is characterized by a decrease of alpha fronto-temporal as well as low frequency intertemporal resting state functional connectivity, together with a loss of local gamma band connectivity. This pattern of changes is different from the changes in functional connectivity in non-demented PD patients but, in contrast, very similar to the abnormalities seen in AD and may reflect degeneration of the cholinergic system as well as local cortical changes, such as atrophy and Lewy body- and tau-pathology. Future studies, addressing the modulatory effects of cholinesterase inhibitors as well as dopaminergic drugs, should clarify the exact contribution of these neuropathological changes.

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