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Millisecond by Millisecond, Year by Year: Normative EEG Microstates and Developmental Stages

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Most studies of continuous EEG data have used frequency transformation, which allows the quantification of brain states that vary over seconds. For the analysis of shorter, transient EEG events, it is possible to identify and quantify brain electric microstates as subsecond time epochs with stable field topography. These microstates may correspond to basic building blocks of human information processing. Microstate analysis yields a compact and comprehensive repertoire of short lasting classes of brain topographic maps, which may be considered to reflect global functional states. Each microstate class is described by topography, mean duration, frequency of occurrence and percentage analysis time occupied. This paper presents normative microstate data for resting EEG obtained from a database of 496 subjects between the age of 6 and 80 years. The extracted microstate variables showed a lawful, complex evolution with age. The pattern of changes with age is compatible with the existence of developmental stages as claimed by developmental psychologists. The results are discussed in the framework of state dependent information processing and suggest the existence of biologically predetermined top-down processes that bias brain electric activity to functional states appropriate for age-specific learning and behavior.

Key Words: **EEG; maturation; microstate; development; normative data.**

INTRODUCTION

Everyday adaptive behavior requires rapid integration of complex, multimodal information with previous knowledge. This may be achieved by extensive distributed neurocognitive networks (Mesulam, 1990; John, 2001) that integrate information by coherent neuronal oscillations in the brain. Coherent firing of a sufficiently large number of neurons produces a detectable and defined voltage field on the scalp. Change of the topography of the electric field thus indicates a change of activation of the underlying networks, while change in amplitude indicates change in the number of coherently active neurons. The topographical analysis of continuous brain electric fields (EEG mapping) thus describes the functional state of neurocognitive networks.

The predominant strategy for analyses of baseline brain activity has been based on frequency transformation, describing EEGs as composed by a set of assumedly stationary oscillatory processes. This approach yielded a systematic, qualitative and quantitative neurophysiological description of normal brain maturation in terms of well-replicated developmental equations of quantitative EEG (Gibbs and Knott, 1949; John *et al.*, 1980; John *et al.*, 1988; Alvarez *et al.*, 1989). Furthermore many clinically relevant conditions including neurological problems and psychiatric disorders (Hughes and John, 1999), varying states of consciousness (John, 2001; Singer, 2001) sleep (Borbely and Achermann, 1999) or neurotropic medication (Herrmann, 1982; Saletu *et al.*, 1994) have been shown to produce specific deviations from these norms.

It is not possible to control for mental activity of subjects during the collection of minutes-long resting baseline recordings. For reasons of practical utility, such sources of variability have been managed by strategies such as *z* transformation (John *et al.*, 1987). This explicitly compensates for momentary fluctuations by incorporating temporal variance of brain activity into analyses. This effectively precludes such methods from analysis of momentary brain activity. However, human information processing takes place in the millisecond time range. It is probable that many brief functional transactions take place in the brain within a single EEG analysis period. In order to investigate these events, it is thus necessary to apply some kind of pattern recognition to determine their on- and offset.

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Using this approach, it becomes possibly to parse EEG data into a series of distinct microstates that are defined as time periods that remain stable in the subsecond time-range and are separated by rapid configuration changes (Lehmann *et al.*, 1987). The duration of these microstates is between 80 and 120 ms, which exceeds the duration that one would expect from a random process (Wackermann *et al.*, 1993; Koenig *et al.*, 1999) and matches the minimal duration of a percept (Efron, 1970). Microstates have been hypothesized to correspond to basic blocks of human information processing (Lehmann, 1990), reflecting the millisecond by millisecond interactions between environmental information and the subject's previous knowledge and internal state. Microstates have been shown to depend on "what just went through the mind" (Lehmann *et al.*, 1998) and consistently abnormal patterns have been reported in disorders affecting cognition such as schizophrenia (Koenig *et al.*, 1999) or dementia (Dierks *et al.*, 1997; Stevens and Kircher, 1998).

Microstates do not only remain stable for a short period of time, but may repeat several times within a second (Wackermann *et al.*, 1993; Koenig *et al.*, 1999). Cluster analysis of microstates reduces the EEG to a consecutive string of repeating short-lasting classes of brain electric states that accounts for a high proportion of the data and enables the sequence of states to be studied (Pascual-Marqui *et al.*, 1995). From this level of description, statistical parameters can be extracted for such measures as mean microstate duration, mean number of microstates per second, or the percentage time covered by each state. These variables can then be further analyzed as function of the experimental condition and microstate class. This analysis provides a gross inventory of the short lasting, phasic brain microstates that were active while the EEG of the subject was recorded (Koenig *et al.*, 1999).

Since it is evident that the high temporal resolution of EEG is likely to provide relevant information in many clinical and research settings, but nonetheless is rarely exploited due to a lack of analytical tools and normative data, we wanted to obtain and provide normative microstate data based on a large database of resting EEG obtained from normally functioning subjects across a large age range. The developmental trajectories of resting EEG microstates are of basic interest because they may contribute to better understanding of normal human cognitive-behavioral maturation from a brain-physiological perspective.

MATERIALS AND METHODS

Subjects

This study was based on normative EEG data from multiple sites (Brain Research Laboratory, NYU Medical School, New York; University Hospital of Clinical Psychiatry, Bern, Switzerland; Cuban Neuroscience Center, La Habana, Cuba), collected under equivalent conditions. Inclusion/exclusion criteria for normal subjects have been described in detail elsewhere (John *et al.*, 1980, 1988; Alvarez *et al.*, 1989). Data from 496 subjects were available; 230 females, 266 males, with an age range from 6 to 80 years. The dataset from New York included 387 subjects between 6 and 80 years, the dataset from Berne included 54 subjects between 10 and 16 years, and the Cuban dataset included 55 subjects between 5 and 69 years. The age range was divided into 18 steps at yearly intervals from ages 6 to 16, where most rapid changes were expected, and at increasing intervals from 16 to 65. These age groups included a minimum of 12 and a maximum of 47 subjects (see Table 1). Informed written consents were obtained from all subjects or their parents if minor.

Data Collection

Eyes closed resting digital EEG data were collected from the 19 electrode sites of the International 10/20 System, referred to linked earlobes, while the subjects were seated, comfortably in a light and sound attenuated room. Amplifiers had a bandpass from 0.5 to 30 or 70 Hz (−3 dB point). A differential eye channel placed on the outer left canthus was used to detect eye movements. All electrode impedances were below 5 KOhms, sampling rate was 128 or 200 Hz. From the digital EEG, artifact-free epochs with a minimal duration of 2 s were selected offline after visual inspection by electrophysiologically expert editors augmented by an automatic artifact rejection algorithm. The minimal total amount of available data was 20 s per subject.

Data Analysis

The selected EEG epochs were remontaged against average reference and digitally band pass filtered from 2–20 Hz, correcting for possible differences in amplifier systems. The Global Field Power (GFP), which quantifies the overall potential variance across the set of electrodes, was computed at each sample in time. Since topography remains stable around peaks of GFP, and changes during the troughs, only topographies at momentary maxima of the GFP were further analyzed. As in previous work (Koenig *et al.*, 1999), four optimally fitted microstate class topographies were computed using a modified version of the K-mean clustering algorithm (Pascual-Marqui *et al.*, 1995). The algorithm was instructed to seek four classes of microstate topography and to assign each EEG topography to one of these classes. This number of classes has previously been found to be optimal, using a cross validation criterion. Microstate class topographies were computed individually and averaged across subjects, using a permutation algorithm that maximized the common variance over subjects (Koenig *et al.*, 1999). Across the sample of

TABLE 1

Microstate Profiles with Their 95% Confidence Intervals for All Age Groups

		Mean microstate duration (ms)					Mean number of microstates (Hz)					Percentage total analysis time covered			
Age	*N*	A	B	C	D	Mean	A	B	C	D	Total	A	B	C	D
6–7	20	97.2 ± 5.4	95.9 ± 7.3	94.6 ± 5.7	90.1 ± 5.2	94.4 ± 3.4	2.81 ± .20	2.64 ± .19	2.56 ± .22	2.52 ± .17	10.52 ± .39	27.3 ± 2.5	25.5 ± 2.8	24.5 ± 3.2	22.7 ± 2.2
7–8	34	91.1 ± 4.8	86.9 ± 5.0	88.0 ± 4.9	89.9 ± 5.2	89.0 ± 3.5	2.88 ± .21	2.81 ± .17	2.72 ± .16	2.86 ± .17	11.26 ± .44	26.0 ± 2.0	24.4 ± 1.9	24.0 ± 1.9	25.7 ± 2.2
8–9	31	87.8 ± 4.0	86.5 ± 4.5	91.4 ± 6.0	86.3 ± 5.6	88.0 ± 3.7	2.91 ± .18	2.67 ± .22	2.91 ± .16	2.89 ± .21	11.38 ± .47	25.5 ± 1.7	23.1 ± 2.2	26.7 ± 2.3	25.0 ± 2.2
9–10	31	87.1 ± 4.4	85.1 ± 5.1	89.1 ± 4.4	89.2 ± 6.0	87.6 ± 3.6	2.80 ± .17	2.63 ± .18	2.98 ± .19	3.02 ± .18	11.42 ± .44	24.3 ± 1.7	22.4 ± 1.8	26.5 ± 2.0	27.1 ± 2.3
10–11	46	86.7 ± 3.8	86.9 ± 4.0	87.3 ± 4.7	86.8 ± 4.7	86.9 ± 3.1	2.91 ± .17	2.84 ± .20	2.91 ± .12	2.88 ± .18	11.53 ± .41	25.3 ± 1.7	24.5 ± 1.8	25.5 ± 1.8	24.8 ± 2.0
11–12	47	86.5 ± 3.8	83.0 ± 4.8	87.4 ± 4.8	87.3 ± 5.1	86.0 ± 3.1	2.89 ± .17	2.67 ± .18	3.08 ± .16	2.93 ± .13	11.57 ± .36	25.2 ± 2.0	22.0 ± 1.6	27.3 ± 2.4	25.8 ± 2.0
12–13	36	81.2 ± 3.7	77.8 ± 3.8	87.6 ± 5.1	84.7 ± 4.9	82.8 ± 2.9	2.92 ± .22	2.55 ± .22	3.34 ± .16	3.18 ± .21	11.99 ± .50	23.8 ± 2.1	19.8 ± 1.9	29.4 ± 2.3	27.0 ± 2.3
13–14	42	81.6 ± 3.5	75.6 ± 3.1	90.5 ± 5.2	83.8 ± 4.3	82.8 ± 2.9	2.82 ± .17	2.56 ± .19	3.41 ± .13	3.24 ± .17	12.02 ± .44	22.8 ± 1.4	19.3 ± 1.6	30.8 ± 2.0	27.3 ± 2.1
14–15	25	81.6 ± 4.8	75.8 ± 5.8	86.8 ± 8.0	87.3 ± 9.6	82.8 ± 4.8	3.09 ± .29	2.60 ± .36	3.23 ± .22	3.17 ± .21	12.08 ± .80	25.0 ± 2.2	19.6 ± 2.7	28.0 ± 3.2	27.6 ± 3.6
15–16	18	79.5 ± 7.9	78.1 ± 7.0	89.7 ± 8.3	79.6 ± 6.8	81.7 ± 5.0	2.90 ± .43	2.76 ± .30	3.35 ± .35	3.12 ± .31	12.13 ± .75	23.2 ± 4.0	21.6 ± 3.0	30.2 ± 4.3	25.2 ± 4.2
16–18	17	78.8 ± 3.6	75.8 ± 6.1	109.4 ± 17.9	78.4 ± 5.2	85.6 ± 5.1	2.62 ± .35	2.51 ± .45	3.47 ± .14	2.80 ± .35	11.39 ± .96	20.6 ± 2.6	19.5 ± 3.9	37.9 ± 6.2	22.1 ± 3.0
18–21	13	80.2 ± 5.2	76.9 ± 7.9	97.5 ± 14.2	78.3 ± 6.5	83.2 ± 6.1	2.79 ± .33	2.60 ± .22	3.62 ± .27	2.84 ± .5	11.85 ± .98	22.2 ± 2.3	20.0 ± 2.6	35.2 ± 5.5	22.6 ± 5.4
21–25	47	78.5 ± 3.1	77.2 ± 3.1	90.9 ± 6.0	80.3 ± 4.3	81.7 ± 3.1	2.85 ± .20	2.81 ± .20	3.47 ± .13	3.04 ± .19	12.18 ± .48	22.4 ± 1.6	21.6 ± 1.6	31.6 ± 2.4	24.6 ± 2.2
25–30	27	76.2 ± 3.1	75.2 ± 5.7	90.6 ± 10.3	81.2 ± 7.8	80.8 ± 5.0	3.01 ± .34	2.87 ± .33	3.47 ± .22	3.02 ± .29	12.36 ± .83	22.7 ± 2.3	21.6 ± 2.6	31.2 ± 3.6	24.7 ± 3.5
30–40	20	78.4 ± 5.0	73.6 ± 4.4	93.9 ± 17.9	88.0 ± 12.8	83.5 ± 6.3	2.91 ± .49	2.68 ± .48	3.25 ± .36	2.95 ± .31	11.79 ± 1.0	23.1 ± 4.5	19.8 ± 3.5	30.6 ± 5.8	26.9 ± 6.0
40–50	12	72.6 ± 4.0	72.9 ± 5.6	89.3 ± 16.3	79.3 ± 10.3	78.5 ± 6.4	3.04 ± .48	2.92 ± .32	3.47 ± .39	3.28 ± .32	12.71 ± 1.2	22.2 ± 3.2	21.2 ± 2.3	31.1 ± 6.4	25.8 ± 4.1
50–65	13	71.4 ± 3.0	68.5 ± 3.4	84.0 ± 18.1	97.9 ± 31.3	80.4 ± 10.3	3.07 ± .84	2.92 ± .79	3.21 ± .40	3.25 ± .29	12.44 ± 1.9	21.8 ± 5.8	19.7 ± 4.6	27.2 ± 7.0	31.8 ± 10.3
65–80	13	81.8 ± 8.3	72.8 ± 7.4	88.2 ± 13.7	70.7 ± 7.5	78.4 ± 6.5	3.47 ± .57	2.88 ± .42	3.49 ± .23	2.78 ± .56	12.61 ± 1.2	28.6 ± 5.1	21.2 ± 3.5	30.7 ± 4.7	20.0 ± 5.0

496 subjects, four classes accounted for 79% of the variance on the average.

Within each subject, microstates were identified as continuous epochs within which all topographies were assigned to the same class. No minimal microstate duration was required. Individual microstate profiles were computed for each class, which consisted of mean microstate duration ("duration"), mean number of microstates per second ("microstates/second") and percentage of total analysis time occupied in that state ("percentage time"). Overall microstate duration and total number of microstates per second were also computed. The extracted parameters are illustrated in Fig. 1. For each variable, mean values and standard errors were computed and plotted for each age group. The statistical significance of the reported age differences in microstate parameters was assessed using ANOVAS, with age as independent variable and microstate class as repeated measure. For future usage, the analysis software used, the normative values and the topographies of the four microstate classes are made available at http://www.puk.unibe.ch/tk2/tk.htm.

To study the possible variability between recording sites, ANOVAS on duration, microstates/second and percentage time were computed using recording site and age group as independent variables and microstate class as repeated measure. Since the data from Berne covered only subjects between 10 and 16 years, and the Cuban data contained mostly subjects between 21 and 30 years, these ANOVAS compared subjects from New York and Berne between 10 and 15 years, and subjects from New York and Cuba between 21 and 30 years. Because no significant effects including recording site were found, the data of the different recording sites were assumed to be similar.

A further aim of the data analysis was to explore the relationship of the obtained microstate developmental data with the "classical" description of EEG maturation in the frequency domain. Therefore, an additional power spectral analysis was applied to the data. Within each subject, relative EEG power was computed in each epoch and channel, averaged over all epochs and pooled over frontal (Fp1, Fp2, F7, F3, Fz, F4, F8) and posterior (T5, P3, Pz, P4, T6, O1, O2) electrodes. In order to keep as many parameters as possible identical to the main microstate analysis, common average reference was used and the bandwidth of the power analysis was kept between 2 and 20 Hz, now subdivided into Delta (2–5 Hz), Theta (5–8 Hz), Alpha (8–12 Hz), and Beta (12–20 Hz). Relative power was used since microstate analysis is independent of total power. Comparisons between microstate results and relative spectral findings were based on Pearson Correlation coefficients between microstate parameters and spectral data and on visual comparisons of the mean values as function of age.

RESULTS

Figure 2 shows the topographies of the four microstate classes which were found. They closely replicated those obtained in previous work (Koenig *et al.*, 1999) and were therefore labeled and arranged in the same order as in the previous publication: Microstate class A had a left occipital to right frontal orientation, class B was from right occipital to left frontal, class C had a symmetric occipital to prefrontal orientation and class D was also symmetric, but with a frontocentral to occipital axis.

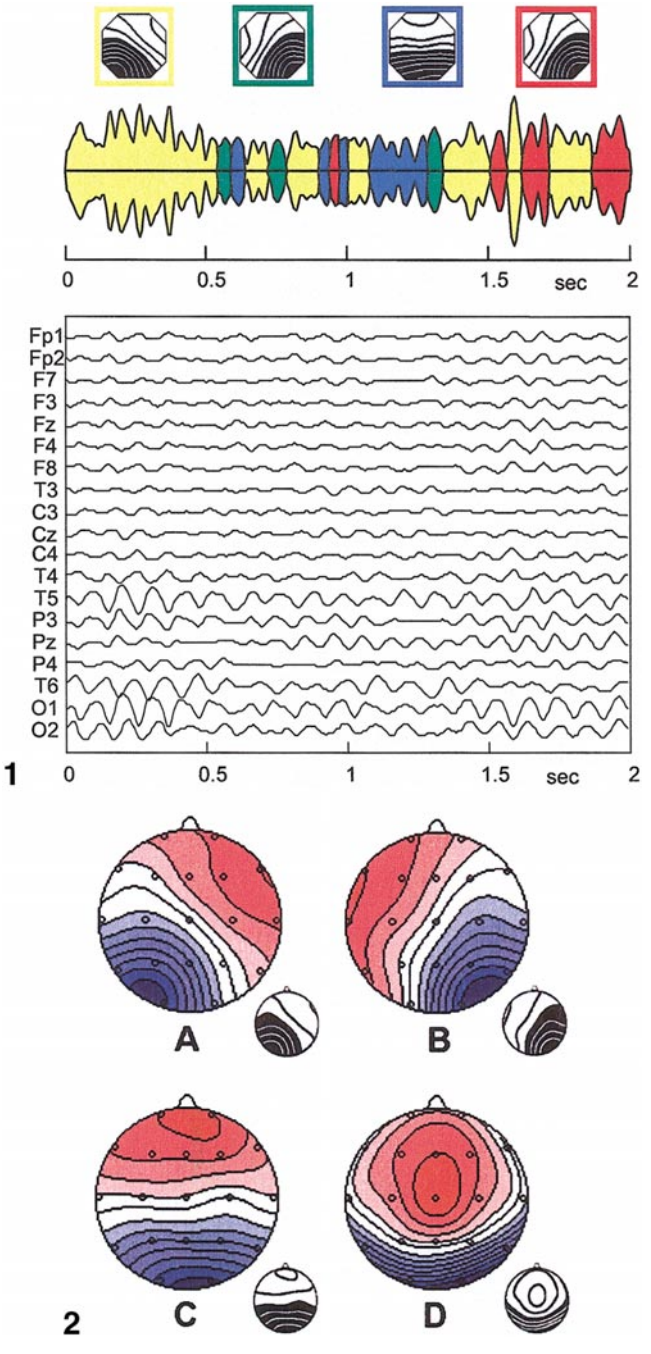

FIG. 1. The tracings show a sample 2-s eyes closed resting EEG displayed against average reference. In the upper part, the assignment of the same EEG to the four microstate class topographies is shown. The color-coded areas indicate the assignment of the momentary EEG topography to the microstate topography with the same color (shown above). The momentary height of the area indicates the amplitude of the momentary EEG field (Global Field Power). Prolonged time epochs assigned to a single topography can clearly be seen. The present analysis established the duration of each of these microstates and the number of times they occurred per second. This was done separately for the different classes. Furthermore, the percentage of total time that was covered by each microstate class was computed. For statistics these measures were averaged over all available EEG epochs of a given subject.

FIG. 2. Normalized mean equipotential contour maps of the four microstate classes (A–D). Map areas of opposite polarity are arbitrarily coded in red and blue using a linear color scale, left ear is left, nose is up. Note that the four topographies extend over wide scalp areas and are likely to represent global brain electric events.

Figure 3 shows microstate duration, microstates per second and percentage time for the four microstate classes as function of age. For future use as a reference, the mean values and the 95% confidence intervals are tabulated in Table 1.

The four microstate classes seemed to follow quite different and complex developmental trajectories. This was statistically substantiated by the results of the ANOVAS, which all were highly significant both for the main effects of age and microstate class as well as for their interaction (Table 2).

Since the microstate profiles followed a lawful, but complex behavior with age, an attempt was made to simplify this developmental trajectory: For each microstate class and variable, the absolute difference between values of adjacent age groups was computed and normalized (divided) by the sum of the same two values. These difference ratios were averaged across microstate classes and variables to yield a single, normalized index of change of microstate profile between adjacent age groups. Plotting this change ratio as function of age showed 3 peaks at ages 12, 16, and 21, as indicated by the vertical lines in Fig. 3. Since the existence of these peaks suggests preferred moments of change, the epochs between these peaks were taken as candidates for putative developmental stages. They will be referred to as: childhood (below 12 years of age); early adolescence (between 12 and 16 years); late adolescence (above 16 and below 21 years) and adulthood (above 21 years).

As a method to validate these putative stages statistically, ANOVAs were computed separately for each of the three microstate variables, treating developmental stage as an independent factor and microstate class as a repeated measure. Significant interactions were hypothesized between microstate class and developmental stage. For all three measures, the ANOVAs yielded significant interactions between microstate class and developmental stage (Table 3). This confirms that the hypothesized developmental stages indeed had statistically different microstate profiles. Similar ANOVAs were computed within each developmental stage, using age group as independent factor and microstate class as repeated measure. Interactions of microstate class with age group would invalidate our hypothesis that within a developmental stage, no significant changes of microstate profile would occur. As hypothesized, the ANOVAs within age group yielded no significant interactions of microstate class with age group, except for an interaction of microstate duration and microstate class during adulthood ($F = 1.71$; $df = 15,381$; $P =$

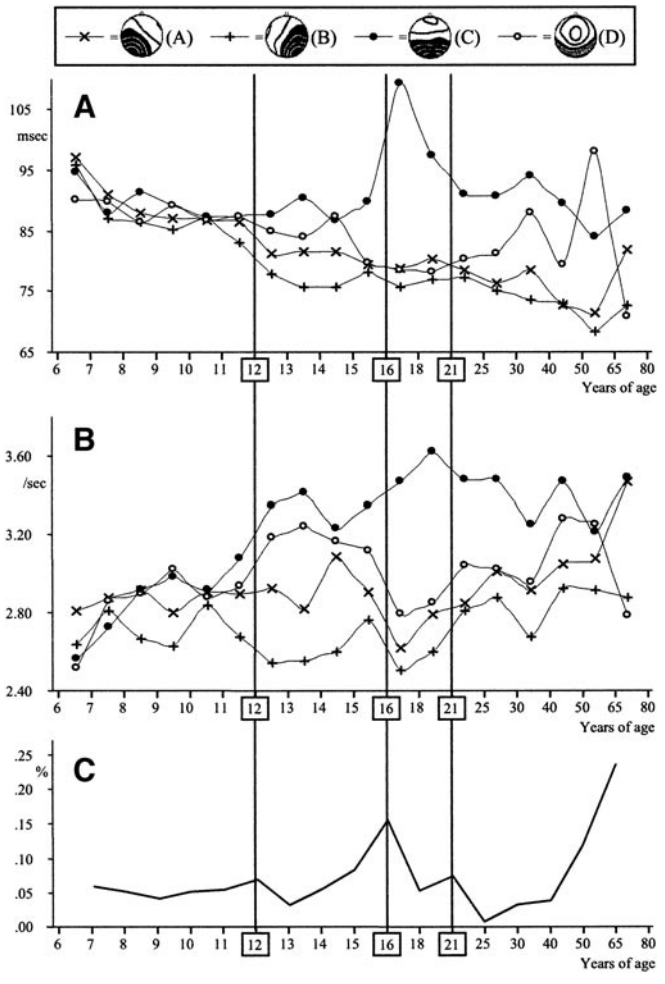

FIG. 3. Mean microstate duration in milliseconds (upper graph A) and number of microstates per second (middle graph B) against age (horizontal). The legend on top indicates the assignment of the used markers to the four microstate classes. The curves show complex trajectories that are incompatible with a continuous, unspecific maturation process. By comparing microstate profiles of adjacent age groups using a microstate change ratio (lower graph C), three peaks were identified which delimited four developmental stages. The vertical lines indicate their borders and latencies.

0.046). Further analysis indicated that changes occurred only after 50 years, suggesting an effect of aging rather than development. The identified developmental stages were thus considered to be stable in microstate profile and are briefly summarized here:

Children between 6 and 12 years showed a relatively undifferentiated pattern. There were only small differences between microstate classes and all microstates were of relatively long duration. At early adolescence, all microstate classes except class C became shorter, resulting in an overall increase of number of microstates per second. The microstate profile now showed a predominance of the (symmetric) microstates classes C and D, which were more frequent and longer than the (lateralized) microstates classes A and B. Late

TABLE 2

ANOVAs with Age Groups and Microstate Class

	df	*F*	*P* level
Microstate duration			
Age	17, 475	3.27	0.000013
Class	3, 1425	51.17	0.000000
Age * Class	51, 1425	3.02	0.000000
Number of microstates			
Age	17, 475	2.48	0.000914
Class	3, 1425	56.30	0.000000
Age * Class	51, 1425	2.79	0.000000
Percentage of time			
Age		Not applicable	
Class	3, 1425	67.16	0.000000
Age * Class	51, 1425	3.11	0.000000

Note. Results of the ANOVAs of microstate duration, number of microstates, and percentage of time, using age as independent variable and microstate class as repeated measure.

adolescence was characterized by very long and frequent microstates of class C, while microstates of class D dropped in duration and incidence. At adulthood, these tendencies were partially reversed, but microstates of class C remained the longest and most frequently observed states. Microstates of class A and B were shortest and least frequent, although again more frequent than during late adolescence.

The mean relative power values as function of age are shown in Fig. 4, separately for the four frequency bands and for anterior and posterior leads. The changes observed are those that are classically reported in the EEG literature, namely a nearly continuous decrease of slow Delta/Theta activity and an opposite development of the faster Alpha/Beta waves, more pronounced in posterior leads. By comparing Figs. 3 and 4, it became apparent that the correspondence between microstate profiles and power spectral

TABLE 3

ANOVAs with Developmental Stage and Microstate Class

	df	*F*	*P* level
Microstate duration			
Stage	3, 489	13.99	0.000000
Class	3, 1467	59.23	0.000000
Stage * Class	9, 1467	10.58	0.000000
Number of microstates			
Stage	3, 489	10.29	0.000001
Class	3, 1467	66.54	0.000000
Stage * Class	9, 1467	10.18	0.000000
Percentage of time			
Stage		Not applicable	
Class	3, 1467	79.50	0.000000
Stage * Class	9, 1467	11.92	0.000000

Note. Results of the ANOVAs of microstate duration, number of microstates, and percentage of time, using developmental stage as independent variable and microstate class as repeated measure.

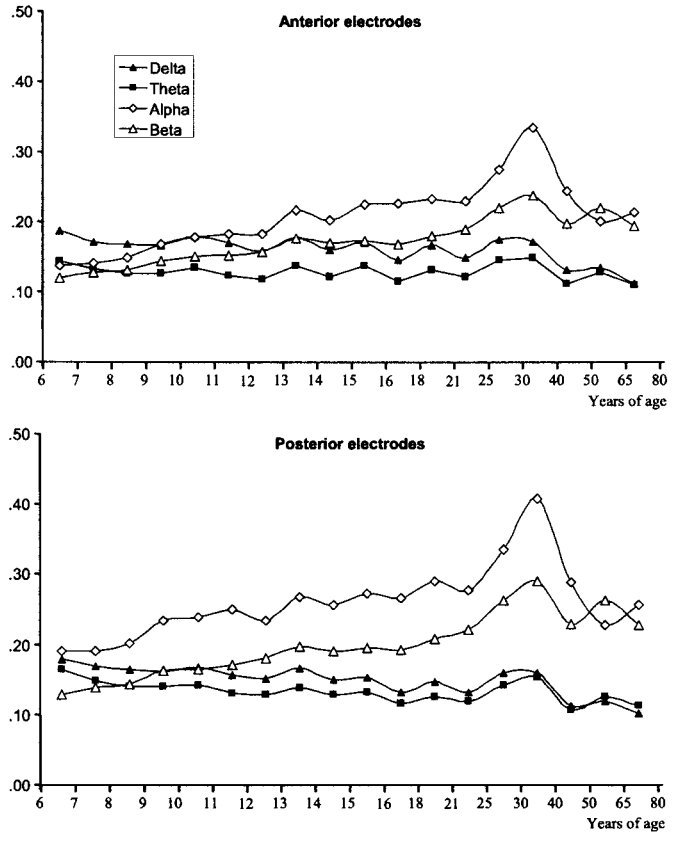

FIG. 4. Mean relative spectral power for Delta, Theta, Alpha, and Beta frequency bands in anterior (upper graph) and posterior (lower graph) electrodes as a function of age. The frequency bands evolve in a quite linear fashion: Alpha and beta power increase in a rather constant, linear fashion from age 6 until the age of about 30, where they begin to decrease again. (The apparent increase in slope after 25 years of age is due to the wider age groups at these ages, which change the pitch of the x-axis.) In the posterior electrodes, slow delta and theta power tend (with some variation) to decrease gradually throughout live.

values was only weak. This was further supported by the correlation coefficients between microstate parameters and power spectral values, which were all below 0.44, indicating that the maximal amount of common variance between a microstate parameter and a power measure did not exceed 20%, although the numbers were extracted from identical EEGs.

DISCUSSION

In the frequency domain, the relations between EEG and brain maturation have long been established (Berger, 1932). The classical observation that was made in these studies was that with increasing age, slow delta and theta waves diminish and the faster alpha and beta waves increase almost linearly (Gibbs and Knott, 1949; John *et al.*, 1980, 1988; Alvarez *et al.*, 1989). This behavior could also be observed in the present data. These continuous changes in the power spectrum may relate to unspecific maturation processes such as increasing thickness of myelination.

However, the time course of microstate profiles depends on microstate class, indicating that there exists relative excess or lack of specific brain states at specific ages. This is statistically corroborated by the significant interactions of microstate class with age and developmental stage. This is incompatible with a continuous, unspecific maturation process because such a process would affect all microstate classes in a similar way. Indeed, the time course of microstate profiles and the time course of relative EEG power are only weakly related.

The discussion of the neural basis of the observed effects remains difficult. In studies on the micro-architecture of developing brain tissue, it has been observed that after an initial excess of relatively unorganized synaptic connections, the number of synapses gradually decreased, while the degree of organization of the connections increased (Huttenlocher, 1979; Rakic *et al.*, 1986). It is thus more likely that the observed changes in microstate profile result form the elimination of non-functional connections rather than from the formation of new ones. Another possible relation of the present results with neurobiological processes comes form the observation that with increasing age, asymmetric microstates diminish, while symmetric microstates increase. Assuming that asymmetric microstates result from predominantly unilateral brain activity, while symmetric microstates indicate predominantly bilateral activity, the observed effects may be related to the growth of the corpus callosum, which continues until late adolescence (e.g., Giedd *et al.*, 1999).

On a behavioral level, children display different behavior and different cognitive styles at different ages. One may therefore speculate that the developmental trajectories of microstates reflect an adaptive biological process that selects those brain functional states optimal for age specific learning and behavior. The stages identified here might thus be neurophysiological correlates of conceptual stages described in the developmental literature. This is supported by the timing of these stages, which coincide with the developmental stages postulated in classical developmental theories (e.g., Piaget, 1954, who discriminated between a concrete operational stage between 7 and 11 years, a formal operational stage between 11 and 15 and a postformal operational stage after 15 years of age). To substantiate this hypothesis, it would however be necessary to correlate EEG data and specific psychological test results obtained in the same children.

From this point of view, abnormal microstate profiles may indicate a possible misfit between activated brain functional states and the subject's environment, hindering age-specific appropriate learning, information processing and adaptive behavior. Microstate analysis

might thus help understanding those cognitive-behavioral disorders that typically appear at a certain developmental stage, such as motor and language deficits, learning and attentional problems, psychosis, mood disorders, or dementia. The currently available studies on microstate classes indeed point into this direction: In a study that compared neuroleptic-naive, first-episode, acute schizophrenic patients with matched controls, microstate duration was reduced selectively for microstates belonging to class D (Koenig *et al.*, 1999). It is noteworthy that in the present data, microstates of class D are shortest (and rarest) between age 16 and 21, where the first signs of a beginning psychosis are usually observed. In the EEG of patients with dementia, it was observed that microstates with asymmetric configurations belonging to class A and B covered increasingly more time with increasing severity of the disease, while the symmetric microstates belonging to class C and D covered less and less time (Koenig *et al.*, in press). This development is basically the opposite of what the current data showed during normal child development.

If microstates assessed using resting EEG show abnormal patterns, but the symptoms of the disorder primarily occur while the subject is engaged in some task or behavior, the results can be interpreted in terms of state dependent information processing. Since information processing strategies and available memory contents crucially depend on the current functional state of the brain (Eich, 1980; Koukkou and Lehmann, 1983; Kondakor *et al.*, 1997; Muller *et al.*, 1999), the presence of an inadequate brain state at rest will result in inadequate processing of incoming stimuli and subsequently to maladaptive experiences and behavior.

The knowledge about the functional significance of microstates may be further extended by studying the behavior of the different microstate classes during varying conditions, which may be spontaneously occurring, stimulus induced, or related to circumscribed dysfunctional and pathological states. Since these normative data is published and the necessary software is free, EEG researchers can quantify and describe normal and abnormal microstate patterns in clinical patients using standard procedures and without the need to evaluate additional control subjects. Before doing so, care should, however, be taken to validate the given normative values in at least 10 locally recorded subjects, as it has been recommended for other electrophysiological measures (e.g., Celesia *et al.*, 1993).

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