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Reduced degree of long-range phase synchrony in pathological human brain

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Abstract. In this paper multivariate spontaneous EEG signals from three broad groups of human subjects - control, seizure, and mania - were studied with the aim of investigating the possible effect of these pathologies on the degree of phase synchronization between cortical areas. The degree of phase synchrony was measured by two recently developed measures which are more suitable than classical indices like correlation or coherence when dealing with nonlinear and non-stationary signals like the EEG. Signals were reduced to seven frequency bands (delta, theta, alpha-1, alpha-2, beta-1, beta-2 and gamma) which were statistically compared between the normal and the other two groups. It was found that the degree of long-range synchrony was significantly reduced for both pathological groups as compared with the control group. No clear differences were found in the degrees of short-range synchrony.

Key words: synchronization, frequency, phase, EEG, healthy, seizure, mania

INTRODUCTION

Synchronization is one of the most ubiquitous phenomena observed in various fields of science (Hugenii 1673, Blekhman 1988, Glass and Mackey 1988). In neurophysiology a major focus is to detect synchronization between neurons (or neuronal assemblies) – within one area of the brain and between different parts of the brain (Singer and Gray 1995). Synchronization seems to be a basic mechanism for neuronal information processing within a brain area as well as for communication between different brain areas (Makarenko and Llinás 1998). Through animal experiments, it was found (Gray et al. 1989) that synchronization of neuronal activity in the visual cortex plays a putative role for the binding of different but related visual feature so that an integrated visual pattern can be recognized as a whole. Further, cognitive acts require the integration of numerous functional areas widely distributed over the brain (Bressler et al. 1993, Roelfsema et al. 1997).

On the other hand, too much of synchrony can cause dynamical disease (Belair et al. 1995) e.g., epilepsy or tremor (Elbe and Koller 1990). In pathological case the nature of neuronal synchronization is usually local (generalized seizure is an exceptional case where large parts of the brain show synchronized spike and wave complexes followed by the loss of consciousness). In the ictal phase of partial epilepsy, high synchronization is found around epileptic foci. Thus, assessment of synchronization is important to obtain a better insight into the physiology of brain functioning in normal as well as in pathological condition.

But how can we tell from observed signals whether the two systems generating the signals are synchronized or not? In identical synchronization, states of the two interacting systems coincide asymptotically when the coupling strength exceeds a certain critical threshold (Pecora and Carroll 1990). The notion of generalized synchronization (Schiff et al. 1996) requires that states of the coupled systems are related by a smooth function; but in real-life signals, it is difficult to detect the functional relationship without having prior knowledge of the underlying dynamics of the interacting systems. Recently, another type of synchronization called phase synchrony has been demonstrated (Rosenblum et al. 1996) in which the synchronization is defined as the appearance of a certain relation between the phases of the interacting systems while the amplitudes may remain uncorrelated.

In neurophysiology the most common measures used to find synchronization are correlation in the time domain and coherence in the frequency domain (Clifford 1987, Petsche and Etlinger 1998). Cross correlations measure the linear correlation between two signals, and coherence is the ratio of the cross-spectrum to the product of auto-spectra. Generally speaking, coherence (χ) measures the phase consistency of the two signals as a function of frequency: at frequency f, $\chi=1$ indicates that the two signals maintain constant phase differences, whereas $\chi = 0$ indicates that the phase differences vary from epoch to epoch. The quality of the coherence-based results depends heavily on variables such as data segmentation, length of signals, the assumption of an underlying linear relationship and stationarity etc. Since coherence mixes the amplitude information with that of phase, it is not a suitable indicator for the detection of phase synchronization, an intrinsic property of neuronal assemblies (Lachaux et al. 1999).

In this paper, we have used two recent approaches (Tass et al. 1998, Mormann et al. 2000) to assess the degree of phase synchrony in multivariate spontaneous and non-paroxysmal EEG signals recorded from human subjects suffering from seizure, and mania. A normal control group was studied as well.

As already mentioned, strong synchronization is associated with generalized seizure. But for focal seizure patients, the seizures are thought to originate from a localized region of the brain, the epileptogenic focus, and rapidly propagate to recruit neighboring cortical regions. During the ictal phase nearly periodic spike-wave complexes appear due to strong synchronization, but the inter-ictal EEG can be irregular like normal background EEG and traditional linear techniques may fail to detect the hidden pathology. There have been a few recent attempts to use nonlinear signal processing techniques (Lehnertz and Elger 1998, Martinerie et al. 1998) to anticipate seizures by analyzing inter-ictal EEG. However, the mathematical assessment of synchrony in the EEG has not been widely reported in states of psychopathology. Shaw et al. (1978) were among the first to apply spectral coherence measures to find differences between psychiatric patients (mainly schizophrenics) and control subjects. Correlations were reported between the coherence change score in the alpha band and the score of the laterality of cerebral function in cognitive tasks. Decreased local coherence values for schizophrenics compared with control subjects have also been reported (Lacroix et al. 1993). Overall, coherence values were highest in controls, intermediate in depression and smallest in mania and schizophrenia (Flor-Henry 1988). So, the measures to assess the

degree of cortical synchronization from noninvasive EEG signals may be useful as diagnostic tools.

The primary aims of this paper are as follows: (i) to investigate and compare the degree of long-range cortical phase synchrony between control and pathological groups, (ii) to probe the role of different frequency bands, and (iii) to compare the performances of two indices measuring phase synchrony. Since phase synchrony is a direct marker of the enhancement of interaction between two brain regions, new insight into the functioning of the normal and diseased brain might be obtained through this approach.

METHOD

Synchronization in periodic oscillators

In the classical case of periodic self-sustained oscillators, phase synchronization is usually defined as the locking of the phases, ϕ_x and ϕ_y of the time series $x(t)$ and $y(t)$, namely

$$\varphi_{m,n} = m\phi_x - n\phi_y = const. \qquad (1)$$

where $\varphi_{m,n}$ is the generalized phase difference or relative phase, and m and n are some positive integers. The detection of phase synchronization in coupled nonlinear chaotic systems calls for a general condition (Rosenblum et al. 1996):

$$\varphi_{m,n} = \left|m\phi_x - n\phi_y\right| < const. \qquad (2)$$

while the amplitudes of the two time series may be completely uncorrelated or linearly independent. The frequency locking condition is $m\omega_x = n\omega_y$ where

$$\omega_{x,y} = \left\langle \frac{d\phi_{x,y}}{dt} \right\rangle$$

are the mean rotation frequencies of the individual oscillator. These requirements are fulfilled within the Arnold tongues (Arnold 1965), for which the $m : n$ resonance limit cycle is stable. Outside the motion of relative phase is quasi-periodic described by a torus.

Noisy/chaotic oscillators

The identification of phase synchrony in EEG signals is complicated by underlying irregularity or chaoticity, noise, and non-stationarity overlying the coordination mechanisms of interest. The direct evaluation of the instantaneous phase differences alone is insufficient to detect the existence of hidden phase synchrony. Fortunately, the properties of phase synchronization in irregular chaotic systems are similar to those of synchronization in periodic oscillators driven by noise; here, the generalized phase difference performs Brownian like motion in a tilted periodic potential, the slope of which is determined by the mismatch in the mean rotation frequency of the two systems. For weak noise, the relative phase oscillates around some constant value, and the mean frequency of both the systems is still locked. When the noise is unbounded, the relative phase remains in the potential well for some time (during this period, the phase locking is found). Afterwards it makes noise-induced slips of 2π from one potential well to another (Stratonovich 1963). So the relative phase of two coupled noisy systems contains segments where the phase is nearly constant, interrupted by noise-induced phase slips. For strong noise, the phase slips occur in both directions ($\pm 2\pi$), and the segments of nearly constant relative phase are very short (Neiman et al. 1999). Thus, the synchronization transition is completely smeared and can be detected through sophisticated analysis.

It may be noted that phase synchronization can be possible without frequency synchronization if the probabilities of phase slips in the upward and downward directions differ. This is in contrast to the classical understanding where phase synchronization was thought to be inseparable from frequency synchronization. Since in this paper the multivariate signals came from the same physiological system, only 1:1 ($m = n = 1$) synchronization is considered and the suffices are dropped for clarity.

Instantaneous phase

The phase of an arbitrary signal $x(t)$ can be determined by using the complex analytic signal (Bendat and Piersol 2000), $X(t)$ as follows

$$\mathrm{X}(t) = x(t) + ix_h(t) = x(t) + i\frac{1}{\pi}\int_{-\infty}^{+\infty}\frac{x(\tau)}{t-\tau}d\tau \qquad (3)$$

where $x_h(t)$ is the Hilbert Transform of $x(t)$, and the integration is performed in the sense of the Cauchy principal value. The analytic signal is further decomposed as $X(t) = a(t)e^{i\phi(t)}$, where $a(t)$ is the instantaneous amplitude, and $\phi(t)$ is the instantaneous phase. Other methods to determine the phase of a time series are also available

(Pikovsky et al. 1997), but Hilbert transform is used here since it does not require the signal to be stationary. The two indices used to measure the degree of phase synchronization are computed as follows.

Statistical phase synchrony

For a pair of signals $\{x_{1,2}(t)\}$, instantaneous phases ($\phi_{1,2}(t)$) are calculated according to Eq. (3) where the phases are defined on the real axis. Relative phase is calculated as $\varphi = |\phi_1 - \phi_2|$ and the distribution function for $\{\varphi \; mod \; 2\pi\}$ is computed. To characterize the strength of phase synchrony, the deviation of the above distribution from the uniform distribution has to be statistically quantified. In order to meet this goal, an index based on Shannon's entropy was computed as follows (Tass et al. 1998)

$$\rho = \frac{H_{\max} - H}{H_{\max}} \tag{4}$$

where entropy of the distribution of $\{\varphi \; mod \; 2\pi\}$,

$$H = -\sum_{i=1}^{M} p_i \ln p_i,$$

M is the number of bins used to obtain the distribution function, and p_i is the probability of finding the relative phase φ within the i-th bin. The maximum entropy ($H_{\max}$) is given by ln M; the optimum number of bins (M) is set as $e^{0.626+0.4\ln(L-1)}$ (Otnes and Enochson 1972) where L is the number of data points.

Mean phase coherence

Here the phases, as computed by Eq. (3), are distributed on the unit circle (restricted to the interval $[0, 2\pi]$) and the relative phase is computed as: $\varphi = \phi_1 - \phi_2$ where $\phi_{1,2}$ are the instantaneous phases of the two signals. The mean phase coherence (Mormann et al. 2000) is defined as:

$$R = \left| \frac{1}{L} \sum_{i=0}^{L-1} e^{i\varphi(t)} \right|$$

which can also be presented as follows,

$$R = \sqrt{\left(\frac{1}{L} \sum_{j=0}^{L-1} \sin(\varphi(j\delta t)) \right)^2 + \left(\frac{1}{L} \sum_{j=0}^{L-1} \cos(\varphi(j\delta t)) \right)^2} \tag{5}$$

where $1/\delta t$ is the sampling rate of the signals.

The values of ρ and R are confined between 0 (no synchrony) and 1 (perfect synchrony) and both the indices monotonically increase with the degree of phase synchrony (Bhattacharya and Petsche 2001).

Recording and processing of data

SUBJECTS

Three different groups: 9 control subjects with no reported psychiatric or neurological disorders, 9 subjects with maniac symptoms, and 8 subjects with seizure were chosen for this study. The subjects were within the age range of 18-65 years with the mean ages of 32.50, 30.44 and 28.44 years for the three groups, respectively (Bhattacharya 2000). All the subjects gave written consent prior to the recording.

DATA

The background EEG signals were recorded from electrode locations Fp1, Fp2, F7, F3, F4, F8, T3, C3, C4, T4, T5, P3, P4, T6, O1, O2 on the scalp (Fig. 1) according to the standard 10-20 International electrode placement system (Jasper 1958). The average signals from the

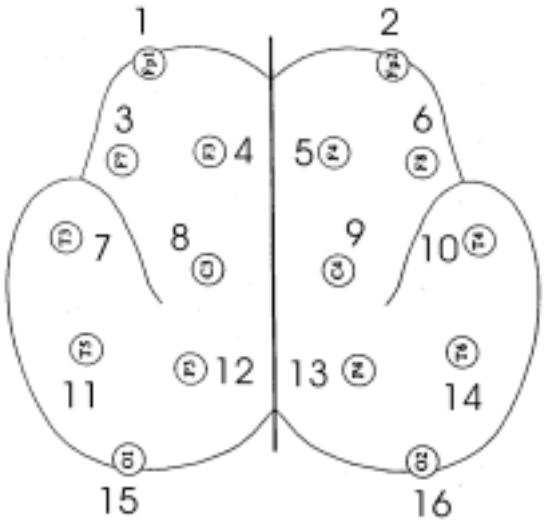

Fig. 1. Positions of the 16 electrodes including their number and their designations. The schemata are based on the internationally established 10-20 system. Midline electrodes are exempted from this study. The following abbreviations are used: Fp for frontopolar, F for frontal (F3 and F4 for midfrontal, F7 and F8 for frontobasal), C for central, T3 and T4 for midtemporal, T5 and T6 for temporo-posterior and O for occipital.

two ear-lobes was used as a reference. The subjects were placed in a sound proof, light attenuated air-conditioned (20°C) room and instructed to relax and close their eyes during the data acquisition period. The sampling frequency was 200 Hz and the signal was filtered between 0.1-70 Hz preceded by a notch filter of 50 Hz.

The total frequency spectrum of the EEG spanning roughly the range from 1 Hz to 70 Hz was divided into seven bands in order to obtain an overview over the total spectrum. Different frequency bands reflect functionally different components of information processing acting on various spatial scales. In this study the seven frequency bands were as follows: delta (1.0-4 Hz), theta (4-7 Hz), alpha-1 (7-10 Hz), alpha-2 (10-13 Hz), beta-1 (13-18 Hz), beta-2 (18-30 Hz) and gamma (30-7 Hz). An epoch length of at least 20 s of EEG data free from any artifacts and visual complexes, (e.g., the spike wave complexes for the seizure patients) were selected. The average (per subject) epoch lengths studied for the three groups were 29, 24, and 26 s, respectively. Baseline drift due to possible electrode movement was removed by subtracting a polynomial of 2nd order. The data were finally band-pass filtered by 6th-order IIR type Butterworth filter in the seven frequency bands.

STATISTICAL ANALYSIS

Both measures of phase synchrony (R and ρ) were computed by a sliding window approach with a window length of 8 s and windows overlapped by 7 s. For each frequency band and in each window, 120 values of ρ were produced considering all possible combination between sixteen electrodes. Based on the physical location of the electrodes, two kinds of synchrony were considered as follows: (i) long-range synchrony between two electrodes, which are either located in opposite hemispheres or are not immediate spatial neighbors, and (ii) short-range synchrony between neighboring electrodes within the same hemisphere (Fig. 2). Phase synchrony values for each electrode pair was compared statistically by non-parametric Wilcoxon rank-sum test ($P \leq 0.05$) between control and other two groups.

RESULTS AND DISCUSSIONS

Examples of EEG signal recorded by the O1 electrode are shown in Fig. 3(A)-(C) for three subjects each belonging to the three different groups. It is clear that all the signals represent spontaneous background activity free from paroxysmal complexes.

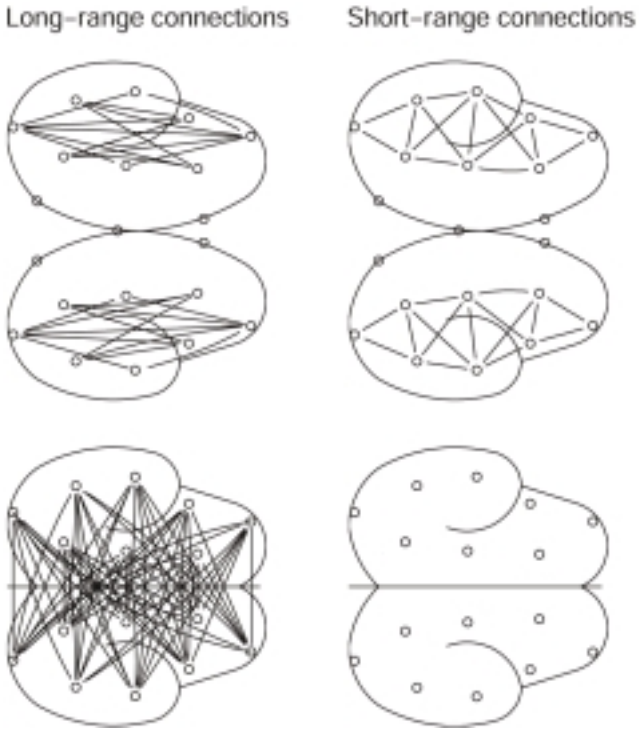

Fig. 2. Possible connections between electrodes for two varieties of synchrony: long-range (left) and short-range (right). Synchrony was classified as short-range if it was calculated between adjacent or neighboring electrodes (within a hemisphere). It was classified as long-range if at least one electrode was situated in between or the two electrodes were from opposite hemispheres.

Long-range synchrony

The total number of electrode pairs showing enhanced and statistically significant long-range phase synchrony, as measured by R, in the control group as compared with seizure group is shown in Fig. 4 (upper). In every frequency band, the degree of long-range synchrony is found to be significantly higher in the control group; the differences are most prominent in the delta, alpha-1, and alpha-2 bands. The comparison between the control and mania groups is also shown in Fig. 4 (lower). Almost no electrode pair showed higher phase synchrony in the subjects with mania compared with control subjects. In all the frequency bands except gamma, an extensive increase in the degree of long-range synchrony was found in control group. Here also the differences are strongest in the alpha bands.

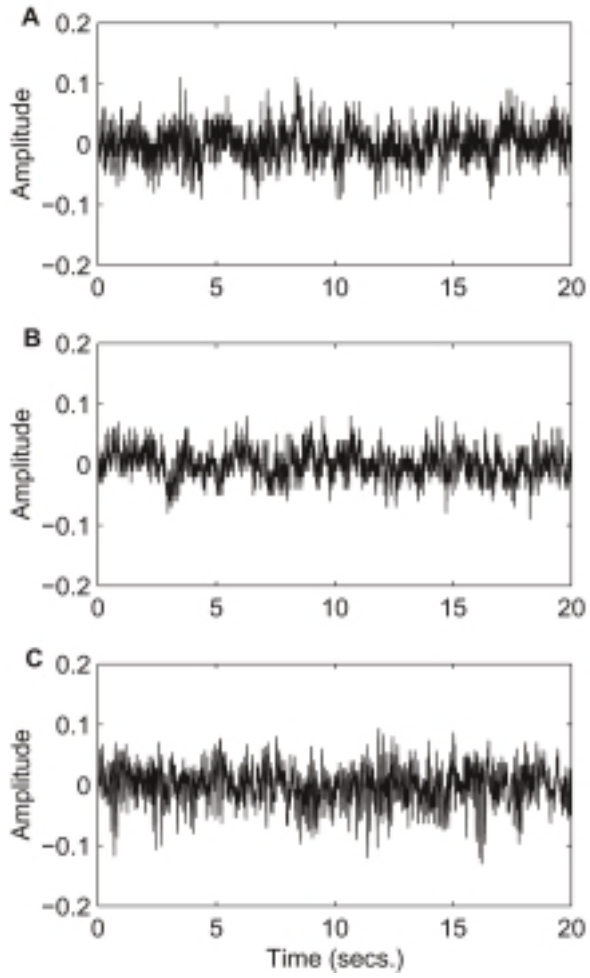

Fig. 3. (A)-(C) An example of 20 s (= 4,000 time samples) of non-filtered EEG signal recorded at electrode O1 from three subjects belong to the healthy, mania, and seizure groups, respectively. Individual signals look irregular and aperiodic and are free from visual complexes.

Thus, the degree of long-range phase synchrony was significantly reduced for pathological subjects as compared with healthy subjects who were without any known neurological problem.

The above analysis was repeated using the other index ρ to measure the degree of phase synchrony. Figure 5 shows the comparison between control and pathological groups in terms of increase (or decrease) in the degree of long-range phase synchrony. The results are strikingly similar to the results obtained using mean phase coherence. The control group shows significant enhancement in the degree of long-range synchrony as compared with both of the pathological groups. Thus, the two indices (ρ and R) are found to be fully compatible and produce equivalent results.

Short-range synchrony

Figure 6 shows the results of the comparison between control and pathological groups in terms of short-range synchrony (measured by R) in the different frequency bands. In sharp contrast to the results of long-range syn-

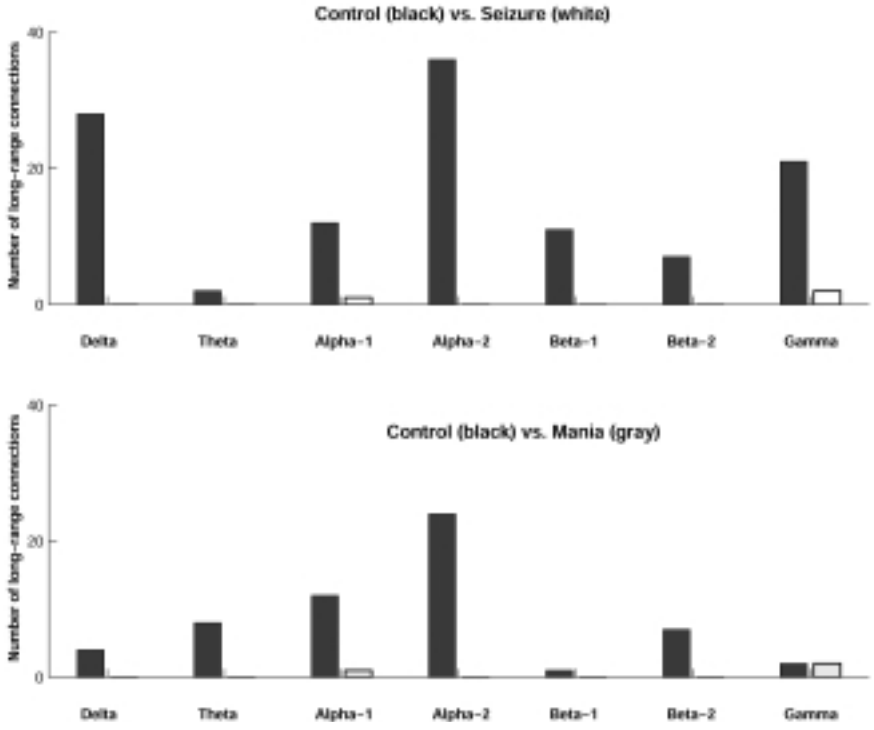

Fig. 4. Comparison in terms of long-range phase synchrony. Upper: Number of electrode-pairs showing significant ($P \leq 0.05$) increase in the degree of long-range phase synchrony while comparing two groups: control (black bar), and seizure (white bar). Phase synchrony was measured by mean phase coherence R (Eq. 5). Lower: same as in upper but while comparing control (black bar) with mania (gray bar) groups. It is to be noted that the phase synchrony measure is symmetric so the effective number of significant electrode-pairs is half of the value shown here. Control group presented stronger long--range synchrony as compared with both pathological groups.

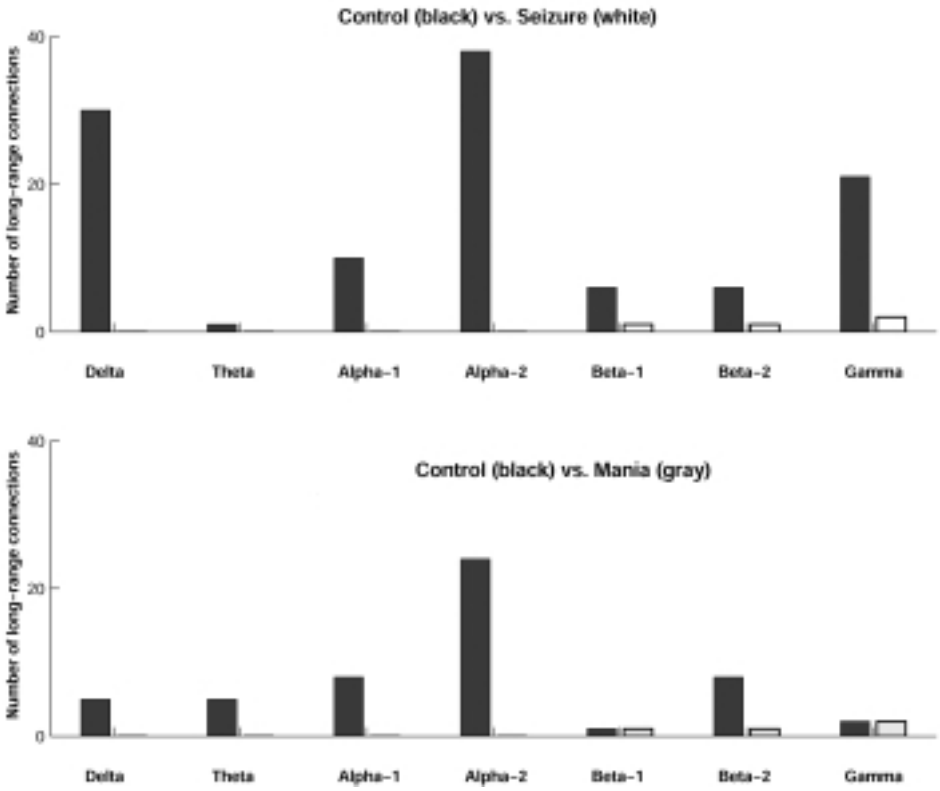

Fig. 5. Similar to Fig. 4 except phase synchrony was measured by the measure ρ (Eq. 4). The results are strikingly similar to Fig. 4.

chrony, no conspicuous differences were found between the control and pathological groups in local or short-range synchronization. The other index ρ produced similar results indicating no clear differences between the control and the other two groups.

Comments on long-range synchrony

Increases in long-range synchrony between distinct cortical areas may result from reentrant interactions between neuronal populations facilitated by cortico-cortical fiber systems (Lopes da Silva 1991, Srinivasan 1999). However, cortical networks can display different states of synchrony, with (or without) oscillations at different frequencies based on the size of the neuronal assemblies involved. In this study the signature of long-range synchrony in the control group is most prominent in the alpha bands. Classically, alpha rhythm is considered as an "idling-rhythm" of the brain, but recently it has been shown that alpha activity (along with other low frequency activity) is related to top-down processing which mediates interactions between distant cortical regions (Von Stein and Sarnthein 2000 and references therein). The alpha synchrony is maximal in situations where cortical processes are not subject to exogenous stimuli but are driven by free floating and spontaneous input. This theory is also supported by the presence of stronger alpha band long-range synchrony in the control group.

Further, in a recent study (Bhattacharya et al. 2000) using a similar data set, alpha waves from a single channel EEG were decomposed into regular and irregular components based on the presence of dominant oscillation. For regular components, a kind of hidden universal mechanism, resembling the critical properties at phase transition, was found in the occipital area of healthy subjects whereas subjects with seizure and mania failed to display this behavior; no difference was found for irregular components. Universality implies that different systems present similar properties near their respective critical points (Stanley 1971, Bhattacharya and Petsche 2001); here, the information is not in the details of the microscopic actions but in the nature of the paths along which order is propagated between subunits. At the critical point, interactions between distant subunits propagate extensively throughout the entire system leading to

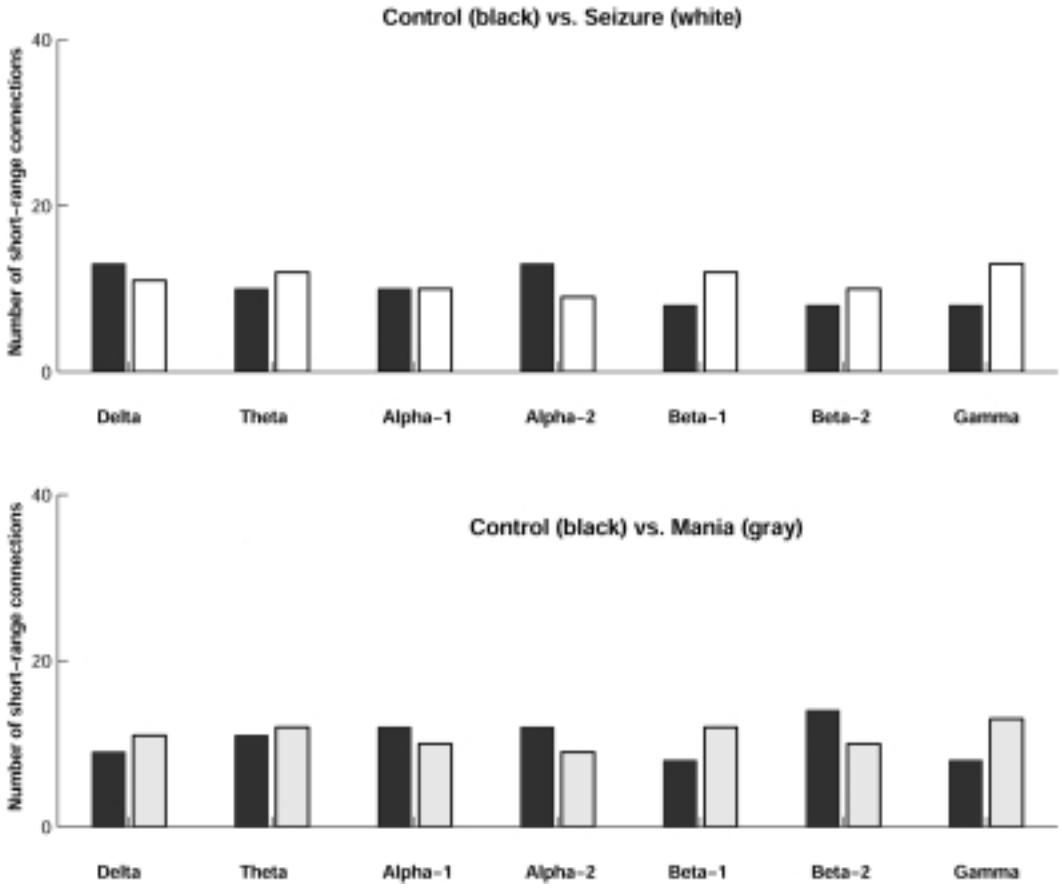

Fig. 6. Similar to Fig. 4 but only short-range phase synchrony (Fig. 3) was considered. No consistent differences were found between the control and pathological groups in the degree of local synchrony.

the emergence of long-range correlation. Correlations decay with exponential term along each path, but the number of such paths increases exponentially and power-law scaling appears primarily out of this competition from the multiplicity of interaction paths connecting neural assemblies in higher dimensions. Long-range phase coupling was also significantly higher in control subjects than subjects with some degree of pathology. So it may be assumed that the co-operation between distant brain areas, manifested by the alpha band phase synchrony, is critically important for maintaining spontaneous functioning of the healthy brain.

Practical remarks

There are a few practical points which need to be discussed. First, only 1:1 synchronization was considered here for the sake of simplicity, which by no means can be claimed to be unique. It will be interesting to search for higher level ($m \neq n$, $m, n > 1$) of phase synchrony among different brain areas. Second, by means of the adopted measures, we cannot prove the existence of actual coupling strength between two cortical areas and neither we can exclude the influences of many other cortical regions. The method of surrogate data might help to provide a confidence limit, which can exclude spurious synchronization detected by any applied index. Third, the division of the groups, as studied here, is too general. It is admitted that neurologically, mania and seizure are too broad to be classified as a single group, but the methods used were still able to discriminate the pathological groups in a conspicuous way based on the degrees of long-range synchrony. Fourth, the degree of long-range synchrony in the control group was mostly prominent in the delta, alpha-1, and alpha-2 bands. Figure 7 shows the total synchrony values, summed over all possible long-range electrode combinations, in these three frequency bands for 10 randomly chosen windows (each window of 8 s length) from each of the three groups. The windows, albeit randomly selected from the healthy

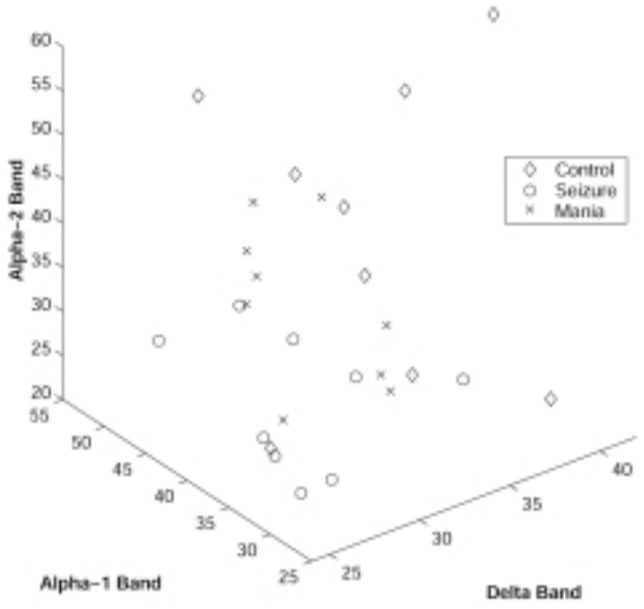

Fig. 7. Scatter plots of synchrony values in 10 randomly picked windows from each of the three groups. The values were summed over all possible combinations of electrodes.

groups, showed a tendency towards higher synchrony as compared with other groups. Finally, a technical question is whether the reported long-range synchrony is really long-range or is effected by the volume conduction between two electrodes. This effect, however, is unlikely for the electrode montage used in this study since the spatial resolution of the EEG is estimated to be approximately 5 cm (Nunez 1995) whereas the average distance between two electrodes within the same hemisphere, considered as long-range (Fig. 2), is 13 cm; further, near and distant electrode pairs were treated in the same way by always comparing the values of identical electrode pairs.

CONCLUSIONS

In the present study we have applied recently developed measures of phase synchronization to time series of brain electrical activity recorded non-invasively from control and pathological groups to investigate whether spatial changes in synchronization across various frequency bands can be related to pathological activity. The results indicate that the degrees of interdependences between cortical areas either distant or from opposite hemispheres are greatly reduced in both of the pathological groups as compared with healthy group, whereas no clear differences were found in the degree of local cortical interactions. Thus, these nonlinear indices based on phase synchrony might be used as a diagnostic tool in discriminating subjects with pathology and further can provide information about the underlying functional relationship between different brain areas leading to the possible localization of pathology. However, we would like to note that further studies are required to quantify the relation between long-range phase synchronization and any clinical state.

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