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Invited review

EEG dynamics in patients with Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by cognitive and intellectual deficits and behavior disturbance. The electroencephalogram (EEG) has been used as a tool for diagnosing AD for several decades. The hallmark of EEG abnormalities in AD patients is a shift of the power spectrum to lower frequencies and a decrease in coherence of fast rhythms. These abnormalities are thought to be associated with functional disconnections among cortical areas resulting from death of cortical neurons, axonal pathology, cholinergic deficits, etc. This article reviews main findings of EEG abnormalities in AD patients obtained from conventional spectral analysis and nonlinear dynamical methods. In particular, nonlinear alterations in the EEG of AD patients, i.e. a decreased complexity of EEG patterns and reduced information transmission among cortical areas, and their clinical implications are discussed. For future studies, improvement of the accuracy of differential diagnosis and early detection of AD based on multimodal approaches, longitudinal studies on nonlinear dynamics of the EEG, drug effects on the EEG dynamics, and linear and nonlinear functional connectivity among cortical regions in AD are proposed to be investigated. EEG abnormalities of AD patients are characterized by slowed mean frequency, less complex activity, and reduced coherences among cortical regions. These abnormalities suggest that the EEG has utility as a valuable tool for differential and early diagnosis of AD.

Keywords: Alzheimer's disease; Electroencephalography; Linear; Nonlinear; Complexity; Diagnosis; Clinical neurophysiology

1. Introduction

Dementia is one of the most common disorders among the elderly population. The prevalence rate of dementia in persons aged 65 years or over has been reported to be about 3.6–10.3% in Western countries and 1.8–10.8% in Asian countries since the mid-1980s (Lee et al., 2002, and the references therein). The prevalence increases markedly with age, so that dementia affects up to 50% of all Americans over the age of 80 (Vicioso, 2002). Among several subtypes of dementia, Alzheimer's disease (AD) is the most frequent cause of dementia. Approximately 50–60% of patients with dementia over 65 years are clinically related to AD. In 2002, 4.3 million individuals are estimated to be with AD in the United States (Lahiri et al., 2002). This number is projected to increase to 15 million by 2050, and consequently the personal and social ramifications of the disease will be more significant. Thus, early diagnosis and effective treatment of AD are critical issues in dementia research.

The neuropathology of AD is characterized by widespread neuronal cell loss, neurofibrillary tangles, and senile plaques in the hippocampus, entorhinal cortex, neocortex and other brain regions (DeCarli, 2001; Selkoe, 1994). Senile plaques are extracellular aggregates of amyloid β-peptides, and neurofibrillary tangles are the aggregation of tau proteins. Hyperphosphorylated tau, produced by an imbalance between protein phosphorylation and dephosphorylation due to a decrease in the activity of protein phosphatase-2A which regulates the activities of tau kinases, is the major protein subunit of neurofibrillary tangles (Iqbal et al., 2002; Smith et al., 2002). Tangles are found mainly in the limbic structures, particularly hippocampal and parahippocampal regions, whereas extensive diffuse and neuritic amyloid plaques form preferentially throughout the neocortex (Price and Morris, 1999; Price et al., 2001). Reduced brain weight, cortical atrophy, and ventricular enlargement are also prominent in the brains of AD patients. The size of the hippocampus and of the temporal horn of the lateral ventricle is associated with the number of neurofibrillary tangles in the hippocampus (DeCarli et al., 1990), whereas cortical atrophy is correlated

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with the amount of senile plaques in the cortex afflicted by AD (Davis et al., 1995).

AD frequently takes a typical clinical course reflecting the underlying expanding neuropathology (Bianchetti and Trabucch, 2001; Förstl and Kurz, 1999; Storey et al., 2002). In the pre-clinical stage of AD, no reliable and valid symptoms are detected to allow a very early diagnosis before the manifestation of irreversible cognitive deficits. In the mild stage, an impairment of learning and memory is usually notable. The declarative recent memory is predominantly affected with early loss of memory for everyday events. Semantic difficulties with word generation and a deterioration of object naming are also prominent. In the moderate dementia stage, language difficulties become more obvious as word finding difficulties, paraphasia, and the circumstanciality increase (Förstl and Kurz, 1999). Deficits in other cognitive abilities, such as judgment, abstract or logical reasoning, planning, and organizing, appear during the progression of the disease (Bianchetti and Trabucch, 2001). One-third of AD patients at this stage develop illusionary misidentifications and other delusional symptoms arise from cognitive deficits (Reisberg et al., 1996). Aimless and restless activity, like wandering and hoarding, is commonly observed (Devanand et al., 1997). In the late stage of illness, almost all cognitive functions are severely damaged, and motor functions including chewing and swallowing are profoundly disturbed. The average duration of survival of AD patients is 5–8 years after clinical diagnosis (Bracco et al., 1994).

Since Hans Berger, the discoverer of the electroencephalogram (EEG), first observed pathological EEG sequences in a historically verified AD patient (Berger, 1931, 1932), a large number of studies about the EEG of AD have been performed. The hallmark of EEG abnormalities in AD patients is slowing of the rhythms and a decrease in coherence among different brain regions. An increase in theta and delta activities and a decrease in alpha and beta activities are repeatedly observed (Brenner et al., 1986; Coben et al., 1983, 1985; Giaquinto and Nolfe, 1986), and a reduced coherence of the alpha and beta bands is frequently found (Dunkin et al., 1994; Leuchter et al., 1987; Locatelli et al., 1998). Furthermore, these abnormalities are correlated with the severity of the disease (Hughes et al., 1989; Kowalski et al., 2001). For the last 2 decades, the EEG has been utilized as a useful tool for diagnosing dementias.

There are several reasons why intensive research has been performed on the EEG in AD. One reason is that AD is a cortical dementia in which EEG abnormalities are more frequently shown. Subcortical dementias exhibit relatively normal EEG patterns compared with cortical dementias (Verma et al., 1987). The EEG abnormalities in AD directly reflect anatomical and functional deficits of the cerebral cortex damaged by the disease. Thus, the investigation of EEG dynamics is expected to provide with fruitful clues about the neuropathology of AD. Another reason is that coherence analysis of the EEG in AD allows noninvasive assessment of synaptic dysfunction. The synaptic plasticity is critical for brain functions, particularly learning and memory. A number of evidence suggest that disturbances of synaptic connections may underlie numerous neurological and psychiatric disorders including AD (Masliah and Terry, 1993), schizophrenia (Feinberg, 1982–1983), epilepsy (Sutula, 1990), and Parkinsonism (Donnan et al., 1991). A decrease in functional connectivity and its correlation with the degree of dementia suggest that EEG coherence studies of AD may help understand the association between synaptic plasticity and cognitive performance (Cook and Leuchter, 1996). In addition to these reasons, it is of physical interest to investigate nonlinear EEG dynamics in AD to understand the role of nonlinearity in brain functions. Nonlinear dynamical analysis (NDA) of the EEG has revealed that a decreased complexity of EEG patterns and reduced functional connections in AD are likely due to decreased nonlinear cell-dynamics and/or nonlinear couplings among cortical areas as well as linear couplings (Jelles et al., 1999b; Jeong et al., 2001b; Villa et al., 2000). Therefore, NDA of the EEG in AD might provide valuable information about the progress of the disease that cannot be assessed by conventional analyses.

This review summarizes main findings about EEG abnormalities in AD patients obtained from linear and nonlinear methods, and considers the clinical neurophysiology of AD underlying the EEG abnormalities. The EEG as a tool for differential diagnosis and early detection of AD and as a measure of functional connectivity among cortical regions is intensively discussed.

2. Slowing of the EEG in AD patients

Since the first observation of Hans Berger, conventional visual analyses of the EEG in AD patients have demonstrated a slowing of the dominant posterior rhythm, an increase in diffuse slow activity (Brenner et al., 1988; Liddle, 1958; Rae-Grant et al., 1987; Soininen et al., 1982), and a reduction in alpha (Gordon and Sim, 1967; Letemendia and Pampiglione, 1958) and beta activities (Letemendia and Pampiglione, 1958; Wiener and Schuster, 1956). There is a good correlation between the degree of the EEG abnormality and cognitive impairment (Brenner et al., 1988; Erkinjuntti et al., 1988; Johannesson et al., 1979; Kaszniak et al., 1979; Liddle, 1958; Merskey et al., 1980; Obrist et al., 1962; Rae-Grant et al., 1987; Roberts et al., 1978; Soininen et al., 1982; Wiener and Schuster, 1956).

Computerized EEG spectral analysis, which provides more quantitative data than does visual analysis, has also shown a decrease in the mean frequency with an increase in delta and theta power and a parallel decrease in alpha and beta power in AD patients compared with those of normal elderly subjects (Bennys et al., 2001; Brenner et al., 1986; Coben et al., 1983, 1985, 1990; Giaquinto and Nolfe, 1986; Ihl et al., 1993; Maurer and Dierks, 1992; Schreiter-Gasser

et al., 1993; Stigsby et al., 1981; Szelies et al., 1992; Visser et al., 1985), even during rapid eye movement (REM) sleep (Hassainia et al., 1997; Montplaisir et al., 1996; Petit et al., 1992, 1993). It is generally thought that the earliest changes are an increase in theta activity and a decrease in beta activity, which are followed by a decrease in alpha activity. Delta activity increases later during the course of the disease. Patients with severe dementia exhibit a decrease in alpha and an increase in delta activity (Coben et al., 1985; Hier et al., 1991; Penttilä et al., 1985; Stigsby et al., 1981), whereas patients with mild dementia show a decrease in beta and an increase in theta activity (Coben et al., 1983, 1985). A good correlation is present between the mean frequency and the severity of dementia (Brenner et al., 1986; Canter et al., 1982; Duffy et al., 1984b; Penttilä et al., 1985; Streletz et al., 1990). Topographic analysis revealed that an increase in slow activity is prominent in the left temporal area of AD patients (Breslau et al., 1989; Rice et al., 1990). Maximal group differences between presenile patients and normal controls are detected in the right posterior temporal area, whereas the largest differences between senile patients and the controls are found in the midfrontal and anterior frontal lobes bilaterally (Duffy et al., 1984b). Studies in which different methods were used on the same population demonstrated that an estimated diagnostic accuracy of spectral and visual EEG analyses is approximately 80% (Brenner et al., 1988; Hooijer et al., 1990).

It is of clinical interest to find that the EEG abnormality is associated with cognitive deficits. A good correlation is found between EEG spectral measures and cognitive deterioration scores, such as the Folstein (Mini-mental) score (Brenner et al., 1986; Elmståhl et al., 1994; Filipovitch et al., 1989; Leuchter et al., 1987; Leuchter et al., 1993; Schreiter-Gasser et al., 1994; Strijers et al., 1997), the global deterioration score (Helkala et al., 1991; Passero et al., 1995; Prichep et al., 1994), and a composite neuropsychological test score (Penttilä et al., 1985). There are, however, some studies reporting only a weak correlation or no correlation between EEG changes and the cognitive decline in AD (Hughes et al., 1989; Prinz and Vitiello, 1989). These discrepancies can be attributed to differences in diagnostic criteria, different EEG techniques, or bottom or ceiling effects of the Folstein score (Jonkman, 1997). The correlation between an EEG slowing and the severity of the disease confirms that a disruption of information processing in cortical networks significantly contributes to the cognitive dysfunction seen in AD.

There are a few longitudinal studies of EEG power spectra in AD patients. Coben et al. (1985) reported that, after 2.5 year follow-up, both delta and theta activities significantly increased, whereas alpha and beta activities decreased. Other studies reported that a progressive EEG showing could be detected in only a proportion of early AD cases, with 50% showing no deterioration at 12 months follow-up, suggesting the heterogeneity of the disease (Rae-Grant et al., 1987; Soininen et al., 1989).

Here, we should note that the healthy elderly also undergo EEG changes during normal aging. A slowing of alpha activity is found particularly over temporal regions in the normal elderly (Busse et al., 1956; Mundy-Castle et al., 1954; Torres et al., 1983). In elderly healthy women aged 75–95 years, theta activity increased with age without any correlation with psychometric features (Elmståhl et al., 1994). Beta activity increases with age in women (Busse, 1983), which is positively correlated with cognitive performance (Williamson et al., 1990). It is reported that, during normal aging, the spatial distribution of EEG activity changes with increasing uniformity across the brain, which is associated with an increase in coupling interactions among cortical areas (Dustman et al., 1985). Although the presence of alterations in the EEG during normal ageing is still controversial (Duffy et al., 1984a; Giaquinto and Nolfe, 1986; Katz and Horowitz, 1982; Pollock et al., 1990), we believe that the only way to investigate the EEG in AD is to compare it with the age-matched normal elderly.

Whether the EEG is a potential predictor of the progression of dementia is of most clinical importance (for a review, see Jelic, 1999). Although Berg et al. (1984) reported that spectral measures of the EEG are not predictive of the progression to moderate or severe dementia, many studies support the possibility of early detection of AD using EEG recordings (Claus et al., 1998, 2000; Helkala et al., 1991; Petrosian et al., 2001; Prinz et al., 1992; Schreiter-Gasser et al., 1994). Helkala et al. (1991) found that AD patients having the EEG abnormality at the early stage of the disease exhibit a different pattern of the cognitive decline from that of AD patients matched for the severity but having normal EEG patterns: AD patients exhibiting deteriorating EEGs show a decline in praxic functions, confrontation naming, and automatic speech functions, whereas AD patients having normal EEGs do not exhibit a deterioration of these functions during the 3 year follow-up period. Schreiter-Gasser et al. (1994) demonstrated that earlier onset produces an increase in theta power and that long duration of the disease decreases alpha power. Higher fronto-central and parieto-occipital theta power, lower parieto-occipital beta power, and lower peak frequency are significantly associated with a more decline in the global cognitive function over the follow-up period (Claus et al., 1998). This suggests that a slowing of the EEG is a marker for the subsequent rate of a cognitive and functional decline in early AD patients.

Current EEG studies on mild cognitive impairment (MCI) have especially aimed toward the detection of pre-clinical AD. MCI is a clinical condition by objective memory disturbances in the absence of other cognitive deficits (Petersen et al., 1999) or more generally characterized by all cognitive changes observed in ageing that are insufficient to meet dementia criteria (Burns and Zaudig, 2002). EEG studies found that theta power (Grunwald et al., 2001; Jelic et al., 1996; Zappoli et al., 1995) as well as other EEG parameters (Elmståhl and Rosen, 1997; Huang et al., 2000; Jelic et al., 1996, 2000) differs significantly between

healthy and MCI subjects, although these EEG parameters for MCI subjects were mostly intermediate between those of controls and dementia subjects with considerable overlap. A recent study found significant theta power differences during haptic tasks between healthy controls and MCI subjects (Grunwald et al., 2002), suggesting that activation paradigms in EEG studies can increase the sensitivity for cases at risk of developing AD.

The EEG, as an effective tool for differential diagnosis of AD from other dementias, has been extensively studied. Particularly, the possibility of differential diagnosis of AD from vascular dementia (VaD) using the EEG has been much investigated. Although neuroimaging analysis of hippocampal atrophy has been proved very effective in detecting AD (de Leon et al., 1989; Erkinjuntti et al., 1993; Jack et al., 1992; Scheltens et al., 1992), the main criteria for distinguishing AD from VaD are usually the case history and neuropsychiatric examination. It is controversial about a diagnostic value of the EEG differentiating AD from VaD (Ettlin et al., 1989; Harrison et al., 1979; Robinson et al., 1994). A number of studies failed to find any significant difference of EEG measures in between AD and VaD (Ettlin et al., 1989; Robinson et al., 1994; Soininen et al., 1982). In contrast, the uneven distribution of EEG abnormalities is clearly observed in VaD patients using multichannel EEG mapping, offering 63% classification accuracy (Saletu et al., 1991). In addition, a higher incidence of focal abnormalities and more preservation of occipital alpha activity are found in VaD patients than those of AD patients (Erkinjuntti et al., 1988; Giannitrapani et al., 1991; Rosen et al., 1993; Sloan and Fenton, 1993; Soininen et al., 1982).

In other dementing illness, the EEG has been examined to test as a differential diagnostic tool. First of all, the EEG is very useful for distinguishing AD patients from patients with senile depression with an accuracy of about 70–85% (Boerman et al., 1994; Brenner et al., 1988, 1989; Hooijer et al., 1990; Moe et al., 1993; Reynolds et al., 1988). Patients with histologically verified fronto-temporal cortical atrophy exhibit normal EEG patterns or a moderate, diffuse increase in relative theta power (Johannesson et al., 1977, 1979). In comparison with controls, patients with fronto-temporal dementia are marked by the absence of an increase in slow EEG activities and a decrease in fast activities, whereas AD patients are marked by an increase in slow activities and a smaller decrease in fast activities (Lindau et al., 2003). This indicates that patients with frontotemporal dementia reveal a different pattern of EEG changes than AD patients, suggesting the usefulness of the EEG for differential diagnoses of frontotemporal dementia and AD. Demented patients with Parkinson's disease have a decrease in relative alpha power in comparison with age- and sex-matched nondemented Parkinsonian patients and healthy subjects (Neufeld et al., 1994a). These results implicate the EEG as a potential tool for differential diagnosis of AD from various dementing illness. A more detailed diagnostic value of the EEG for AD is presented in other reviews (Jonkman, 1997; Rosen, 1996).

What is the pathophysiological origin of the EEG slowing in AD? A major promising candidate is the cholinergic deficit. AD is thought to be a syndrome of neocortical disconnection, in which profound cognitive losses arise from the disrupted structural and functional integrity of long cortico-cortical tracts (Leuchter et al., 1992). Senile plaques and neurofibrillary tangles of AD prominently involve the origins and terminations of long cortico-cortical association fibers (Esiri et al., 1986; Lewis et al., 1987; Pearson et al., 1985; Rogers and Morrison, 1985). The brain of AD patients exhibits a significant reduction in markers of cholinergic transmission (Bartus et al., 1982; Collerton, 1986; Coyle et al., 1983). The atrophy of basal forebrain cholinergic neurons innervating the neocortex and hippocampus among others is also observed in AD (Bartus et al., 1982; Coyle et al., 1983). Since several studies demonstrated that acetylcholine (ACh) and the basal forebrain system maintain desynchronized EEG activity (Celesia and Jasper, 1966; Cuculic et al., 1968; Kanai and Szerb, 1965; Metherate et al., 1992; Spehlmann and Norcross, 1982), a loss of cholinergic innervation of the neocortex might play a critical role in the EEG slowing of AD.

The critical role of the cholinergic deficit in the EEG slowing in AD is also supported by EEG studies using scopolamine (for a review, see Ebert and Kirch, 1998). Scopolamine is a nonselective muscarine receptor antagonist that blocks the stimulation of post-synaptic receptors. After the scopolamine administration, an increase in delta and theta power and/or a decrease in alpha and beta power are detected in healthy subjects (Ebert et al., 2001; Neufeld et al., 1994b; Sannita et al., 1987; Sloan and Fenton, 1992). Studies using rats presented that the scopolamine administration results in an increase in power of slow EEG waves (Bartus et al., 1982; Buzsaki et al., 1988). Furthermore, scopolamine induces a pattern of memory and cognitive deficits in young healthy subjects, markedly similar to the changes occurring in mild AD patients (Drachmann et al., 1974; Weingartner, 1985; Wesnes, 1988).

The hypothesis that basal forebrain neurons are severely affected in AD and result in a cerebral cholinergic deficit that underlies the memory loss and other cognitive symptoms, the so-called cholinergic hypothesis, was first proposed nearly 25 years ago (Bartus et al., 1982; Davies and Maloney, 1976; Perry et al., 1977). This hypothesis has been the stimulus for a great deal of effort in experimental pharmacology and a large number of clinical trials, and has served as the rationale for the development of drugs currently approved for AD treatment. Primary treatment strategies of AD have focused on boosting acetylcholine by the development of cholinesterase inhibitors. The loss of cholinergic neurons in the basal forebrain of AD patients results in up to 90% reduction in activity of choline acetyltransferase (ChAT), an enzyme needed for the synthesis of acetylcholine (Murphy et al., 1998). Acetylcholinesterase (AChE) inhibitors work by

reversibly binding to the choline binding subsite of AChE, and consequently preventing degradation of acetylcholine. Currently, cholinesterase inhibition proves the most effective approach for treating the symptoms of AD (Imbimbo, 2001). Until now, 4 drugs for AD have been approved for prescription use by US Food and Drug Administration: tacrine, donepezil, rivastigmine, and galantamine. These drugs all belong to the drug category of AChE inhibitors. Although they do not halt progression of the disease, all have been shown to improve memory and cognitive functions in patients with mild and moderate AD (for reviews on a therapeutic value of AChE inhibitors in AD, see Lahiri et al., 2002; Sramek et al., 2002).

The reversal of EEG slowings induced by cholinergic drugs also supports the cholinergic deficit as the cause of the EEG slowing in AD. Neuropsychological and neurophysiological studies reported that the acute administration of cholinergic drugs improving memory and attention (physostigmine, pyridostigmine bromide, and edrophonium chloride) exhibits a tendency to shift the EEG into more normal patterns (Agnoli et al., 1983), whereas anticholinergic drugs (scopolamine and orphenadrine) induce opposite effects (Agnoli et al., 1983; Neufeld et al., 1994b). Treatment with tacrine (or 1,2,3,4-tetrahydro-5-aminoacridine, THA) induces a decrease in slow wave activity and an increase in the mean frequency of the EEG (Alhainen and Riekkinen, 1993; Jelic et al., 1998; Nordberg et al., 1998; Perryman and Fitten, 1991; Shigeta et al., 1993).

Long-term treatment with donepezil results in a significant decrease in the mean absolute power of theta activity (Kogan et al., 2001), decreases in the mean alpha and delta power (Reeves et al., 2002), and a lesser EEG deterioration (Rodriguez et al., 2002), mainly in frontal and/or temporoparietal areas in mild AD patients, accompanied by a milder neuropsychological decline. Similar effects are reported with treatment of rivastigmine (Adler and Brassen, 2001). In addition, the acetylcholine agonist nicotine significantly shifts the EEG toward normal values by reducing slow wave (relative delta and theta) power and augmenting fast (relative alpha-1, alpha-2, beta-1) wave power (Knott et al., 2000a). This EEG restoration by drugs depends on the duration of treatment. For example, Shigeta et al. (1993) found that the early EEG improvement with THA reverts to the pretreatment value within 30 weeks. These significant effects of cholinergic drugs on the EEG and on memory and cognitive functions in AD patients suggest that EEG abnormalities of AD patients are highly associated with a decline in memory and cognitive function by cholinergic deficits.

However, solely the cholinergic dysfunction is not sufficient to produce cognitive and electrophysiological symptoms of AD. Davis et al. (1999) found that patients with the early stages of AD who are already experiencing the characteristic symptoms of AD at death show no evidence of deficiency of either ChAT or AChE activity. This work suggests that the AD symptoms, at least in the early stages, are not primarily caused by a loss of cholinergic transmission, even though there is a large body of evidence that such deficits do occur as the disease progresses. Most surprisingly, elevated ChAT activity suggesting upregulation of cholinergic systems is found in the frontal cortex and hippocampus of individuals with MCI (DeKosky et al., 2002). There is now increasing evidence for the hypothesis that cholinergic neurons in MCI are not normally regulated (Sarter and Bruno, 1999, 2002). Although the number of cholinergic terminals is either unchanged or even increased in MCI, their trophic factor regulation is disrupted (Chen et al., 1997; Sarter and Bruno, 1999; Sarter and Turchi, 2002). These recent findings suggest a more subtle dysregulation of basal forebrain neurons rather than substantial cell death in the basal forebrain early in AD.

It is generally thought that more widespread degenerative processes involving both cholinergic and monoaminergic (and possibly other) systems are necessary to produce a dementia-like behavior and a global loss of EEG activation (Dringenberg, 2000). AD patients exhibit great reductions in noncholinergic neurotransmitters including serotonin (Baker and Reynolds, 1989; Bowen and Davison, 1986; Cross, 1990; Rossor and Iversen, 1986), glutamate (Greenamyre, 1986; Maragos et al., 1987; Myhrer, 1998), and noradrenaline (Baker and Reynolds, 1989; Cross et al., 1981; Rossor and Iversen, 1986). Since significant monoaminergic deficits occur in AD as well as the atrophy of cholinergic neurons, drug therapies aimed at concurrently stimulating cholinergic and monoaminergic neurotransmission can be more effective in reversing the EEG slowing than cholinergic therapy alone. Dringenberg et al. (2000a,b) showed that EEG restoration by tacrine can be enhanced in all frequency bands by co-administration of tacrine and the monoamine-oxidase inhibitor pargyline or deprenyl. Accordingly, complex interactions among cholinergic and other neurotransmitter systems should be considered to understand the biochemical basis of cognitive and electrophysiological symptoms of AD.

3. Decreased complexity of the EEG in AD

NDA has been widely applied to various physiological data to comprehend complex dynamics of the underlying processes for the last 2 decades. In particular, the EEG, one of the most complex biological signals, requires the use of new mathematical methods. Applying NDA to the EEG has offered valuable information on cortical dynamics.

The fundamental assumption of NDA is that EEG signals are generated by nonlinear deterministic processes with nonlinear coupling interactions between neuronal populations. Nonlinear deterministic systems may show a sensitive dependence on initial conditions, implying 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 behave very irregular and complex, similar to stochastic systems. Given the highly nonlinear nature of

neuronal interactions at multiple levels of spatial scales, it is quite natural to apply nonlinear methods to the EEG.

Complex dynamical systems like 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. Based on this theorem, now we can extract information as to the underlying cortical dynamics by analyzing a bunch of the trajectories (i.e. the attractor) reconstructed from the time series (i.e. EEG). This procedure is referred to as the inverse problem. The geometric and dynamical properties of the trajectories in the phase space are quantified by nonlinear measures. Theoretical concepts and algorithms of NDA in detail are well presented in other technical review articles (Abarbanel and Rabinovich, 2001; Cerutti et al., 1996; Faure and Korn, 2001; Kantz and Schreiber, 1997; Schreiber, 1999), and C-code programs estimating nonlinear measures are available at many websites including one developed by Hegger et al. (1999).

One of the major contributions of NDA in neuropsychiatry is to the EEG in AD. A number of studies offer growing evidence that NDA of brain electrical activity in AD patients is capable of providing potentially useful diagnostic information (for a review, see Jeong, 2002). Woyshville and Calabrese (1994) demonstrated, using single-channel EEGs, that AD patients have reduced values of the correlation dimension (D_2) in the occipital EEG compared with those of healthy subjects, and that, within AD patients, autopsy-confirmed AD patients have more reduced D_2 values than probable AD patients. The D_2 reflects the number of independent variables that are necessary to describe the dynamics of the system. In nonlinear EEG analysis, the D_2 is considered to be a reflection of the complexity of the cortical dynamics underlying EEG recordings. Thus, reduced D_2 values of the EEG in AD patients indicate that brains injured by AD exhibit a decrease in the complexity of brain electrical activity. 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 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) found markedly reduced spatio-temporal brain activity in AD patients in comparison with that in normal controls. All these findings indicate globally decreased complexity of brain electrical activity in AD patients.

Pathophysiological implications of the decreased EEG complexity in AD are not clear. A decrease in dynamic complexity of the EEG in AD patients might arise from neuronal death, deficiency of neurotransmitters like acetylcholine, and/or loss of connectivity of local neuronal networks. The reduction of the dimensionality in AD is possibly an expression of the inactivation of previously active networks. Also, a loss of dynamical brain responsivity to stimuli might be responsible for the decrease in the EEG complexity of AD patients. Pritchard et al. (1991, 1993) found that AD patients do not have D_2 differences between in eyes-open and eyes-close conditions, whereas normal subjects have prominently increased eyes-open D_2 values compared with eyes-closed D_2 values. These results suggest that AD patients exhibit a loss of brain responsivity to changing environmental stimuli. Therefore, given that EEG patterns reflect cortical activity (information processing) of the brain, the reduced EEG complexity in AD suggests the deficient information processing of the cortex due to the inactivation of previously active networks or a loss of dynamical brain responsivity to external stimuli.

Using the first positive Lyapunov exponents (L_1), Jeong et al. (1998) and Stam et al. (1995) demonstrated the decreased complexity of brain activity in AD patients compared with that of age-matched healthy subjects. The L_1 describes the divergence of trajectories starting at nearby initial states. While the D_2 is a static, geometric measure, the L_1 is relatively a dynamic measure. It is true that both D_2 and L_1 are used as a measure of complexity in NDA, but the L_1 of the EEG can be often interpreted as a measure of flexibility of information processing of the brain (Fell et al., 1995). The 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 indicate a drop in the flexibility of information processing of the AD brains.

The surrogate data method has been applied to investigate nonlinearity of the EEG in AD patients. Surrogate data are constructed by phase randomization of original EEG signals (Schreiber and Schmitz, 2000). In this way, linear properties (e.g. power spectrum) of the surrogate data are unchanged, but their nonlinear structure that may be present is destroyed. Therefore, statistical differences of a nonlinear measure between the original data and their surrogate data indicate the presence of nonlinearity in the original data. Both normal subjects and AD patients exhibit significant D_2 differences between original and their surrogate EEG data (Jelles et al., 1999b; Stam et al., 1995), indicating the presence of nonlinearity in the EEG. Besides, Jelles et al. (1999b) found smaller differences between original and the surrogate EEG data in AD patients than in healthy subjects. This indicates that the decrease in the EEG complexity of AD patients may be attributable to decreased nonlinear neurodynamics underlying the EEG, which might be associated with the cognitive decline. In another study, Jelles et al. (1999a) detected no change in the nonlinear structure between healthy subjects and patients with mild AD. This suggests that linear dynamics of the EEG

changes first in the course of AD followed by changes in nonlinear dynamics.

Nonlinear measures are quite efficient as a diagnostic indicator of AD. Pritchard et al. (1994) assessed the classification accuracy of the EEG using nonlinear measures and a neural-net classification procedure in addition to linear methods. The combination of linear and nonlinear analyses improves the classification accuracy of the AD/control status of subjects up to 92%. Besthorn et al. (1997) reported that the D_2 correctly classified AD and normal subjects with an accuracy of 70%. Good correlations are found 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). Furthermore, the global entropy can quantify EEG changes induced by drugs (Pezard et al., 1998), suggesting a possibility that nonlinear measures is capable of quantifying the effect of drugs on the course of the disease. Taken together, we believe that nonlinear measures are a potentially useful indicator for diagnosis of AD, assessment of neuropsychological deficits, and pharmacological treatment evaluations.

There are a few studies on 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 VaD (Jeong et al., 2001a). VaD patients appear to have an uneven distribution of the D_2 values over the regions relative to AD patients and normal controls, even though the statistics did not confirm this. In the early stage of AD, nonlinear EEG abnormalities in AD patients, i.e. the decreased complexity and increased predictability, are observed mainly in frontal and temporal areas (Jelles et al., 1999a). It is of importance to determine whether NDA can provide additional information helpful for differential and early diagnosis of AD in future.

With an increasing body of evidence for the usefulness of NDA in AD patients, there are several limitations on NDA to solve. First of all, the fundamental assumption of NDA that the EEG generates by a deterministic process is still disputable. Much research has proven the nonlinear, deterministic character of cortical dynamics. The EEG has a finite noninteger correlation dimension (D_2) and a positive value of averaged local Lyapunov exponents, indicating the presence of deterministic chaos in the EEG (Babloyantz et al., 1985; Kowalik, 2000; Soong and Stuart, 1989). The surrogate data method capable of detecting nonlinear determinism within a time series also revealed that EEG recordings have a nonlinear structure (Ehlers et al., 1998; Jelles et al., 1999b; Kowalik, 2000; Pritchard et al., 1995; Rombouts et al., 1995; Stam et al., 1999). These findings support the hypothesis that brain oscillators are governed by nonlinear, deterministic processes. In contrast, there have been several studies reporting that the EEG may not be produced by a low-dimensional chaotic system (Pritchard et al., 1995; Rapp et al., 1993; Theiler and Rapp, 1996; Theiler et al., 1992). They demonstrated that filtered noise could mimic low-dimensional chaotic attractors as the EEG data do. Recently, more direct methods have been applied to detect nonlinear determinism within the EEG (Jeong et al., 1999, 2002a,b) to show that the EEG might not be generated by a low-dimensional deterministic process. Despite no compelling evidence for deterministic nature of the EEG, a large number of studies have shown that nonlinear dynamical methods allow characterization of different physiological and pathological brain states (for intensive reviews, see Le Van Quyen et al., 2001; Sarbadhikari and Chakrabarty, 2001; Wackermann, 1999). Therefore, nonlinear measures are meaningful only when they are used as a relative measure of complexity to quantify an irregular behavior of the brain, instead of being used as an absolute measure to differentiate between periodic, chaotic and stochastic dynamics.

Another limitation of NDA is that the absolute values of nonlinear measures depend sensitively on algorithms used or parameters in the algorithms, such as the embedding dimension, the time delay, the number of data point, the cut-off noise level. Thus, in order to diagnose AD accurately, a large pool of sample data for autopsy-confirmed AD patients and the age- and sex-matched healthy controls and other patient groups are needed to compare their nonlinear measures with the algorithm and the parameters fixed. Furthermore, a large number of data points are required to reconstruct the whole attractor (i.e. entire dynamics of the system) in the phase space and thus to obtain reliable results. Unfortunately, the data length required for reliable results in principle is beyond the experimental possibility for physiological data.

Thirdly, given that nonlinear measures like the D_2 or L_1 reflect nonlinear dynamics of the attractor in the phase space reconstructed from the EEG, the physiological implications of the changes in these measures in pathological brain states are not clear. For example, the D_2 of the EEG indicates the number of parameters pertaining to the underlying cortical dynamics, but it does not provide any information on the physiological correspondence of each parameter. This shortcoming appears to limit the usefulness of NDA. Furthermore, the number of the degrees of freedom revealed by the D_2 estimation of the EEG in AD is about 6–10 (Jeong, 2002), which is too high to develop a mathematical model to produce the EEG in AD patients. Although there have been several studies attempting to build up empirical, dynamical models based on raw EEG data and information obtained from NDA (Kadtke, 1995; Kadtke and Kremliovsky, 1996, 1997), mathematical theory and analysis methods for high-dimensional, physiological systems should be further developed and established (Cremers and Hubler, 1981; Crutchfield and McNamara, 1987).

Finally, it is noteworthy that nonlinear dynamics of the EEG is possibly influenced by many physiological factors including age (Anokhin et al., 1996, 2000; Meyer-Lindenberg, 1996), sex (Anokhin et al., 2000) and intelligence

(Anokhin et al., 1999; Lutzenberger et al., 1992), as well as by the severity of the disease. Although the effect of normal aging on EEG dynamics is somewhat disputable (Angeleri et al., 1997; Dustman et al., 1993; Visser, 1991), the effect of these factors should be considered with caution during analysis to obtain reliable results and to have appropriate interpretations. In addition, nonlinear properties of EEG dynamics are also associated with their linear properties like power spectrum (Osborne and Provenzale, 1989). For example, the EEG slowing in AD patients might lead to decreased complexity of the EEG. Thus, its physiological interpretation should be made with caution.

Nonlinear dynamics and chaos theory suggest that AD can be a dynamical disease which is characterized by changes in the qualitative dynamics of physiological processes, leading to abnormal dynamics and disease (Belair et al., 1995; Mackey and Milton, 1987). Ageing and age-related diseases often accompany a wide-ranging loss of physiological complexity from molecular to cellular, and from tissue to organismic levels (Kyriazis, 2003). The disruptions of fractal and nonlinear physiological properties leads to an increase in regularity and stochasticity (i.e. an increase in uncorrelated true randomness), a situation encountered during ageing and age-related diseases (Goldberger et al., 2002a,b; Lipsitz and Goldberger, 1992; Toussaint and Schneider, 1998). An underlying dysfunction of several individual subsystems, such as synaptic and receptor alterations and other molecular changes, might result in a loss of complex properties seen in ageing or AD brains (Narayanan et al., 2001; Yates, 2002). The deceased EEG complexity in AD might reflect a loss of physiological complexity at molecular or cellular level with wide-ranging cognitive changes. Interestingly, Nakayama et al. (2001) demonstrated that morphological patterns of senile plaques are very fractal. Therefore, it is significant to monitor alterations in EEG complexity in AD as the disease progresses, and furthermore, to reverse this loss and reinstate physiological complexity by applying multiple external physiological stimuli (Dokoumetzidis et al., 2001; Lipsitz, 2002).

4. Reduced degrees of functional connectivity in AD brains

Coherence analysis of the EEG has been used to estimate the degree of functional connectivity among cortical areas. 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 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 or reduced common modulation of two areas by one-third.

EEG coherence analysis in AD has been applied to examine whether the cognitive decline is associated with changes in functional connections between cortical regions and whether different types of dementia are related to specific changes. A well-established feature in AD is a decrease in coherence of the alpha and beta bands in various types of dementia between both close and distant channels, suggesting functional disconnections among cortical regions (Besthorn et al., 1994; Dunkin et al., 1994; Leuchter et al., 1987, 1992; Locatelli et al., 1998; O'Conner et al., 1979; Sloan et al., 1994). This deceased coherence of fast bands is significantly correlated with cognitive impairment (Dunkin et al., 1994; Jelic et al., 1996). This might result from a loss of long cortico-cortical association fibers, because long-distance anatomical connections between different cortical regions are obviously required for functional interactions. In this view, the decreased EEG coherence in AD patients supports the hypothesis that AD is a neocortical disconnection syndrome.

In addition to anatomical disconnections of long cortico-cortical fibers, changes in synaptic couplings among cortical neurons might be of importance. A decrease in synaptic couplings can reduce long-distance functional connections even when the anatomical connections are intact. A distinct feature of AD is a loss of acetylcholine, an excitatory neurotransmitter of the cerebral cortex. Synaptic blockade of the cholinergic system by the application of scopolamine, an anticholinergic drug, reduces the EEG coherence in humans (Kikuchi et al., 2000). If the decreased EEG coherence in AD is simply due to a loss of cortical neurons, it would be difficult to explain why all frequencies are not equally affected (Stam et al., 2003). In patients with the most severe cognitive impairment, coherence of slow EEG rhythms is unaffected (Besthorn et al., 1994), or reduced (Knott et al., 2000b), or rather increased (Comi et al., 1998; Locatelli et al., 1998). An increase in the slow band power in AD patients is associated with a 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 and Fenton, 1992). In addition, an animal study (Villa et al., 2000) showed that a loss of acetylcholine results in a decrease in high-frequency couplings and an increase in low-frequency couplings. Thus, it is possible that the decrease in EEG coherence of AD results from both anatomical disconnections among different cortical regions and reduced cholinergic coupling interactions between cortical neurons.

Recently, the mutual information (MI) (Jeong et al., 2001b) and synchronization method (Stam et al., 2003) have been applied to the EEG in AD patients. While coherence measures only linear dependencies in electrical activity across different brain regions, MI and synchronization analyses take into account both linear and nonlinear dependencies. MI analysis showed that

the interdependencies between different electrodes are reduced in AD patients in comparison with those in normal controls, particularly over frontal and antero-temporal regions (Jeong et al., 2001b). A decrease in the MI between distant electrodes and between inter-hemispheric electrodes is prominently found in AD patients. Stam et al. (2003) found a significant loss of EEG synchronization in the beta band and its correlation with MMSE scores in subjects with MCI as well as AD. Since the MI and synchronization of the EEG reflect linear and nonlinear functional connections among cortical regions, a decrease in these measures in AD suggests an impairment of information transmission among cortical regions.

In fact, clear evidence for the presence of the nonlinear couplings in long cortico-cortical fibers is rarely found. Villa et al. (2000) detected indirect evidence for the existence of nonlinear, functional cortico-cortical interactions. 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, which provokes a selective loss of NGFr-positive basal forebrain cholinergic neurons similar to the loss of its integrity in the AD brain, a decrease in choline acetyltransferase activity and an increase of the phase coupling in low frequencies are found. This indicates a decrease in functional cortico-cortical interactions, and suggests that nonlinear coupling is present among long cortico-cortical fibers. Since neurodynamics includes many highly nonlinear processes (McKenna et al., 1994), MI analysis or other methods capable of measuring nonlinear dependencies among multichannel signals should be utilized to quantify both linear and nonlinear coupling interactions among cortical areas. The investigation of nonlinear interactions among cortical areas and their functional role will be, therefore, a critical issue in multichannel analysis.

5. Perspectives

EEG abnormalities of AD patients have been extensively studied for several decades. The role of the EEG in diagnosis and clinical evaluations of AD has become more significant. One of the most critical issues of EEG studies on AD is improvement of the accuracy of differential diagnosis of AD and early detection in the pre-clinical stage. As mentioned earlier, the diagnostic accuracy of the EEG based on a broad survey of the literature is currently about 80%. One of the proposed ideas for increasing the diagnostic accuracy is to use structural and functional neuroimaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron-emission tomography (PET), and functional magnetic resonance imaging (fMRI), in combination with the EEG. This multimodal approach has been found predominant for diagnosing dementias (for reviews, see Albert, 2003; DeCarli, 2001; Jagust, 2000; Kantarci and Jack, 2003; Kumari et al., 2002; Petrella et al., 2003; Scheltens and Korf, 2000). For example, the combination of EEG and PET variables results in approximately 90% of overall correct classification with a specificity of 100% (Jelic et al., 1999). EEG and MRI measurements of the hippocampus obtain the highest scores of abnormalities in patients with probable AD (Jonkman, 1997). Furthermore, CT- and MRI-based measurements of hippocampal atrophy provide a useful early marker of AD (Scheltens, 1999). These neuroimaging techniques can offer not only supplementary information for diagnosis of AD, but also an opportunity to explore structural, functional, and biochemical changes in the brain leading to new insights into the pathogenesis of AD.

The possible usefulness of the EEG in early detection of AD can be fully evaluated by examining EEG alterations in subjects having risk factors for AD. Particularly, EEG studies on MCI might facilitate the ability to diagnose AD at a very early stage, preferably before dementia symptoms are apparent. Although structural volumetric MRI, PET, and SPECT are currently most commonly used neuroimaging modalities in MCI studies, quantitative EEGs also have potential to become a valuable tool in early diagnosis of AD (Wolf et al., 2003). There is growing evidence from prospective studies that increased theta activity, decreased alpha and beta activities, and slowed mean frequency may be predictors of dementia in subjects with MCI (Huang et al., 2000; Jelic et al., 2000) On the other hand, recent studies investigated whether or not genetic heterogeneity of 4 allele of apolipoprotein E (APOE), a major biological risk factor for late onset AD, affected the EEG in AD patients (Alvarez et al., 1999; Jelic et al., 1997; Lehtovirta et al., 1996, 2000; Riekkinen et al., 1997). Jelic et al. (1997) found that AD patients homozygous for the APOE 4 allele have reduced right and left temporoparietal, right temporofrontal, and left occipitoparietal coherence, indicating that APOE 4 seems to be associated with selective decreases in functional connectivity as assessed by EEG coherence. Additionally, we expect that novel methods for EEG analysis will help improve the accuracy of early detection of AD (Musha et al., 2002; Stam et al., 2003).

Another important issue is to quantify the severity of the disease using the EEG to provide demented patients and their families with a more reliable prediction of the disease's course and appropriate clinical treatments and to facilitate planning for necessary social resources. Long-term follow-up studies of the EEG in subjects with MCI are quite necessary. Besides, quantitative changes of EEG dynamics in AD patients with treatment of drugs should be investigated.

Finally, the use of new mathematical methods is required to explore the abnormal cortical dynamics underlying

the EEG in AD. Nonlinear dynamical methods might provide a useful tool to help in understanding brain electrical activity in terms of the collective dynamics of neurons, as well as improvement of the accuracy of differential and early diagnosis of AD. 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 are rarely investigated. For instance, the association between nonlinear EEG dynamics and cognitive performance, longitudinal changes in nonlinear dynamics of the EEG during the progression of the disease, drug effects on nonlinear neurodynamics, and nonlinear functional connectivity among cortical areas afflicted by AD should be further examined. EEG studies on these issues using nonlinear dynamical methods might contribute to a deeper understanding of pathophysiology of AD in ways that are not possible by conventional spectral analysis.

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