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Dynamic regulation of EEG power and coherence is lost early and globally in probable DAT

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Abstract Electroencephalographic (EEG) findings in dementia of Alzheimer type (DAT) include slowing of alpha frequency, loss of alpha band power, increased theta and delta power and reduced coherence. Here it is evaluated whether a) EEG acquisition during different functional states facilitates the detection of DAT-associated EEG changes, and b) EEG changes in mild DAT are topographically confined or global. Power spectra and coherence of EEGs from 29 patients with mild probable DAT and 28 age- and sex-matched controls were compared during three cognitive states. Group differences in power spectra and coherence were largest during resting with eyes open, yielding a 77 % correct classification result. Already in early stages of probable DAT, EEG changes were topographically wide-spread. The task-related up- and down-regulation of power and coherence was impaired already in mild probable DAT. We propose to augment clinical EEG assessment by including a quantitative analysis of the dynamic power and coherence changes from rest, eyes closed to eyes open in suspected DAT.

Key words Dementia of Alzheimer type (DAT) · EEG · Spectral power · Coherence

Introduction

The diagnosis of early dementia of the Alzheimer's Type (DAT) poses a major diagnostic challenge to clinicians and researchers. Recently, a number of non-invasive procedures were introduced that may enhance the accuracy for predicting DAT. These include nuclear magnetic resonance volumetry of the hippocampal structures (Fox et al. 1999), biochemical assays for, e. g., Chromogranin A and serum- homocysteine (Gottfries et al. 1998), SPECT measurements of brain metabolism (Julin et al. 1995), and genotyping for ApoE4 (Mayeux et al. 1998). The latter was claimed to have a predictive accuracy of 85 %. For comparison, the accuracy of clinical diagnosis at first evaluation is around 20–30 % (Mayeux et al. 1998), while NINCDS-ADRDA criteria (McKhann et al. 1984) of possible DAT have been reported to be 77 % accurate in a prospective study (Jobst et al. 1998). However, the above mentioned technical investigations are not readily available, as well as costly and demanding for the patient. A non-invasive tool for the detection of small physiological changes is the EEG. It is easy to administer and, when abnormal, may justify further investigations.

DAT is accompanied by a number of characteristic EEG changes, including an increase of slow EEG power (mainly in the 3–7 Hz or theta range) (Signorino et al. 1995) and reduced alpha and beta activity (Coben et al. 1985; Rosen et al. 1993). Changes in EEG spectral composition correlate with the clinical state (Coben et al. 1985). EEG coherence analysis focuses on the pairwise correlation of power spectra obtained from different EEG leads and is thought to gauge cooperation of the respective cortical brain areas. (However, there are other measures of neuronal cooperation, like phase coherence). Lesions of thalamo-cortical projections and the nucleus reticularis thalami (NRT) have been shown to reduce coherence more than lesions of cortico-cortical projections (Contreras and Steriade, 1997). The earliest neuropathological changes in AD are apparent in the entorhinal cortex (which maintains projections to almost all sensory and associative cortices), in neuromodulatory nuclei like the magnocellular basal forebrain nuclei and the ventral tegmental and raphe nuclei (which also maintain projections to all cortical areas), and the NRT (Braak and Braak, 1991; Braak et al. 1996). In agreement with these histopathological findings, Dunkin et al.

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(1995) reported topographically diffuse alterations of EEG coherence in many frequency bands in moderately demented patients with probable DAT, scoring an average of 17.5 points in the MMSE (Mini-Mental Status Examination) (Folstein et al. 1975).

A further consistent EEG finding in DAT patients is a reduced alpha blocking upon eyes opening (Pritchard et al. 1994; Signorino et al. 1995). This suggests that DAT-related EEG abnormalities might be more apparent in dynamic EEG examination under different cognitive states.

In the present study we compare EEG recordings of patients with mild DAT and healthy controls during three different states, each lasting 5 min: rest, eyes closed, eyes open and watching a pendulum. Although all tasks are passive, we chose these deliberately, as we had found earlier that cognitively impaired subjects may not comply with active tasks like mental arithmetic. We calculated differences in coherence and power spectra within and between groups and determined the diagnostic value across the tasks. We hypothesized that a) the choice of an appropriate functional state will facilitate the detection of EEG changes specific for DAT, and b) that there are wide spread, diffuse abnormalities in power spectra and coherence in mild probable DAT because of early involvement of diffusely projecting neuromodulatory nuclei.

Methods

Subjects

All subjects (ss) were recruited from the outpatient clinic and through a newspaper advertisement offering a memory test. Thirty-seven patients with possible DAT and 28 age- and sex-matched controls were recruited. The patients suffered from mild dementia of possible or probable DAT according to the NINCDS-ADRDA (McKhann et al. 1984) report with an MMSE score above 15 and below 25 points, which corresponds to mild cognitive impairment. Controls were required to score above 46 points in the Structured Interview for the diagnosis of Dementia of Alzheimer type, Multiinfarct dementia and other etiology (SIDAM, Zaudig et al. 1990) and above 24 points in the MMSE. Eight of the subjects with mild dementia had to be excluded due to artifact-ridden EEGs. Table 1 represents the data of the remaining participants (29 patients and 28 controls). All participants were right-handed (Questionnaire for Handedness, Bryden, 1977) above 50 years of age, without current psychopharmacological medication and without prior or current psychiatric diagnosis (other than DAT in the patients) or neurological disease, such as multiple sclerosis, brain trauma, stroke or parkinsonism.

Psychological testing for all ss included the SIDAM, which assigns diagnoses according to DSM-III-R (American Psychiatric Association 1987) and ICD–10 (World Health Organisation, WHO 1992), the MMSE, and the Geriatric Depression Scale (GDS, Yesavage et al. 1983) (a GDS score < 10 was required). The SIDAM assigns the following categories: "unimpaired" (score 47–55), "cognitive deficits" (score 33–46), and "demented" (score < 33). In comparison, a MMSE score of < 24 is considered to indicate cognitive impairment, a score < 21 signals mild, a score < 16 moderate and a score < 9 severe dementia. Ten of 29 DAT patients consented to a CCT, which showed slight cortical atrophy in 4 cases and periventricular hypodensities in 3 cases, (one patient showed both); 4 patients did not show radiological changes. Each participant gave informed written consent.

Table 1 Sample descriptors. Demographic and cognitive characteristics of patients with mild DAT and healthy controls. Unless indicated otherwise, mean, standard deviation (SD) and median are denoted. The SIDAM subscores are orientation (0–10), memory (comprising immediate reproduction, short- and long-term memory, 0–20), intellectual capacity (0–5) and higher cortical function (verbal and arithmetic abilities, visu-spatial abilities, aphasia and apraxia, each 0–20).

	Probable DAT	Controls	Mann-Whitney U-test (p)
Number of cases	29	28	
Age (years)	69.5 ± 9.5 (70)	68.0 ± 8.2 (69)	n. s.
Gender (male /female)	10/19	10/18	
MMS score	21.1 ± 5.5 (22)	29.1 ± 1.0 (29)	P<0.001
SIDAM score			
Below: SIDAM subscores	35.8 ± 10.4 (36)	51.9 ± 2.3 (53)	P<0.001
Orientation	7.0 ± 3.1 (8)	10.0 ± 0.5 (10)	P<0.001
Memory	10.4 ± 3.5 (10)	18.0 ± 2.5 (18)	P<0.001
Intellectual capacity	3.5 ± 1.7 (4)	4.9 ± 0.1 (5)	P<0.001
Higher cortical function	14.9 ± 4.1 (15)	18.8 ± 1.2 (19)	P<0.001
Duration of illness (months)	21	n/a	

EEG recording and analysis

Subjects were comfortably seated in a reclining chair in a soundproof, electrically insulated room, illuminated with white light of medium brightness. Instructions were read aloud by the technician. Prior to data acquisition, a 5 min period of resting EEG with closed eyes was observed to allow for adaptation. Then 5 min of EEG during rest with their eyes closed (RC), followed by 5 min of eyes open (RO) were recorded. Vigilance was controlled through a video circuit. With eyes open, the subjects gazed at an amber-colored wall. In a third block of EEG recording (5 min), a chaotic pendulum was placed in front of the subjects at 0.8 m distance. The pendulum measured 24 × 16 cm and was electromagnetically driven. It consisted of two large metallic spheres, connected through a metallic tube hinged in the middle. Between the hinge and the balls were fitted on either side of the axis, two smaller satellite pendulums, also consisting of an axis bearing spheres at the ends. The main pendulum swung around the middle axis, while the satellites rotated in chaotic movement. The subjects were instructed to keep their gaze on the axis of the main pendulum (PW). The purpose of the device was to keep the subjects attention engaged and the gaze fixed. EEGs were recorded using 19 electrodes placed according to the 10/20 convention at the following sites: FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2. Standard electrode positions were achieved by using the Electrocap® system (Geli-Med, Munich). The data were recorded using a Neurofile® digital EEG machine (Nihon-Kohden, Bad Homburg, Germany). Vertical and horizontal eye movement (EOG) as well as electrocardiogram (ECG) were recorded through bipolar leads and stored together with the EEG. Events were marked in a separate channel. Linked ears served as the reference. The EEG were band-pass filtered from 0.5 to 64 Hz, digitized at 1 kHz and stored at 256 samples per second. From each task, two periods of 16 s of continuous artifact-free EEG were chosen by visual inspection. The segments were taken from the center of each task. For each EEG channel the FFT was calculated, using a 2 s frame shifted in 1 s steps and applying a Hanning-window. Power spectra were calculated as absolute power (V^2) for the following bands: delta (0.5 to 3.5 Hz), theta (3.5 to 7.5 Hz), slow alpha (7.5 to 9.5 Hz), fast alpha (9.5 to 12.5 Hz), slow beta (12.5 to 19.5 Hz) and fast beta (19.5 to 29.5 Hz). Total power was calculated by summing up the EEG power within each frequency band over the EEG channels (Coben et al. 1985). Relative power, representing spectral composition of the EEG, was derived by dividing the power within each frequency band by the total power (Coben et al. 1985). Since we were interested in the topographic distribution of coherence abnormalities, coherence was calculated for immediate adjacent electrodes in an arbitrarily chosen anterior-posterior pattern, covering the skull evenly. A left-right orientation of the electrode pairs (data not shown) yielded similar results, due to apparently directionally homogenous coupling

within the brain. EEG coherence was thus calculated from pairs of electrodes following the method described by Dunkin et al. (1995). Briefly, the square of the cross-spectrum of the channels divided by the product of the power spectra of the individual channels was computed separately for each of the six frequency bands and for the following pairs of electrodes, covering the skull in 5 parallel rows running from frontal to occipital: F3-C3, C3-P3, P3-O1 (row 1), F7-T3, T3-T5 (row 2), Fz-Cz, Cz-Pz (central) and F4-C4, C4-P4, P4-O2 (row 4), F8-T4, T4-T6 (row 5), in addition, coherence was calculated for O1-O2 covering both primary visual areas. In addition to these local measures of coherence (between electrode pairs), a global measure of coherence was derived by calculating average coherence (over all electrode pairs) for each frequency band.

Statistics

All dependent variables were approximately normal distributed (Kolmogorov-Smirnov distribution test; for all variables $p>0.6$). Separate MANOVAs were run for total and relative power and coherence, respectively; then effects within each frequency band were analyzed by post hoc tests. Diagnosis, condition and electrode sites were factors and frequency band the multiple measure. In all MANOVAs contrasts were of the repeated type for condition and of the deviation type for electrode pairs and diagnosis. Significance was assumed at $p<0.05$. Degrees of freedom were corrected according to Huynh-Feldt (only corrected p values are reported, but original df). Univariate and post hoc effects are reported only when the main effect was significant. Post hoc tests were corrected following the Bonferroni method. For statistical analysis SPSSPC® Vers. 9 (SPSS Inc. Chicago, U. S. A.) was used.

Results

Absolute power

A significant effect for diagnosis was observed only in the theta band (increased in patients). Effects involving diagnosis and diagnosis*condition and the respective F-'df- and p-values are summarized in Table 2. A significant condition effect was found ($F12,210=10.36$, $p<0.001$), due to a decrease of theta power from RC to RO and PW ($F2,55=9.73$, $p<0.001$). There was a similar decrease of slow alpha ($F2,55=43.46$, $p<0.001$), fast alpha ($F2,55=42.26$, $p<0.001$) and slow beta ($F2,55=9.59$, $p<0.001$) power over the conditions. The interaction diagnosis*condition was significant ($F12,210=2.020$, $p<0.02$), due to less reduction of fast alpha, slow and fast beta power in patients as compared to controls (Fig. 1, Table 2). Analysis of the diagnosis*electrode site multivariate contrasts revealed that the effects were topographically distributed, with largest effects over fronto-temporal and central sites (all df=1,55: FP $F=5.1$, $p<0.02$, F3 $F=4.6$, $p<0.03$, F4 $F=5.3$, $p<0.02$, P4 $F=4.5$, $p<0.03$, O1 $F=5.9$, $p<0.01$, T4 $F= 4.01$, $p<0.05$, T5 $F=4.2$, $p<0.05$, Cz $F=11.3$, $p<0.001$, Pz $F=5.3$, $p<0.03$).

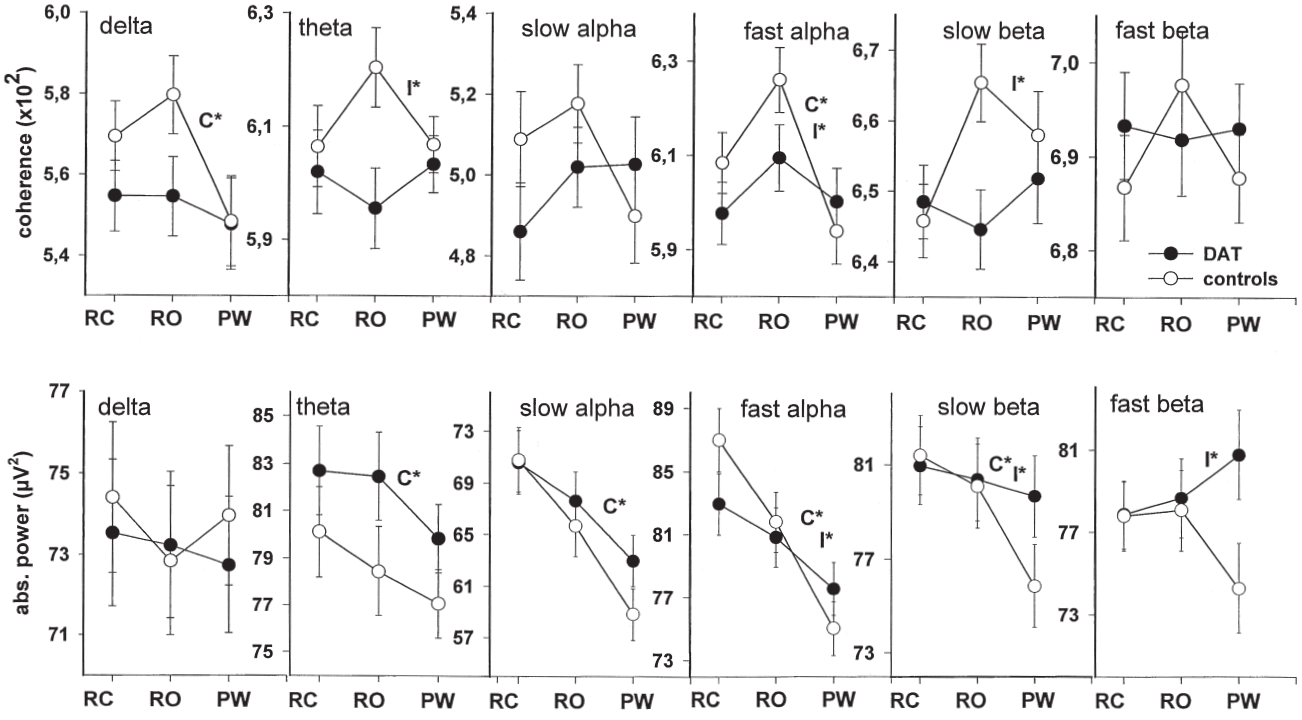

Fig. 1 The upper half represents *EEG coherence* (averaged coherence values within each frequency band over all electrode pairs x10^2 and SEM) for each task (*RC* rest, eyes closed, *RO* rest, eyes open, *PW* pendulum watching) and group. Effects are denoted as C* (condition, $p<0.05$) or I* (interaction diagnosis*condition, $p<0.05$). Diagnosis effects were found for the RO condition in all frequency bands except delta and are *not* indicated in the figure.
The lower half represents absolute *EEG spectral power* values (averaged over all electrodes) for each condition and frequency band. Again, condition (C) and interaction effects (I) are marked. The results suggest differential regulation of EEG spectral power in patients as compared to controls.

Table 2 Summary of EEG findings. The statistical findings from analysis of absolute and relative EEG power and coherence are summarized by indicating F-values, df and p for effects involving diagnosis. There are apparently more effects in relative than in absolute power analysis, but because changes of power in one frequency band will entail changes of relative power in all other frequency bands, the findings concerning absolute power seem more valid. Note that while coherence yields main effects for diagnosis only in the theta range, significant effects in many frequency bands are observed when dynamic regulation of coherence is considered (interaction effects diagnosis*condition).

	Effect	df	delta F, p	theta F, p	slow alpha F, p	fast alpha F, p	slow beta F, p	fast beta F, p
Absolute power	Diagnosis	1,55	0.0, n. s.	3.78, p<0.05	0.83, n. s.	0.1, n. s.	0.01, n. s.	1.3, n. s.
	Diagnosis x cond.	2,110	0.43, n. s.	0.59, n. s.	2.01, n. s.	6.13, p<0.01	3.95, p<0.04	5.92, p<0.02
Relative power	Diagnosis	1,55	1.01, n. s.	5.04, p<0.02	1.18, n. s.	6.10, p<0.02	0.01, n. s.	0.12, n. s.
	Diagnosis x cond.	2,110	5.78, p<0.005	10.7, p<0.001	0.37, n. s.	4.98, p<0.01	4.92, p<0.01	5.18, p<0.01
Coherence	Diagnosis	1,55	3.146, p=0.08	3.85, p<0.05	1.11, n. s.	1.07, n. s.	1.07, n. s.	2.31, n. s.
	Diagnosis x cond.	2,110	0.73, n. s.	3.86, p<0.05	1.29, n. s.	4.12, p<0.05	5.02, p<0.03	2.58, p=0.08

Relative power

Since between-subject comparisons may be confounded by wide inter-individual variation of absolute power, the analysis was repeated for relative power. The comparison of spectral composition yielded a significant effect for diagnosis ($F_{6,49}=2.73$, $p<0.02$), due to increased relative theta and reduced fast alpha power in the patients (Table 2). Effects for the interaction diagnosis*condition were found in all except the slow alpha band. In the delta range the controls showed significantly reduced power in the RO condition as compared to RC and PW, while the patients showed no change. In the theta range, controls showed more power in the PW condition as compared to RO and RC, while patients showed less power in PW. In the fast alpha range, controls showed a significant reduction of fast alpha power from RC to RO to PW, while the patients reduced fast alpha power much less. In the slow and fast beta range, both controls and patients increased power from RC to RO, but controls displayed reduced power in the PW condition, while patients showed an increase.

Coherence

An effect for diagnosis was found only in the theta band with reduced average coherence (all electrode pairs) in the patients (Table 2). A significant condition effect was present ($F_{12,210}=3.43$, $p<0.05$), due to a rise in coherence in all frequency bands from RC to RO and a drop from RO to PW. Post-hoc analysis indicated that the effect was most prominent in the delta ($F_{2,110}=3.94$, $p<0.05$) and the fast alpha bands ($F_{2,110}=11.72$, $p<0.001$). Effects for the interaction diagnosis*condition were found in the theta, fast alpha and the slow beta bands. In detail, from RC to RO the controls showed a large increase of coherence in all frequency bands, which was absent (delta, theta, slow and fast beta) or diminished (slow alpha, fast alpha) in patients. Then, the statistical power of each single task (RC, RO or PW) to discriminate between controls and patients was considered by comparing the effect sizes obtained for diagnosis in each condition. In the RC and PW conditions there was no significant effect for diagnosis, nor for the interaction, but coherence during the RO condition indicated a significant difference between the groups ($F_{1,55}=5.62$, $p<0.02$). The diagnosis*frequency-band*electrode pair interaction was significant ($F_{60,3300}=1.94$, $p<0.001$). Post hoc tests localized the effects to many electrode pairs and frequency bands: in the theta band effects were found at C3-P3 (all $df=1,55$, $F=5.8$, $p<0.02$) and F4-C4 ($F=5.6$, $p<0.02$), in the slow alpha range at T3-T5 ($F3.37$, $p<0.07$), C4-P4 ($F=18.6$, $p<0.01$), F8-T4 ($F=5.2$, $p<0.02$), in the fast alpha band at P3-O1 ($F=4.4$, $p<0.04$), T3-T5 ($F=7.8$, $p<0.01$) and Cz-Pz ($F=4.6$, $p<0.04$), in the slow beta range at P4-O2 ($F=4.5$, $p<0.05$) and T4-T6 ($F=6.3$, $p<0.01$), and in the fast beta range at F3-C3 ($F=4.1$, $p<0.05$), C3-P3 ($F=5.1$, $p<0.02$), P3–01 ($F=3.84$, $p<0.05$), F7-T3 ($F=6.8$, $p<0.01$), F4-C4 ($F=9.07$, $p<0.01$), T4-T6 ($F=3.57$, $p<0.06$). In the PW condition there was no significant effect for diagnosis, nor for the interactions. To further evaluate the ability of RO coherence to discern patients and controls, a discriminant analysis was calculated. Since a large number of classification variables guarantees good, but spurious classification results, we restricted the discriminant function to three variables. Average RO coherence in the fast alpha, slow beta and fast beta bands were calculated from those (symmetric) electrode pairs which had yielded the largest MANOVA effects: F3-C3, C3-P3, P3-O1, F4-C4, C4-P4, P4-O2, Fz-Cz. The data set was split into two, one set for deriving the discriminant coefficients and one for evaluation. The evaluation set was augmented by the RO episodes from those 8 mildly demented patients, who, lacking usable RC or PW EEG sequences, had originally been excluded. The 3-variable discriminant function achieved an accuracy of 77 % (21/27) correct classifications in the evaluation set, a sensitivity of 0.8 (ratio of cases predicted vs. actual cases) and a specificity of 0.75 (ration of controls predicted vs. actual controls).

Discussion

The diagnosis of early DAT still poses a major challenge in clinical psychiatry. The present study addressed two issues: whether the choice of an appropriate functional

state might improve EEG-based diagnosis, and, whether alterations of EEG power and coherence are initially confined to certain brain regions, as the cortical pattern of disease progression suggests (Braak and Braak 1991). We evaluated patients with very mild dementia (MMSE median score = 22) with possible DAT.

The most salient finding was that coherence in the rest, eyes open condition, as compared to eyes closed and a passive observation task, yielded the best results in discriminating patients from controls. Earlier reports of a reduced alpha blocking reaction (Berger effect) in DAT patients had already suggested impaired EEG-reactivity. Reduced coherence in early stages of dementia may be more evident in the eyes open state than with eyes closed, as the latter state is normally accompanied by low coherence. In terms of EEG dynamics, the present experiment shows that in controls coherence increases in all frequency bands when going from rest, eyes closed to eyes open, while it increases in patients only slightly and only in the alpha frequency range. This difference in EEG dynamics between patients and controls was less evident in the power spectra. The findings suggest that, already in early stages of dementia, the large scale coordination of cortical areas is impaired. Studies using EEG microstates (segments of quasistationary EEG activity) in DAT patients with more severe dementia had indicated a similar dynamic restriction (Stevens and Kircher, 1998; Strik et al. 1997). Reduced coherence in DAT patients has been reported in a number of EEG studies involving more severely impaired patients (Dunkin et al. 1995; Besthorn et al. 1994), but dynamic assessment of coherence has to the best of our knowledge not yet been evaluated. To assess a possible clinical use, we performed a discriminant analysis based on coherence during RO, which achieved 77 % accuracy in an independent evaluation sample. By comparison, single photon emission computed tomography (SPECT) yielded 83 % accuracy in a prospective study of patients with moderate cognitive impairment (Jobst et al. 1998). In practice, of course, clinical findings, neuropsychology, EEG and CT are combined to establish a diagnosis.

Another relevant finding of the present study was that, already in early stages of dementia, both power and coherence are globally altered, that is, over many, topographically distributed electrode sites. Prior studies had reported that both long- (fascicular) and short-range coherence is reduced in patients with moderate to severe DAT (Leuchter et al. 1987; Leuchter et al. 1992; Jelic et al. 1996, Coben et al. 1985; Rosen et al. 1993; Rodriguez et al. 1998; Pucci et al. 1999; Soininen et al. 1989); however there is no systematical topographic analysis of coherence between adjacent pairs of equidistant electrodes covering the scull. Both EEG power and coherence rely on synchronization among cortical neurons and dynamic changes of power and coherence accordingly on some regulation of neuronal coupling (Schwarz et al. 2000). This regulation is thought to be under neuromodulatory and thalamo-cortical control (Perry et al. 1999; Larson et al. 1998). As an explanation for the topographically diffuse abnormalities in early stages of probable DAT, a dysfunction of thalamic or neuromodulatory nuclei seems therefore more likely than assuming widespread cortical pathology, which is also in agreement with the pattern of brain destruction in DAT (Braak and Braak, 1991) and the current understanding of frequency and phase coupling in the brain (Contreras et al. 1997; Hoppensteadt and Izhikevich, 1998).

There are several limitations to the study. The most evident drawback is that the diagnosis of possible or probable DAT is unconfirmed, e. g., by a follow-up assessment. Such a study is currently under way. Also, measurements of coherence are susceptible to influences of the electric reference and may vary with the length of the EEG epochs used. Finally, fluctuation of vigilance may alter EEG spectral composition and coherence. However, given the task-related changes of spectral power and coherence, the present findings are unlikely to be explained by reduced vigilance in the patients.

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