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Cognitive decline unlike normal aging is associated with alterations of EEG temporo-spatial characteristics

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Abstract The diagnosis of beginning dementia is based mainly on neuropsychological testing. Several measures of EEG spectral composition, coherence and complexity (correlation dimension) have been shown to correspond to cognitive function. Only a few studies have evaluated EEG changes in normal aging, and no quantitative study has addressed changes in EEG during cognitive tasks in demented elderly. In this study the quantitative descriptors of EEGs from 31 demented or cognitively impaired elderly persons, 30 healthy elderly (mean age 69 years) and 35 young controls (mean age 31 years) were compared. The EEGs were recorded during two resting conditions (eyes closed and eyes opened) and two tasks (mental arithmetics and a lexical decision). The goal of the study was to evaluate which temporal and spatial EEG descriptors change with cognitive decline and with normal aging, respectively. Cognitive categories (unimpaired, impaired, demented) were based on Structured Interview for the Diagnosis of Dementia of Alzheimer Type (SIDAM) scores. The EEGs were analysed using adaptive segmentation of continuous EEG, which quantifies the succession of distinct stable topographic voltage patterns (EEG microstates). The main findings were a significant increase in the number of ultra-short EEG microstates and, independently, a reduction in the average duration of EEG microstates in the cognitively impaired and demented patients. In addition, cognitive impairment was associated with a reduction or loss of EEG reactivity normally observed when the resting states with closed and with opened eyes are compared. No alterations in temporal or spatial EEG descriptors were found in normal aging. Cognitive tasks did not add to information already obtained during the resting states. The reduction in EEG microstate duration correlated with loss of cognitive function. Temporo-spatial analysis of EEG therefore is a useful indicator of cortical dysfunction in dementia, correlating with the degree of cognitive impairment. Normal aging seems not to be accompanied by changes in temporo-spatial EEG patterns. The data suggest that fragmentation of the electrophysiological processes underlies cognitive dysfunction in Alzheimer's disease.

Key words Dementia · Cognitive testing · Alzheimer's disease · Quantitative EEG · Adaptive segmentation

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Introduction

Dementia is a frequent ailment of the elderly, with an annual incidence of 4–7% in persons above 65 years of age [6] and a doubling of incidence for every 5 years of age beyond 65 years. Dementia can be classified as either cortical or subcortical on the grounds of clinical and psychopathological findings [13]. In cortical dementia lesions of the cortex predominate, as in Pick's disease and Alzheimer's disease (AD). Subcortical dementia is characterized by lesions of subcortical structures, such as basal ganglia, thalamus or subcortical white matter, clinically showing impaired reasoning, disturbance of affects and working memory. The diagnosis of dementia is usually a clinical one, based on assessments of cognitive performance and neurological examination. Neuroimaging is of limited value in the early stages of the disease, unless sophisticated procedures, such as nuclear magnetic resonance (NMR) volumetry or functional neuroimaging, such as single photon emission tomography (SPECT), are employed. In contrast, spectral analysis of the EEG discriminates AD effectively from healthy elderly as well as from other types of dementia. In AD a consistent increase in delta and theta power and a parallel decrease in alpha power have been reported [2, 31, 38]. Slow-wave ampli-

tude was found to correlate inversely with cerebral glucose metabolism determined by positron emission tomography (PET) and with cognitive impairment. In addition to changes in spectral power, spectral coherence was found to be reduced in AD, most pronouncedly above the frontal and central cortex [5, 21]. Dunkin et al. [16] noted that reduced spectral coherence paralleled cognitive impairment. It is still controversial, however, whether EEG changes occur in normal aging, and if so, which ones. Duffy et al. [15] reported increased EEG beta power and Christian [12] a slowing of alpha activity with normal aging. These findings, however, were not replicated by Dierks et al. [14].

The present study was undertaken to study quantitative EEG in normal and in pathological aging. The following hypotheses were tested:

1. The quantitative descriptors of EEG are unchanged in normal aging compared with a group of young controls.
2. Cognitive impairment correlates with altered topography and temporal dynamics of the brain electric microstates.
3. EEGs recorded during active cognitive tasks are more useful for diagnosing dementia than resting EEGs.

Adaptive segmentation of continuous EEG [20] served as the method for EEG analysis. Adaptive segmentation is not based on frequency bands, but describes temporal and spatial features of the EEG in terms of the temporal extension and topography of characteristic voltage distributions. The rationale for choosing this method of quantitative EEG analysis is the aspect of the cerebral cortex as a vast array of neuronal oscillators, which may be functionally coupled and uncoupled through cortico-cortical and subcortical connections [11, 25]. In order to produce a signal in the magnitude of EEG currents, a large number of the cortical oscillators must fire simultaneously, and in the case of rhythmic, topographical stable EEG patterns, with a fixed-phase relationship. Large systems of partly synchronized oscillators may produce macroscopic interference patterns spontaneously without apparent relationship to ongoing processing of information. On the other hand, numerous studies suggest that information processing requires a temporally coordinated activity of neurons [11, 28], and disturbed timing of neuronal events is thought to impair information processing [24]. Impairment of cognitive function, as in dementia, may thus be associated with a loss of the temporo-spatial coordination of cortico-electrical activity. Adaptive segmentation identifies in an automated and algorithmic way EEG segments (EEG microstates), during which stable topographic patterns are maintained. Numerous previous reports have demonstrated the technique to be reliable and consistent [19, 32–34].

Subjects and methods

Three groups of subjects were investigated: (a) elderly patients with dementia or cognitive impairment; (b) healthy elderly; and (c) healthy young controls. In order to include both demented and healthy elderly, a total of 86 elderly persons (mean age 69 years) were recruited from two different sources: 38 of the elderly participants were referred to the Klinik für Psychiatrie und Psychotherapie Tübingen for diagnostic evaluation of suspected cognitive impairment. In addition, 48 elderly volunteers were recruited through a newspaper advertisement, offering psychological tests of cognitive and memory functions as well as an EEG. The sample of elderly participants met the following criteria: right-handed, above 50 years of age, no current psychopharmacological medication, no prior or current psychiatric diagnosis, and no known neurological disease, such as multiple sclerosis, brain trauma, stroke and parkinsonism. All participants were asked to provide information about their medical history, social position and living circumstances. These data were gathered by means of a structured interview. From each participant informed written consent was obtained. All participants were assessed by the same skilled psychologist. Radiological diagnoses (CCT) were done by a specialist. Psychological testing included the Structured Interview for the Diagnosis of Dementia of Alzheimer Type (SIDAM), multi-infarct dementia and other aetiology [39] according to DSM-III-R and ICD-10, the Mini-Mental State Examination (MMSE) [17], which is also part of the SIDAM, and the Geriatric Depression Scale (GDS) [30]. Ten of 86 patients were excluded due to the presence of a major depressive episode, 2 due to a history of alcohol abuse and 2

Table 1 Psychopathological, clinical and radiological findings *(CCT)*. *MMSE* Mini-Mental State Examination; *SIDAM* Structured Interview for the Diagnosis of Dementia of Alzheimer Type; *n.a.* not applicable

	Elderly patients (cognitively impaired or demented)	Elderly controls (healthy)	Young controls (healthy)
N	31	30	35
Gender (male/female)	11/20	9/21	12/23
Age (years)	69.6 ± 12.3	68.6 ± 10.4	31.1±8.7
CCT: lacunar infarction	4/21	n.a.	n.a.
Cortical atrophy	14/21	n.a.	n.a.
Periventricular hypodensities	2/21	n.a.	n.a.
Normal	1/21	n.a.	n.a.
MMSE			
Demented	16	0	n.a.
Impaired	6	0	n.a.
Unimpaired	9	30	n.a.
SIDAM			
Demented	14	0	n.a.
Impaired	17	0	n.a.
Unimpaired			n.a.
Clinical diagnosis			
Cortical dementia	10	None	None
Subcortical dementia	4	None	None
Combined cortical/ subcortical	17	None	None

due to being left-handed (according to a translated version of Bryden's [8] questionnaire for handedness). Eleven more patients had to be excluded on the grounds of tremor or movement artefacts in the EEG recordings. Thus, 61 elderly patients remained in the study and were assigned to the following diagnostic categories, according to their SIDAM scores: "unimpaired" (score 47–55), "cognitive deficits" (score 33–46) and "demented" (score < 33). In comparison, an MMSE score of 24 is considered to indicate cognitive impairment, and a score 21 signals dementia. The SIDAM scores classified 14 subjects as demented, 17 as cognitively impaired and 30 as normal. Using MMSE scores, 16 were regarded demented, 6 cognitively impaired and 39 normal. As noted in a previous study, there is moderate agreement between the tests on the diagnosis level, but good agreement on the raw-score level [27]. Twenty-one of the 31 patients with SIDAM scores below 47 (cognitively impaired) agreed on a CCT, which revealed cortical atrophy in 14 cases, lacunar infarction in 4, only periventricular hypodensities in 2 cases, and 1 case without any pathology. Based on CCT, clinical and psychological results, clinical diagnoses according to DSM-III-R were assigned by a psychiatrist (T.K.). Ten patients were diagnosed as suffering probably from dementia of the Alzheimer type (cortical dementia), 4 from lacunar state or Binswanger's disease (subcortical dementia) and 17 from dementia with combined cortical and subcortical lesions or uncertain diagnosis. These data were compared with 35 young controls (mean age 31 years), who were recruited through a similar advertisement in the same year. None of the young participants were offered a CCT or psychological testing. Ten patients had no professional qualification but had finished regular school, 16 were skilled workers and 9 had academic qualifications, thus spanning a normal range of professional training. Inclusion criteria were the same as for the healthy elderly sample, and the medical, psychiatric and psychiatric family history were obtained in the same way. Table 1 represents the demographic and psychological data of the entire sample.

EEG recordings

Electroencephalograms were recorded from patients resting in a reclined chair, using 21 electrodes placed according to the 10/20 convention at the following sites: FP1, FP2, FPz, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, Oz. Standardized electrode positioning was achieved by using the Electrocap® (Geli-med, Munich) system. Linked ears served as reference, transformed off-line to average reference to eliminate spatial offset. Impedance was 5 kOhms. The data were amplified, digitized at 128 Hz and stored on optical discs. Vertical and horizontal eye movement as well as ECG were recorded by bipolar leads. The EEGs were inspected without knowledge of age and diagnosis, and five epochs, each spanning 2 s of artefact-free EEG, were selected from the centre of each condition. The EEGs were recorded during a resting condition with closed eyes, then with open eyes, during a simple mental arithmetic task and a lexical decision paradigm. The instructions were given verbally in a stereotyped form. For the resting condition the participants were asked to sit relaxed with closed eyes, then to gaze straight ahead (at a white sheet of cloth). Illumination was dimmed white light during the whole recording. For mental arithmetic the subjects were asked to subtract silently and repeatedly 3 from 102, to announce when zero was reached and to keep their eyes open all the time. For the lexical decision task, the subjects were instructed to press the left of two buttons located at the right index finger when the group of letters presented on a computer monitor was recognized as a common German noun, and the right button, if the subject decided that it was not a noun. The letters formed either a noun (50%) or a non-word (50%), each consisting of six to ten letters. They were presented on a computer screen 1 m in front of the subjects, the letters measuring 8 cm in height, white on a black background. A test series served to ascertain sufficient visual and reading capabilities. Words and non-words presented for 1000 ms each in five series of ten single words/non-words with an interstimulus interval of 500 ms.

EEG analysis

The data were automatically processed as described by Lehmann et al. [20], Strik and Lehmann [35] and Stevens et al. [32, 33]. The EEG was digitally filtered from 2 to 34 Hz. For every sampling point (at 128 Hz) the global field power (GFP) was determined and the maps with maximum field strength (maximal GFP) were selected. The GFP is computed as the N-weighted standard deviation of the voltages measured at all electrodes vs one of the N electrodes. The GFP is zero for a completely flat field (the voltages are approximately equal at all recording sites), and rises with increasing hilliness of the field, thus indicating how distinct the field configuration is [20]. Field topography is described by the coordinates of the two centroids, which indicate the centre of gravity of positive and negative field areas. The coordinates are given as x- and y-values, the x-value corresponding to a left–right gradient, and the y-value to an anterior–posterior gradient. The units are electrode distances (10/20 system) with a left frontal origin, i.e. 1.3 describes the T3 electrode site. To avoid indicating x and y pairs of coordinates for each set of centroids, and to provide information on the shape of the field, the Cartesian coordinates of the centroid pairs are translated into a polar system with the location of the origin, the rotational angle of the axis connecting the centroids (clockwise from ear to ear = 0°) and the radius from the origin. During each EEG microstate the field oscillates repeatedly while maintaining its topography; thus, the polarity of the centroids changes repeatedly. A new microstate is assumed when one of the centroids moves out of a circular area (the topographical window), the location of which was set by the preceding centroid locations. The circular window allows for a certain amount of topographical variance within which the field is maintained. For all subjects and condition the same window size (r = 0.5 electrode distances) was used. The optimum window size was determined from the EEGs of healthy controls under resting conditions [34]. The number of GFP peaks/s indicates the frequency of field strength maxima. Since the GFP shows two peaks per oscillatory cycle (one positive, one negative), the number of GFP peaks/s is double the carrier frequency of the EEG. The EEG microstates are characterized by their duration (ms) and their topography. The summary topography in Table 2 indicates for each diagnostic group the centre of gravity of the centroid locations during the respective condition (denoted in the x/y coordinate system described previously) and the average orientation of the axis connecting the two centroids (in degrees, clockwise from ear to ear = 0°). The number of single-peak segments/s represents the frequency of fields containing only one GFP maximum. Single-peak segments are thought to represent non-stationary EEG signals, e.g. when the electric field transforms into another configuration or moves. In normal EEGs only few single-peak segments/s are interspersed between long (150–170 ms) periods during which the brain's electric field oscillates repeatedly without any changes in its topography, thus resembling a standing wave. Only multipeak segments are used for the spatial clustering and the calculation of average microstate duration.

Statistical analysis

The data were tested for normal distribution and homogeneity of variance, then they were analysed by one multivariate repeated-measures ANOVA for the temporal and one for the topographic EEG descriptors as dependent variables. The between-groups fac-

tor was "cognitive category" according to the SIDAM levels, the within factor was "condition". The effect of age and gender were assessed as covariate and additional factor, respectively. Significance was assumed at $p < 0.05$. Only when a significant main or interaction effect was found was it located by post-hoc univariate analysis to variables and by contrasts or modified least significant difference tests to groups, thus taking into account multiple group comparisons. Only corrected *p*-values are reported.

Results

As the data set includes four conditions (resting eyes opened, resting eyes closed, mental arithmetics and lexical decision task), the results of the ANOVAs (one for the temporal and one for the topographic parameters) were broken down into several comparisons. Figure 1 and Table 2 summarize the results.

When only the resting conditions were considered, a large and significant effect emerged for the groups ($F12,267 = 3.04$, $p < 0.001$) as well as for the interaction "group x condition" ($F12,267 = 2.59$, $p < 0.003$). The main effect was due to a shortened duration of EEG microstates and an increased frequency of single-peak segments (see below). The interaction effect was attributed to a large shift in the temporal EEG descriptors occurring in the young controls and the healthy elderly (resting with closed eyes vs resting with opened eyes, concerning the following variables: EEG microstate duration (univariate $F3,32 = 39.4$, $p < 0.001$), single-peak segments/s ($F3,32 = 34.6$, $p < 0.001$) and GFP peaks/s ($F3,32 = 10.9$, $p < 0.002$). This shift occurred only to a lesser degree in the cognitively impaired elderly and the demented [contrasts cognitively impaired ($t = 1.98$, $p < 0.05$), demented ($t = 1.87$, $p < 0.05$)]. All groups showed a uniform shift of centroids towards the anterior in the eyes-open state ($F1,91 = 18.0$, $p < 0.001$). Inclusion of the mental arithmetic task yielded again a significant effect for the groups ($F12,249 = 2.15$, $p < 0.01$), due to an increase in the number of single-peak segments/s (ultra short microstates; univariate $F3,90 = 3.60$, $p < 0.02$) in both the cognitively impaired and the demented as compared with the young controls as well as the healthy elderly. Also, the average duration of EEG microstates was reduced in both the demented patients and the cognitively impaired ($F3,90 = 2.99$, $p < 0.04$). There was no effect for age (within-cell regression $F4,84 = 0.45$, n.s.) or gender on any of the temporal or spatial EEG descriptors, and the topographical descriptors of the EEG do not differ between groups. Considering the mental arithmetic task alone, all elderly participants (most prominently the demented) showed significantly shortened EEG microstate duration [modified least significant difference (LSD) test] as compared with the young controls. The topography descriptors during calculation revealed no differences between the groups. The lexical decision task was mastered by 9 of 14 demented patients and by all subjects of the remaining groups. Similar as during mental arithmetics the EEG microstates during the lexical task were shortened (one-way $F3,89 = 5.25$, $p < 0.001$) in all elderly patients including the healthy, as compared with the young controls, but the demented and the cognitively impaired showed the largest reduction [modified least significant difference (LSD) test]. The number of single-peak segments/s was greatly increased ($F3,89 = 5.5$, $p < 0.001$) in the demented. The carrier frequency during the lexical task was accelerated in all elderly patients as compared with young controls but most pronouncedly in the demented ($F3,89 = 5.8$ $p < 0.001$). The interaction group x topography was, as in the mental arithmetic paradigm, not significant. Reaction times

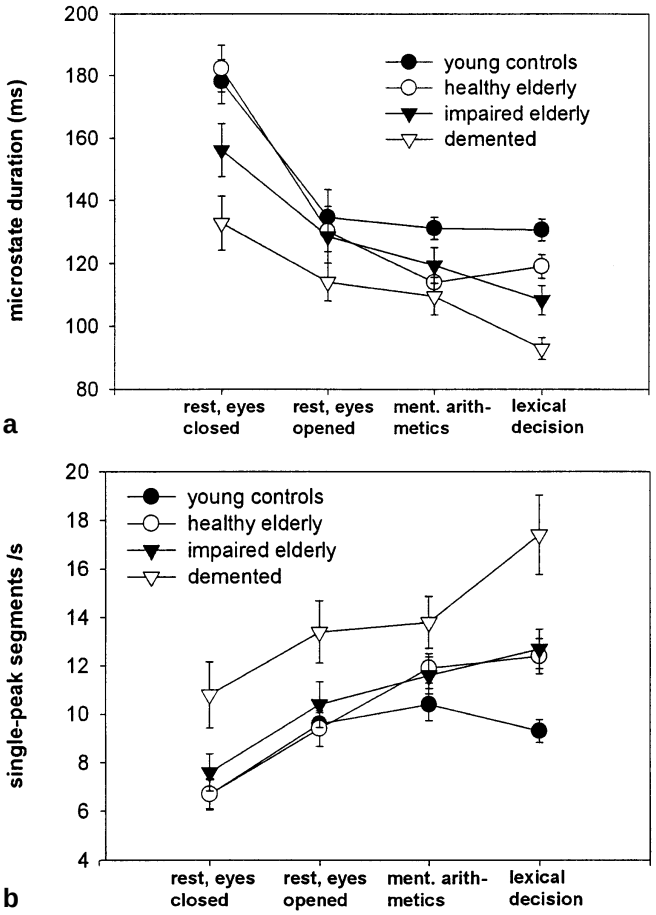

Fig. 1 **a** The mean values and SEM of the microstate duration are represented for each group and condition. The groups are best differentiated by, in this order, the resting condition with eyes closed (*far left*) and the lexical decision task (*far right*). Microstate duration is reduced in the cognitively impaired and the demented patients. **b** The mean values and SEM of the number of single-peak segments/s are represented. In the demented, and to a lesser degree in the cognitively impaired, the number of ultra-short EEG segments (single-peak segments) is increased as compared with the young controls. In the lexical task further fragmentation of the EEG is evident in the demented. Note that the increased number of ultra-short segment/s does not correspond to decreased microstate duration, since only multipeak segments were used for its calculation

Table 2 Temporal and topographic EEG descriptors. Represented are mean values and standard deviations according to SIDAM categories. *GFP* Global field power

Time variables	Elderly subjects (< 50 years)			Young controls (n = 35)
	Demented (n = 14)	Impaired (n = 17)	Healthy (n = 30)	
Microstate duration (ms)				
Rest, eyes closed	132.8 ± 32.4	156.1 ± 35.3	182.3 ± 41.5	178.1 ± 41.9
Rest, eyes opened	114.1 ± 22.3	128.6 ± 61.5	130.2 ± 35.2	134.7 ± 20.5
Mental arithmetic	109.6 ± 22.3	119.4 ± 23.4	114.0 ± 24.4	131.2 ± 21.2
Lexical task	92.9 ± 13.1	108.4 ± 19.3	119.1 ± 20.6	130.7 ± 20.8
Single-peak segments/s				
Rest, eyes closed	10.8 ± 5.1	7.6 ± 3.2	6.7 ± 3.3	6.7 ± 3.8
Rest, eyes opened	13.4 ± 4.8	10.4 ± 3.9	9.4 ± 4.0	9.6 ± 2.7
Mental arithmetic	13.8 ± 4.03	11.6 ± 3.2	11.9 ± 3.4	10.4 ± 4.0
Lexical task	17.4 ± 6.1	12.7 ± 3.4	12.4 ± 4.0	9.3 ± 2.8
GFP peaks/s (carrier frequency)				
Rest, eyes closed	22.7 ± 3.3	22.2 ± 3.1	20.9 ± 3.6	20.5 ± 2.2
Rest, eyes opened	24.8 ± 3.9	22.4 ± 4.2	23.5 ± 3.1	21.3 ± 2.2
Mental arithmetic	25.6 ± 2.8	24.3 ± 3.8	24.5 ± 3.6	22.1 ± 3.0
Lexical task	28.2 ± 3.2	24.8 ± 3.2	25.6 ± 4.1	21.8 ± 3.1
Topography variables Centroid x-position (EP)				
Rest, eyes closed	2.99 ± 0.17	2.95 ± 0.09	2.98 ± 0.16	2.95 ± 0.6
Rest, eyes opened	2.98 ± 0.16	2.98 ± 0.09	2.97 ± 0.07	2.96 ± 0.08
Mental arithmetic	2.98 ± 0.08	2.98 ± 0.11	2.98 ± 0.08	2.98 ± 0.06
Lexical task	2.95 ± 0.11	2.96 ± 0.08	3.00 ± 0.06	3.00 ± 0.10
Centroid y-position (EP)				
Rest, eyes closed	3.11 ± 0.09	3.13 ± 0.19	3.19 ± 0.15	3.19 ± 0.12
Rest, eyes opened	3.01 ± 0.10	3.07 ± 0.11	3.01 ± 0.08	2.98 ± 0.06
Mental arithmetic	3.02 ± 0.17	3.04 ± 0.11	3.04 ± 0.14	2.99 ± 0.08
Lexical task	2.91 ± 0.11	3.02 ± 0.10	3.02 ± 0.10	2.97 ± 0.10
Lexical task performance				
Reaction time (ms)	2614 ± 2200	1954 ± 681	1295 ± 620	633 ± 150
Errors (n)	11.0 ± 11.6	7.07 ± 12.8	2.84 ± 3.8	3.1 ± 4.7

in all elderly patients were significantly prolonged, the most in the cognitively impaired (threefold) and the demented (fourfold). The error rate was similar in young controls and healthy elderly, but double- and threefold increased in the cognitively impaired and the demented. Reaction time correlated with both the number of single-peak segments/s ($r = 0.50$, $p < 0.001$) and EEG microstate duration ($r = –0.37$, $p < 0.01$). The error rate correlated with the number of single-peak segments/s ($r = 0.26$, $p < 0.04$).

Pearson correlation coefficients for SIDAM total score vs microstate duration (resting with closed eyes) were $r = 0.34$ ($p < 0.006$), and $r = –0.36$ ($p < 0.005$) for SIDAM scores vs the number of single-peak segments/s. Of the SIDAM subscores (orientation, memory, intellectual capacity, higher cognitive function scores) memory performance correlated with microstate duration ($r = 0.30$, $p < 0.02$ after correction for multiple correlations), whereas intellectual performance correlated best with single-peak segments /s ($r = –29$, $p < 0.02$).

In a second run, the clinical diagnoses instead of the cognitive function levels were employed as grouping factor. Comparison of the EEGs during resting with eyes opened, resting with eyes closed and mental arithmetic indicated an effect for the clinical diagnosis ($F16,336 = 1.98$, $p < 0.01$), due to significantly reduced EEG microstate duration (univariate $F4,84 = 4.16$, $p < 0.004$) and an increased number of single-peak segments/s (univari-

Table 3 Classification results (based on resting with closed eyes microstate duration and single-peak segments/s)

Actual group	N	Predicted group (n)			
		Cortical dementia	Subcortical dementia	Combined dementia	Healthy elderly
Cortical	10	4 (40)	4 (40)	2 (20)	0
Subcortical	4	0	3 (75)	1 (25)	0
Combined	17	4 (24)	2 (12)	6 (35)	5 (29)
Healthy	30	4 (13)	2 (6)	6 (20)	18 (60)

Numbers in parentheses are percentages

ate $F_{4,84} = 2.62$, $p < 0.04$) in the probable AD patients and in those with combined dementia. The 4 patients with subcortical dementia showed an opposite pattern of EEG alterations with increased EEG microstate duration and decreased number of single-peak segments/s.

In order to analyse the discriminative value of microstate segmentation, a discriminant analysis using only two variables (microstate duration and number of single-peak segments/s during the resting state with eyes closed) was run over the EEGs of the elderly participants, using clinical diagnosis as classification goal. The results are given below (Table 3). The overall classification success was moderate (0.51 as compared with a guessing probability of 0.25). However, 84% all demented patients were classified correctly (sensitivity = 84%, specificity = 60%).

Discussion

The main interest of this study was a comparison of quantitative EEG descriptors in normal aging and in dementia. The EEGs of 61 persons beyond age 50 years (31 with and 30 without cognitive impairment; mean age 69 years) and of 35 young controls (mean age 31 years) were analysed during rest and during two cognitive tasks. The first major result was that neither temporal nor spatial characteristics of the EEG, as recorded during rest as well as during cognitive tasks, change with normal aging. This observation extends findings of Dierks et al. [14], who found that the spectral composition as well as equivalent dipole localization in resting EEGs are unchanged in healthy aging. Whereas some previous investigations reported an increase in EEG beta power [15] or slowing of alpha activity with normal aging [12], in our study only cognitive decline was associated with alterations in EEG temporo-spatial structure. In contrast, both in cognitively impaired and in demented patients, a shortening of EEG microstate duration and an increased frequency in single-peak segments were observed.

A reduction in EEG microstate duration is regarded as electrophysiological evidence of a fragmentation of quasi-stationary EEG periods. Single-peak segments represent clearly defined (by sharp voltage gradients) fields that prevail for less than one oscillatory cycle. Their increased occurrence in cognitively impaired and demented patients also supports an interpretation in terms of EEG fragmentation. The changes in the temporal EEG descriptors correlated with some (overall memory function and overall intellectual capacity), but not all, SIDAM subscores. A similar correlation was found between cognitive function and EEG coherence (the correlation of spectral band power between electrode sites) by Besthorn et al. [5] and Dunkin et al. [16], which is thought to gauge the functional cooperation between cortical areas in the frequency domain. One report [18], however, has found increased duration of quasistationary EEG segments in dementia. However, the average duration for the segments was 40 ms, which is well below the duration of 100–200 ms cited in numerous comparable EEG investigations [33, 34, 36]. Using a non-linear measure of signal complexity (correlation dimension), Pritchard et al. [29] and Besthorn et al. [4] have shown that EEG correlation dimension is reduced in AD, which indicates a predominance of processes with simple temporo-spatial structure. Several studies have demonstrated a correlation between alterations of EEG power-spectra topography and cognitive decline [2, 31]. In the present study, neither aging nor cognitive decline was associated with changes in EEG microstate topography, suggesting that the same brain areas are activated in dementia as in healthy controls. Another result of the present study is a reduced dynamic response to eyes opening in cognitively impaired patients. Pritchard et al. [29] have described a similar phenomenon using EEG spectral power as well as EEG correlation dimension analysis.

Contrary to our expectations, “dynamic testing” over a range of tasks did not add to the variance explained by the diagnostic group (Fig. 1). It is conceivable, however, that tasks putting more load on intermediate or long-term memory instead of working memory might have yielded different results. The lexical task showed at least that decreased microstate duration and single-peak microstates correlated with bad performance. Reduced EEG microstate duration was prominent in patients with probable AD, but it was not found in the 4 patients with pure subcortical dementia (instead, microstate duration was increased) and was present to a lesser extent in the group with combined cortical and subcortical dementia.

We evaluated the usefulness of adaptive segmentation in predicting clinical diagnosis from the EEG. Using only two EEG parameters, the sensitivity was high (84%) but the specificity only moderate (60%) for predicting the four clinical diagnoses (healthy elderly, probably AD, subcortical dementia, combined dementia). These results are comparable to those obtained with a six-variable spectral-power-based prediction [29]. In the same report [29], however, superior classification results were achieved using a neural net prediction. Leuchter et al. [21] reported correct spectral-power-based classification of dementia patients (as opposed to normals) in 80%, and correct prediction of different dementias in 66% of cases.

How reduced coherence and decreased microstate duration are linked with impaired cognitive functioning is presently not clear. Presumably, dementia of Alzheimer type leads to an inability to maintain coordinated activity in large sets of cortical neurons. Llinas [24], Burgess et al. [9], and Barnes and Asselman [3] have compiled evidence to the effect that information at higher levels is processed discontinuously, with cycle lengths of 100–400 ms. Disruption of the cycle periods would result in loss of infor-

mation, especially in memory processes [23]. Electroencephalogram fragmentation, loss of spectral coherence and reduction in EEG correlation dimension may arise from disrupted cortico-cortical connections, as in subcortical dementia, from dysfunction of cortical neurons themselves or from defective neuromodulation. Given the extensive damage to cholinergic neurons early in AD [7] and the ability of cholinergic input to stabilize neurons in their respective firing mode [10, 22, 26], a cholinergic deficit could provoke alterations in EEG spectral composition as well as the temporo-spatial abnormalities observed in probable AD.

In summary, we propose that analysis of temporo-spatial EEG structure may be helpful in the recognition of AD and offer a theory linking defective neuromodulation, EEG activity and cognition.

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