Scale-Free Dynamics of Global Functional Connectivity in the Human Brain

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Abstract: Higher brain functions depend upon the rapid creation and dissolution of ever changing synchronous cell assemblies. We examine the hypothesis that the dynamics of this process displays scale-free, self-similar properties. EEGs (19 channels, average reference, sample frequency 500 Hz) of 15 healthy subjects (10 men; mean age 22.5 years) were analyzed during eyes-closed and eyes-open no-task conditions. Mean level of synchronization as a function of time was estimated with the synchronization likelihood for five frequency bands (0.5–4, 4–8, 8–13, 13–30, and 30–48 Hz). Scaling in these time series was investigated with detrended fluctuation analysis (DFA). DFA analysis of global synchronization time series showed scale-free characteristics, suggesting neuronal dynamics do not necessarily have a characteristic time constant. The scaling exponent as determined with DFA differed significantly for different frequency bands and conditions. The exponent was close to 1.5 for low frequencies (δ , θ , and α) and close to 1 for β and γ bands. Eye opening decreased the exponent, in particular in α and β bands. Fluctuations of EEG synchronization in δ , θ , α , β , and γ bands exhibit scale-free dynamics in eyes-closed as well as eyes-open no-task states. The decrease in the scaling exponent following eye opening reflects a relative preponderance of rapid fluctuations with respect to slow changes in the mean synchronization level. The existence of scaling suggests that the underlying dynamics may display self-organized criticality, possibly representing a near-optimal state for information processing. *Hum. Brain Mapp.* 22:97–109, 2004.

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INTRODUCTION

There is increasing evidence that integration of information processed in widely distributed neural systems in the brain depends, at least in part, upon the formation of synchronized cell assemblies. In particular, synchronized activ-

ity in various frequency bands has been proposed to be an important mechanism for binding [Basar et al., 2001]. Gamma band synchronization is now believed to play a role in higher brain functions such as perception, attention, working memory, sensory motor integration, associative learning, and conscious awareness [Engel and Singer, 2001; Singer, 2001]. Synchronized activity in slower frequencies, in particular the θ band, has been implicated in working memory [Sarnthein et al., 1998; Stam et al., 2002a]. In addition, there are a number of studies that suggest functional interactions between θ and γ band synchronization [Fell et al., 2003; Schack et al., 2002]. An explicit model of θ - γ interactions has been proposed by Lisman and Idiart [1995].

Despite their obvious importance for cognition, synchronous oscillations provide, at best, only an incomplete expla-

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nation of underlying mechanisms. Flexible information processing requires not only the formation, but also the dissolution of synchronous cell assemblies. This notion of consecutive synchronization and desynchronization processes underlying higher brain function has been suggested by several authors. Friston has introduced the notion of a “labile brain” and has stressed the importance of short-lived neural transients and non-linear coupling dynamics [Friston, 2000]. Some of the predictions of Friston’s model, in particular the non-linear nature of functional connectivity, were recently confirmed in MEG and EEG data [Stam et al., 2003a]. The alternation of synchronization and desynchronization has also been proposed by Varela et al. [2001]. Experimental support was found in an EEG study on γ synchronization induced by Mooney faces [Rodriguez et al., 1999]. Freeman demonstrated the spontaneous occurrence of so-called “wave packets” both in animal and human EEG data [Freeman and Rogers, 2002; Freeman et al., 2003].

Several mechanisms have been proposed to explain the rapid creation and dissolution of synchronous cell assemblies. Modeling work of Breakspear has shown that nonlinearly coupled chaotic oscillators can display intermittent dynamics, with alternating strong and weak synchronization even when the coupling strength remains constant [Breakspear et al., 2003]. Hopfield and Brody [2001] have shown in their network models how transient γ band synchronization events can function as a computational tool to detect spatio-temporal patterns. Relative coordination between periodic oscillators is another proposed mechanism for critical dynamics and fluctuating connectivity levels [Bressler and Kelso, 2001]. Finally, several authors have suggested that the complex dynamics of synchronization and desynchronization processes in the brain might be due to so called “self-organized criticality” [Bak et al., 1987; Freeman et al., 2003; Le van Quyen, 2003].

A crucial question in relation to the dynamics of these synchronous cell assemblies is whether or not they have a characteristic time scale. Some data seem to suggest that these transient synchronization patterns have a characteristic life span of a few hundred milliseconds [Freeman and Rogers, 2002; Rodriguez et al., 1999; van Putten, 2003]. Modulation of γ synchronization by θ carrier waves also points in the direction of a characteristic time scale [Burgess and Ali, 2002]. The alternative view is that synchronization events in the brain do not have a characteristic time scale but rather display scale-free, self-similar dynamics [Gong et al., 2003].

The present study was undertaken to address this question by examining the dynamics of large-scale synchronization events in ongoing, no-task EEG of healthy human subjects. We used the synchronization likelihood as a tool to obtain high-resolution time series of large-scale EEG synchronization levels [Stam and van Dijk, 2002]. Time series of synchronization likelihood were examined for scale-free dynamics with detrended fluctuation analysis, which is especially suitable to detect scaling properties in non-stationary physiological signals [Peng et al., 1992, 1995].

SUBJECTS AND METHODS

Ten male and five female students (mean age: 22.5 ± 0.7 years, range: 18–27 years) gave written informed consent to participate in this study. All subjects (except one left-handed male) were right-handed. EEG was recorded during no-task eyes-closed and eyes-open conditions from 64 tin electrodes placed according to the international 10–10 system with linked mastoids as a reference (QuikCap, Neurosoft, El Paso, TX). During the recording, the subjects were seated in a comfortable chair in a sound-attenuated and electrically shielded testing chamber. Impedance was kept below 10 k Ω . Filters were set at 0.15 and 70 Hz, and signals were digitized at a rate of 500 Hz with 16-bit A/D precision (SynAmps amplifiers, Neuroscan software v. 4.1; Neurosoft, El Paso, TX).

Data Analysis

For every subject and each condition, artifact-free epochs were selected manually. These epochs started 3 sec after presentation of the instruction for eye closure in order to minimize eye-blink artifacts. A selection of 19 electrodes (O1, O2, Pz, P3, P4, P7, P8, Cz, C3, C4, T7, T8, Fz, F3, F4, F7, F8, Fp1, Fp2) was referenced to an average reference electrode (which included these 19 electrodes). The length of the epochs was 4,096 samples (about 8 sec). The EEG was digitally filtered off-line in the following frequency bands: δ , 0.5–4 Hz; θ , 4–8 Hz; α , 8–13 Hz; β , 13–30 Hz; and γ , 30–48 Hz.

Synchronization Likelihood

The synchronization likelihood (SL) is a measure of the statistical interdependencies between two time series, for instance two EEG channels. The synchronization likelihood takes on values between p_{ref} (a small number close to 0) in the case of independent time series and 1 in the case of fully synchronized time series. The synchronization likelihood is sensitive to linear as well as non-linear interdependencies, and can be computed with a high time resolution, making it suitable for tracking time-dependent changes in the synchronization level. For a technical description of the method and its properties, we refer to Stam and van Dijk [2002]. Here we explain the general principles.

Assume we have two time series x_i and y_i , where the index i denotes discrete time. From each of these time series and for each time i , we construct vectors X_i and Y_i in state space with the method of time-delay embedding [Takens, 1981]. These vectors can be thought of as representing the “state” of the system underlying the time series at a moment in time. Synchronization likelihood is now defined as the conditional likelihood that Y_i and Y_j will be very close together (“close together” means that the distance between Y_i and Y_j in state space is smaller than some critical cut-off distance), given that X_i and X_j are very close together. In other words, the synchronization likelihood is the likelihood that if system X is (almost) in the same state at two different times i and j , that system Y will also be (almost) in the same

state at i and j . In the case of maximal synchronization, this chance is 1; in the case of independent systems, it is a small, but nonzero number, namely p_{ref} . This small number is the likelihood that two *randomly* chosen vectors Y (or X) will be

closer than the cut-off distance. In practice, the cut-off distance is chosen such that the likelihood of random vectors being close is fixed at p_{ref} , which is chosen the same for X and for Y .

In the present study, we computed the synchronization likelihood averaged over all possible pairs of channels ($19 \times 18/2$) for each sample time. This resulted in a time series of 4,096 consecutive synchronization values reflecting the spontaneous dynamics of global synchronization levels in each epoch. The parameters used for the computation of the synchronization likelihood were: time lag = 10; embedding dimension = 10; Theiler correction = 10; $w_2 = 407$ samples; $\text{pred} = 0.05$. These parameters were the same as in a number of previous studies [Stam et al., 2002a,b, 2003a,b].

Detrended Fluctuation Analysis

Detrended fluctuation analysis (DFA) is a technique to characterize the correlation structure of non-stationary time series. It was first introduced to characterize long-range correlations between nucleotide sequences [Peng et al., 1992]. It has subsequently been applied in the analysis of physiological time series, such as heart-beat intervals [Peng et al., 1995] and EEG [Hwa and Ferree, 2002; Lee et al., 2002; Linkenkaer-Hansen et al., 2001; Shen et al., 2003; Watters, 1998]. Here we closely follow the description of the method as given in Peng et al. [1995]. A schematic explanation is shown in Figure 1.

The analysis is applied to a discrete time series $x(i)$, $i = \{1..N\}$, which in the present study represents the synchronization likelihood averaged over all pairs of channels for each time sample ($N=4096$). In the first step, the mean is subtracted from this time series and it is integrated:

$$y(k) = \sum_{i=1}^k [x(i) - \langle x \rangle] \quad (1)$$

where $\langle x \rangle$ is the average of the synchronization likelihood time series. Next, the integrated, de-meant time series $y(k)$

Figure 1.

Schematic explanation of detrended fluctuation analysis (DFA). The analysis is applied to a time series of interest (A). In the present study, this was the time series of the global synchronization likelihood. First, the mean is subtracted from this time series and it is integrated (B). Then the de-meant, integrated time series is divided into segments of length n . In each of these segments, a linear fit through the data is determined (C). The fluctuation at scale n is then determined as the mean squared deviation from these local linear fits through the integrated time series; this results in a fluctuation estimate F_n for each scale n . Finally, the logarithm of F_n is plotted as a function of n (D). If there is a linear scaling region, then this is evidence for scale-free properties of the fluctuations in the data set. The slope of the plot is determined by a linear fit. The slope of the scaling region is the scaling or self-similarity exponent, which is 0.5 for uncorrelated noise, 1 for $1/f$ noise, and 1.5 for Brownian noise.

is divided in a number of segments with length n (n represents a time scale of observation). For each of these segments, the local least-squares linear fit is determined. The ensuing piece wise linear fit is designated $y_n(k)$. Then the integrated time series $y(k)$ is detrended by subtracting the local linear fit $y_n(k)$ for each segment. The root mean square fluctuation of this integrated and detrended time series is given by:

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2} \quad (2)$$

Subsequently, this determination of $F(n)$ is repeated for a range of different scales n (in the present study n ranged from 4 samples to 2,048 samples). In a final step, the logarithm of $F(n)$ is plotted as a function of the logarithm of the time scale n (we used logarithms with a base of 2). If the time series $x(i)$ has self-similar, scale-free (fractal) properties, this plot will display a linear scaling region. The slope of the plot of $\text{Log}_2(F(n))/\text{Log}_2(n)$ is called the scaling or self-similarity coefficient. This exponent is 0.5 if $x(i)$ is uncorrelated white noise; it is 1.5 if $x(i)$ is Brownian noise, and it is 1 if $x(i)$ is $1/f$ noise.

Test Signals

To illustrate the combined synchronization likelihood and detrended fluctuation analysis, we applied this analysis to two different sets of test signals. First, we considered two uncorrelated time series of white noise (Fig. 2A). For the first 500 samples, the amplitudes of the two time series were the same; for the last 500 samples, the amplitude of one of the two time series was multiplied by five. The synchronization likelihood was computed as a function of time for these two time series (Fig. 2B). As can be seen in Figure 2B, the synchronization likelihood fluctuated around the expected value for uncorrelated time series of $p_{\text{ref}} = 0.05$ over the whole range of 1,000 samples. Thus, the sudden increase in amplitude of one of the two time series did not affect the synchronization likelihood. Detrended fluctuation analysis was then applied to a time series of synchronization likelihood determined from four consecutive epochs such as shown in Figure 2A. The results (Fig. 2C) show only moderate scaling and a scaling exponent close to 0.5, which suggest little or no correlations between successive values of the synchronization likelihood time series.

Next, a similar analysis was applied to a set of two white noise signals that were uncorrelated for the first 500 samples, and strongly correlated for the next 500 samples, while the amplitudes were the same (Fig. 3A). Here, the synchronization likelihood is close to 0.05 for the first 500 samples, and shows a clear and sustained increase after sample 500, reflecting the increased coupling. The detrended fluctuation analysis of a synchronization likelihood time series determined from four concatenated epochs such as the one in Figure 3A shows no scaling, but rather reflects the characteristic time scale (500 samples) on which the coupling strength fluctuates (Fig. 3C).

Finally, we considered the influence of the montage on the synchronization likelihood and the DFA analysis. An EEG epoch of a representative subject was filtered in the β band (13–30 Hz) and was reformatted in four different montages: linked pre auricular electrode (A1/A2), common average (based upon all electrodes except Fp2 and Fp1; this montage was used in the rest of this study), bipolar chain with short electrode distances (bipolar), and a source, constructed by subtracting the voltage at each electrode from the mean of the four surrounding electrodes (source). Results are shown in Figure 4. Figure 4A shows the DFA plots for the four different montages. There is only a modest influence of montage, which is most clear for long time scales. The slope is steepest for A1/A2, and then decreases for average, bipolar, and source. The slope of a linear fit through the first four points of the DFA plot (the procedure used in this study) is shown in Figure 4B. For all montages, the slope is close to one. Montage has a stronger influence on the mean synchronization likelihood: the SL is highest for the A1/A2 montage, and substantially lower for the other three montages. The A1/A2 montages accentuate long-distance coupling at the cost of small-scale detail, while the reverse is true for the source montage. The average montage has intermediate properties and was used in the rest of this study [Nunez et al., 1992].

Statistical Analysis

Statistical analysis was done with SPSS for Windows, version 10.0. The dependence of the mean synchronization likelihood (averaged over all pair-wise combinations of channels and over all time samples) on frequency band (within-subjects factor with five levels: δ , θ , α , β and γ) and condition (within-subjects factor with two levels: eyes closed and eyes open) was examined with a two-way repeated-measures ANOVA with Greenhouse-Geisser corrected degrees of freedom (in the results section the uncorrected degrees are given). Sub effects were examined with t -tests. The results for the scaling exponent were tested similarly.

RESULTS

Synchronization Likelihood

Results for the mean synchronization likelihood are shown in Figure 5. The main effect of band was significant ($F_{4,56} = 16.363$, $P < 0.001$). The main effect of condition failed to reach significance ($F_{1,14} = 0.153$, $P = 0.702$), whereas the interaction of band $\times$ condition was significant ($F_{4,56} = 7.262$, $P = 0.006$).

To explore the significant main effect of band on the synchronization likelihood, pair-wise comparisons were made between all five frequency bands. This showed a clear distinction between the bands: a low-frequency range (consisting of the δ , θ , and α bands) with relatively high SL, and a high-frequency range (consisting of the β and γ bands) with relatively low SL. All comparisons within either the low-frequency or the high-frequency range were not signif-

Figure 2.

Insensitivity of synchronization likelihood to changes in amplitude. **A:** Two different, uncorrelated time series of white noise. For the first 500 samples, the amplitude of both time series is the same; for the last 500 samples, the amplitude of the upper time series is increased by a factor five. **B:** The time series of the synchronization likelihood of the time series shown in A (parameters for synchronization likelihood: lag = 10; embedding dimension = 10; V1 or Theiler correction = 100; V2 = 400; $p_{\text{ref}} = 0.05$). The synchronization likelihood fluctuates around the expected value of

p_{ref} (0.05) as expected for uncorrelated time series. Note that the synchronization likelihood is not at all affected by the sudden increase in amplitude of the upper time series at time sample 500. **C:** Detrended fluctuation analysis of synchronization likelihood determined from two time series of 4,000 samples, constructed by pasting together four different time series pairs such as shown in A. The bold plot is F_t as a function of time. The dotted line is a linear fit through the first four points. The scaling exponent (0.548) is close to 0.5 expected for a random time series.

Figure 3.

Figure 4.

Influence of the montage on synchronization likelihood and slope of the DFA plot. Results are shown for a representative subject for the β band (13–30 Hz). Four different montages were used: linked pre auricular electrodes (A1/A2), common average (based upon all electrodes except Fp2 and Fp1; this montage was used in the rest of this study), bipolar chain with short electrode distances (bipolar), and a source, constructed by subtracting the voltage at each electrode from the mean of the four surrounding electrodes (source). **A:** DFA plots. The plots show a modest influence of montage on the slope, especially for long time intervals. The slope of a linear fit decreased slightly going from the A1/A2, to the average, the bipolar, and finally the source montage. **B:** The slope of a linear fit through the first four points of the DFA plot is close to 1, and decreases as indicated above. Montage has a stronger influence on the mean synchronization likelihood: this is substantially higher for the A1/A2 montage, and much lower for the average, bipolar, and source montages.

icant, whereas all comparisons of SL between bands of the low-frequency range on the one hand and the high-frequency range on the other hand were significant with $P \leq 0.001$. (The mean synchronization likelihood in the δ , θ , and α band was higher than that in the β and γ band.)

The band $\times$ condition interaction was further examined by testing the condition effect within each frequency band

separately with t -tests. In the θ band, the synchronization likelihood was higher during eyes open than during eyes closed ($t_{14} = -2.619$, $P = 0.020$). An opposite effect was found in the α band ($t_{14} = 3.917$, $P = 0.002$) and the β band ($t_{14} = 2.546$, $P = 0.028$). In the other bands, no significant condition effects were found. Thus, the band $\times$ condition interaction for the synchronization likelihood is due to the

Figure 3.

Sensitivity of synchronization likelihood to changes in coupling strength. **A:** Two different time series of white noise. For the first 500 samples, the time series are uncorrelated; for the last 500 samples, the time series are strongly coupled, but the amplitudes are unaltered. **B:** The time series of the synchronization likelihood of the time series shown in A (parameters for synchronization likelihood: lag = 10; embedding dimension = 10; W1 or Theiler correction = 100; W2 = 400; $p_{ref} = 0.05$). The synchronization likelihood fluctuates around the expected value of p_{ref} (0.05) for the first 500 samples as expected for uncorrelated time series. The synchronization likelihood shows a sharp and strong increase

after sample 500, reflecting the increase in coupling between the two time series. **C:** Detrended fluctuation analysis of synchronization likelihood determined from two time series of 4,000 samples, constructed by pasting together four different time series pairs such as shown in A. The bold plot is F_t as a function of time. The dotted line is a linear fit through the first four points. The scaling exponent (0.620) of the first part of the DFA plot is close to 0.5 expected for a random time series. The plot as a whole is not described by a single linear fit, which suggests the existence of a characteristic time scale. This characteristic time scale is due to the strong and weak coupling, which alternate every 500 samples.

Figure 5.

Mean synchronization likelihood in different frequency bands (δ = 0.5–4 Hz; θ = 4–8 Hz, α = 8–13 Hz, β = 13–30 Hz, and γ = 30–48 Hz) and conditions (EC = eyes closed; EO = eyes open). Error bars indicate the standard deviation.

opposite effects of condition in the θ band (increase in SL) as opposed to the α and β band (decrease in SL).

Scaling Exponent

Detrended fluctuation analysis was applied to time series of SL for different frequency bands and different conditions. This resulted in one scaling exponent per band per condition for each of the 15 subjects. In all subjects, the plot of $\text{Log}_2(F_n)$ as a function of $\text{Log}_2(n)$ showed a clear scaling region, which allowed for determining a scaling and a slope. The actual slope was determined from a linear fit through the first four points of the plot (n ranging from 4 to 32 samples, corresponding to time scales of 8 to 64 milliseconds). Results for the α and β band of the first subject are shown in Figure 6 (note that the actual scaling region extends far beyond the time scale of 64 milliseconds). The scaling behavior in the other subjects was comparable.

Mean results for the scaling exponent are shown in Figure 7. The main effect of band was highly significant ($F_{4,56} = 525.444$, $P < 0.001$). The scaling exponent was generally lower during the eyes-open condition than during the eyes-closed condition (significant main effect of condition, $F_{1,14} = 5.815$, $P = 0.030$). Finally, the band $\times$ condition interaction showed only a trend ($F_{4,56} = 3.039$, $P = 0.088$).

The main effect of band was further examined by pairwise comparisons of the scaling exponent in the five different frequency bands pooled over conditions. All comparisons were significant at the $P < 0.001$ level, that is: the scaling exponent in each of the five bands differed significantly from that in all other bands. The exponent was highest in the θ band (mean = 1.580, S.E. = 0.008) followed by the α band (mean = 1.520, S.E. = 0.008), the δ band (mean = 1.322, S.E. = 0.024), the γ band (mean = 1.045, S.E. = 0.014), and finally the β band (mean = 0.976, S.E. = 0.012). The condition effect within each frequency band was examined with a t -test. Eye opening resulted in a significant decrease of the scaling exponent in the α band ($t_{14} = 4.716$, $P < 0.001$) and the β band ($t_{14} = 2.801$, $P = 0.014$). Condition effects within the other bands failed to reach significance.

DISCUSSION

The most important finding of the present study is the scale-free, self-similar dynamics of global EEG synchronization levels. Scale-free dynamics were found for fluctuations of synchronization in δ , θ , α , β , and γ bands, and for eyes-closed as well as eyes-open no-task states. The scaling exponents of synchronization fluctuations differed significantly for the different frequency bands. Also, the scaling

Figure 6.

Detailed results of a representative subject. **Left:** The time series of the synchronization likelihood (averaged over all pair-wise combinations of channels for each time sample) for the α and the β band (scale Y-axis arbitrary). **Right:** The corresponding plot of the $\text{Log}_2(F_n)$ vs. $\text{Log}_2(n)$ are shown. Time is indicated in samples;

time in milliseconds is twice this value. Linear scaling can be seen in both plots. The scaling exponent was determined by a linear fit through the first four points of the plot. Note, however, that the actual linear scaling region was longer and extended to the longest time scale for the β band.

exponent decreased during eyes open as compared to eyes closed, especially in the α and β band. Before we discuss these findings in relation to scaling in more detail, we briefly discuss the changes in the mean synchronization levels in different frequency bands and conditions.

The overall synchronization strength, averaged over all pair-wise combinations of channels as well as over time, resulting in a single value for each analyzed epoch, displayed significant differences between frequency bands and conditions (Fig. 2). On the basis of synchronization levels, a slow frequency range (comprising the δ , θ and α bands) and a fast frequency range (including the β and γ bands) could be distinguished. Synchronization levels did not differ between bands within each of these groups. However, the synchronization of the bands in the low-frequency range was significantly higher than that of the bands with high frequencies. This pattern of differences in synchronization strength between different bands is known from other stud-

ies using the synchronization likelihood, although it was not tested formally in these studies [Stam et al., 2002a,b, 2003b].

Eye opening resulted in a significant increase in synchronization in the θ band, as well as a significant decrease of synchronization in the α and β bands. Large-scale desynchronization of α and β band during the eyes-open state probably is a non-specific reflection of more activated cortical networks. This is in agreement with the well-known finding that local desynchronization of the α band (event-related desynchronization, or ERD) is a good measure of local cortical activation [Pfurtscheller and Aranibar, 1997]. The increase in θ synchronization, although less strong than the α desynchronization, is of interest because it is a reminder of the increased θ synchronization that has been described during working memory tasks [Sarnthein et al., 1998; Stam et al., 2002a]. Although in the present study, the eyes-open condition was not associated with a specific task, it is possible that the increased processing of visual input

Figure 7.

Mean scaling exponent in different frequency bands (δ = 0.5–4 Hz; θ = 4–8 Hz, α = 8–13 Hz, β = 13–30 Hz, and γ = 30–48 Hz) and conditions (EC = eyes-closed; EO = eyes=open). Error bars indicate the standard deviation.

during the eyes-open state also activates working-memory processes to a certain extent.

Although changes in time-averaged synchronization levels provide some insight in the functional connectivity of ongoing EEG during eyes-closed and eyes-open states, they do not reveal the small-scale nature of the underlying dynamics. The principal question we wanted to address is whether ongoing EEG reflects a rapid succession of synchronized and desynchronized networks, and whether these events display scale-free dynamics, or have a characteristic time scale instead. To address this question, we considered time series of the synchronization likelihood, where the averaging is only done over all pair-wise combinations of channels (providing a “global” index of synchronization) but not over time. Examples of such synchronization time series, computed from EEG filtered in the α or β band, are shown in Figure 6. The presence of scale-free fluctuations in these time series was examined with detrended fluctuation analysis (DFA), because this method is robust when applied to possibly non-stationary physiological data [Peng et al., 1995]. We found linear scaling in a double logarithmic plot of the fluctuations of the mean synchronization level as a function of the observation time scale, which indicates scale-free, self-similar dynamics in all frequency bands and in

both eyes-closed and eyes-open conditions (for a representative example, see Fig. 6). This means that, in ongoing EEG during a no-task state, synchronization events do not seem to have a characteristic time scale, but rather show fluctuations that are correlated over a whole range of time scales. However, we should note that in the case of the α rhythm, the scaling breaks down at longer time scales, whereas for the β band it seems to hold on all time scales considered.

Although scaling behavior was found for all frequency bands and in both conditions, there were differences between the frequency bands studied in the scaling exponent determined from the slope of the double logarithmic plot of fluctuations vs. time scale. This is in contrast to the time-averaged synchronization, which only showed a differentiation between a slow (δ , θ , and α) and a fast (β and γ) range. A large scaling exponent reflects slow fluctuations and a small scaling exponent reflects more rapid fluctuations in the synchronization time series. The largest mean scaling exponent was found for the θ band (1.580), followed by the α (1.520) and δ (1.322) bands. The smallest scaling exponents were found for the γ (1.045) and β (0.976) bands. Thus, the value of the scaling exponent is not related to the frequency band in a trivial, predictable way, because in that case it would be expected that the exponent would be highest for

the δ band, and systematically decreasing with increasing frequency. For the two lowest frequency bands, the value of the exponent is close to 1.5, which is the theoretical value for fractal Brownian noise. Interestingly, for the β and γ bands the scaling exponent is close to 1, which is the theoretical value for so-called $1/f$ noise.

The scaling exponent was also affected by the transition from the eyes-closed to the eyes-open state. There was a general tendency for the exponent to decrease during eye opening, which was most significant in the α band and somewhat less significant in the β band. Decrease in the scaling exponent reflects a relative preponderance of rapid fluctuations with respect to slow fluctuations in the mean synchronization level. This finding is in agreement with a view of information processing in the brain as a state of rapid changes in the synchronization level [Stam et al., 2002b, 2003a].

The scale-free nature of global synchronization dynamics is in agreement with the suggestion of self-organized criticality by Freeman et al. [2003] and Le van Quyen [2003]. A few studies have described scale-free patterns in spontaneous fluctuations in coupling between EEG channels [Bullock et al., 1995; Gong et al., 2003; Leopold et al., 2003]. Bullock et al. [1995] found that fluctuations of coherence between intracranial EEG electrodes in human subjects with temporal lobe epilepsy showed large fluctuations without clear periodicity. Leopold et al. [2003] studied band-limited field power of local field potentials in the visual cortex. They found fluctuations of the band-limited power at many time scales, which were strongly coherent between electrodes, particularly in the γ band, but did not depend upon the behavioral condition. Finally, Gong et al. [2003] demonstrated scale-free dynamics of α -band intermittent phase synchrony in the scalp EEG of six healthy subjects. The study of Gong et al. [2003] was the only one of these three in which the scaling was explicitly demonstrated.

Our results agree with the main conclusion of these other studies, namely that fluctuations in coupling/synchronization levels between different brain regions do not have a characteristic time scale, but rather have scale-free dynamics. Apparently, the same conclusion is reached in animals and human subjects, with both intracranial and scalp recordings and using either coherence, phase synchronization, or synchronization likelihood as a measure of coupling. In addition to the other studies, however, we could demonstrate that the scaling exponent differs significantly between eyes-closed and eyes-open states. The scaling exponent is thus not a pure "trait" measure, but also reflects "state" characteristics.

Further support comes from a series of studies that have demonstrated scaling behavior in local EEG [Hwa and Ferree, 2002; Lee et al., 2002; Shen et al., 2003; Watters, 1998] and MEG time series [Linkenkaer-Hansen et al., 2001]. Although fluctuations of the power of individual EEG channels do not contain information about long-distance coupling between brain regions, it can be considered to reflect the small-scale synchrony of the cortex. The presence of self-similar features

in local as well as long-distance synchronization fluctuations suggests that the same or a similar kind of dynamics may be responsible for both.

At first sight our results seem to be in disagreement with a number of studies that have reported or suggested the existence of a characteristic time scale or modulation frequency of synchronous cell assemblies [Burgess and Ali, 2003; Rodriguez et al., 1999; Schack et al., 2002]. However, a possible explanation for this discrepancy might be the difference in the experimental approach between studies that do and studies that do not find characteristic time scales. All the studies that suggest the existence of distinct synchronous cell assemblies with durations of a few hundred milliseconds use very short EEG segments averaged over many (stimulus-locked) trials. In contrast, all the studies that do not report characteristic time scales but scale-free dynamics are based on the analysis of non-averaged, spontaneous, ongoing EEG signals of much longer duration [Bullock et al., 1995; Gong et al., 2003; Leopold et al., 2003]. It may be that the analysis of rapid connectivity changes in averaged, evoked, or induced trials selects a specific component with a specific time scale out of an ongoing dynamics that in itself is scale-free, which can only be revealed on long time scales and without averaging.

In this context, it is appropriate to point out that the so-called "no-task" eyes-closed/eyes-open states cannot be merely be considered as simple "resting" states in which no information processing is going on. Even when there is no task, there is still consciousness and internal thinking. Recently, a complex network of activated brain areas has been revealed during a no-task state with fMRI analysis [Greicius et al., 2003]. This finding stresses the fact that no-task states are better described by the acronym REST (random episodic spontaneous thought) coined by Nancy Andreasen. Such states are not simply noise, but may reveal properties of brain dynamics that are "averaged away" in the typical averaged trial approach. The relevance of the scale-free synchronization dynamics of neural networks for information processing is suggested by the observation that behavioral measures during a long-lasting cognitive task also display scale-free, $1/f$ statistics [Gilden et al., 1995].

If we assume that, at least in the REST state, brain dynamics are characterized by scale-free fluctuations of synchronization levels, this raises the question how this kind of dynamics can be explained. Leopold et al. [2003] suggested that slow fluctuations in large-scale connectivity patterns could be due to slow changes in brain-stem noradrenergic and cholinergic activating systems. From a more theoretical point of view, it is known that scale-free behavior can arise in dynamic systems operating in the vicinity of a bifurcation or phase transition. In a model of the α rhythm, it has been shown that the infrequent occurrence of weakly non-linear α bursts could point to dynamics of the underlying neural networks close to a bifurcation [Stam et al., 1999]. However, in general, it would require delicate fine-tuning of control parameters to keep a system at the bifurcation point.

An alternative explanation for scale-free dynamics in large-scale dynamic systems has been suggested by Bak et al. [1987]. They have shown that, under some very general conditions, systems that consist of a large number of interacting non-linear elements automatically evolve to a critical state with fluctuations at all spatial and temporal scales. This phenomenon is called “self-organized criticality” and has been suggested as an explanation of scale-free dynamics in the brain by several authors [Freeman, 2003; Gong et al., 2003; Le van Quyen, 2003; Linkenkaer-Hansen et al., 2001]. In support of this idea, Corral et al. [1995] have shown that self-organized criticality can emerge in networks of coupled relaxation oscillators that reflect the integrate-and-fire properties of neurons. Further studies should be directed at demonstrating the universal character of scale-free synchronization dynamics in the brain, the factors that determine the scaling exponent, its possible relation to behavioral measures, and optimal information processing.

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