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Research Overview

Nonlinear Dynamics of EEG in Alzheimer's Disease

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Strategy, Management and Health Policy				
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ABSTRACT Nonlinear dynamical analysis has been widely applied to a variety of physiological data for last two decades. One of its major contributions is to the electroencephalogram (EEG) in Alzheimer's disease (AD). A number of studies using nonlinear dynamical methods have shown the globally decreased complexity of EEG patterns in AD patients. A prominent decrease in information transmission among cortical areas quantified by information-theoretic measures like mutual information is also found. These findings indicate decreased nonlinear processes underlying the EEG in AD. This review article focuses on nonlinear EEG abnormalities in AD patients obtained from nonlinear methods and their clinical implications. We suggest that nonlinear dynamical analysis may contribute to a deeper understanding of the neuropathological mechanism of AD in ways that are not possible by conventional spectral analysis. Drug Dev. Res. 56:57–66, 2002. © 2002 Wiley-Liss, Inc.

Key words: Alzheimer's disease; nonlinear dynamics; EEG; complexity; information transmission

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease, characterized by progressive impairments in cognition and memory. These clinical features are accompanied by characteristic histological changes in the brain, which include widespread cortical atrophy, intracellular deposition of neurofibrillary tangles, and extracellular deposition of senile plaques, particularly in the hippocampus and the cerebral cortex [Selkoe, 1994].

The electroencephalogram (EEG) has been used as a tool for diagnosing dementias for several decades. Typical EEG abnormalities in AD are characterized by a slowing of the rhythms and a decreased coherence among cortical areas: an increase in theta and delta activity, a decrease in alpha and beta activity, and a reduced coherence of the alpha and beta bands. These abnormalities are found to be associated with the severity of the disease. A number of studies have demonstrated that the EEG is useful for diagnosing AD [for review, Rosen 1996; Jonkman, 1997].

Nonlinear dynamical analysis (NDA) has been widely applied to various physiological data to investigate complex dynamics of the underlying processes for last two decades. In particular, applying NDA to EEG recordings has been demonstrated to offer fruitful information about the cortical dynamics underlying EEG signals. One of the major contributions of NDA is to the EEG in AD. Nonlinear abnormalities of the EEG in AD are characterized by the decreased complexity of EEG patterns and lowered functional connectivity among cortical areas. These results indicate decreased nonlinear processes and coupling interactions underlying the EEG in AD. Many studies have provided a growing body of evidence that NDA of brain electrical activity in AD patients is capable of offering potentially valuable diagnostic information and better understanding of the neuropathological mechanism of AD.

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In this article, we briefly review theoretical background and concepts of nonlinear dynamical methods and summarize nonlinear abnormality of the EEG in AD obtained by these nonlinear methods as well as spectral abnormality of the EEG. The clinical and neurophysiological implications of these findings are discussed.

NONLINEAR DYNAMICAL ANALYSIS OF THE EEG IN AD

Characterizing Nonlinear Dynamical Changes of the EEG

The fundamental assumption of NDA is that EEG signals are generated by nonlinear deterministic processes with coupled nonlinear interactions between neuronal populations. Nonlinear deterministic systems may show a sensitive dependence on initial conditions, indicating that different states of a system, being arbitrarily close initially, can become exponentially separated in sufficiently long times. This behavior is called deterministic chaos. These systems look highly irregular and complex, similar to stochastic systems. Given the highly nonlinear nature of neuronal interactions at multiple levels of spatial scales, it is natural to apply nonlinear dynamical methods to the EEG.

Complex dynamical systems such as the brain commonly involve a large number of interrelated variables that are impossible to measure directly. Thus, the major problem is how to analyze multidimensional dynamics knowing only a few variables that can be measured. Takens [1981] has shown that if we measure any single variable with sufficient accuracy for a long period of time, it is possible to reconstruct the underlying dynamic structure of the entire system from the behavior of that single variable using delay coordinates and the embedding procedure.

The first step of the embedding procedure in nonlinear EEG analysis is to transform the one-dimensional EEG data into multidimensional phase space. The concept of phase space is central to the analysis of nonlinear dynamics. In a hypothetical system governed by n variables, the phase space is n-dimensional. Each state of the system corresponds to a point in the phase space whose n-coordinates are the values assumed by the governing variables for this specific state. If the system is observed for a long period of time, the sequence of points in the phase space forms a trajectory. This trajectory fills a subspace of the phase space, called the system's attractor. The reconstruction of the attractor in the phase space is carried out through the technique of delay coordinates. To unfold the projection back to a multivariate state space that is a representation of the original system, the delay coordinates $y(t)=[x_j(t),\ x_j(t+\tau,),\ x(t+2\tau),\ldots,\ x_j(t+\ (d-1)\tau)]$ from a single time series x_j is used, where $y(t)$ is a point of the trajectory in the phase space at time t, $x_j(t+i\tau)$ is the coordinate in the phase space corresponding to the time-delayed values of the time series, τ is the time delay between the points of the time series considered, and d is the embedding dimension [Kantz and Schreiber, 1997].

The choice of an appropriate time delay τ and embedding dimension d is important for the success of reconstruction with finite data. For the time delay τ, the first zero-crossing time of the autocorrelation or the first local minimum of the average mutual information of the EEG is often utilized. Mutual information measures linear and nonlinear dependence of two variables, while the autocorrelation estimates linear dependence. It has been shown that the mutual information provides a more reliable delay time than does autocorrelation [Fraser and Swinney, 1986]. The optimal embedding dimension can be obtained using the method developed by Kennel et al. [1992]. The algorithm of this method is based on the idea that in the passage from dimension d to dimension $d+1$, one can differentiate between points on the orbit that are true neighbors and those which are false. A false neighbor is a point in the dataset that is a neighbor solely because we are viewing the orbit (the attractor) in too small an embedding space ($d<d_{min}$). When a large enough embedding space has been achieved ($d\geq d_{min}$), all neighbors of every orbit point in the multivariate phase space will be true neighbors. A properly fixed value ranging 5–15 or a minimum value obtained from Kennel's method is often used for the embedding dimension in NDA.

The geometric and dynamical properties of the trajectories in the phase space can be quantified by nonlinear measures. An important measure is the dimensionality of the attractor, referred to as the correlation dimension (D_2) or dimensional complexity. The D_2 reflects the number of independent variables that are necessary to describe the dynamics of the system. For instance, the D_2 of the attractor is zero in the case of steady-state behavior and the D_2 of the periodic attractor is one. In chaotic states, the D_2 usually takes on noninteger values. The larger the D_2 of the attractor, the more complicated the behavior of the nonlinear system. D_2 is therefore a measure of complexity of the process being investigated and characterizes the distribution of points in the phase space. The D_2 of the EEG is generally considered to be a reflection of the complexity of the cortical dynamics underlying EEG recordings [Röschke and Aldenhoff, 1991].

The D_2 of the attractors from the EEG is commonly evaluated using the Grassberger-Procaccia Algorithm (GPA) [Grassberger and Procaccia, 1983]. This algorithm determines the D_2 by counting the relative number of pairs of points in the phase-space that are separated by a distance less than r:

$$D_2 = \lim_{r\to 0}\lim_{N\to\infty}\frac{\log C(r, N)}{\log r} \tag{1}$$

where the correlation integral $C(N, r)$ is defined by:

$$C(r) = \frac{1}{N^2}\sum_{\substack{i,j=1\\ i\neq j}}^{N}\theta\left(r - |\vec{y}_i - \vec{y}_j|\right) \tag{2}$$

where y_i and y_j are the points of the trajectory in the phase space, N is the number of data points in the phase space, the distance r is a radius around each reference point y_i, and Θ is the Heaviside function, defined as 0 if $y<0$, and 1 if $y\geq 0$. For small r, the correlation integral exhibits the scaling property: $C(N, r)\propto r^{D2}$. For the fractal attractor the local scaling exponent is constant; this region is called a scaling region. If this plateau is convincing enough, this scaling exponent (i.e., the slope of the $C(r)$ on a log–log plot) can be used as an estimate of D_2.

As another measure of complexity, Lyapunov exponents estimate the mean exponential divergence or convergence of nearby trajectories of the attractor in the phase space. This reflects the sensitive dependence on initial conditions. A system possessing at least one positive Lyapunov exponent is chaotic. Lyapunov exponents are usually ordered in a descending fashion from L_1 (the highest value) to L_n (the lowest value), where n is equal to the dimensionality of the phase space. Positive L_1 of a time series indicates the presence of chaoticity in the underlying dynamics of the time series. The larger the positive L_1 of the attractor, the more complicated the behavior of the nonlinear system. While D_2 is a static, geometric measure, L_1 is a relatively dynamic measure of conditions [Fell et al., 1993].

The L_1 of time series is usually computed using the Wolf algorithm [Wolf et al., 1985]. The Wolf algorithm calculates the initial vector distance $\delta(0)$ of two nearby points and evolves its length $\delta(t)$ at a certain propagation time t. If the vector length between the two points becomes too large, a new reference point is chosen with properties minimizing the replacement length and the orientation change. Then the two points are evolved again, and so on. After m propagation steps, the first positive Lyapunov exponent, L_1, results from the sum over the logarithm of the ratios of the vector distances divided by the total evolving time:

$$L_1 = \frac{1}{m}\sum_{i=1}^{m}\frac{\ln\frac{\delta_i(t)}{\delta_i(0)}}{t\cdot\ln 2}\,(bits/s) \tag{3}$$

where t is the evolving time, $\delta(0)$ and $\delta(t)$ are the initial and the final separations between the points in the fiducial trajectory and in the nearest-neighbor trajectory separated in time t, respectively. A graphic presentation of the nonlinear methods is given in Fig. 1.

The surrogate data method is often used to help detect nonlinear deterministic structure within the data. Surrogate data can be constructed by phase randomization of the original signals. In this way, surrogate data are produced whose linear properties, such as power spectrum and histogram, are unchanged, whereas nonlinear properties that may be present are destroyed. Statistical differences of nonlinear measures between the original data and its surrogate data indicate the presence of nonlinear structure in the original data. The detailed algorithm for generating the surrogate data is presented in Schreiber and Schmitz [2000]. More detailed algorithms of NDA are present in other reviews [Pritchard and Duke, 1992; Cerutti et al., 1996; Kantz and Schreiber, 1997; Schreiber, 1999; Abarbanel and Rabinovich, 2001; Faure and Korn, 2001]. C-code programs estimating nonlinear measures are available at the website developed by Hegger et al. [1999].

As a matter of fact, whether the EEG has a deterministic component or not is still controversial. Much research has proven the nonlinear character of cortical dynamics. The EEG has a finite noninteger D_2 and a positive value of averaged local Lyapunov exponents, indicating the presence of deterministic chaos in the EEG [Babloyantz, 1985; Soong and Stuart, 1989; Kowalik, 2000]. The surrogate data test distinguishing between original- and randomized-phase time-series has revealed that EEG recordings are nonlinear [Pritchard et al., 1995; Elhers et al., 1998; Jelles et al., 1999b; Kowalik, 2000]. These findings support the hypothesis that brain oscillators are governed by deterministic, nonlinear dynamics. By contrast, Theiler et al. [1992, 1996] and Pritchard et al. [1995] have found, using the surrogate data method, that the EEG is not produced by low-dimensional chaos. In addition, filtered noise can mimic low-dimensional chaotic attractors as the EEG data do [Rapp et al., 1993]. Recently, more direct methods have been applied to detect determinism within the EEG [Jeong et al., 1999]. Based on the observation that nearby trajectories reconstructed from the behavior of deterministic systems in the phase space behave similarly under time evolution, smoothness of

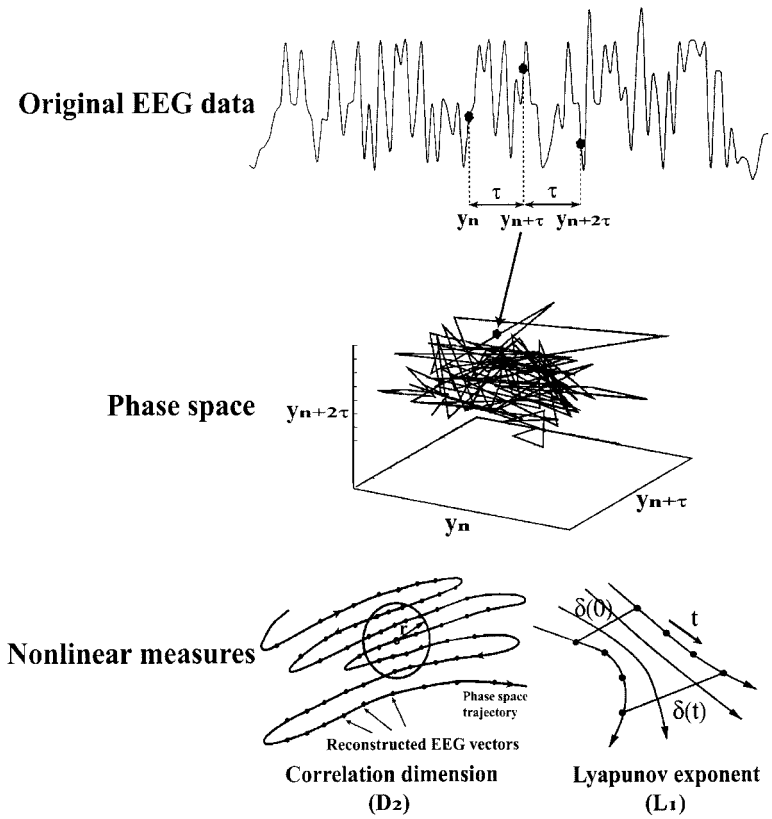

Fig. 1. A schematic diagram of nonlinear dynamical analysis of the EEG. The first step is to transform the EEG data into multidimensional phase space using delay coordinates. Nonlinear measures like the first positive Lyapunov exponent and correlation dimension are estimated from the attractor in the phase space reconstructed from the EEG data.

trajectories of the EEG is estimated. No smoothness is found in the trajectories reconstructed from the EEG, indicating that the EEG is not generated by a low-dimensional deterministic process.

Although no compelling evidence for a deterministic nature of the EEG has been adduced, nonlinear dynamical methods have been proven to allow characterization of different physiological and pathological brain states [for review, see Jansen, 1996; Wackermann, 1999; Le Van Quyen et al., 2001; Sarbadhikari and Chakrabarty, 2001]. Therefore, these nonlinear measures are used now as a measure of complexity to quantify complex behavior of the brain, instead of using it as an absolute measure to differentiate between periodic, chaotic, or stochastic dynamics.

Decreased Complexity of the EEG in AD

Since the first observation of Hans Berger, conventional spectral analysis of the EEG in AD patients has demonstrated a slowing of EEG rhythms. The decreased mean frequency with an increase in delta and theta power and a parallel decrease in alpha and beta power are observed in AD patients compared to that of normal elderly subjects [Stigsby et al., 1981; Coben et al., 1983, 1985; Brenner et al., 1986; Giaquinto and Nolfe, 1986; Maurer and Dierks, 1992; Szelies et al., 1992; Schreiter-Gasser et al., 1993; Ihl et al., 1993]. The earliest changes are an increase in theta activity and a decrease in beta activity, which are followed by a decrease in alpha activity, and then an increase in delta activity [Stigsby et al., 1981; Coben et al., 1983, 1985; Penttilä et al., 1985; Hier et al., 1991]. The increase in slow activity in AD patients is prominent in the left temporal area compared with elderly normal subjects [Breslau et al., 1989; Rice et al., 1990]. These EEG abnormalities are associated with cognitive deficits. Good correlations between EEG spectral measures and cognitive deterioration scores such as the Folstein (Mini-Mental) score [Brenner et al., 1986; Leuchter et al., 1987, 1993; Filipovitch et al., 1989; Elmståhl et al., 1994; Schreiter-Gasser et al., 1994; Strijers et al., 1997], the Global Deterioration Score [Helkala et al., 1991; Prichep et al., 1994; Passero et al., 1995], and a composite neuropsychological test score [Penttilä et al., 1985] are found. The close

correlation between an EEG slowing and the severity of the disease suggests that a disruption of processing in cortical networks contributes importantly to the behavioral disorganization present in AD [Dringenberg, 2000]. Studies in which different methods are used on the same population demonstrate that a total accuracy of approximately 80% is a realistic obtainable value by spectral analysis of the EEG [Brenner et al., 1988; Hooijer et al., 1990]. Diagnostic value of the EEG in AD is presented in other articles in detail [Rosen, 1996; Jonkman, 1997].

NDA of brain electrical activity in AD patients has provided supplementary useful diagnostic information that cannot be obtained by spectral analysis. Woyshville and Calabrese [1994] have demonstrated, using single-channel EEG, that AD patients exhibit reduced D_2 values of the occipital EEG compared with those of healthy subjects, indicating that brains injured by AD exhibit a decrease in complexity of electrical activity. Moreover, within AD patients autopsy-confirmed AD patients have significantly reduced D_2 values relative to probable AD patients. Besthorn et al. [1995] and Jeong et al. [1998] used multichannel EEG recordings and a time-delay embedding method to show that AD patients have significantly lower D_2 values than those of age-approximated healthy subjects in almost all electrodes. Using a spatial embedding method, Stam et al. [1995] and Yagyu et al. [1997] demonstrated prominently reduced spatiotemporal brain activity of AD patients compared with normal controls. These findings indicate the globally decreased complexity of brain electrical activity in AD patients.

Neurophysiological implications of decreased complexity of the EEG are not certain. The decrease in dynamical complexity of the EEG in AD patients might arise from neuronal death, deficiency of neurotransmitter such as acetylcholine, and/or loss of connectivity of local neuronal networks. Thus, the reduction of the dimensionality in AD might be an expression of the inactivation of previously active networks. In addition, it is likely due to a loss of dynamical brain responsivity to stimuli. Pritchard et al. [1991, 1993] found that AD patients do not have significant D_2 differences between in eyes-open and eye-closed conditions, whereas normal subjects have markedly increased eyes-open D_2 values compared with eyes-closed D_2 values. These results support the hypothesis that AD patients exhibit a loss of dynamical brain responsivity to the environmental stimuli. Given that complex EEG dynamics reflect the cortical activity (information processing) underlying EEG recordings, the reduced complexity of the EEG in AD may indicate the deficient information processing of the AD brain due to the inactivation of previously active networks or a loss of dynamical brain responsivity to stimuli.

Using the first positive Lyapunov exponents, Stam et al. [1995] and Jeong et al. [1998] have shown a decreased complex brain activity in AD patients compared with that of age-matched healthy subjects. Although both D_2 and L_1 are a measure of complexity, the L_1 of the EEG can be interpreted as a measure of flexibility of information processing in the brain [Fell et al., 1995]. Flexibility is understood as the facility of the central nervous system to reach different states of information processing from similar initial states [Röschke and Aldenhoff, 1991]. In this context, decreased L_1 values in AD patients in comparison with healthy subjects indicate a drop in the flexibility of information processing in AD brains.

The surrogate data method has been applied to investigate nonlinearity of the EEG in AD patients. Both normal subjects and AD patients exhibit significant D_2 differences between original and surrogate EEG data [Stam et al., 1995; Jelles et al., 1999b], indicating the presence of nonlinearity in the EEG. Yet Jelles et al. [1999b] found less difference between original EEG data and the surrogate data in AD patients compared with those of healthy subjects. This indicates that the decrease in complexity of the EEG in AD may be attributable, at least in part, to different nonlinear neurodynamics underlying the EEG. In another study, Jelles et al. [1999a] found no significant change in nonlinear structure between healthy subjects and AD patients in the early stage of the disease. This implies that linear dynamics of the EEG changes first in the course of AD followed by changes in nonlinear dynamics.

Nonlinear measures as a diagnostic indicator of AD has been investigated. Pritchard et al. [1994] assessed the ability of adding nonlinear measures to spectral analysis and using a neural-net classification procedure to improve the classification accuracy of subjects. The addition of D_2 improves the classification accuracy of the AD/control status of subjects up to 92%. Besthorn et al. [1997] also reported that the D_2 correctly classified AD and normal subjects in approximately 70%. In addition, good correlations between nonlinear measures and the severity of the disease [Besthorn et al., 1995; Yagyu et al., 1997], a slowing of EEG rhythms [Besthorn et al., 1995], and neuropsychological performance [Ikawa et al., 2000] are found. Furthermore, it has shown that a high dose of drug (experiment molecule) increases the complexity of the brain activity in frontotemporal areas measured by the global entropy compared with a placebo condition [Pezard et al., 1998]. This result suggests a possibility

that nonlinear measures can quantify the effect of drug on the course of the disease. Taken together, we believe that nonlinear measures are a potentially useful indicator for the diagnosis of AD, assessment of neuropsychological deficits, and pharmacological treatment evaluations.

There are few studies about differential and early diagnosis of AD using nonlinear methods. AD patients exhibit lower L_1 values than those of Parkinson patients [Stam et al., 1994, 1995] and lower D_2 and L_1 values than those of patients with vascular dementia (VaD) [Jeong et al., 2001a]. VaD patients appear to have an uneven distribution of the D_2 values over the regions than AD patients and normal controls do, even though the statistics did not confirm this. In the early stage of AD, nonlinear EEG abnormalities in AD patients, like decreased complexity and increased predictability, are observed particularly in the frontal and temporal areas [Jelles et al., 1999a]. These findings indicate that NDA provides additional information helpful for differential and early diagnosis of AD.

It is noteworthy that nonlinear dynamics of the EEG is influenced by age [Meyer-Lindenberg, 1996; Anokhin et al., 1996, 2000], sex [Anokhin et al., 2000], and intelligence [Anokhin et al., 1999; Lutzenberger et al., 1992]. Although the effect of normal aging on the EEG dynamics is controversial [for review, see Visser, 1991; Dustman et al., 1993; Angeleri et al., 1997], the effects of these factors should be considered with caution in the analysis to obtain reliable results and to have proper interpretations.

Decreased Degrees of Functional Connectivity in AD

The degree of functional connectivity among cortical areas has been estimated using coherence of the EEG. EEG coherence is defined as the square of the cross-spectrum of the electrodes divided by the product of the power spectra of the individual electrodes. It is often estimated separately for each of the six frequency bands and for specific pairs of electrodes such as F3-C3, or averaged over all electrode pairs for each frequency band as a global measure of connectivity. Decreased coherence reflects reduced functional connections between cortical areas beneath the electrodes. Coherence analysis of the EEG in AD has reported a decrease in coherence of the alpha and beta bands in various types of dementia in both the short- and long-distance connections [O'Conner et al., 1979; Leuchter et al., 1987, 1992; Besthorn et al., 1994; Dunkin et al., 1994; Sloan et al., 1994; Locatelli et al., 1998]. This deceased coherence of fast bands is significantly correlated with cognitive impairment [Dunkin et al., 1994; Jelic et al., 1996]. The decrease in EEG coherence indicates functional disconnections among cortical areas resulting from axonal pathology or death of cortical neurons.

By contrast, coherence of slow EEG rhythms is unaffected [Besthorn et al., 1994] or rather increased [Locatelli et al., 1998; Comi et al., 1998], particularly in patients with the most severe cognitive impairment [Locatelli et al., 1998]. Locatelli et al. [1998] interpreted this as that an increase in coherence of slow bands depends on cortical deafferentation from subcortical structures. It is shown that an increase in slow band power in AD patients is associated with cortical loss of choline acetyltransferase [Reinikainen et al., 1988; Soininen et al., 1992]. Anticholinergic drugs in healthy subjects induce an increase in coherence of slow bands [Sloan et al., 1992]. These findings indicate that the increase in coherence of slow bands in AD is associated with the disruption of long cortico-cortical cholinergic connections.

Recently, the mutual information (MI) method was applied to the EEG in AD patients [Jeong et al., 2001b]. While coherence measures only linear dependencies in the electrical activity across different areas, MI analysis takes into account both the linear and nonlinear dependencies among those same brain regions. MI analysis has shown that the information transmission between different electrodes is reduced in AD subjects in comparison with that in normal controls, in particular over frontal and anterotemporal regions. Furthermore, a prominent decrease in the MI between distant electrodes and between interhemispheric electrodes is observed in AD patients. A prominent decrease in the information transmission between interhemispheric electrodes in AD patients is a novel finding, supporting the usefulness of the MI analysis.

As a matter of fact, clear evidence for the presence of nonlinear coupling in long cortico-cortical fibers in the cortex is not found. Villa et al. [2000] detected indirect evidence for the nonlinear functional cortico-cortical interaction. They used bispectral analysis to measure the shift of phase-coupled frequencies (somewhat analogous to frequencies of resonance) in multiple local field potentials in the rat temporal cortex. After the application of the immunotoxin 192 IgG-saporin (SAP), which provokes a selective loss of NGFr-positive basal forebrain cholinergic neurons similar to the loss of its integrity associated with human AD, a decrease in choline acetyltransferase activity and an increase of phase coupling in the low frequencies are found, indicating a decrease in functional cortico-cortical interaction. This result supports the hypothesis that nonlinear coupling is present in long cortico-cortical fibers in the cortex. Because neural dynamics include many highly nonlinear processes [McKenna

TABLE 1. Summary of Main Findings of EEG Studies on Nonlinear Dynamics in AD Patients

Authors (year)	Sample	Analysis methods	Main findings
Pritchard et al. [1991, 1993]	20 ADs, 12 young controls, 7 elderly controls	D_2	A loss of dynamical brain responsivity to stimuli in AD patients.
Pritchard et al. [1994]	14 ADs, 25 controls	D_2 and neural network	The addition of the D_2 improves the classification accuracy of the AD/control status of subjects up to 92%.
Woyshville and Calabrese [1994]	6 probable ADs, 6 autopsy-confirmed ADs, 8 controls	D_2	Lower D_2s in ADs than those of controls. Lower D_2s in autopsy-confirmed ADs than those of probable ADs.
Stam et al. [1994]	15 demented patients, 17 Parkinson patients, 20 controls	D_2, spatial embedding	Lower D_2s in demented patients than those of controls and Parkinson patients. A positive correlation of D_2 with beta power, and a negative correlation with delta and theta power.
Besthorn et al. [1995]	50 ADs, 42 controls	D_2	Lower D_2 values in AD patients than in controls.
Stam et al. [1995]	9 demented patients, 13 Parkinson patients, 9 controls	K_2, L_1, D_2, spatial embedding, surrogate data method	The presence of nonlinear structure in the EEG. Lower D_2 and L_1 in demented patients than those of controls. Higher L1 in Parkinson patients than in demented patients.
Besthorn et al. [1997]	50 ADs, 42 controls	D_2, back propagation neural network, PCA	The D_2 correctly classified AD/normal subjects in about 70%. A maximum of 86.6% correct classifications is reached using PCA.
Yagyu et al. [1997]	21 ADs, 29 mild cognitive impairment, 29 subjective memory complaint	D_2, spatial embedding	Lower D_2s in AD patients than those of mild cognitive impairments and subjective memory complaints, A positive correlation between D_2 and cognitive performance (MMSE and WAIS-R scores).
Pezard et al. [1998]	12 ADs	Entropy	A significant effect of the drug (an experimental molecule: S 12024-2) are found compared with placebo. An increase in entropy for the highest dose (200 mg).
Jeong et al. [1998]	12 ADs, 12 controls	D_2, L_1, optimal embedding dimension method	Lower D_2 and L_1 values in AD patients than in controls.
Jelles et al. [1999a]	24 probable ADs, 22 controls	D_2, surrogate data method	Lower D_2 in AD patients than in controls. D_2 differences between original and surrogate data are significant in both groups. Smaller differences between original and surrogate data are found in AD patients.
Jelles et al. [1999b]	42 controls, 7 ADs	D_2, nonlinear prediction, surrogate data method	Lower D_2 and higher predictability in demented subjects than in normal subjects. Major differences between demented and healthy subjects are not due to nonlinearity
Ikawa et al. [2000]	24 ADs.	D_2, neuropsychological tests	Significant correlations between D_2 and neuropsychological test scores.
Jeong et al. [2001a]	12 ADs, 12 VaDs, 14 controls	D_2, L_1	Lower D_2s and L_1s in VaD patients than in AD patients, and controls in some channels. An uneven distribution of D_2s and L_1s in VaD patients.
Jeong et al. [2001b]	15 ADs, 15 controls	Mutual information	Lower MIs in AD patients than in controls, in particular over frontal and antero-temporal regions, in distant electrodes in he right hemisphere, and between interhemispheric electrodes.

AD, Alzheimer's disease; VaD, vascular dementia; D_2, correlation dimension; K_2, Kolmogorove entropy; L_1, the first positive Lyapunov exponent; PCA, principal component analysis; MI, mutual information.

et al., 1994], MI analysis or other methods capable of measuring nonlinear dependencies among multichannel signals should be utilized to quantify not only linear but also nonlinear coupling interactions among cortical areas that cannot be assessed by conventional coherence methods. Clear evidence for the presence of

nonlinear interactions among cortical areas and its functional role should also be further investigated (Table 1).

PERSPECTIVES

EEG abnormalities in AD patients have been extensively studied for several decades. The role of the EEG in diagnosis and clinical evaluations of AD becomes more important. The complex behavior of the EEG requires the use of new mathematical methods to investigate the cortical dynamics underlying EEG signals. Nonlinear dynamical methods might provide useful tools to help in understanding brain electrical activity in terms of the collective dynamics of neurons. While spectral analysis of the EEG in AD patients has been intensively performed, many critical issues relating to nonlinear dynamics of the EEG in AD remain to be investigated. For instance, the association between nonlinear EEG dynamics and cognitive performance, longitudinal changes in nonlinear dynamics of the EEG in AD, the drug effect on nonlinear neurodynamics, and nonlinear functional connectivity among cortical areas afflicted by AD should be examined. Nonlinear dynamics might also help in improvement of the accuracy of differential diagnosis of AD and early detection in the preclinical stages. We expect that nonlinear dynamical analysis may contribute to deeper understanding of neuropathological mechanism of AD in ways that are not possible by conventional spectral analysis.

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