

Invited review

Nonlinear dynamical analysis of EEG and MEG: Review of an emerging field

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Abstract

Many complex and interesting phenomena in nature are due to nonlinear phenomena. The theory of nonlinear dynamical systems, also called ‘chaos theory’, has now progressed to a stage, where it becomes possible to study self-organization and pattern formation in the complex neuronal networks of the brain. One approach to nonlinear time series analysis consists of reconstructing, from time series of EEG or MEG, an attractor of the underlying dynamical system, and characterizing it in terms of its dimension (an estimate of the degrees of freedom of the system), or its Lyapunov exponents and entropy (reflecting unpredictability of the dynamics due to the sensitive dependence on initial conditions). More recently developed nonlinear measures characterize other features of local brain dynamics (forecasting, time asymmetry, determinism) or the nonlinear synchronization between recordings from different brain regions.

Nonlinear time series has been applied to EEG and MEG of healthy subjects during no-task resting states, perceptual processing, performance of cognitive tasks and different sleep stages. Many pathologic states have been examined as well, ranging from toxic states, seizures, and psychiatric disorders to Alzheimer’s, Parkinson’s and Creutzfeldt-Jakob’s disease. Interpretation of these results in terms of ‘functional sources’ and ‘functional networks’ allows the identification of three basic patterns of brain dynamics: (i) normal, ongoing dynamics during a no-task, resting state in healthy subjects; this state is characterized by a high dimensional complexity and a relatively low and fluctuating level of synchronization of the neuronal networks; (ii) hypersynchronous, highly nonlinear dynamics of epileptic seizures; (iii) dynamics of degenerative encephalopathies with an abnormally low level of between area synchronization. Only intermediate levels of rapidly fluctuating synchronization, possibly due to critical dynamics near a phase transition, are associated with normal information processing, whereas both hyper—as well as hyposynchronous states result in impaired information processing and disturbed consciousness. © 2005 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Keywords: Nonlinear dynamics; chaos; complexity; self-organization; time series analysis; EEG; MEG

1. Introduction

1.1. The emergence of nonlinear brain dynamics

Recently there is an increasing interest in neurophysiological techniques such as EEG and MEG that are eminently suitable to capture the macroscopic spatial temporal dynamics of the electro magnetic fields of the brain. The following citation from Jones reflects this new elan: ‘Now that neuroscientists are beginning seriously to contemplate higher levels of brain functioning in terms of neuronal

networks and reverberating circuits, electroencephalographers can take satisfaction in the knowledge that after some time of unfashionability their specialty is once again assuming a central role. As they suspected all along, there does appear to be important information about how the brain works contained in the empirically useful but inscrutable oscillations of the EEG’ (Jones, 1999).

This renewed interest in EEG and MEG has two different sources: (i) the realization that a full understanding of the neurophysiological mechanisms underlying normal and disturbed higher brain functions cannot be derived from a purely reductionistic approach and requires the study of emergent phenomena such as large scale synchronization of neuronal networks in the brain (Bressler, 2002; Le van Quyen, 2003; Schnitzler and Gross, 2005; Varela et al.,

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2001); (ii) the introduction of new techniques, concepts and analytical tools which make it possible to extract more and more meaningful information from recordings of brain electro magnetic activity. Examples of such new developments are the use of combined recording of EEG and fMRI, wavelets, analysis with artificial neural networks, and advanced source modelling (Benar et al., 2003; Durka, 2003; Gabor and Seyal, 1992; Robert et al., 2002; Vrba et al., 2004).

Another example of a new approach, and perhaps one of the most ambitious attempts to decipher Jones' 'inscrutable oscillations of the EEG', is the application of concepts and time series analysis techniques derived from nonlinear dynamics (also called 'chaos theory') to the study of EEG and MEG. The application of nonlinear dynamics to electroencephalography has opened up a range of new perspectives for the study of normal and disturbed brain function and is developing toward a new interdisciplinary field of nonlinear brain dynamics (Elbert et al., 1994; Korn and Faure, 2003; Le van Quyen, 2003; Rey and Guillemant, 1997; Sarbadhikari and Chakrabarty, 2001; Stam, 2003). The purpose of the present review is to provide an introduction in the basic concepts and analytical techniques of nonlinear EEG analysis, and to give an overview of the most important results that have been obtained so far in the study of normal EEG rhythms, sleep, epilepsy, psychiatric disease and normal and disturbed cognition.

1.2. Historical background

Nonlinear EEG analysis started in 1985, when two pioneers in the field published their first results. Rapp et al. described their results with 'chaos analysis' of spontaneous neural activity in the motor cortex of a monkey (Rapp et al., 1985), and Babloyantz and co-workers reported the first observations on the so called correlation dimension of human sleep EEG (Babloyantz et al., 1985). In these early days, super computers were required for even the most basic types of nonlinear EEG analysis. However, the pioneering work of Rapp and Babloyantz did not only depend upon the availability of super computers, but also upon progress in the physics and mathematics of nonlinear dynamical systems.

One might say that nonlinear dynamics was born in 1665 when Christiaan Huygens, lying ill in his bed, observed that two clocks hanging from the same wall tended to synchronize the motion of their pendulums exactly in phase (Huygens, 1967a,b). Synchronization of dynamical systems is a key nonlinear phenomenon, and as we will see it has become increasingly important in recent developments in nonlinear EEG analysis. Despite Huygens' early observations, the status of founding father of 'chaos theory' is usually given to the French mathematician Henri Poincaré, who in 1889 showed that a simple gravitational system of three interacting bodies can display completely unpredictable behaviour (Poincaré, 1892–1899). This unpredictable behaviour arises despite the fact that the

(nonlinear) equations describing the system are completely deterministic. This paradoxical phenomenon of unpredictable behaviour in deterministic dynamical systems is now called 'deterministic chaos' (Li and Yorke, 1975). Poincaré was far ahead of his time, and in the first decades of the twentieth century progress in nonlinear dynamics was slow and overshadowed by developments in relativity and quantum physics. Important work was done by Russian mathematicians such as Lyapunov and Kolmogorov, and the Dutch physicist Balthasar van der Pol, but the impact of their work only became clear later.

Things changed rapidly due to a number of developments between 1960 and 1980. First, advances in computer technology allowed to study nonlinear dynamical systems with a technique called numerical integration. This computationally demanding procedure is one of the few ways to study the behaviour of a dynamical system when there is no closed solution for the equations of motion. Next, the meteorologist Edward Lorenz, studying a simple nonlinear model of the atmosphere using numerical integration, rediscovered Poincaré's chaotic dynamics and published the first graph of a strange attractor, the now famous 'Lorenz attractor' shown in Fig. 1 (Lorenz, 1963). Then Packard et al. showed how a time series of observations could be transformed into a representation of the dynamics of the system in a multi-dimensional state space or phase space, and the Dutch mathematician Floris Takens proved that the reconstructed attractor has the same basic properties as the true attractor of the system

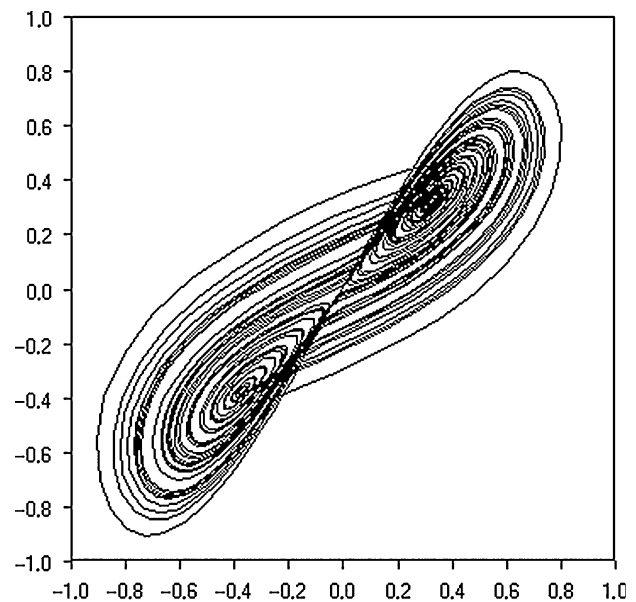


Fig. 1. Two dimensional phase portrait of the Lorenz attractor. This attractor was discovered by Edward Lorenz in 1963 in a system of three coupled nonlinear differential equations, representing a simplified model of the atmosphere. The attractor is a fractal object made up of an infinite number of lines representing the trajectory of the dynamical system. The trajectory segment connects consecutive states of the system. Due to the fractal geometry nearby trajectory segments come infinitely close but never intersect. [units of X and Y axis are arbitrary]

(Packard et al., 1980; Takens, 1981). The final breakthrough came in 1983 when Grassberger and Procaccia published an algorithm to compute the correlation dimension of a reconstructed attractor (Grassberger and Procaccia, 1983a). This made it possible to apply chaos theory to almost any set of observations, and resulted within two years to the first applications to EEG by Rapp and Babloyantz. The atmosphere of enthusiasm and optimism of the early period of chaos theory is very well captured by Gleick, Basar and Duke and Pritchard (Basar, 1990; Duke and Pritchard, 1991; Gleick, 1987).

The early phase of nonlinear EEG analysis, roughly between 1985 and 1990, was characterized the search for low-dimensional chaotic dynamics in various types of EEG signals. Around 1990 some of the limitations of various algorithms for nonlinear time series analysis became clear, and the method of ‘surrogate data testing’ was introduced to check the validity of the results (Jansen and Brandt, 1993; Osborne and Provenzale, 1989; Pijn, 1990; Pijn et al., 1991; Theiler, 1986; Theiler et al., 1992a,b). Subsequently, early claims for ‘chaos’ in the brain were critically re examined and often rejected (Pritchard et al., 1995a; Theiler, 1995). Since then, nonlinear EEG analysis has redirected its focus in two less ambitious but more realistic directions: (i) the detection, characterization and modelling of nonlinear dynamics rather than strict deterministic chaos; (ii) the development of new nonlinear measures which are more suitable to be applied to noisy, non stationary and high-dimensional EEG data. This approach has paid off and has led in the late nineties of the last century to a whole new range of EEG measures based upon phase synchronization and generalized synchronization as well as a number of emerging applications in the monitoring of sleep, anesthesia and seizures. Ironically, while ‘chaos in brain?’ is no longer an issue, research in nonlinear EEG analysis is booming (Lehnertz and Litt, 2005; Lehnertz et al., 2000).

2. Nonlinear dynamical systems

2.1. The concept of a dynamical system

In the historical overview several concepts such as dynamical system, nonlinear, attractor and deterministic chaos were already mentioned. In this section the conceptual framework of nonlinear dynamics is explained in a more structured way. The emphasis is on an intuitive understanding of the concepts, not on mathematical rigor. For detailed mathematical backgrounds the reader is referred to specialist texts (Eckmann and Ruelle, 1985; Kantz and Schreiber, 2003; Kaplan and Glass, 1995; Ott, 1993; Schuster, 1995).

The principal concept to be dealt with is that of a dynamical system. A dynamical system is a model that determines the evolution of a system given only the initial state, which implies that these systems possess memory: the

current state is a particular function of a previous state. Thus a dynamical system is described by two things: a state and a dynamics. The state of a dynamical system is determined by the values of all the variables that describe the system at a particular moment in time. Consequently, the state of a system described by m variables can be represented by a point in an m -dimensional space. This space is called the state space (or phase space) of the system. The dynamics of the system is the set of laws or equations that describe how the state of the system changes over time. Usually this set of equations consists of a system of coupled differential equations, one for each of the systems variables. The actual dynamical evolution of the system corresponds to a series of consecutive states (points) in its state space; the line connecting these consecutive points in state space is called the trajectory of the system.

Various phenomena can be described as dynamical systems. For example, the amount of interest your money is earning in the bank, or the growth of the world’s human population. One should also think of systems like the weather, the sun and the planets, chemical reactions, or electronic circuits. Even though these are very different phenomena, they can all be modeled as a system governed by a consistent set of laws that determine the evolution over time, i.e. the dynamics of the systems.

Dynamical systems come in different flavours: we can distinguish between linear and nonlinear systems, and conservative and dissipative systems. A dynamical system is linear if all the equations describing its dynamics are linear; otherwise it is nonlinear. In a linear system, there is a linear relation between causes and effects (small causes have small effects); in a nonlinear system this is not necessarily so: small causes may have large effects. A dynamical system is conservative if the important quantities of the system (energy, heat, voltage) are preserved over time; if they are not (for instance if energy is exchanged with the surroundings) the system is dissipative. Finally a dynamical system is deterministic if the equations of motion do not contain any noise terms and stochastic otherwise. These are rather technical definitions; what should concern us in the present context is that realistic biological systems such as the neural networks of the brain are likely to be nonlinear dissipative systems. Whether they are more deterministic or stochastic is one of the questions dealt with by nonlinear analysis (Section 3).

2.2. Attractors and their properties

A crucial property of dissipative deterministic dynamical systems is that, if we observe the system for a sufficiently long time (after the initial transients have died out), the trajectory will converge to a subspace of the total state space. This subspace is a geometrical object which is called the attractor of the system. It is called attractor since it ‘attracts’ trajectories from all possible initial conditions. The Lorenz attractor shown in Fig. 1 is an example of such

an attractor. In a linear dissipative deterministic system only one type of attractor can exist: a simple point in state space or ‘point attractor’. This implies that such a system will converge to a steady state after which no further changes occur, unless the system is disturbed from the outside.

In contrast, nonlinear deterministic dissipative systems may display a much more interesting repertoire of dynamics. Apart from point attractors, three more types of attractor can occur: (i) limit cycles; (ii) torus attractors; (iii) chaotic or strange attractors. Limit cycle attractors are closed loops in the state space of the system. They correspond to period dynamics. Torus attractors have a more complex ‘donut like’ shape, and correspond to quasi periodic dynamics. This type of dynamics is a superposition of different periodic dynamics with incommensurable frequencies. The chaotic or strange attractor is a very complex object with a so-called fractal geometry. The dynamics corresponding to a strange attractor is deterministic chaos. Deterministic chaos is a kind of dynamics that is on the one hand deterministic (remember we are dealing here with nonlinear, deterministic dissipative systems) but on the other hand seemingly random. Chaotic dynamics can only be predicted for short time periods. A chaotic system, although its dynamics is confined to the attractor, never repeats the same state. This paradox is made possible by the fractal structure of the attractor. Examples of the four basic types of attractor are shown in Fig 2. What should have become clear from this description is that attractors are very important objects since they give us an image or a ‘picture’ of the systems dynamics; the more complex the attractor, the more complex the corresponding dynamics.

2.3. Characterization of attractors

To characterize the properties of attractors, and thus of the corresponding dynamics more exactly, several measures are used. The first is the dimension of the attractor. The dimension of a geometric object is a measure of its spatial extensiveness. The dimension of an attractor can be thought of as a measure of the degrees of freedom or the ‘complexity’ of the dynamics. A point attractor has dimension zero, a limit cycle dimension one, a torus has an integer dimension corresponding to the number of superimposed periodic oscillations, and a strange attractor has a fractal dimension. A fractal dimension is a non integer number, for instance 2.16, which reflects the complex, fractal geometry of the strange attractor.

Dimensions are static measures of attractors which provide no information on the evolution of trajectories over time. Lyapunov exponents and entropy measures on the other hand can be considered ‘dynamic’ measures of attractor complexity. Lyapunov exponents indicate the exponential divergence (positive exponents) or convergence (negative exponents) of nearby trajectories on the attractor. A system has as many Lyapunov exponents as there are directions in state space. Continuous dynamical systems

always have at least one exponent that is exactly zero. The concept of entropy is closely related to that of Lyapunov exponents. Its is defined as the rate of information loss over time and is equal to the sum of all positive Lyapunov exponents.

With the concepts of Lyapunov exponents and entropy it is now possible to give more exact definitions of conservative and dissipative dynamics and chaos. Conservative dynamics refers to a system with no resistance or loss of energy over time; one can think of a frictionless pendulum which swings in a vacuum. Conservative dynamics has a zero entropy and the sum of all its Lyapunov exponents is also zero. Conservative systems do not have attractors. In contrast, dissipative systems are systems with ‘resistance’ or energy loss. One can think of a swinging pendulum in air which will slow down the motion of the pendulum. In such systems the sum of all Lyapunov exponents is negative; one might say that the dynamics is ‘contracted’ in state space to a subset which is the attractor of the system. In the case of the damped pendulum without driving the attractor would be a point attractor corresponding to the pendulum hanging motionless. In general, dissipative systems, in contrast to conservative systems, do have attractors. Finally chaotic dynamics can be defined in terms of Lyapunov exponents and entropy: chaotic dynamics is characterized by (i) the existence of at least one positive Lyapunov exponent, or, equivalently: (ii) a positive entropy. The positive Lyapunov exponent / entropy reflect the tendency of small disturbances to grow exponentially. This is what is meant by ‘sensitive dependence on initial conditions’ of chaotic systems, and limits their prediction horizon.

2.4. Control parameters, multi stability, bifurcations

The final concepts we need to deal with are control parameters, multi stability and phase transitions or bifurcations. Control parameters are those system properties that can influence the dynamics of the system and that are either held constant or assumed constant during the time the system is observed. Parameters should not be confused with variables, since variables are not held constant but are allowed to change. For a fixed set of control parameters a dynamical system may have more than one attractor. This phenomenon is called multistability. Each attractor occupies its own region in the state space of the system. Surrounding each attractor there is a region of state space called the basin of attraction of that attractor. If the initial state of the system falls within the basin of a certain attractor, the dynamics of the system will evolve to that attractor and stay there. Thus in a system with multi stability the basins will determine which attractor the system will end on. External disturbances may ‘push’ a system out of the basin of one attractor and move it to the basin of another attractor.

In a multi stable system the total of coexisting attractors and their basins can be said to form an ‘attractor landscape’

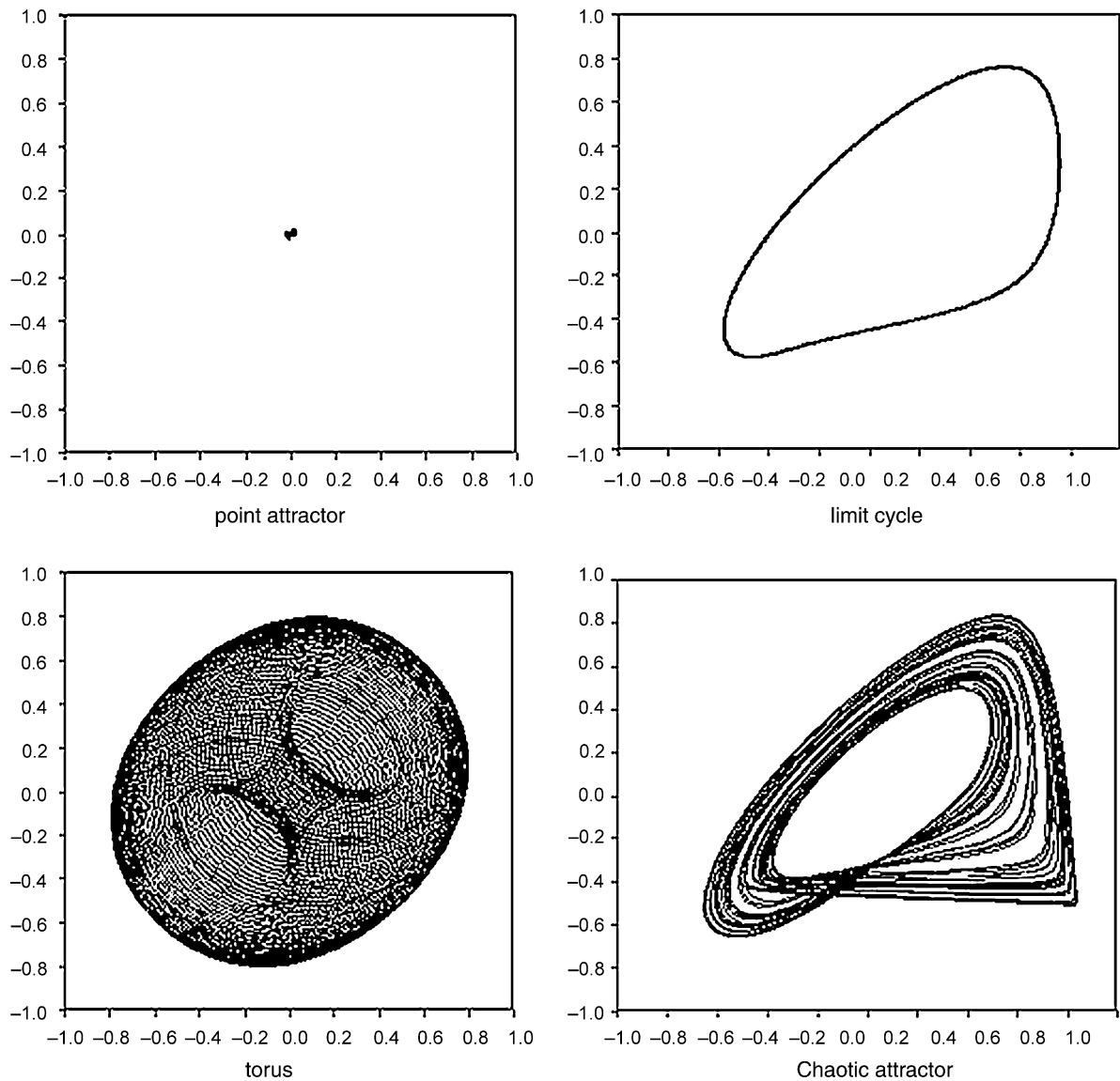


Fig. 2. Examples of the four basic types of attractor [units of X and Y axis are arbitrary]. At the top left the simplest type of attractor, a single point in state space, is shown. This point attractor corresponds to a system that remains in a single state after the initial transients have died out. At the top right a limit cycle attractor is shown. A limit cycle is a closed loop of any shape, and corresponds to a periodic system. At the bottom left a torus attractor is shown. A torus attractor corresponds to quasi periodic motion due to the superposition of periodic oscillations with incommensurate frequencies. In this example two oscillations, a fast and a slow one, are superimposed producing a torus with a donut like shape. At the bottom right a strange or chaotic attractor is shown. This attractor has a fractal geometry and corresponds to deterministic chaos in the dynamical system. A chaotic system is characterized by sensitive dependence on initial conditions, which is reflected by the exponential divergence of nearby trajectory segments on the attractor. [Adapted from Stam, *Am. J. END Technol.* 2003 43: 1–17]

which is characteristic for a set of values of the control parameters. If the control parameters are changed this may result in a smooth deformation of the attractor landscape. However, for critical values of the control parameters the shape of the attractor landscape may change suddenly and dramatically. At such transitions, called bifurcations, old attractors may disappear and new attractors may appear. At first sight these concepts may seem very abstract and esoteric. However, as we will see, current attempts to understand how seizures can arise out of seemingly normal brain activity make extensive use of these concepts (Lopes da Silva et al., 2003a,b).

3. Nonlinear time series analysis

3.1. From 'bottom up' to 'top down'

In the previous section we discussed dynamical systems from a 'bottom up' perspective: what can be observed in nonlinear dynamical systems if we know the set of equations governing the basic systems variables. However, the starting point of any investigation in clinical neurophysiology is usually not a set of differential equations, but rather a set of observations in the form of an EEG or MEG record. We do not know the nature of the underlying

dynamics, its complexity, control parameters, sensitivity to disturbances or closeness to a bifurcation. The way to get from the observations of a system with unknown properties to a better understanding of the dynamics of the underlying system is nonlinear time series analysis. This is more or less a ‘top down’ approach, starting with the output of the system, and working back to the state space, attractors and their properties.

One approach within nonlinear time series analysis is a procedure that consists of three distinct steps: (i) reconstruction of the systems dynamics in state space; (ii) characterization of the reconstructed attractor; (iii) checking the validity (at least to a certain extent) of the procedure with ‘surrogate data testing’. Here we attempt to give an intuitive explanation of what is involved in each of the three steps, and focus on the question what can and cannot be concluded from the analyses. A more extensive discussion with mathematical details can be found in a few review papers (Grassberger et al., 1991; Schreiber, 1999) as well as some textbooks on nonlinear time series analysis (Abarbanel, 1996; Diks, 1999; Galka, 2000; Kantz and Schreiber, 2003). Useful information can also be found on the following websites: <http://www.ieap.uni-kiel.de/plasma/ag-pfister/privat/galka/nonlintimserann.html> and <http://www.mpiipks-dresden.mpg.de/~tisean/>

3.2. *Embedding: reconstruction of dynamics from observations*

The first and most crucial step in nonlinear analysis is to reconstruct, from one or a few time series of observations, an attractor in the state space of the underlying system. The problem is that our measurements usually do not have a one to one correspondence with the system variables we are interested in. For instance, the actual state space may be determined by ten variables of interest, while we have only two time series of measurements; each of these time series might then be due to some unknown mixing of the true system variables. At first sight it seems a hopeless task to reverse this process, but the procedure of embedding allows us to reconstruct an equivalent attractor of the underlying dynamical system. With embedding one time series or a few simultaneous time series are converted to a series or sequence of vectors in an m -dimensional embedding space. If the system from which the measurements were taken has an attractor, and if the embedding dimension m is sufficiently high (more than twice the dimension of the systems attractor), the series of reconstructed vectors constitute an ‘equivalent attractor’ (Whitney, 1936). Takens has proven that this equivalent attractor has the same dynamical properties (dimension, Lyapunov spectrum, entropy) as the true attractor (Takens, 1981). This result, sometimes called ‘Takens embedding theorem’ is the heart of nonlinear time series analysis. It means that we can obtain valuable information about the dynamics of the system, even if we don’t have direct access to all the systems variables.

Two different embedding procedures exist: (i) time-delay embedding; (ii) spatial embedding (for a technical review see: Sauer et al., 1991). In the case of time-delay embedding we start with a single time series of observations. From this we reconstruct the m -dimensional vectors by taking m consecutive values of the time series as the values for the m coordinates of the vector. By repeating this procedure for the next m values of the time series we obtain the series of vectors in the state space of the system. The connection between successive vectors defines the trajectory of the system. In practice, we do not use values of the time series of consecutive digitising steps, but use values separated by a small ‘lag’ l . Thus time-delay embedding is characterized by two parameters: the time lag l , and the embedding dimension m . The proper choice of these parameters is an important but difficult step in nonlinear analysis. A pragmatic approach is to choose l equal to the time interval after which the autocorrelation function (or the mutual information) of the time series has dropped to $1/e$ of its initial value, and repeat the analysis (for instance, computation of the correlation dimension) for increasing values of m until the results no longer change; one assumes that is the point where $m > 2d$ (with d the true dimension of the attractor). More sophisticated procedures have been proposed both for choosing the lag (Rosenstein et al., 1994) as well as choosing the embedding dimension (Kennel et al., 1992). A comparison of different approaches to choosing embedding parameters can be found in Cellucci et al. (2003). Whatever approach is chosen, the important thing about l and m is that they are interdependent. The product of l and m , called the embedding window, is the length of the segment of the time series used to reconstruct a single state space vector. According to Albano and Rapp the embedding window should be chosen as the time after which the autocorrelation function of the time series becomes zero (Albano and Rapp, 1993). Takens has suggested to choose l such that it captures the smallest details of interest in the time series, and m such that the embedding window captures the largest phenomena of interest (Takens, personal communication). The procedure of time-delay embedding is explained schematically in Fig. 3.

If we have m time series of independent measurements instead of a single one it is also possible to use spatial embedding to reconstruct the attractor of the system (Babloyantz, 1989; Eckmann and Ruelle, 1985). In this case the m coordinates of the vectors are taken as the values of the m time series at a particular time; by repeating this for consecutive time points a series of vectors is obtained. In this case the embedding dimension m is equal to the number of channels used to reconstruct the vectors. The spatial equivalent of the time lag l is the inter electrode distance. The advantage of spatial embedding is that it achieves a considerable data reduction, since the dynamics of the whole system is represented in a single state space. The alternative would be to do a separate time delay embedding on each of the m time series. The disadvantage

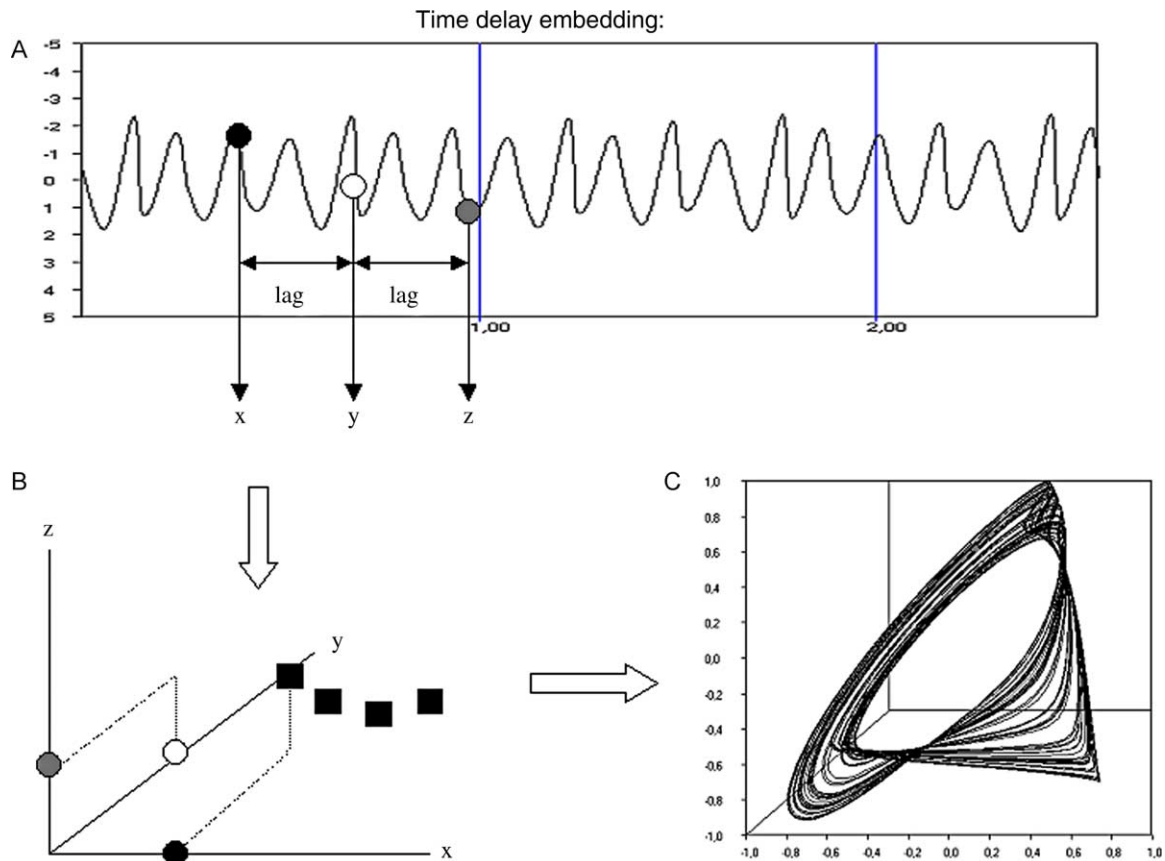


Fig. 3. Schematic explanation of time delay embedding. In A a small part of a time series is shown. To embed this time series in a 3-dimensional state space (shown in B) three coordinates are needed for each point in the state space. These coordinates are obtained by taking the amplitude values of the time series at three consecutive times x , y and z , separated by a time lag. The segment of the time series between x and z is called the embedding window. The values at x , y and z (indicated by the black, white and grey spheres) are plotted in the three dimensional space shown in B, and give the coordinates of a single point in state space, represented by the black square. Next, x , y and z are moved to the right one step, three new values are read from the time series, and the next point in state space is reconstructed, shown by the next black square. By repeating this procedure for the whole time series, an equivalent attractor can be reconstructed, as shown in C. [units of X , Y and Z axis are arbitrary]

of this approach is that the spatial 'lag', that is the distance between EEG electrodes or MEG sensors, is usually given, and cannot be chosen in an optimal way. There is no simple answer to the question which approach is right; it depends strongly on the kind of question one wants to answer. For instance if the purpose of the analysis is to study interactions between different brain regions, it is often necessary to employ separate time-delay embeddings for all of the time series (see below in the discussion of synchronization measures). Some groups have strongly advocated spatial embedding (Lachaux et al., 1997). However, Pritchard et al. have suggested it may not even be a valid embedding procedure at all (Pritchard et al., 1996a; see also: Pezard et al., 1999; Pritchard, 1999).

3.3. Characterization of the reconstructed attractor

3.3.1. Phase portraits, Poincaré sections and recurrence plots

Once the attractor has been reconstructed with time-delay or spatial embedding the next step is to characterize it.

The simplest way to do this is to visualize it with a phase portrait or a Poincaré section. A phase portrait is simply a 2- or 3-dimensional plot of the reconstructed state space and the attractor. The graphs shown in Fig. 1 and 2 are examples of 2-dimensional phase portraits. For higher-dimensional attractors a visual characterization using a "simple" 2- or 3-dimensional representation of a high-dimensional object can lead to misinterpretations depending on the chosen projection. A Poincaré section is a 2-dimensional section through an m -dimensional state space; it shows where the trajectory segments of the attractor cross the plane of section. For example, in the case of a 3-dimensional state space with three variables x , y and z , a Poincaré section can be obtained by plotting the values of x and y each time $z=c$, with c some constant.

A more complex but very informative way to display the reconstructed trajectory segments is the recurrence plot (Eckmann et al., 1987; Koebbe and Mayer-Kress, 1992). This is a 2-dimensional graph, with both axes corresponding to time. Each point in the graph corresponds to a combination of the two times (the values of the x and y

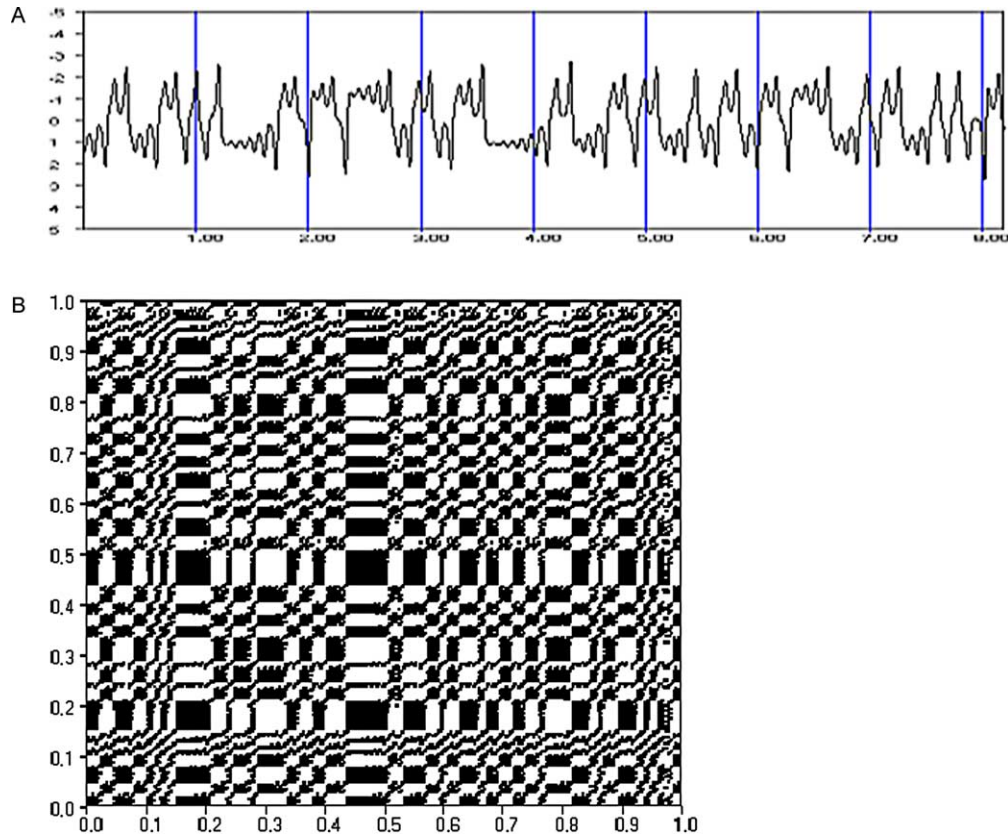


Fig. 4. Example of a recurrence plot. In A a time series from a Lorenz system is shown [units of X and Y axis are arbitrary] In B the recurrence plot based upon this time series is displayed. The two axes of the recurrence plot correspond to time. Each point in the plot corresponds to a combination of two times, one on the X -axis and one on the Y -axis. This point is made black in the plot if the two reconstructed vectors corresponding to the times on the X and Y -axis are closer together than a small cut-off distance; otherwise it is left blank. The recurrence plot thus shows patterns of recurrence of states of the Lorenz system. Vectors are reconstructed from the time series using time-delay embedding (as described in Fig. 3). Note that the plot is symmetric around the diagonal running from the lower left to the upper right.

coordinates). When the state space vectors corresponding to these time points are closer together than some small cutoff distance, the point is made black in the graph, otherwise no point is plotted. Recurrence plots provide information on the stationarity of the dynamics as well as more detailed structure such as periodic components (Babloyantz, 1991). A quantitative assessment of non stationarity using the phenomenon of recurrence has been described by Rieke et al. (2002, 2004). A modification called cross recurrence plots has been proposed as a tool to study nonlinear interdependencies in bivariate data sets (Marwan and Kurths, 2002). An example of a recurrence plot is shown in Fig. 4.

3.3.2. Classic measures: dimension, Lyapunov exponents and entropy

Following embedding and perhaps visualization of the reconstructed attractor the next step is to attempt to characterize it in a quantitative way. Currently many different algorithms are available to do this, and new measures are introduced frequently in the physics literature. The discussion here is intended to give a brief overview and to focus on an intuitive understanding; mathematical details

can be found in the technical papers referred to. First we address the three most basic measures of attractors which were already introduced in Section 2.3: the dimension, the Lyapunov exponents and the entropy. In Section 3.3.3 we will discuss a number of more recent, ‘non classical’ measures, and in Section 3.3.4 we will deal with nonlinear measures of statistical interdependencies between time series.

The first and the most frequently used measure is the correlation dimension D_2 introduced by Grassberger and Procaccia (1983a,b). The correlation dimension is not the only type of dimension that can be computed, but it is computationally simpler than for instance the information dimension (for a tutorial review see: Pritchard and Duke, 1995). The correlation dimension is based upon the correlation integral. The correlation integral C_r is the likelihood that any two randomly chosen points on the attractor will be closer than a given distance r ; usually C_r is determined for a range of values r , and plotted as a function of r in a double logarithmic plot. The crucial point of the Grassberger and Procaccia algorithm is that, for a sufficiently high embedding dimension m , the slope of a linear scaling region of $\log(C_r)/\log(r)$ is an estimate of the

correlation dimension D_2 . To determine what is a sufficiently high m , the procedure is repeated for increasing values of m until the value of the correlation dimension no longer increases. This phenomenon is called saturation of the correlation dimension with increasing embedding dimension. Computation of the correlation dimension is illustrated schematically in Fig. 5.

The algorithm to compute the correlation dimension is deceptively simple, although it is rather time consuming. However it has turned out that the proper computation and interpretation of the D_2 involves many pitfalls. First, the computation of the D_2 can be biased by autocorrelation effects in the time series. This can be avoided by discarding vector pairs with time indices less than the autocorrelation time (Theiler, 1986). Insufficient length of the time series can bias the dimension estimate (Eckman and Ruelle, 1992). The computation of the correlation dimension can be influenced by noise (Möller et al., 1989). Jedynek et al. showed that the correlation dimension could not be

computed reliably in a model system with a dimension of five (Jedynek et al., 1994). Osborne and Provenzale showed that certain types of noise can give rise to linear scaling regions of the plot and saturation with increasing embedding dimensions, spuriously suggesting the existence of a low-dimensional attractor (Osborne and Provenzale, 1989).

Several authors have proposed modifications and improvements of the original correlation dimension (Judd, 1992). The point correlation dimension is an algorithm that allows to compute the dimension as a function of time (Skinner et al., 1994). Faster and more efficient algorithms to compute attractor dimensions were proposed by several authors (Grassberger, 1990; Theiler, 1987; Theiler and Lookman, 1993; Widman et al., 1998). Other modifications were directed at the computation of correlation dimensions from noisy or non stationary data sets or preliminary nonlinear noise reduction (Bröcker et al., 2002; Havstad and Ehlers, 1989; Nolte et al., 2001; Saermark et al., 1997; Schouten et al., 1994a,b).

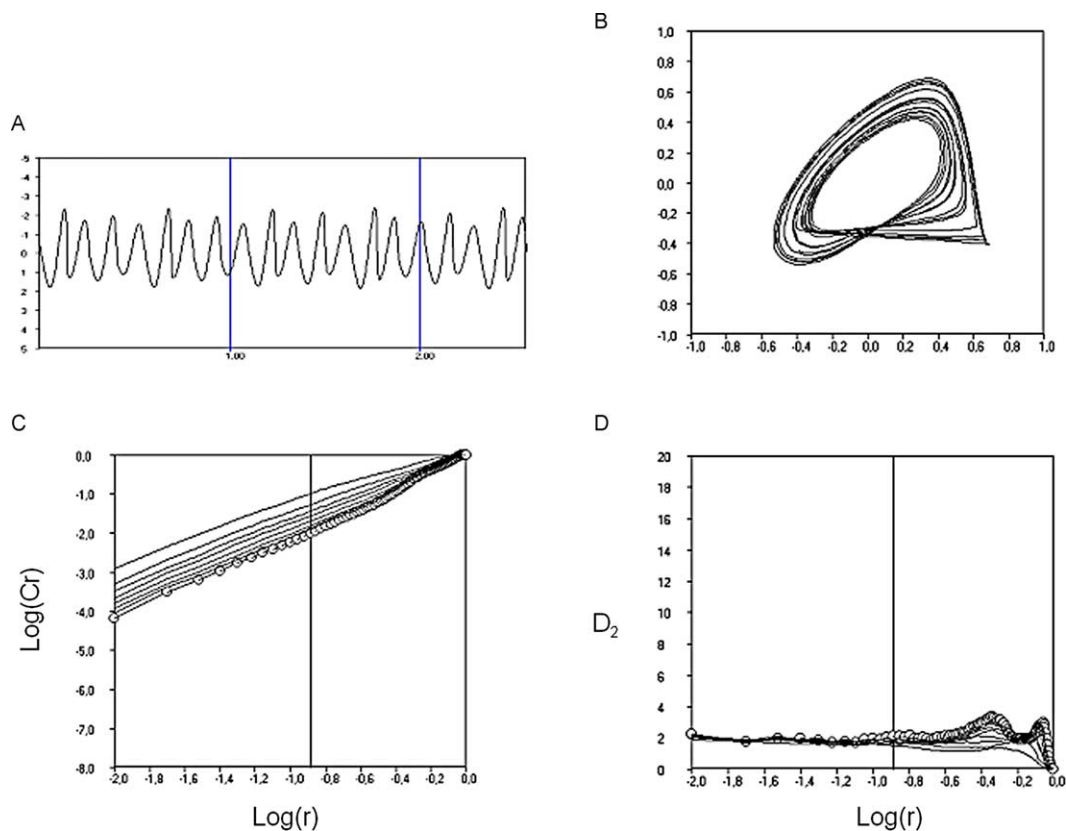


Fig. 5. Computation of the correlation integral and correlation dimension. In A the time series to be analyzed is shown. From this time series trajectories in state space are reconstructed as shown in B (time-delay embedding is explained in Fig. 3). The next step is the computation of the correlation integral. The correlation integral C_r is the likelihood that two randomly chosen points on the attractor will be closer than a certain distance r , as a function of r . The correlation integral is determined from the distribution of all pair-wise distances of points on the attractor. In C the correlation integral is plotted in a double logarithmic plot, with the X-axis corresponding to $\log(r)$ and the Y-axis corresponding to $\log(C_r)$. The different lines in the plot correspond to the correlation integral for increasing embedding dimensions, starting with $m=2$ for the uppermost plot, $m=3$ for the one below it, and so on. The plot with the small circles corresponds to the highest embedding dimension considered. The slope of the correlation integral in the linear scaling regions corresponds to the value of the correlation dimension D_2 . This can be seen in a different way in D. Here the first derivative of the correlation integral (which corresponds to the local slope of the plot in C) is plotted as a function of $\log(r)$. It can be clearly seen in D that this first derivative converges to a value around two for increasing embedding dimensions and small values of $\log(r)$. The estimated value of the correlation dimension of this system is thus close to 2.

The basic principle behind most algorithms to compute Lyapunov exponents is to consider two or a small number of nearby points on the attractor, and to quantify the exponential increase or decrease of the inter vector distances over time intervals. The algorithm of Wolf et al. was one of the earliest practical implementations of this idea (Wolf et al., 1985). Later simpler and faster algorithms to compute the largest Lyapunov exponent were introduced by Kantz and by Rosenstein et al. (Kantz, 1994; Rosenstein et al., 1993). The algorithm of McCaffrey et al. is based upon non parametric regression (McCaffrey et al., 1992). Kowalik and Elbert proposed a modification where the largest exponent is computed in a time-dependent way (Kowalik and Elbert, 1995). Other algorithms aim at a determination of the full spectrum instead of only the largest exponent (Brown et al., 1991; Sano and Sawada, 1985). Many of the problems involved in the computation of the correlation dimension, such as the proper choice of embedding parameters, length and stationarity of the time series and noise, are also relevant for the computation of Lyapunov exponents. Other problems such as resonance phenomena are specific for the computation of Lyapunov exponents (Fell and Beckmann, 1994). While a positive largest exponent in principle is an indicator of chaotic dynamics, it should be realized that noise time series can also give rise to spurious positive exponents (Tanaka et al., 1998). One way to control for this has been proposed by Parlitz (Parlitz, 1992).

The entropy of an attractor is the rate of information loss of its dynamics. The entropy is equal to the sum of all positive Lyapunov exponents, and a positive entropy indicates chaotic dynamics. A wide variety of algorithms for the computation of entropy measures have been introduced. Grassberger and Procaccia (1983b, 1984) showed that the entropy can be determined from the correlation integral. Other entropy measures that have been suggested are the entropy based upon nonlinear forecasting (Pezard et al., 1997; Wales, 1991), approximate entropy (Pincus et al., 1991), maximum likelihood entropy (Schouten et al., 1994b), coarse grained entropy rates (Palus, 1996a, 1997) and multi resolution entropy (Torres et al., 2001). In extended systems it is also possible to determine a spatial entropy, defined as the loss of information per unit length (Van der Stappen et al., 1994). Like the other nonlinear measures, entropy estimates have their limitations when applied to EEG recordings (Dünki, 1991). The problem of noise can be dealt with to some extent by the approach of Nolte et al. (Nolte et al., 2001).

3.3.3. Novel measures

The classic measures described above have in common that they allow us to draw far reaching conclusions on the nature of the systems dynamics, for instance with regard to its degrees of freedom, the presence of chaotic dynamics, and the rate of information loss. However, it has now become clear that when these measures are computed from

filtered, noisy, nonstationary time series of limited duration and precision spurious results can occur such as a false suggestion of low-dimensional structure or chaos (Rapp, 1993; Rapp et al., 1993). These problems can be dealt with in three different ways (or combinations of them): (i) still compute classic measures, but refrain from an interpretation in terms of dimensions or deterministic chaos, and consider them as tentative indices of different brain states; (ii) check the validity of the results with surrogate data (this will be discussed under 3.4); (iii) use novel nonlinear measures which attempt to characterize some of the structure of the reconstructed trajectories without making strong assumptions about the nature of the underlying dynamics. The development and testing of new nonlinear measures is now a major effort in nonlinear dynamics, and dozens of new algorithms have been proposed over the last decade. It is impossible to discuss all of these but we will attempt to indicate the major categories, and point to the key references for more details. A brief overview of new measures is given in Table 1. Although any subdivision at this stage is necessarily arbitrary, we will try to group the new methods in the following categories: (i) nonlinear prediction; (ii) tests for determinism; (iii) tests for reversibility; (iv) characterization of spatio temporal chaos; (v) other measures.

One of the earliest attempts to bypass the shortcomings of classic nonlinear EEG measures was the algorithm of nonlinear forecasting or prediction (for a review see: West and Mackey, 1992). The idea was originally developed by Farmer, and later made popular in a more simple form by Sugihara and May (Farmer and Sidorowich, 1987; Sugihara and May, 1990). The basic idea is to consider a point on the attractor and to predict the future course of this point by fitting a local linear model to the dynamics. The simplest way to do this is to search for a number of nearest neighbours of the reference point. This cloud of nearest neighbours is then advanced in time, and its ‘center of gravity’ is taken as a prediction of the future location of the reference point. The difference between actual and predicted future states is usually expressed as a prediction error, which can be plotted for different values of the prediction horizon. Nonlinear prediction has now been widely studied (Andrzejak et al., 2001a; Gallez and Babloyantz, 1991; Hernandez et al., 1995; Murray, 1993; Tsonis and Elsner, 1992). It has become clear that nonlinear forecasting can be applied to, and sometimes distinguish between deterministic and stochastic systems. In particular, nonlinear forecasting can be used to distinguish between added noise and chaos (Elsner and Tsonis, 1992). Blinowska and Malinowska have compared nonlinear forecasting to linear forecasting (Blinowska and Malinowski, 1991). Elsner showed that neural networks can also be used for the nonlinear forecasting (Elsner, 1992). Nonlinear prediction was used by Dushanova and Popivanov to analyze single trial data in a readiness potential paradigm (Dushanova and Popivanov, 1996).

Table 1
Overview of some of the new nonlinear time series methods

Measure:	Property measured:	Key references:
Nonlinear forecasting	Prediction of future states of the system	Farmer and Sidorowich, 1987 Sugihara and May, 1990
Local deterministic properties of dynamics	Local deterministic properties of dynamics	Kaplan and Glass, 1992
Deterministic versus stochastic modelling	Determination of optimal predictability by Gaussian versus deterministic models	Casdagli and Weigend, 1993
Cross recurrence		Zbilut et al., 1998
False nearest neighbours	Determination of optimal embedding dimension	Kennel et al., 1992
S	Statistic for time irreversibility as indicator of nonlinear dynamics	Diks et al., 1995
Nonlinear cross prediction	Detection of amplitude and time asymmetry based on nonlinear forecasting	Stam et al., 1998
	Test for irreversibility based upon symbolic dynamics	Daw et al., 2000
Dimension density	Dimension per unit size in systems with spatiotemporal chaos	Zoldi and Greenside, 1997
Unstable periodic orbits	Characterization of dynamics in terms of unstable periodic orbits	So et al., 1996, 1998
Phase synchronization	Interdependencies of instantaneous phases of two time series	Rosenblum et al., 1996
Phase synchronization in multivariate systems	Phase synchronization in multivariate systems	Allefeld and Kurths, 2004
Cross prediction	Measure of generalized synchronization	Schiff et al., 1996
S	Measure of generalized synchronization	Le van Quyen et al., 1998 Arnhold et al., 1999 Quian Quiroga et al., 2000
Synchronization likelihood	Measure of generalized synchronization	Stam et al., 2002a,b
Mutual dimension	Estimate of the shared degrees of freedom of two dynamical systems	Buzug et al., 1994 Meng et al., 2001 Wojcik et al., 2001

Palus et al. used a nonlinear prediction approach in combination with surrogate data testing (Palus et al., 1995).

A different but closely related group of measures attempts to detect deterministic structure in experimental time series. Since predictability, (at least on short time scales in the case of chaotic systems), is the hallmark of determinism, these measures typically share some similarity with the forecasting algorithms discussed above. Several attempts to introduce a ‘determinism’ statistic were described by Kaplan and Glass (Kaplan, 1993, 1994; Kaplan and Glass, 1992, 1995). One approach was based on the observation that determinism is associated with some preferred orientation of the tangents to a trajectory in a given region of state space (Kaplan and Glass, 1992). Closely related methods have been proposed by other authors (Ortega and Louis, 1998; Salvino and Cawley, 1994; Wayland et al., 1993). All these methods are based on the assumption that mathematical properties such as parallelism, smoothness, differentiability, or continuity of some vector field in state space indicate determinism. In their textbook Kaplan and Glass described an approach based upon a nonlinear prediction statistic and fitting models of varying order to the local dynamics (Kaplan and Glass, 1995). A somewhat related approach called ‘deterministic versus stochastic modeling’ was described by (Casdagli and Weigend, 1993). In yet another study, Kaplan defined a statistic for exceptionally predictable events in a time series

(Kaplan, 1994). A measure of the sensitive dependence on initial conditions was used by Schittenkopf and Deco to detect deterministic chaos (Schittenkopf and Deco, 1997). Zbilut et al. used the phenomenon of cross recurrence to search for deterministic structure (Zbilut et al., 1998). The concept of false nearest neighbours (attractor points that are close with an embedding dimension m , but distant with an embedding dimension $m + 1$) was already encountered as a tool to determine the optimal embedding dimension in Section 3.2 (Kennel et al., 1992). Hegger and Kantz used this phenomenon as a basis for their test for determinism (Hegger and Kantz, 1999). Jeong et al. devised a test based upon the local smoothness of the trajectories in state space and used this in combination with surrogate data to test for deterministic structure (Jeong et al., 1999, 2002a,b).

Yet another group of nonlinear measures is based upon the fact that linearly filtered gaussian noise is time reversible, that is the statistical properties of such a time series do not depend on the direction of time. Diks et al. developed a statistic that can detect significant time irreversibility, which can be an indication of nonlinear dynamics in the system generating the time series (Diks et al., 1995). Stam et al. introduced the nonlinear cross prediction which is based upon the predictability of a time series and its time reversed copy (Stam et al., 1998).

A symbolic expression of the dynamics was used by Daw et al. to search for ‘irreversibility’ (Daw et al., 2000).

In systems with a significant spatial extent and many degrees of freedom chaotic dynamics can have spatial as well as temporal structure (Cross and Hohenberg, 1994). This phenomenon has been studied especially in chemical systems (Baier and Sahle, 1998). However, neural networks may also qualify as systems that can display spatial temporal chaos (Lourenco and Babloyantz, 1996). The proper characterization of spatial temporal chaos is an especially challenging topic (Bauer et al., 1993; Chate, 1995; Shibata, 1998). One problem is that such systems cannot be characterized with the usual measures of dimension and entropy, since dimension and entropy in such systems are extensive quantities that depend upon system size (Torcini et al., 1991; Tsimring, 1993). The alternative is to estimate measures such as ‘dimension density’ (Zoldi and Greenside, 1997).

Many other measures have been proposed which may share some similarity to the algorithms discussed above, but are otherwise difficult to classify. Here we mention some of the more interesting and important proposals. Takens proposed to use the correlation integrals themselves, and not derivative measures such as the correlation dimension or entropy, to test for nonlinear structure in combination with surrogate data (Takens, 1993). Jansen and Nyberg (1993) used a clustering technique to measure the similarity of trajectories. Another classification scheme was proposed by Schreiber and Schmitz (Schreiber and Schmitz, 1997). Any chaotic dynamical system can be thought of as the superposition of a large number of unstable periodic orbits. This suggests that such systems can be characterized in terms of the unstable orbits (So et al., 1996, 1998). Identification of unstable orbits is also an important step in controlling chaotic systems (Ding and Kelso, 1991; Moss, 1994; Ott et al., 1990).

3.3.4. Measures of nonlinear interdependency

The brain can be conceived as a complex network of coupled and interacting subsystems. Higher brain functions, and in particular cognition depend upon effective processing and integration of information in this network. This raises the question how functional interactions between different areas in the brain take place, and how such interactions may be changed in different types of pathology. These questions currently are a field of intense interest and research in neuroscience (Glass, 2001; Schnitzler and Gross, 2005; Varela et al., 2001). In Section 5 the concept of the brain as a network of coupled dynamical systems is discussed in more detail. Here we introduce various measures of synchronization that have been introduced in the context of nonlinear time series analysis.

3.3.4.1. Phase synchronization. The discovery of synchronization between oscillating systems by Christiaan Huygens marked one of the important early discoveries in nonlinear dynamics. A number of recent discoveries in the theory of

synchronization have revived interest in this phenomenon and have resulted in the introduction of a wide variety of new measures of nonlinear interdependencies. It should be noted here that the original rather narrow neurophysiological definition of synchronization as two or many subsystems sharing specific common frequencies has been replaced by the broader notion of a process, whereby two or many subsystems adjust some of their time-varying properties to a common behavior due to coupling or common external forcing (Brown and Kocarev, 2000). Overviews of the current state of knowledge on synchronization and nonlinear interdependency can be found in a number of review papers (Boccaletti et al., 2002; Breakspear, 2004; Rosenblum and Pikovsky, 2003; Rosenblum et al., 2004) and a textbook (Pikovsky et al., 2001). In this section, we discuss phase synchronization and in the next section we discuss generalized synchronization.

A important breakthrough in the theory of synchronization was the discovery that synchronization not only occurs between regular, linear oscillators, but also between irregular, chaotic systems (Pecora and Carroll, 1990). By now a hierarchy of increasingly general synchronization types has been proposed from complete synchronization via lagged synchronization and phase synchronization to generalized synchronization, although this concept is still controversial (Boccaletti et al., 2002). Due to the widened scope of the concept of synchronization, a new definition is required. Boccaletti et al. suggest the following definition: ‘Synchronization of chaos refers to a process, wherein two (or many) systems (either equivalent or nonequivalent) adjust a given property of their motion to a common behavior due to a coupling or to a forcing (periodical or noisy)’ (Boccaletti et al., 2002). These new types of synchronization require new tools to detect them in empirical data.

In 1996, Rosenblum et al. showed that coupled chaotic oscillators can display phase synchronization even when their amplitudes remain uncorrelated (Rosenblum et al., 1996). Phase synchronization is characterized by a non uniform distribution of the phase difference between two time series; in contrast to coherence it is not dependent upon the amplitudes of the signals and may be more suitable to track non stationary and non linear dynamics. Phase synchronization can be computed using the Hilbert transform (Mormann et al., 2000; Tass et al., 1998) or by means of wavelets analysis (Lachaux et al., 1999). Mormann et al. used the circular variance to characterize the distribution of phase differences, while Tass et al. used a Shannon information entropy measure (Mormann et al., 2000; Tass et al., 1998). More recently it has been shown that phase synchronization can also be used to detect the direction of coupling between two systems (Cimponeriu et al., 2003; Rosenblum and Pikovsky, 2001; Smirnov and Bezruchko, 2003). Witte and Schack discussed methods to study nonlinear interactions between different frequencies (Witte and Schack, 2003). Thanks to its high time resolution phase

synchrony can also be used to track rapid changes in the level of coupling between dynamical systems (Breakspear et al., 2004; Kozma and Freeman, 2002; Van Putten, 2003a,b). Finally attempts have been made to extend the concept of phase synchronization from the bi variate to the multi variate case (Allefeld and Kurths, 2004).

3.3.4.2. Generalized synchronization. The concept of phase, and as a consequence, that of phase synchronization makes only sense in oscillatory, periodic systems. In 1995 Rulkov et al. introduced the concept of generalized synchronization which does not assume this property of the interacting systems (Rulkov et al., 1995). Generalized synchronization exists between two interacting systems if the state of the response system Y is a function of the state of the driver system X : $Y = F(X)$. Both Rulkov et al. and several other groups have proposed algorithms to measure generalized synchronization in real data sets (Le van Quyen et al., 1998; Rulkov et al., 1995; Schiff et al., 1996). Some of these algorithms make use of the idea of cross prediction: this is the extent to which prediction of X is improved by knowledge about Y . One of the most basic statistics for generalized synchronization, the nonlinear interdependence, was proposed by Arnhold et al. (Arnhold et al., 1999). However, as the authors themselves and Pereda et al. pointed out, the nonlinear interdependence is not a pure measure of coupling but is also affected by the complexity or degrees of freedom of the interacting systems (Pereda et al., 2001). The synchronization likelihood was developed to avoid this bias (Stam and van Dijk, 2002). Quian-Quiroga et al. also discussed the limitations of the similarity index and proposed modifications (Quian Quiroga et al., 2000). Since then further improvements of algorithms for the assessment of generalized synchronization, and the detection of driver response relationships have been described (Bhattacharya et al., 2003; Feldmann and Bhattacharya, 2004; Hu and Nenov, 2004; Terry and Breakspear, 2003). One of the attractive properties of many measures based upon generalized synchronization is the fact that they can detect asymmetric interactions. A alternative approach to do this is based upon the notion of Granger causality (Chen et al., 2004). Chavez et al. have used the idea of Granger causality in a dynamical systems framework, although only weak effects were found in epileptic EEG data (Chavez et al., 2003).

A somewhat related approach makes use of the fact that the dimension in a combined state space is lower than the sum of the dimensions of two interacting systems if there is some degree of synchronization. One of the first implementations of this idea was the mutual dimension described by Buzug et al. (Buzug et al., 1994). Later other authors have proposed measures based upon the same principle (Meng et al., 2001; Wojcik et al., 2001). One attractive feature of this approach is that it also allows the detection of driver (lower dimension) and response (higher dimension) systems. However, a drawback is that these measures are hampered by the usual problems connected to

dimension estimates from noisy, non stationary data (see Section 3.3.2).

Finally a few other measures of nonlinear interdependencies between time series need to be mentioned, although they do not fall in the strict categories of phase synchronization or generalized synchronization. A nonlinear equivalent of the correlation coefficient, the nonlinear h^2 , was introduced by Pijn (Pijn, 1990). This h^2 allows the determination of time lags between time series, but does not make use of the embedding procedure. Quian-Quiroga introduced the event synchronization which may be particularly suited for time series with spikes or other recurring well-defined events (Quian Quiroga et al., 2002a). Schreiber proposed a measure for information transfer between time series (Schreiber, 2000). Other measures are directed at detecting the nonlinearity in the coupling between systems (Hoyer et al., 1998; Tanaka et al., 2000).

With the availability of so many different measures to assess the nonlinear interdependencies between time series a natural question is whether any of these measures can be considered superior over the others, and if so, under what circumstances. Quian-Quiroga analysed a real data set (epileptic EEG recorded in rats) with several synchronization measures and could not demonstrate clear superiority of any of the measures (Quian Quiroga et al., 2002b). David et al. used a model of the EEG based upon the original alpha rhythm model of Lopes da Silva to test synchronization measures. They also concluded that most measures performed quite well with the exception of mutual information (David et al., 2004). Mormann et al. compared 30 univariate and bivariate measures in predicting seizures in recordings of five subjects. Bivariate measures performed better than univariate, but linear measures were at least as good as nonlinear ones (Mormann et al., 2005). The authors suggest a combination of bivariate and univariate measures might be the most promising approach. However, more systematic comparisons in larger data sets are still required before any definite conclusions can be drawn.

3.4. Checking the validity of the analysis: surrogate data testing

As indicated above (Section 3.3.3) the interpretation of nonlinear measures can sometimes present problems since filtered noise time series can give rise to a spurious impression of low-dimensional dynamics and chaos (Albano and Rapp, 1993; Rapp et al., 1993). One of the most important tools to safeguard against this is the use of so-called surrogate data (Schreiber and Schmitz, 2000). The basic principle is straightforward: a nonlinear measure (dimension, entropy, or one of the new measures) is computed from a time series of interest and from a control or surrogate time series. The surrogate time series is constructed to have the same linear properties (power spectrum / autocorrelation function) as the original time series but no other (nonlinear) structure. If the outcome of

the nonlinear analysis is clearly different for original and surrogate data it can be concluded that the original data contain some interesting nonlinear structure. The comparison between original and surrogate data can be subjected to a formal statistical test by constructing not one but a whole set of surrogate data, and by determining whether the value of the nonlinear statistic for the original data lies within the distribution of values obtained for the ensemble of surrogate data. Demonstration of nonlinearity is important since only nonlinear dynamical systems can have attractors other than a trivial point attractor (Section 2.2). Chaos can only occur in nonlinear dynamical systems.

An elegant way to construct surrogate data with the same power spectrum as the original data is to perform a Fourier transform, randomise the phases, and then perform an inverse Fourier transform (Fig. 6). This idea was first proposed by Pijn and Theiler et al. (Pijn, 1990; Theiler et al., 1992a,b). Theiler et al. also proposed a slightly more sophisticated type of surrogate data that preserve the amplitude distribution as well as the power spectrum (Dolan and Spano, 2001; Theiler et al., 1992a,b). In the case of nonlinear analysis based upon spatial embedding or using statistics sensitive to couplings between channels

a modified type of surrogate data is required (Dolan and Neiman, 2002; Prichard and Theiler, 1994; Palus, 1996b). Here not only the power spectra but also the coherence needs to be preserved. This can be achieved by adding the same random number in each channel to the phase of a particular frequency (different random numbers for different frequencies).

Although surrogate data testing represents an enormous advance compared to uncontrolled nonlinear analysis, even surrogate data can give rise to spurious results. For instance, if the amplitude distribution of the original data is non Gaussian, simple phase randomisation will tend to make this distribution Gaussian which can lead to spurious differences between real data and surrogate data (Rapp et al., 1994). One way to control for this is the use of amplitude adjusted surrogate data (Theiler et al., 1992a,b). An even more sophisticated approach has been proposed by Schreiber and Schmitz (Schreiber and Schmitz, 1996). Here, an iterative procedure is used to preserve both the power spectrum as well as the amplitude distribution as good as possible. However even this type of surrogate data has problems due to a spuriously low variance of the test statistic in the surrogate data set (Kugiumtzis, 1999, 2001). Another

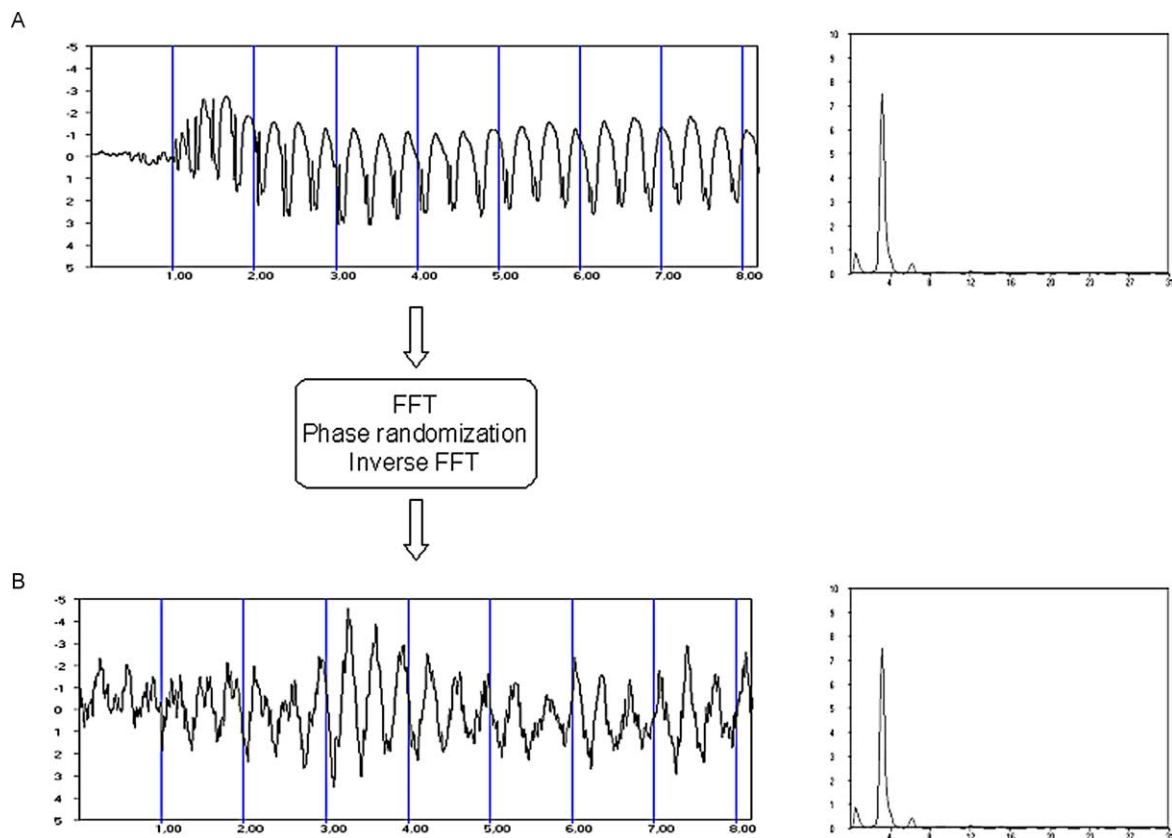


Fig. 6. Illustration of phase randomised surrogates. In A, the original time series is shown on the left and the corresponding power spectrum (X-axis in Hz; Y-axis arbitrary units) on the right. The time series is a small EEG epoch with spike-wave discharges. From this EEG a phase randomized surrogate signal is constructed by (i) a Fourier transform of the signal in A; (ii) a randomization of all the phases of the complex Fourier transform; (iii) an inverse Fourier transform. The resulting signal with its corresponding power spectrum are shown in B. Note that the spike-wave structure present in A is destroyed in the surrogate signal in B. Also note that the power spectrum is the same in A and B. The phase randomization procedure thus destroys all the nonlinear (phase dependent) structure in the signal, but preserves the power spectrum.

problem is the issue of non stationarity. The usual surrogate data test the null hypothesis that the original data cannot be distinguished from linearly filtered stationary noise. Thus a significant difference between the original data and the surrogate data can be due to nonlinearity, non stationarity or a combination of both. This problem has been discussed by several authors (Popivanov and Mineva, 1999; Rieke et al., 2003; Timmer, 1998). Surrogate data based upon wavelets could present a possible way out (Breakspear et al., 2003a). Another problem arises in the case of almost periodic time series (Small and Tse, 2002; Theiler et al., 1993). One possible solution to this problem, and possibly also to the problem of non stationarity, is to use time reversed copies of the original signal as ‘surrogate data’ (Stam et al., 1998).

3.5. Scope and limitations of nonlinear time series analysis

Before considering an overview of the actual applications of nonlinear analysis to EEG and MEG it may be appropriate to briefly recapture the most salient characteristics of this approach. First, the central and most important step in the analysis is embedding: nonlinear analysis deals with ‘states’ in ‘state space’ and not with amplitudes, powers and frequencies. The motivation for this is that states may provide more information on the underlying system than amplitudes. Second, although there is an enormous number of different classical and novel nonlinear measures, almost all of them depend somehow on computing distances between vectors (states) in states space; the notion of recurrence—the tendency of systems to visit almost the same state over and over again—lies at the heart of nonlinear analysis, as some type of recurrence indicates structure in the dynamics. Third, a strict interpretation of nonlinear measures in terms of attractor dimensions, deterministic chaos and entropy as bits / second is almost never justified. However, the classic measures can still be used as ‘tentative indices’ of different brain states, and the newer measures often allow a less ambitious but more straightforward interpretation. Finally, surrogate data testing, despite its limitations, is the most important safeguard against incorrect conclusions from the results of nonlinear analysis. While surrogate data testing may not be necessary for all types of analysis, it is unavoidable if conclusions are to be drawn about the existence of nonlinear dynamics in the underlying system.

4. Nonlinear dynamical analysis of EEG and MEG

4.1. Normal resting-state EEG

Nonlinear analysis of normal, resting-state EEG has been primarily directed at the question what kind of dynamics underlies the normal EEG and in particular the alpha rhythm. Before it was realized that filtered noise can mimic low-dimensional chaos and before surrogate data testing

was introduced as an antidote to premature enthusiasm, many investigators considered the possibility that normal EEG rhythms might reflect dynamics on low-dimensional chaotic attractors (Babloyantz and Destexhe, 1988; Dvorak et al., 1986; Mayer-Kress and Layne, 1987; Pritchard and Duke, 1992; Rapp et al., 1989; Soong and Stuart, 1989). With the advent of surrogate data testing these early claims for chaos underlying the normal EEG were critically re-examined. The general conclusion that emerges from a large number of studies is that there is no evidence for low-dimensional chaos in the EEG (Palus, 1996c; Pritchard et al., 1995a; Theiler and Rapp, 1996). At the same time it has become clear from many studies that the normal EEG does reflect weak but significant nonlinear structure (Gautama et al., 2003; Gebber et al., 1999; Maurice et al., 2002; Meyer-Lindenberg, 1996; Palus, 1996c; Pritchard et al., 1995a; Rombouts et al., 1995; Stam et al., 1999; Stepien, 2002). Some authors have suggested that the alpha rhythm might reflect (noisy) limit cycle attractors in cortical networks (Gebber et al., 1999; Palus, 1996c). In a study based upon the alpha rhythm model of Lopes da Silva (1974) it was shown that linear type I alpha epochs could be explained by a point attractor in the model and nonlinear type II alpha epochs by a noisy limit cycle (Stam et al., 1999). It was also suggested that normal EEG might reflect critical dynamics close to a bifurcation between these two types of attractor. Further support for the existence of critical brain dynamics comes from studies of fluctuations of nonlinear EEG measures (Stam and de Bruin, 2004; Tirsch et al., 2004).

A related problem is whether the statistical interdependencies between EEG signals recorded over different brain regions reflect nonlinear interactions. A few studies using the multivariate surrogate data proposed by Pritchard and Theiler have shown evidence for weak but significant nonlinear coupling in multichannel EEG and MEG (Breakspear, 2002; Breakspear and Terry, 2002a,b; Stam et al., 2003a). Epochs with significant nonlinear coupling occurred only infrequently and were characterized by more regular alpha with a sharp peak in the power spectrum, suggestive of ‘type II alpha’ (Breakspear and Terry, 2002a). In a direct comparison of EEG and MEG recorded in the same subjects it was shown that nonlinear interactions could be more easily demonstrated with MEG (Stam et al., 2003a).

Relative little is known about the changes in nonlinear dynamics with maturation and ageing. Nonlinear analysis of the neonatal EEG has only just started (Hecox et al., 2003; Witte et al., 2004). Meyer-Lindenberg studied resting-state EEGs of 54 healthy children and 12 adults (Meyer-Lindenberg, 1996). Using surrogate data testing significant nonlinear structure could be found in 60–70% of the examined epochs, even in newborns. The correlation dimension was shown to increase with ageing. Other studies also addressed the relationship between ageing and ‘brain complexity’ (Anokhin et al., 1996; Anokhin et al., 2000; Choi et al., 2000). Anokhin et al. could confirm the increase of EEG

dimension with age, especially in frontal regions. They interpreted this as a consequence of the increase in the number of independent synchronous networks in the brain (Anokhin et al., 1996).

4.2. Sleep

The first study ever published on nonlinear analysis of the human EEG dealt with sleep recordings (Babloyantz et al., 1985). Since then sleep has become a major research focus in nonlinear dynamics (Coenen, 1998). Many authors studied the correlation dimension and often also the largest Lyapunov exponent during the various sleep stages (Cerf et al., 1996; Fell et al., 1993; Kobayashi et al., 1999, 2001; Niestroj et al., 1995; Pradhan et al., 1995; Pradhan and Sadasivan, 1996; Roschke, 1992; Rösche and Aldenhoff, 1991; Rösche et al., 1993). In many of these studies it was suggested that sleep EEG reflects low-dimensional chaotic dynamics, but these claims were not backed up by surrogate data testing. The general pattern that emerges from these studies is that deeper sleep stages are almost always associated with a ‘lower complexity’ as exemplified by lower dimensions and lower values for the largest Lyapunov exponent. This type of finding has suggested the possible usefulness of nonlinear EEG analysis to obtain automatic hypnograms.

More recently, claims for chaos and nonlinearity in the sleep EEG have been examined with surrogate data testing. In an analysis of an all night sleep recording Achermann found evidence for weak nonlinear structure but not low-dimensional chaos (Achermann et al., 1994a,b). A similar result was obtained by Fell et al. (1996a). In two studies, Ferri et al. (2002, 2003) used the nonlinear cross prediction (NLCP) to search for nonlinear structure in sleep EEGs of adults and infants. In the first study, nonlinear structure was found during CAP (cyclic alternating pattern) stages A1 and to a lesser extent A2 both during NREM II and slow wave sleep (Ferri et al., 2002). In contrast, sleep EEG of young infants showed nonlinear structure only sporadically, mostly during quiet sleep (Ferri et al., 2003). The study of Shen et al. also suggests that nonlinearity depends upon sleep stage (Shen et al., 2003). These authors found the strongest indications for nonlinear structure during NREM II.

Another way to probe the relative importance of nonlinear sleep EEG measures is to compare them to appropriate linear measures. Fell et al. studied the performance of nonlinear (correlation dimension and largest Lyapunov exponent) and spectral measures in distinguishing between sleep stages (Fell et al., 1996b). The nonlinear measures were better in discriminating between stages I and II, whereas the spectral measures were superior in separating stage II and slow wave sleep. This makes sense in view of the findings of Ferri et al. and Shen et al. mentioned above which suggests nonlinear structure may be most outspoken in stage II. Pereda et al. compared the correlation dimension of sleep EEG with the fractal

dimension of the EEG curve (Pereda et al., 1998). The fractal dimension of the EEG curve (which should not be confused with the correlation dimension) is a linear measure which can be derived from the power spectrum (fractal dimensions are used to characterize irregular lines of boundaries such as coastlines). The correlation dimension in this studied correlated strongly with the fractal dimension, suggesting a considerable part of the information in the sleep EEG can be captured by a linear measure. In another study these authors also found strong correlations between nonlinear measures and spectral band power (Pereda et al., 1999). Shen et al. found a correlation between the correlation dimension and the exponent of detrended fluctuation analysis, which is a linear measure related to the fractal dimension mentioned above (Shen et al., 2003).

A few studies have addressed the problem of functional interactions between different brain regions during sleep. Pereda et al. showed that the nonlinear interdependence proposed by Arnhold et al. (Arnhold et al., 1999) may be influenced by changes in the complexity of the local dynamics, and suggested to use surrogate data to obtain unbiased estimates of coupling (Pereda et al., 2001). Using this approach they could demonstrate nonlinear and asymmetric coupling during slow wave sleep in infants (Pereda et al., 2003). In this study the strength of the coupling increased with deeper sleep stages. Terry et al. used a comparable approach and found age-dependent nonlinear interactions between left frontal and right parietal regions (Terry et al., 2004).

4.3. Coma and anaesthesia

Considering the fact that many studies have shown a systematic decrease of nonlinear measures such as the correlation dimension and the largest Lyapunov exponent with deeper sleep stages it might be logical to investigate the usefulness of nonlinear EEG analysis for the characterization of other types of impaired consciousness. However this issue has only been addressed in a few studies so far.

The earliest study to suggest a relationship between changes in consciousness and the correlation dimension of the EEG was published by Nan and Jinghua (Nan and Jinghua, 1988). Matousek et al. (1995) studied the correlation dimension (based upon a spatial embedding) in a small group of 14 healthy subjects aged from 1.5 to 61 years. They found an increase of the dimension during drowsiness as compared to the awake state. Kim et al. (1996) showed that nonlinear analysis can be used to differentiate between normal alpha rhythm and pathological alpha coma. Witte et al. (1999) investigated interrelations between different EEG frequency components in sedated patients during burst suppression episodes in the EEG. An EEG entropy measure was used by Tong et al. to characterize the EEG of patients after cardiac arrest (Tong et al., 2002).

The usefulness of nonlinear EEG analysis as a tool to monitor anesthetic depth was first suggested by Watt and Hameroff (Watt and Hameroff, 1988). Widman et al. showed that the correlation dimension correlated with the estimated level of sevoflurane in the brain (Widman et al., 2000a). The usefulness of the correlation dimension as an estimate of anesthetic depth was confirmed by the PhD thesis of Van den Broek (2003). Bruhn et al. examined various entropy measures such as the approximate entropy and the Shannon information entropy (Bruhn et al., 2000, 2001a,b). However, one nonlinear measure, the bispectral index (BIS) has dominated this field. It has been shown to be a reliable measure for practical clinical purposes in clinical trials (Myles et al., 2004). Its usefulness outside the operating theatre remains to be demonstrated (Frenzel et al., 2002).

4.4. epilepsy

4.4.1. The dynamic nature of seizures

Epilepsy is probably the most important application for nonlinear EEG analysis at this moment (Elger et al., 2000a, b). This has to do with the fact that epileptic seizures, in contrast to normal background activity, are highly nonlinear phenomena. This important fact opens up the way for localization of the epileptogenic zone, detection and prediction of epileptic seizures. In this section we discuss

the studies that deal with the dynamic nature of seizures and the events that characterize the transition between interictal and ictal EEG activity (Fig. 7). In the next section use of nonlinear analysis to detect and predict seizures will be discussed.

Babloyantz and Destexhe were the first to report on the nonlinear analysis of an absence (3 Hz spike and wave discharge) seizure (Babloyantz and Destexhe, 1986). The correlation dimension of this seizure was substantially lower than the dimension of normal waking EEG, which suggested that epileptic seizures might be due to a pathological ‘loss of complexity’. The decrease of the largest Lyapunov exponent during an epileptic seizure reported by Iasemidis et al. was in agreement with this concept (Iasemidis et al., 1990). Frank et al. also analysed the EEG of absence seizures and suggested the existence of an underlying chaotic attractor (Frank et al., 1990). However, the same data set was later re analysed by Theiler with appropriately constructed surrogate data (Theiler, 1995). He concluded that the dynamics of spike and wave discharges is not chaotic but could reflect a noisy limit cycle. The idea that the regular spike and wave discharges of absence epilepsy are related to limit cycle dynamics has since been confirmed in a number of studies (Feucht et al., 1998; Friedrich and Uhl, 1996; Hernandez et al., 1996; Schiff et al., 1995). Analysis of spike wave discharges with

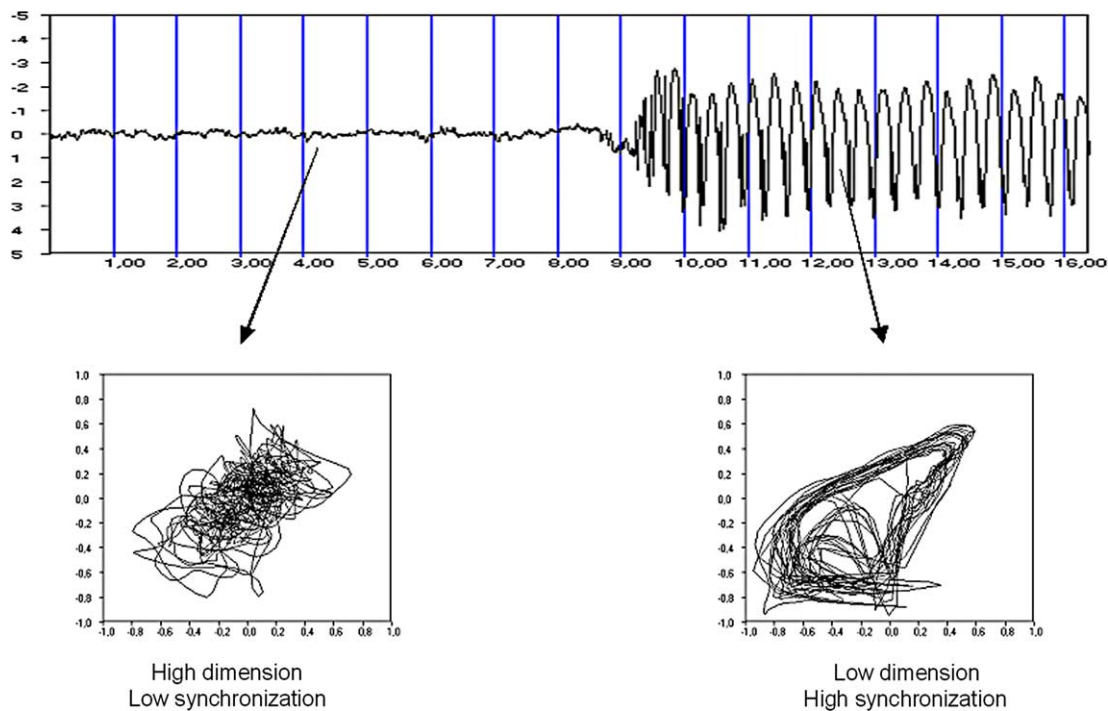


Fig. 7. This EEG time series shows the transition between inter ictal (to the left) and ictal (to the right) brain dynamics. The attractors corresponding to the inter ictal and ictal parts are shown at the lower left and right. The attractor corresponding to the inter ictal state is high dimensional and reflects a low level of synchronization in the underlying neuronal networks. In contrast, the attractor reconstructed from the ictal part on the right shows a clearly recognizable structure. This attractor is more low dimensional and reflects a high level of synchronization in the underlying neuronal networks. One of the key questions in the nonlinear dynamics of epilepsy is how the transition between these two types of dynamics takes place. [Adapted from Stam *Am. J. END Technol.* 2003 43: 1–17]

unstable orbits is also in agreement with this view (Le van Quyen et al., 1997a,b).

Many studies have used some sort of surrogate data testing to explore the nonlinear nature of seizures. As a consequence there is now fairly strong evidence that seizures reflect strongly nonlinear brain dynamics (Andrzejak et al., 2001b; Casdagli et al., 1997; Ferri et al., 2001; Pijn et al., 1991, 1997; Van der Heyden et al., 1996). Of interest, the interictal spike and waves of hypsarhythmia show no evidence for nonlinear dynamics (Van Putten and Stam, 2001). Epileptic seizures are also characterized by nonlinear interdependencies between EEG channels. Other studies have investigated the nature of interictal brain dynamics in patients with epilepsy. Lehnertz et al. showed that, in intracranial recordings, the epileptogenic are is characterized by a loss of complexity as determined with a modified correlation dimension (Lehnertz and Elger, 1995). The localizing value of interictal complexity loss or changes in other nonlinear measures was later confirmed in several studies (Feucht et al., 1999; Jing and Takigawa, 2000; Jing et al., 2002; Silva et al., 1999; Weber et al., 1998; Widman et al., 2000b). Kowalik et al. showed that a time dependent Lyapunov exponent calculated from interictal MEG recordings could also be used to localize the epileptic focus (Kowalik et al., 2001). Interestingly this interictal complexity loss of the epileptogenic zone can be influenced by anti epileptic drugs (Kim et al., 2002; Lehnertz and Elger, 1997).

The fact that seizure activity is highly nonlinear and probably low-dimensional, and interictal EEG is high-dimensional and only weakly nonlinear raises the question how the interictal ictal transition takes place (Le van Quyen et al., 2000, 2003a). There are two aspects of this transition: changes in local dynamics and changes in interregional coupling. With respect to the first aspect the theory of nonlinear dynamical systems suggests that this transition is likely to be due to one or more bifurcations due to changes in critical control parameters such as the balance between excitation an inhibition in the neuronal networks involved (Velazquez et al., 2003). The dynamics of seizure generation were reviewed by Lopes da Silva et al. (2003a, b). He proposed three different scenario's: (i) sudden emergence of seizure out of normal background activity; this would be characteristic of absence seizures; (ii) reflex epilepsy: transition to another attractor induced by an external stimulus (Parra et al., 2003); (iii) gradual transition from normal to seizure activity through a series of bifurcations and an 'pre ictal' state. The last scenario opens up the way for seizure prediction which will be discussed in the next section.

Apart from changes in the local dynamics of attractors, seizures may also be characterized by changes in the coupling between different brain areas (Arnhold et al., 1999; Chavez et al., 2003; Le van Quyen et al., 1998, 1999a,b; Mormann et al., 2000; Palus et al., 2001). Here is should be taken into account that these studies involve different (types

of) patient samples, and different synchronization measures, which might have influenced the results. Ferri et al. showed that nocturnal frontal lobe seizures are characterized by an early increase in alpha band synchronization and a late, partially post ictal, rise in delta band synchronization (Ferri et al., 2004). Although seizures are generally characterized by an increase in coupling between different brain areas, there are indications that in some types of seizures there is actually a decrease in the level of coupling preceding the seizure (Mormann et al., 2003a,b). This phenomenon has been replicated with experimental seizures (Netoff and Schiff, 2002). It is currently unknown how the three scenario's proposed by Lopes da Silva et al. are related to increases or decreases in interregional synchronization predicting seizures.

4.4.2. Seizure detection and prediction

Prediction or anticipation of epileptic seizures with nonlinear EEG analysis has become hot science. In the last few years many reviews of nonlinear seizure anticipation have appeared (Iasemidis, 2003; Lehnertz et al., 2001, 2003; Le van Quyen, 2005; Le van Quyen et al., 2001a; Litt and Echaz, 2002; Litt and Lehnertz, 2002). The importance of seizure prediction can easily be appreciated: if a reliable and robust measure can indicate an oncoming seizure twenty or more minutes before it actually starts, the patient can be warned and appropriate treatment can be installed. Ultimately a closed loop system involving the patient, a seizure prediction device and automatic administration of drugs could be envisaged (Peters et al., 2001). However the early enthusiasm should not distract us from a critical analysis of the facts (Ebersole, 2005).

In 1998, within a few months time, two papers were published that, in retrospect, can be said to have started the field of seizure prediction. The first paper showed that the dimensional complexity loss L^* , previously used by the same authors to identify epileptogenic areas in interictal recordings, dropped to lower levels up to 20 min before the actual start of the seizure (Elger and Lehnertz, 1998; Lehnertz and Elger, 1998). This phenomenon was most outspoken at the electrode contacts closest to the seizure onset zone. The second paper was published in *Nature Medicine* by a French group and showed that intracranially recorded seizures could be anticipated 2–6 minutes in 17 out of 19 cases (Martinerie et al., 1998). Schiff spoke about 'forecasting brainstorms' in an editorial comment on this paper (Schiff, 1998). The initial results were followed up by improvements in the analysis method (Le van Quyen et al., 1999b). It was shown that seizure prediction was also possible with surface EEG recordings (Le van Quyen et al., 2001b). This was a significant observation, since the first two studies both involved high quality intracranial recordings. Next, it was shown that seizure anticipation also worked for extra temporal seizures (Navarro et al., 2002). This early phase was characterized by great enthusiasm and a hope for clinical applications (Lehnertz et al., 2000).

Inspired by the results of the German and French groups, many others epilepsy centers got involved in nonlinear EEG analysis. Several algorithms for nonlinear seizure prediction were proposed, involving amongst others the use of correlation integrals, correlation dimensions, Lyapunov exponents, entropy measures and phase clustering for the assessment of changes in the local dynamics (Iasemidis et al., 2001, 2004; Kalitzin et al., 2002; Li et al., 2003; Litt et al., 2001; Moser et al., 1999; Osorio et al., 2001; Schindler et al., 2001; Schindler et al., 2002; Van Drongelen et al., 2003; Van Putten, 2003a,b). Other approaches focused on estimating changes in nonlinear coupling between different brain regions with phase synchronization (Mormann et al., 2003a,b). In some studies the focus was more on the less ambitious but perhaps more realistic goal of detecting rather than predicting seizures (Altenburg et al., 2003; Celka and Colditz, 2002; Lerner, 1996; Smit et al., 2004; Yaylali et al., 1996). Many of the results of the early studies were discussed on a conference in Bonn in 1999 (Lehnertz et al., 2000) and in the review papers mentioned above (Iasemidis, 2003; Lehnertz et al., 2001; Lehnertz et al., 2003; Le van Quyen et al., 2001a; Litt and Echaz, 2002; Litt and Lehnertz, 2002).

However, the initial optimism was followed by a few sobering experiences. The approach initially described by Lehnertz and Elger using the complexity loss L^* was replicated by Aschenbrenner-Scheibe et al. (2003). These authors showed that with an acceptable false positive rate the sensitivity of the method was not very high. In the same year the Bonn group also reported on a diminished predictive performance of a number of their univariate measures (including L^*) when being applied to continuous long-term recordings (Lehnertz et al., 2003). The results of Martinerie et al. were also critically re-examined. McSharry et al. suggested that the measure used by Martinerie et al. was sensitive to signal amplitudes and that the good results might also have been obtained with a linear method (McSharry et al., 2003; for a response see: Martinerie et al., 2003). Another group attempted to replicate the results of Le van Quyen et al. in predicting seizures from surface EEG recordings (De Clercq et al., 2003). These authors could not replicate the results in their own group, although they could predict a seizure in a data set provided by the French group. Several explanations for the failed replication, most of a methodological nature, were suggested (Le van Quyen et al., 2003b). Even so, it has become clear that further progress in this field would depend upon the development of appropriate statistical tests (for the assessment of sensitivity and false positive rates) and benchmarks in the form of shared data sets. Exactly these topics were addressed at the First International Collaborative Workshop on Seizure Prediction, held in Bonn in April of 2002. Reports of this workshop can be found in a recent issue of this journal (D'Allesandro et al., 2005; Ebersole, 2005; Esteller et al., 2005; Harrison et al., 2005; Iasemidis et al., 2005; Jerger et al., 2005; Jouny et al., 2005; Lehnertz

and Litt, 2005; Le van Quyen et al., 2005b; Mormann et al., 2005).

Several authors have now undertaken a direct comparison of one or more linear and nonlinear measures for seizure prediction. Kugiumtzis and Larsson compared linear and nonlinear measures of seizure prediction in a small sample of seven subjects, and found no clear superiority of the nonlinear measures (Kugiumtzis and Larsson, 2000). McSharry compared a linear and a nonlinear measure and showed under what circumstances the nonlinear measure could be expected to provide additional information (McSharry et al., 2002). Jerger et al. compared seven different linear and nonlinear measures, and found comparable results for both classes of measures (Jerger et al., 2001). In this study seizures could be anticipated one or two minutes before they started. Phase synchronization seemed to be the most robust measure, probably due to its insensitivity to amplitude effects. Winterhalder et al. described a 'seizure prediction characteristic' for the comparison of different seizure prediction algorithms (Winterhalder et al., 2003). This seizure prediction statistic was used to compare three nonlinear seizure prediction methods (Maiwald et al., 2004). A statistical test for the existence of a 'pre ictal state' was introduced by Andrzejak et al. (Andrzejak et al., 2003). A new type of surrogate data, measure profile surrogates, was introduced by the same group to test the performance of seizure prediction measures (Kreuz et al., 2004). With the use of comparative tests and statistical control methods, such as the examples mentioned above, realistic aims can be said for the future and further progress in predicting and detecting seizures should be possible within the next few years.

4.5. Mental states and psychiatric disease

4.5.1. Psychopharmacology

Various pharmacological agents can influence normal brain function. Quantitative EEG analysis is a well established tool to characterize such effects ('pharmacology EEG'). A number of studies have explored the usefulness of nonlinear EEG analysis for this purpose. One of the best studied agents is alcohol. In a well designed study using linear and nonlinear measures (time asymmetry, determinism, and redundancy) in combination with surrogate data, Ehlers et al. showed that the EEG in a placebo condition had significant nonlinear structure which was significantly decreased after the administration of ethanol (Ehlers et al., 1998). The subjective feeling of intoxication was correlated with the nonlinear and not with the linear measures. Viewing alcohol pictures as compared to non alcohol beverage pictures induced an increase in the D_2 of the EEG in social drinkers and alcoholics in the study of Kim et al. (Kim et al., 2003). Moderate alcohol use has also been shown to increase nonlinear coupling between EEG channels in the theta and the gamma band (De Bruin et al., 2004).

Klonowski et al. used a dimension estimate based upon the Karhunen Loeve expansion to determine the influence of diazepam on the EEG (Klonowski et al., 1999). In the small study with four subjects no effects could be demonstrated. Using surrogate data Pritchard et al. found significant nonlinearity in the EEG of healthy subjects, but no influence of smoking (nicotine) on the nonlinear structure (Pritchard et al., 1995b). Wackermann et al. compared a placebo condition with different doses of Piracetam, and showed a decrease of the global dimensional complexity (correlation dimension determined from spatial embedding) under influence of higher drug doses (Wackermann et al., 1993).

4.5.2. *Perceptual and emotional states*

In a large series of papers Aftanas and coworkers explored almost the whole spectrum of nonlinear EEG measures in order to characterize changes in brain function related to emotion and affect (Aftanas et al., 1994, 1997a,b, 1998, 2002). They showed a fronto central increase in dimension during imagination compared to perception; an emotional condition was associated with a more posterior increase in dimension (Aftanas et al., 1994). Using nonlinear forecasting, negative emotions were shown to be associated with higher EEG predictability especially in posterior regions (Aftanas et al., 1997a). Kolmogorov entropy and the largest Lyapunov exponent were increased after viewing positive or negative movies compared to viewing neutral movies (Aftanas et al., 1997b). Using the mutual dimension D_m as a measure of nonlinear coupling they showed that negative emotions were associated with a left frontal decrease in coupling, whereas positive emotions were associated with a more posterior central increase in coupling (Aftanas et al., 1998). A state of meditation was shown to be associated with a decrease in dimensional complexity (Aftanas and Golocheikine, 2002).

Studies by other others have used various types of stimulation to investigate changes in brain complexity. Kondakor et al. showed that simple visual processing (eyes-open compared to eyes-closed) was associated with an increase in global dimensional complexity (Kondakor et al., 1997). Memory for personal pain was shown to be characterized by an increase in dimensional complexity (Lutzenberger et al., 1997). In some cases nonlinear measures were less sensitive than linear ones. This was the case in the study of Yagyu et al. where the effect of chewing gum with different flavours was shown with a linear complexity measure, but not with a correlation dimension determined from a spatial embedding (Yagyu et al., 1997a). Following stimulating with light and sound the largest Lyapunov exponent was reported to decrease (Jin et al., 2002). In another study EEG nonlinearity was shown with surrogate data, and an increase of the EEG dimension was found after repetitive transcranial magnetic stimulation (Jing and Takigawa, 2002). In an experiment, where control subjects and patients with anorexia nervosa were exposed to gustatory stimuli, the EEG of anorexia patients had a

lower-dimensional complexity compared to the controls (Toth et al., 2004).

4.5.3. *Depression and schizophrenia*

The potential usefulness of a nonlinear dynamical systems framework for psychiatry was recognized in the early nineties (Globus and Arpaia, 1994; Schmid, 1991). This research has been directed at EEG changes in depression and schizophrenia. In major depression, abnormalities of sleep EEG and an increased predictability of waking EEG have been described, but the number of studies is still quite limited (Nandrino et al., 1994; Pezard et al., 1996; Rösche et al., 1994).

In comparison, nonlinear EEG analysis in schizophrenia has received much more attention. The majority of these studies focused upon the question whether schizophrenia is characterized by a loss of dynamical complexity or rather by an abnormal increase of complexity, reflecting a 'loosening of neural networks'. Many and especially more recent studies have found a lower complexity in terms of a lower correlation dimension or lower Lyapunov exponent (Jeong et al., 1998a; Kim et al., 2000; Kotini and Anninos, 2002; Lee et al., 2001a; Rockstroh et al., 1997). In the only MEG study so far similar changes were found (Kotini and Anninos, 2002). However, increases in dimension and Lyapunov exponent have also been reported in the older studies (Elbert et al., 1992; Koukkou et al., 1993; Saito et al., 1998). During sleep, nonlinear measures of complexity were decreased in schizophrenic patients (Rösche and Aldenhof, 1993). In one study it was shown that the particular method used for embedding might explain some of these discrepancies (Lee et al., 2001b). Lee et al. showed that the dimension computed with time delay embedding was increased in schizophrenic patients, whereas the dimension determined from a spatial embedding was decreased in patients (Lee et al., 2001b). Other considerations are the type of schizophrenia and the influence of treatment on nonlinear EEG measures (Kang et al., 2001).

One general pattern that becomes evident from the studies is that the abnormalities are usually most outspoken in the frontal areas, and in particular in the left hemisphere, suggesting a left frontal dysfunction (Breakspear et al., 2003b; Elbert et al., 1992; Jeong et al., 1998a; Kang et al., 2001; Kim et al., 2000; Lee et al., 2001b). A few studies used surrogate data testing to investigate the presence of nonlinear structure in the EEG of schizophrenics (Lee et al., 2001a). Finally, two studies used nonlinear measures of interdependency to investigate abnormal interactions between brain regions in schizophrenia (Breakspear et al., 2003b; Kang et al., 2001). Using an asymmetric measure of nonlinear coupling (mutual cross prediction) Kang et al. (2001) showed that under influence of clozapine the driving system was located more frontally. In the same study, the correlation dimension and the largest Lyapunov exponent proved to be less sensitive to the influence of clozapine on the EEG. Breakspear et al. (2003b) investigated changes in

nonlinear EEG interdependencies in a large study with 40 schizophrenia patients and 40 matched controls. The authors found no evidence for a general loss of coupling between brain regions, but nonlinear couplings tended to occur in larger ‘clusters’ in patients compared to controls, especially in the left hemisphere.

4.6. Normal cognition

Nonlinear EEG analysis has been applied extensively to study the cortical dynamics underlying various types of cognitive processing. These studies have addressed the question whether brain dynamics becomes more or less complex during cognitive tasks, and have attempted to relate changes in brain dynamics complexity to the nature and complexity of the task, as well as the intelligence of the subject. Finally, nonlinear methods have been used to explore changes in functional interactions between brain regions.

Intuitively it would seem logical that performance of some cognitive task is associated with more complex brain dynamics. Indeed, several studies report an increase in the correlation dimension or related complexity measures during cognitive tasks (Bizas et al., 1999; Meyer-Lindenberg, 1998; Micheloyannis et al., 1998, 2002; Molle et al., 1995; Stam et al., 1996a; Tomberg, 1999). This phenomenon has been shown in various arithmetic tasks (Micheloyannis et al., 1998, 2002; Stam et al., 1996a), but also in visual tasks (Bizas et al., 1999) and a silent reading condition (Tomberg, 1999). However, decreases in complexity have also been reported, most notably during a working memory task (Molnar et al., 1995; Sammer, 1996, 1999). Molle et al. suggested that changes in the level of EEG complexity might be related to the particular mode of thinking involved (Molle et al., 1996, 1997, 2000). Of interest, work on the influence of nicotine on brain complexity suggests the existence of a state of optimal complexity (Houlihan et al., 1996). When nonlinear measures are computed from narrow band filtered data, increases as well as decreases may be found during the same task. For instance, the multichannel correlation dimension of EEG filtered in the lower alpha band increased and the dimension of theta band EEG decreased during a visual working memory task (Stam, 2000).

For those tasks which are associated with increased EEG complexity, the level of difficulty of the task seems to be correlated to the magnitude of the EEG complexity increase (Gregson et al., 1990, 1992; Lamberts et al., 2000; Muller et al., 2003). This relationship between task complexity and brain dynamics complexity has also been shown for fMRI data (Dhamala et al., 2002). Imagery was shown to be related to more complex brain dynamics than perception (Lutzenberger et al., 1992a). Jeong et al. showed that the power spectrum of music was related to the nature of the induced changes in brain dynamics. So-called ‘one over f’ type music decreased complexity, whereas white or

Brownian noise increased brain complexity (Jeong et al., 1998b). The fact that various cognitive tasks induce changes in brain complexity, which are sometime related to the difficulty of the task of the type of thinking involved, raises the question whether EEG complexity might be related to intelligence. A correlation between nonlinear EEG measures and IQ has been suggested by a few authors (Anokhin et al., 1999; Lutzenberger et al., 1992b; Stam, 2000). In the study of Anokhin et al. a negative correlation between IQ and EEG dimension was found, whereas Lutzenberger et al. described a positive correlation, but only during a resting state (Anokhin et al., 1999; Lutzenberger et al., 1992b). In the study of Stam working memory capacity correlated with a lower theta band multichannel dimension (implying stronger coupling between EEG channels!) during the no-task condition, but only in female subjects (Stam, 2000). The latter finding seems to be in agreement with the observation of Anokhin et al. that theta band coherence correlated with a higher IQ (Anokhin et al., 1999).

These observations suggest that linear and nonlinear measures of coupling between brain regions might be more relevant to understand cognitive processing than local measures of complexity. In a series of investigations Bhattacharya et al. workers have shown that activities such as listening to music, watching paintings and mental rotation are associated with changes in functional coupling between brain regions, especially in experts and most outspoken in the gamma band (Bhattacharya and Petsche, 2001, 2002; Bhattacharya et al., 2001a,b,c). The fact that changes in functional connectivity were different in experts as compared to non experts suggests that these changes reflect to some extent properties of long term, possibly implicit memory stores. Using the mutual dimension as a nonlinear measure of coupling, Meyer-Lindenberg showed increased coupling between both temporal regions and the right frontal area during a mental arithmetic task (Meyer-Lindenberg, 1998). An increase in mutual dimension during arithmetic was also shown by Stam et al. (Stam et al., 1996a). During the retention interval of a visual working memory task, an increase in theta band coupling and a decrease in lower alpha band coupling was found (Stam et al., 2002a). Micheloyannis showed increased coupling in the gamma band during a complex visual discrimination task (Micheloyannis et al., 2003). While these studies are heterogeneous in several aspects, there seems to be agreement that cognition involves complex spatio temporal networks, and that gamma band plays an especially important role. This issue will be taken up in the discussion of brain dynamics in dementia, and in the general discussion in Section 5.

4.7. Disturbed cognition and dementia

A natural extension of the use of nonlinear analysis to study the dynamics of normal cognition is its application to

neurological disorders characterized by disturbed cognition, in particular dementia. An extensive review of nonlinear EEG analysis in dementia can be found in two recent papers by Jeong (2002, 2004). One of the pioneering studies in this field was published by Pritchard et al. (1991). In this study, the increase in D_2 accompanying eye opening in non demented subjects was diminished in Alzheimer patients, which was interpreted as a ‘lack of dynamical responsivity’. A few years later it was shown that a loss of dynamical complexity can already be demonstrated in Alzheimer patients in an eyes-closed resting state (Besthorn et al., 1995; Jelles et al., 1999a; Jeong et al., 1998c, 2001a; Stam et al., 1994, 1995; Yagyu et al., 1997b). Support for the concept of ‘complexity loss’ underlying cognitive dysfunction in dementia comes from several studies showing correlations between nonlinear EEG measures and performance on neuropsychological tests. In the study of Yagyu et al. a lower global dimensional complexity of the EEG correlated with lower scores on the MMSE and the WAIS-R (Yagyu et al., 1997b). Ikawa et al. (2000) described two region-specific correlations between DC (dynamical complexity) and neuropsychological performance in 25 AD patients: one between the DC value in the left frontal, central and mid-temporal areas and intellectual function; and another between the DC value in the left central, parietal and post-temporal areas and verbal memory.

Nonlinear EEG analysis has also been applied to other forms of dementia. The periodic discharges in the EEG of patients with Creutzfeldt-Jakob disease have been shown to reflect low dimensional, highly nonlinear dynamics (Babloyantz and Destexhe, 1987; Stam et al., 1997). Compared to controls patients with vascular dementia had a higher dimension but a lower Lyapunov exponent in the study of Jeong et al. (2001a). Babiloni et al. demonstrated a loss of functional connectivity in patients with vascular dementia (Babiloni et al., 2004). Parkinson patients could be distinguished from Alzheimer patients by a higher Lyapunov exponent of the EEG; in both PD and AD the correlation dimension was lower than in non demented controls (Stam et al., 1994, 1995). Anninos et al. (2000) studied the correlation dimension of the MEG in Parkinson patients and found an increase in dimensional complexity after external magnetic stimulation. Muller et al. (2001) studied 17 Parkinson patients and 12 controls during a resting condition and during execution or imagining of a complex motor task. No differences were found in the resting condition, but the dimensional complexity in PD patients was increased compared to controls in the motor execution/imagining task. Pezard et al. (2001) described a higher entropy and increased nonlinearity of the EEG in L-Dopa naive Parkinson patients.

While many of the studies mentioned above suggest changes in nonlinear measures in various types of dementia, it remains unclear to what extent these findings are influenced by the linear properties of the EEG. Correlations between nonlinear and linear measures, including the Neural

Complexity measure of Tononi et al. (1994), have been demonstrated (Stam et al., 1994; Van Cappellen van Walsum et al., 2003). Jelles et al. showed that the EEG in Alzheimer’s disease has less significant nonlinear structure than in non demented controls (Jelles et al., 1999a). Also, linear changes might occur earlier than nonlinear changes (Jelles et al., 1999b). Of practical interest is the question whether combining linear and nonlinear measures might increase the diagnostic usefulness of the EEG in distinguishing between demented and non demented subjects. Two studies have shown that such a combination might be effective (Pritchard et al., 1994; Stam et al., 1996b).

Recently there is an increased interest to study abnormal brain dynamics in Alzheimer’s disease in terms of disturbed functional interactions between brain regions. This approach is motivated by the hypothesis that Alzheimer’s disease has many features of a ‘dysconnection syndrome’ (Delbeuck et al., 2003). Jeong et al. used the cross mutual information to study correlations between EEG channels and found a decrease of functional interactions over frontal and anterior temporal regions in Alzheimer patients (Jeong et al., 2001b). In a study using MEG lower levels of between area synchronization were found in Alzheimer patients in upper alpha, beta and gamma bands (Stam et al., 2002b). Coherence analysis of the same data only showed a non significant trend in the same direction. These results were later confirmed in several EEG studies (Babiloni et al., 2004; Pijnenburg et al., 2004; Stam et al., 2003b; Stam et al., 2005). In the last study lower levels of EEG beta band synchronization correlated with lower scores on the MMSE. Consequently, studies of nonlinear synchronization of MEG and EEG in Alzheimer’s disease support the hypothesis of disturbed functional connectivity underlying the ‘dysconnection syndrome’ of Alzheimer’s disease.

5. The brain as network of coupled dynamical systems

In the previous sections a large number of papers have been discussed that deal with nonlinear EEG or MEG analysis of normal and various abnormal brain states. While some patterns are emerging—for instance the fact that many epileptic seizures are characterized by highly nonlinear, synchronous brain dynamics—the overall picture is yet far from clear. At present, there is no such thing as a general theory of nonlinear brain dynamics. Many studies are based on restricted and ad hoc hypotheses, such as the idea that cognitive processing is likely to be associated with ‘more complex’ brain dynamics. However, a general conceptual framework might help to integrate the results of the various studies done so far, and to point the way to future work. Here we attempt to provide a highly preliminary-sketch of such a framework.

5.1. Functional sources, functional connectivity, functional networks

Before addressing the main findings with respect to brain dynamics in normal and abnormal brain states it is necessary to clarify the terminology. Nonlinear analysis can be applied to time series of brain activity, whether these are surface recordings (EEG, MEG), measurements of field potentials, or even single unit recordings. Nonlinear analysis can also be applied to other types of measurements, such as fMRI BOLD time series (Dhamala et al., 2002; Friston et al., 1995; Wang et al., 2003). The present review was limited to EEG and MEG, but a general framework should be able to deal with all types of measurements. An important distinction is that between the analysis of a local time series, and the analysis of relations between two or more time series. With respect to the latter type of analysis the notion of ‘functional connectivity’ has been introduced (for review see: Lee et al., 2003). Functional connectivity is a pragmatic concept which simply refers to any type of correlation between time series of brain activity. The underlying assumption is that functional connectivity reflects, as least to some extent, functional interactions between different brain regions.

In line with this approach we can introduce two new concepts. The first is the functional source, which is defined as the part or parts of the brain that contribute to the activity recorded at a single sensor. A functional source is an operational concept, that does not have to coincide with a well defined anatomical part of the brain, and is neutral with respect to the problems of source localization and volume conduction; it is simply a shorthand for denoting the part of the brain being measured at a single recording site. Functional connectivity can now be defined as any correlation between the activity of two functional sources. The second concept, that of a functional network, is then defined as the full matrix of all pair-wise correlations between functional sources.

In this terminology, a functional source is the lowest level of spatial resolution of a particular type of measurement. Evidently, functional sources of scalp recorded EEG will be much larger than those of MEG, or intracranial EEG recordings, with the single neuron level constituting a natural lower bound. Consequently, functional sources at a low level of resolution are functional networks at a higher level of resolution. The functional sources of this higher level of resolution, in their turn, are the functional networks of the next level of resolution, and so on, till the single neuron level. What constitutes a functional source, and what a functional network, is thus determined by the spatial resolution of the recording setup. This feature can be called the nestedness of functional networks. For a given level of resolution the analysis can be directed at interactions within the functional network, or the local dynamics of functional sources; however, the local dynamics of a functional source is equivalent to the global dynamics of a functional network one level down.

5.2. Complexity

Another concept that needs clarification before we can attempt to interpret and integrate the results of nonlinear EEG / MEG analysis is the notion of ‘complexity’. Complexity is a frequently used, but often ill-defined concept. However, many nonlinear EEG studies use such notions as ‘dynamical complexity’, usually in relation to estimates of the correlation dimension, so we need to be clear about the interpretation. An excellent discussion of different notions of complexity can be found in the textbook of Badii and Politi, and the review paper of Tononi et al. (Badii and Politi, 1997; Tononi et al., 1998). In the paper of Tononi et al. two notions of complexity are discussed. The first interprets complexity as degree of randomness, or degrees of freedom in a large system of interacting elements. A gas at high temperature is an example of a complex system in this sense. The second, more sophisticated notion interprets complexity as a state intermediate between randomness and order. This second concept has been called ‘neural complexity’ by the authors and was first described in 1994 (Tononi et al., 1994). The neural networks in the brain, with their structure intermediate between randomness (gas) and order (crystal) are considered an example of complexity in this sense of the word.

Although neural complexity is the more interesting interpretation it seems that what is being measured by nonlinear analysis is more closely related to the first concept. We will come back to the notion of neuronal complexity later and will define ‘dynamical complexity’ as the randomness or lack of interactions between the elements of a dynamical system. This definition can be easily translated to the functional source / functional network terminology introduced above: ‘dynamical complexity’ of a functional network is related to the lack of correlations between its functional sources. Alternatively we can state: the higher the level of synchronization between functional sources in a functional network, the lower its dynamical complexity.

5.3. Interpretation of nonlinear measures

With this definition of terminology we can now address the interpretation of nonlinear measures. Here we consider a functional source to be a dynamical system, and a functional network a system of coupled dynamical systems. Nonlinear measures derived from single time series provide information on the dynamics of the functional source, and thus of the lower level nested functional networks within this functional source. Estimates of the correlation dimension of a single time series thus give an indication of the ‘dynamical complexity’ of the functional source, which is equivalent to the randomness or degrees of freedom of the functional network one level down. Alternatively, explicit measures of coupling or synchronization between time series provide information about the dynamical complexity of the highest

level functional network. In other words: both within and between channel analyses deal with levels of synchronization or cooperativity, but only at different spatial scales. Local measures of dynamical complexity are indirect, since we cannot ‘see’ the underlying lower level functional sources, and global measures of dynamical complexity are explicit since we can measure the time series of all the functional sources that constitute the functional network. As will become clear in the following discussion, measures of coupling in functional networks may be more reliable estimators of synchronization levels than local estimates of dynamical complexity.

5.4. The brain as a self-organizing dynamical system

Taking the terminology and concepts defined above as a starting point we can now attempt to summarize what is known about the dynamics of various brain states as determined by nonlinear EEG or MEG analysis and integrate these findings in a single scheme (Fig. 8). In this discussion we will focus on three exemplary states: (i) normal, ongoing brain activity in resting or cognitive states; (ii) epileptic seizures; (iii) degenerative brain disease, with an emphasis on Alzheimer’s disease.

As discussed in sections 4.1 and 4.2, ongoing brain activity during the awake state in healthy adults is characterized by a relatively high-dimensional complexity, both with respect to the functional network as with respect to the functional sources. In other words, the nested networks of interacting dynamical systems and subsystems characteristic of normal ongoing brain activity are

characterized by a relatively weak level of synchronization between the interacting elements. However, although the interactions are weak, they do exist, and impose a certain structure on spontaneous brain dynamics. This structure is revealed in two ways: (i) ongoing brain activity during the awake state is not random noise, but has weak nonlinear properties, both at the level of functional networks as well as the level of functional sources; (ii) levels of synchronization of functional networks and functional sources are not constant over time, but show characteristic fluctuations, which have a scale-free character. These scale free fluctuations of synchronization levels have been demonstrated for local (Linkenkaer-Hansen et al., 2001; Nikulin and Brismar, 2004, 2005) as well as global dynamics (Stam and de Bruin, 2004), and might be due to self-organized criticality or critical dynamics near a phase transition. The scale-free dynamics might even be preserved under pathological conditions (Stam et al., 2005; Worrell et al., 2002). The resulting image of ongoing brain dynamics suggests a self-organizing system of nested functional networks with high-dimensional, weakly nonlinear, critical dynamics and constantly changing spatial patterns of synchronization.

This basic pattern of ongoing brain dynamics can be modulated in a physiological way by perceptual or cognitive processing, or by changes in the level of consciousness. Changes related to perceptual or cognitive processing can be in the direction of increased or decreased levels of synchronization, and may occur independently at the functional network and functional source level. To complicate matters further, changes can be in opposite

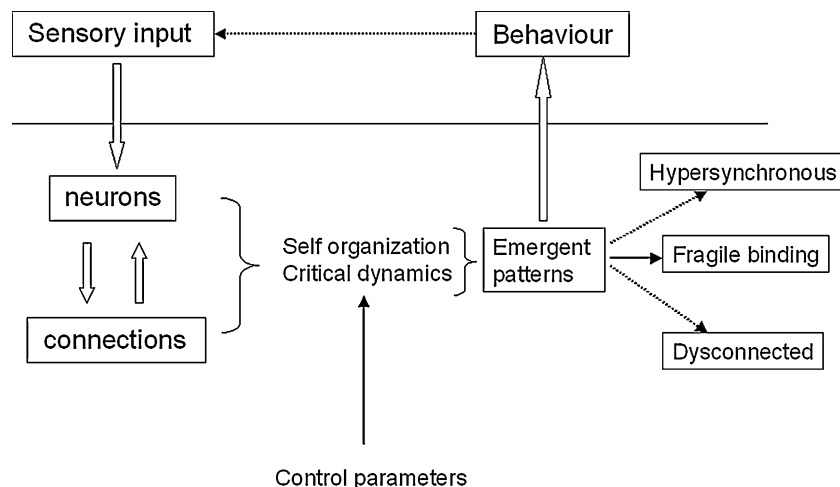


Fig. 8. Schematic illustration of a conceptual model of the relation between brain dynamics and self-organization. The basic elements are functional networks of neurons (or groups of neurons) and their connections. Neurons receive part of their input from internal as well as external sensory systems. The connections restrict the degrees of freedom of the network. Through a process of self-organization patterns of activity (attractors) emerge in the neuronal networks. The process of self-organization is influenced by different control parameters, such as the balance between excitation and inhibition. When the system is close to a bifurcation the dynamics is critical, and different patterns are formed on all spatial and temporal scales. This critical state is hypothesized to underlie information processing in the awake resting state. Its dynamics can be indicated as ‘fragile binding’. Under pathological circumstances the control parameters move to an abnormal range, and pattern formation is either excessive (hypersynchronous state characteristic of seizures) or broken down (disconnected state corresponding to various types of degenerative brain disease). The emergent patterns (attractor states of neuronal networks in the brain) organize the behaviour of the individual. Part of this behaviour may influence the sensory input, thereby closing the loop.

directions in different frequency bands. The direction and distribution of the changes seems to depend crucially upon the exact nature of the perceptual or cognitive task. We should stress however that the relative changes in local and global synchronization levels are very small compared to the synchronization levels of ongoing brain activity. Furthermore, it has become clear that the awake no-task state to which ongoing brain dynamics corresponds is not a simple ‘blank’ state of the brain, but is characterized by intensive ongoing cognitive processing involving in particular memory systems (Andreasen et al., 1995). This notion has led to the concepts of ‘resting state networks’ and ‘default networks’ (Gusnard and Raichle, 2001). Consequently ongoing brain dynamics with its rapidly changing synchronous functional networks reflects intensive spontaneous information processing, and sensory processing or performing a cognitive task induce only minor modifications in the basic pattern.

What happens during sleep is less clear. Analysis at the level of functional sources seems to suggest a loss of dynamical complexity or an increase in the level of synchronization. However, estimates of dynamical complexity based upon the correlation dimension might have been biased by spectral changes during slow wave sleep. Slow wave sleep is difficult to discriminate from filtered noise, which is difficult to understand if slow wave sleep would represent a truly hypersynchronous state. If there is any evidence for nonlinear structure in sleep EEG it is limited to NREM II. Assessments at the level of functional networks during sleep suggest only minor changes in synchronization levels. Thus sleep seems to be characterized primarily by ‘slowing down’, and hardly by significant changes in synchronization levels. The significance of this pattern is not clear, but it is of interest that sleep, like the ‘resting state’ is not a blank state of the brain but may involve significant information processing (Hobson and Pace-Schott, 2002). In particular it has been suggested that sleep may involve spontaneous ‘replay’ of functional networks activated during cognitive tasks before falling asleep (Huber et al., 2004).

Pathological changes of brain dynamics can be divided into two broad categories, one characterized by increased and one by decreased levels of synchronization. Epileptic seizures constitute the clearest example of the first category. As discussed in Section 4.4, many studies have shown that during epileptic seizures brain dynamics is characterized by a loss of dynamical complexity, strong nonlinearity and increased levels of synchronization. Hypersynchronization has been shown at the level of functional networks and functional sources. Transition between normal, high-dimensional brain dynamics, and abnormal low-dimensional seizures states may be abrupt, having the character of a Hopf bifurcation, or more gradual, involving various intermediate stages, possibly with a decrease in interregional synchronization before the seizure (Lopes da Silva et al., 2003a,b; see also the more extensive discussion in Section

4.4). The occurrence of bifurcations suggests a critical change in one of the systems control parameters, which might be the ratio of excitatory to inhibitory connections. Depending upon the type of seizure, the dynamics may change during the course of the epileptic discharges, and usually decreases in complexity towards to end of the seizure (Pijn et al., 1997). Of importance, hypersynchronous brain dynamics such as occurs during seizures may interfere with normal information processing, and may affect the level of consciousness. Even brief epileptiform discharges have been implicated in transient cognitive impairment (Binnie, 2003).

Loss of neurons in degenerative brain disease may disrupt anatomical connectivity at the level of functional sources and functional networks. Consequently one might expect that brain dynamics in such disorders, in particular Alzheimer’s disease, is characterized by a lower level of synchronization of ongoing brain activity, and that this loss of functional connectivity interferes with normal information processing (Delbeuck et al., 2003). Support for the dysconnection hypothesis of dementia has been found in studies at the functional network level. However, at the level of functional sources many studies have reported a loss of dynamical complexity which would suggest increased local levels of synchronization. The problem seems to be the same as with the local analysis of slow wave sleep: spectral changes, in particular an increase in slow wave activity may bias estimates of the correlation dimension, and wrongly suggest a loss of dynamical complexity. The results of surrogate data testing suggest that local brain dynamics in Alzheimer’s disease is more complex (more noise like, less nonlinear and less synchronized) than in healthy subjects, which is more consistent with the findings at the functional network level (Jelles et al., 1999a). In general it seems that coupling measures applied at the functional network level are more reliable estimators of synchronization levels than measures applied at the functional source level; this makes sense since the interacting elements of the functional source can only be assessed indirectly.

In summary, the image that arises from the analysis of normal and disturbed brain dynamics is the following. The brain can be conceived of as a nested network of coupled dynamical systems. This network probably has critical dynamics, which gives rise to constantly changing, weakly synchronized patterns of functional networks. This dynamical process of creating and destructing functional networks, which has been designated as ‘fragile binding’, is hypothesized to underly the spontaneous information processing of the ‘resting state’. The spatio temporal dynamics of the resting state is intermediate between randomness and order, and may have properties consistent with the concept of ‘neuronal complexity’ discussed above. Physiological changes in this state, whether they are related to perceptual or cognitive performance, or to falling asleep, involve only minimal changes in the level of synchronization, although sleep is characterized by a general slowing. In contrast,

significant changes in the level of synchronization always seem to interfere with information processing, and sometimes also with consciousness. Pathological dynamics with either abnormally high or abnormally low levels of synchronization seems to be brought about by changes in a critical control parameter of the neural networks in the brain. Changes in the control parameter move the system away from the optimal dynamics which is hypothesized to be near the phase transition between low and high levels of synchronization.

No doubt, this model of normal and disturbed brain dynamics is still very crude and simple. However, it may allow to establish a common framework to interpret the results of the many studies on nonlinear brain dynamics in normal and pathological conditions. And finally it may allow the formulation of more specific hypotheses which can serve as the starting point for future studies.

6. Conclusions and future perspectives

Progress in nonlinear dynamics and nonlinear time series analysis has reached a stage, where fruitful applications to EEG and MEG have become a reality. Studies in this field have shown however that the initial hypothesis of a low-dimensional chaotic attractor explaining brain dynamics is too simple. The only type of brain state that comes close to this is the brain dynamics of epileptic seizures. Other types of normal and abnormal brain dynamics have proven to be both more complex and less stationary than expected. Furthermore, extensive experience in applying nonlinear methods to various types of signals, backed up by hypothesis testing with surrogate data, is pointing the way to a proper interpretation of these tools. In particular, measures of nonlinear coupling between time series may allow a more straightforward interpretation than local measures of complexity or chaos. Several years of experience with nonlinear analysis have shown that the proper question to be asked is not whether a low-dimensional chaotic attractor can be identified, but to what extent nonlinear phenomena, such as the level of synchronization between different network elements, contribute to a particular brain state.

The future of nonlinear EEG / MEG analysis will depend upon progress in three directions: (i) development of better tools for nonlinear time series analysis; (ii) a better theoretical understanding of the dynamics of normal and pathological brain states; (iii) clinical application of nonlinear analysis to such problems as seizure anticipation / detection and diagnosis of psychiatric and neurological disorders.

Development of new and improved methods for non-linear time series has been a field of intense research in the past years, and will probably continue like this in the years to come. Development of new methods is driven by the need to study newly discovered features of nonlinear dynamical systems in real data. One example is the discovery of ‘generalized synchronization’ which has inspired the

development of a whole series of new measures for the assessment of nonlinear coupling between time series. Also, EEG and MEG time series present problems due to non stationarity, noise levels and high dimensionality. New methods will have to be developed that can deal with this type of data and produce robust results which allow a meaningful interpretation in terms of the underlying brain dynamics. Finally, the field of nonlinear analysis can be broadened by applying the techniques to different measures of brain activity, such as the fMRI BOLD time series.

At a fundamental level, nonlinear analysis aims at an understanding of the dynamic processes underlying normal and pathological brain states. Although some basic insights have been obtained – in particular the importance of ‘fragile binding’ for normal brain functioning – further work is required to obtain a more detailed understanding of brain dynamics. In particular, a better understanding of the relationship between brain dynamics at the one hand, and structural properties as well as behavioural performance on the other hand, should be looked for. Current research using simulated neural networks as well as animal experiments can help to test various hypothesis concerning normal and disturbed brain dynamics, and its relations to control parameters such as the ratio between inhibition and excitation.

Finally, for the clinical neurophysiologist, the proof of the pudding is the clinical application. At this stage, nonlinear analysis is still a research field. However, several clinical problems present suitable targets for clinical application. In the short term, the most likely clinical application is in the field of epileptology, in particular the anticipation and detection of epileptic seizures. Automatic analysis of sleep stages is also a promising field, although the understanding of nonlinear dynamics during sleep is still in an early stage. One of the biggest challenges for the future is to use nonlinear analysis as a tool to better understand cognitive dysfunction, and to aid in the diagnosis and differential diagnosis of dementia.

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