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Mutual information analysis of the EEG in patients with Alzheimer's disease

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Abstract

Objective: Mutual information provides a measure of both the linear and nonlinear statistical dependencies between two time series. Cross-mutual information (CMI) is used to quantify the information transmitted from one time series to another, while auto mutual information (AMI) in a time series estimates how much on average the value of the time series can be predicted from values of the time series at preceding points. The aim of this study is to assess information transmission between different cortical areas in Alzheimer's disease (AD) patients by estimating the average CMI between EEG electrodes.

Methods: We recorded the EEG from 16 scale electrodes in 15 AD patients and 15 age-matched normal controls, and estimated the local, distant, and interhemispheric CMIs of the EEG in both groups. The rate of decrease (with increasing delay) of the AMI of the EEG was also measured to evaluate the complexity of the EEG in AD patients.

Results: The local CMI in AD subjects was lower than that in normal controls, especially over frontal and antero-temporal regions. A prominent decrease in information transmission between distant electrodes in the right hemisphere and between corresponding interhemispheric electrodes was detected in the AD patients. In addition, the AMIs throughout the cerebrums of the AD patients decreased significantly more slowly with delay than did the AMIs of normal controls.

Conclusions: These results are consistent with previous findings that suggest the association of EEG abnormalities in AD patients with functional impairment of information transmission in long cortico-cortical connections.

Keywords: Information transmission; EEG; Mutual information; Alzheimer's disease; Functional connectivity; Complexity

1. Introduction

The EEG is a time series of electrical potentials representing the sum of a very large number of neuronal dendritic potentials in the brain. Dendrites of cortical pyramidal neurons generate local field potentials (LFP) that summate on the scalp and are measured as EEG potentials (Gevins et al., 1983; Mitzdorf, 1985; Picton and Hillyard, 1988). Rhythmicities of the EEG seem to depend upon dynamical interactions among cortical cells as well as on rhythmic inputs to the cortex from the brain stem (Steriade et al., 1990). LFPs in the 40–50 Hz frequency range are correlated with action potentials of the neurons (Eckhorn et al., 1988; Gray et al., 1989). In addition, distinct states of brain activity are associated with various temporal characteristics of these EEG potentials that can be quantified using linear or nonlinear measures such as the power spectrum, entropy, or the correlation dimension. (Gevins et al., 1983; Babloyantz et al., 1985; Basar, 1988; Niedenmeyer and Lopes da Silva, 1993). These associations suggest that EEG activity can be considered to reflect differential information processing in the brain.

The aim of this study is to use mutual information analysis in the multi-channel EEG to measure the transmission of information between various cortical areas of Alzheimer's disease (AD) patients. Mutual information (MI) detects linear and nonlinear statistical dependencies between time series, whereas the more standard correlation function measures only their linear dependence. The MI between measurement x_i generated from system X and measurement y_j generated from system Y is the amount of information that measurement x_i provides about y_j. Thus, MI is a measure of dynamical coupling or information transmission between X and Y, and when applied to the EEG it may be postulated to

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be one measure of functional connectivity. If one system is completely independent of another, then and only then the MI between the time series generated from these dynamical systems is zero.

When we consider the MI between two different systems X and Y, this MI is called the cross mutual information (CMI). The CMI quantifies the information transmitted from one system to another. In contrast, the MI between two measurements taken from a single time series $x(t)$ separated by time τ is called the auto mutual information (AMI). The AMI estimates the degree to which $x(t + \tau)$ on average can be predicted from $x(t)$, or the mean predictability of future points in a time series from past points. The rate of decrease of the AMI with increasing time delays is a normalized measure of the complexity of the time series. The first local minimum of the AMI of a time series has been used in non-linear analyses of dynamical systems to determine the optimal time delay that makes the coordinates for an embedding procedure less pairwise dependent in a well controlled manner (Fraser and Swinney, 1986). While the CMI is a nonlinear analogue of the cross-correlation function between the two times series, the AMI may be considered a nonlinear version of the auto-correlation function.

Since its introduction by Shannon (Shannon and Weaver, 1949), MI has been used in diverse fields as a measure of coupling or information transmission between different systems (Cover and Thomas, 1991). However, few previous studies have investigated information transmission in the brain using mutual information analysis. Notably, Xu et al. (1997) described information transmission among different cortical areas in waking and sleep states by estimating the complexity of the CMI among 8 electrodes of the EEG. They showed that information transmission in waking states with eyes open was greater than in deep sleep states, while no significant differences were detected between waking states with eyes closed and states of light sleep.

In this study, we investigate the information transmission among different cortical areas in both AD and healthy control subjects by estimating the CMI between EEG electrodes. CMIs of the EEG between local, distant, and interhemispheric electrodes are calculated. The rate of decrease of the AMI is also measured to estimate the complexity of the EEG in both groups.

2. Subjects and methods

2.1. Subjects

EEGs recordings were obtained from 15 patients (8 females and 7 males; age = 70.35 ± 3.14 years, mean ± SD) with 'Alzheimer's Disease' diagnosed using criteria of the National Institute of Neurological Disorders and Stroke Association and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (Mckhann et al., 1984). EEGs were also obtained in 15 healthy controls (8 females and 7 males; age = 69.72 ± 4.31 years). All subjects underwent the following examinations: general physical and clinical neurological examination; Mini-Mental Status Examination (MMSE) (Kwon and Park, 1986); assessment of depressive symptoms using the Hamilton Depression scale (Hamilton, 1960); extensive laboratory tests to exclude secondary causes of dementia; and clinical magnetic resonance imaging (MRI) or computed tomography (CT) of the brain. Each AD patient had been free of psychotropic medications for at least one week before the EEG recording. The AD subjects had a mean MMSE score = 9.4 ± 3.43 (possible range 0–30), indicating severe dementia. They also had scores <4 on the modified ischemia scale (Rosen et al., 1980). The average age at onset of dementia was approximately 65.2 ± 3.11 years, and the average length of the illness was 61.2 ± 7.32 months. The controls had a mean MMSE score of 27.3 ± 0.57. All subjects and the caregivers of the patients provided written informed consent for participation.

2.2. EEG recording

EEGs were recorded from 16 scalp loci (F7, T3, Fp1, F3, C3, P3, O1, F8, T4, T5, T6, Fp2, F4, C4, P4, and O2) of the international 10-20 system. With the subjects in a relaxed state and eyes closed, 16 seconds of recording (4000 data points, sampling frequency of 250 Hz) were acquired and digitized using a 12-bit analog-digital converter on an IBM PC. Potentials from the 16 channels referenced against linked earlobes were amplified on a Nihon Kohden EEG-4421K recording unit using a time constant of 0.1 s. All data were digitally filtered with a band pass of 1.0–35.0 Hz. Overall amplification was 20 000-fold. Each EEG record was judged to be free from electrooculographic and movement artifacts and to contain minimal electromyographic (EMG) activity.

2.3. Mutual information analysis

MI quantifies the information gained about one system from the measurement of another. Given measurement x_i drawn from a set $X = \{x_i\}$, the information in bits is defined as

$$\log_2 \frac{1}{P_X(x_i)} = -\log_2 P_X(x_i) \quad (1)$$

where $P_X(x_i)$ is the probability that an isolated measurement will find the system in the ith element of the bin, and $P_X(x)$ is the normalized histogram of the distribution of values observed for the measurement x. We evaluate these probabilities by constructing a histogram (from 4000 data points) of the variations of the measurement x_1.

The average amount of information obtained from any observation of X is the entropy H of a system

$$H(X) = -\sum_{x_i} P_X(x_i)\log_2 P_X(x_i) \quad (2)$$

Before any measurement of X, this information is called uncertainty. Under the condition $Y = y_j$, $H(X)$ has to be replaced by the conditional uncertainty on X

$$H(X|Y = y_j) = -\sum_{x_i} \frac{P_{XY}(x_i, y_j)}{P_Y(y_j)} \log_2 \frac{P_{XY}(x_i, y_j)}{P_Y(y_j)} \quad (3)$$

where P_{XY} (x_i, y_j) is the joint probability density for the measurements of X and Y that produce the values X and Y. $H(X|Y = y_j)$ indicates the amount of uncertainty in a measurement of x, given that y has been measured and found to be y_j. From this, we get the mean conditional uncertainty on X over y_j, under the condition that Y is known

$$H(X|Y) = \sum_{y_j} P_Y(y_j) H(X|Y = y_j) \quad (4)$$

$$= -\sum_{x_i, y_j} P_{XY}(x_i, y_j)\log_2[P_{XY}(x_i, y_j)/P_y(y_j)] \quad (5)$$

$$= H(X, Y) - H(Y) \quad (6)$$

where

$$H(X, Y) = -\sum_{x_i, y_j} P_{XY}(x_i, y_j)\log_2[P_{XY}(x_i, y_j)] \quad (7)$$

While the a priori uncertainty on X is $H(X)$, the a posteriori uncertainty on X, given a measurement of y, is $H(X|Y)$. Hence the amount that a measurement of y reduces the uncertainty of x is

$$I_{XY} = H(X) - H(X|Y) \quad (8)$$

$$= H(X) + H(Y) - H(X, Y) \quad (9)$$

which can be rewritten as

$$I_{XY} = \sum_{x_i, y_j} P_{XY}(x_i, y_j)\log_2 \frac{P_{XY}(x_i, y_j)}{P_X(x_i)P_Y(y_j)} \quad (10)$$

This is the cross mutual information (CMI) I_{XY}, the average MI between measurements of X and measurements of Y. It is the answer to the question, 'Given a measure of y, how many bits on average can be predicted about x?' (Fraser and Swinney, 1986).

If the measurement of a value from X resulting in x_i is completely independent of the measurement of a value from Y resulting in y_j, then $P_{XY}(x, y)$ factorizes: $P_{XY}(x, y) = P_X(x)P_Y(y)$ and the amount of information between the measurements, the MI, is zero. One of the properties of the MI is that $I_{XY} = I_{YX}$. The detailed derivation of these equations and the history of information theory are presented elsewhere (Fraser and Swinney, 1986; Cover and Thomas, 1991; Palus, 1994).

The principal difficulty in calculating the CMI from experimental data is estimating $P_{XY}(x,y)$ from histograms (Fraser and Swinney, 1986). For a given number of data points, using larger sampling bins to construct the histograms produces more accurate estimates of the average probability, but then the estimate of $P_{XY}(x,y)$ is too flat, underestimating I_{XY}. Using smaller bins is better for indicating changes in $P_{XY}(x,y)$ over short distances, but produces fluctuations because the sample size is small, thus overestimating I_{XY}. In this study, we used 64 bins to construct the histograms, which provides stable estimates. The auto mutual information (AMI), the MI between x_i and $x_{i+\tau}$ is

$$I_{XX_\tau} = \sum_{x(t), x(t+\tau)} P_{XX_\tau}(x(t), x(t+\tau))\log_2 \frac{P_{XX_\tau}(x(t), x(t+\tau))}{P_X(x(t))P_{X_\tau}(x(t+\tau))} \quad (11)$$

We computed the time-delayed CMI, $I_{X(t)Y(t+\tau)}$ – i.e. the MI of the EEG between different electrodes as a function of a time delay. The average time-delayed CMIs between all electrodes (over time delays of 0–500 ms) were calculated as the information transmission between different cortical areas. In order to assess whether the changes of the MI were mostly associated with impaired transmission of information over short or long distances, or within and between hemispheres, local, distant, and interhemispheric CMIs were calculated. We estimated the mean CMI values between electrodes located over frontal and antero-temporal regions as the local CMI for pairs of anterior brain region (Fp1–F7, Fp2–F8, Fp1–F3, Fp2–F4, Fp1–C3, Fp2–C4, F7–C3, F8–C4, F3–C3 and F4–C4). The local posterior CMIs between temporal, parietal, and occipital regions were also measured (O1–P3, O2–P4, O1–T5, O2–T6, O1–C3, O2–C4, P3–C3, P4–C4, T5–C3 and T6–C4). The distant CMI's were calculated between pairs of electrodes across the central line (O1–Fp1, O2–Fp2, O1–F7, O2–F8, O1–F3, O2–F4, P3–Fp1, P4–Fp2, P3–F7, P4–F8, P3–F3, P4–F4, T5–Fp1, T6–Fp2, T5–F7, T6–F8, T5–F3 and T6–F4). The interhemispheric MI was also estimated between all pairs of interhemispheric electrodes. These definitions of local, distant, and interhemispheric CMIs are the same as those used by Locatelli et al. (1998), who estimated local and distant coherences of the EEG in AD patients.

We also estimated the AMI of the EEG for 16 channels from both AD patients and normal subjects. The rate of decrease of the AMI was calculated and used as a measure of EEG complexity. The slope of the AMI was estimated using a least-squares fitting method assuming a first order monomial, $Y = aX + 1$, where x is the time delay (s) and y is the CMI. The slope was computed from a time delay of 0 to the first minimum value of the CMI.

2.4. Statistical analysis

The normality of the distributions of the CMI values for both groups was tested using the Kolmogorov–Smirnov test. Group differences of each CMI were analyzed using a repeated measure analysis of variance (ANOVA) with a group factor (patients vs. controls) and a within subject factor (electrode). Because this involved performing 7 distinct tests of significance, a Bonferroni correction was

employed and a probability value <0.0071 was required for statistical significance. Post-hoc group comparisons of local, distant and interhemispheric CMIs were performed using unpaired Student's t tests (SPSS version 6.0). Spearman rank order correlation coefficients were used to evaluate the associations of MMSE score with each CMI.

Group differences in AMIs were assessed using a repeated measures analysis of variance (ANOVA) with a group factor (patients vs. controls) and a within subject factor (electrodes). Unpaired Student t tests were used to analyze group differences in the rates of decrease of the AMIs with increasing time delays. A two-tailed P-value <0.05 was considered significant. Associations of MMSE scores with the rates of decrease in the AMIs were assessed using Spearman rank order correlation coefficients.

3. Results

3.1. CMI analysis

Fig. 1 presents a typical CMI between electrode T3 and increasingly time-delayed T6 electrode obtained from the EEG of an AD patient. The CMIs generally showed large fluctuations that gradually decreased with time. In most cases, a maximum peak in the CMI was present near a time delay of 100–450 ms, which may be considered as a time of peak effectiveness for the transmission of information across brain regions. The average CMIs between all electrodes over a time delay of 500 ms were calculated to represent information transmission across different cortical areas (Figs. 2 and 3). The channel on the y-axis was time-delayed. Although the CMI is not symmetric with the time delay, i.e. $I_{X(t)Y(t+\tau)} \neq I_{Y(t)X(t+\tau)}$, the average CMI distribution is nearly symmetric, suggesting the presence of fast bi-directional transmission of information between brain areas. The average CMI distribution between all pairs of channels in the AD patients was different from that in the normal subjects. For both groups, MI values had a Gaussian distribution, with MI decreasing as the distance between electrodes increased (Kolmogorov–Smirnov test: $P < 0.05$ for all the pairs of channels). Compared with normal subjects, the CMI of the EEG in the AD patients decreased markedly as the distance between electrodes increased (Figs. 2 and 3). In general, the AD patients had lower CMI values than the normal subjects, a finding that is more evident between frontal and antero-temporal electrodes. This indicates that the transmission of information between frontal and antero-temporal regions was reduced in the brains of AD patients than in the brains of normal controls.

An ANOVA with GROUP as an independent factor and ELECTRODE (local, distant and interhemispheric) as a

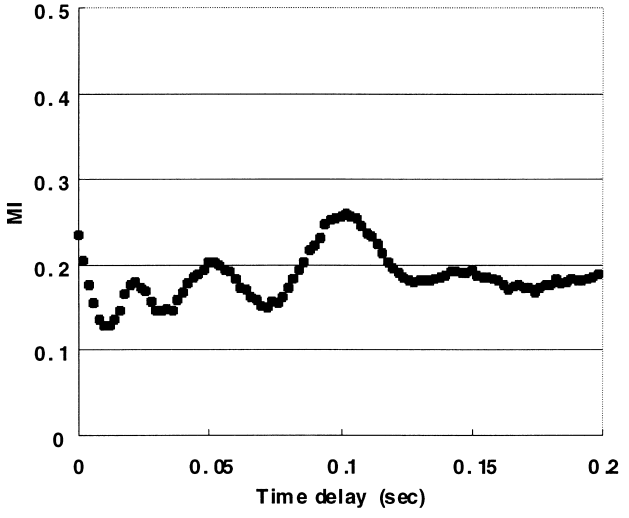

Fig. 1. The CMI between the EEG at T3 and the time-delayed EEG (4000 data points) at T6 from an AD patient.

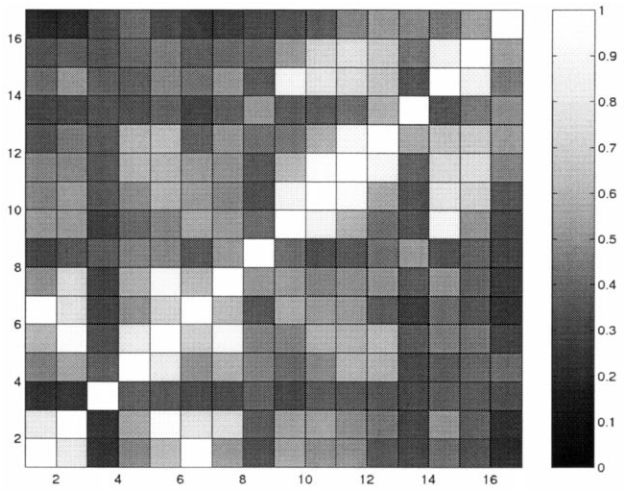

Fig. 2. Distribution of the average CMI values between all pairs of channels in the normal subjects. The numbers (1–16) correspond to F7, T3, T5, Fp1, F3, C3, P3, O1, Fp2, F4, C4, P4, O2, F8, T4, and T6.

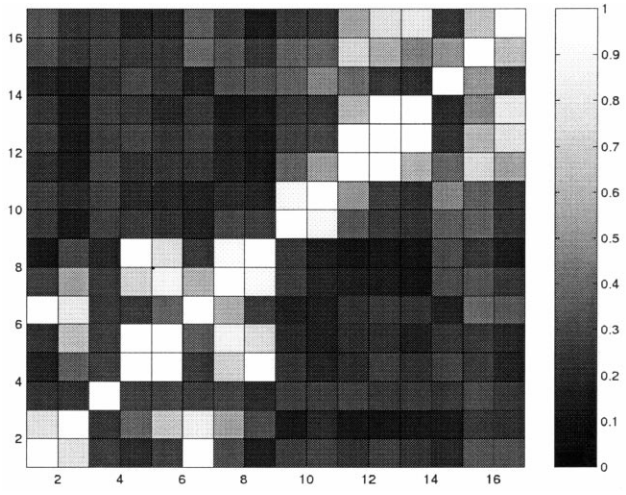

Fig. 3. Distribution of the average CMI values between all pairs of channels in AD patients.

Table 1
The average values and standard deviations of the local, distant and interhemispheric CMIs in the AD and normal subjects[a]

Mean ± SD	Local anterior		Local posterior		Distant		Interhemispheric*
	Right*	Left*	Right	Left	Right*	Left*	
Controls	0.78 ± 0.15	0.75 ± 0.13	0.58 ± 0.11	0.49 ± 0.11	0.41 ± 0.08	0.44 ± 0.08	0.42 ± 0.09
AD	0.66 ± 0.13	0.61 ± 0.11	0.52 ± 0.13	0.44 ± 0.09	0.25 ± 0.09	0.38 ± 0.08	0.21 ± 0.08

[a] *$P < 0.0071$ (two tailed t test).

repeated-measure factor yielded significant main effects for the factor GROUP ($F = 6.89$, d.f. = 1, 196; $P < 0.01$) and for the factor ELECTRODE ($F = 2.96$, d.f. = 6, 196; $p < 0.01$). No significant interaction for GROUP × ELECTRODE was found ($F = 1.59$, d.f. = 6, 196; $P = 0.083$). Table 1 presents the post-hoc comparisons of the local, distant, and interhemispheric CMIs between groups. Statistical analyses showed that anterior local and distant CMIs in the AD patients were significantly lower than those in normal subjects. A trend toward reduction in local posterior CMI values was also observed ($P < 0.07$). MMSE scores correlated significantly with CMIs, in particular with distant and interhemispheric CMIs (P's < 0.01) (Table 2).

3.2. AMI analysis

Fig. 4 shows typical AMI profiles of the EEGs (using 4000 data points) from an AD patient and a normal subject as a function of time delay. Both profiles exhibited transient oscillation and then decreased gradual with time, and approached nonzero stable values after long time delays. Since AMI profiles were normalized, the AMI value was 1 at a time delay of 0. In AD patients, the AMI decreased more slowly than in normal controls, indicating that the EEGs in the normal subjects were more complex than those in AD patients. The means and standard deviations of the AMI rates of decrease in each group are summarized in Table 3. An ANOVA performed on the rate of AMI decrease revealed significant main effects for GROUP ($F = 6.95$, d.f. = 1, 448; $P < 0.01$) and for ELECTRODE ($F = 1.86$, d.f. = 15, 448; $P < 0.05$). No GROUP × ELECTRODE interaction was found ($F = 1.26$, d.f. = 15, 448; $P = 0.088$). Spearman rank order correlation analyses in the AD group indicated that AMI's declined more slowly with time in the more demented subjects (Table 4).

4. Discussion

4.1. CMI analyses

Analyses of the CMI's of the EEG demonstrated that CMIs as a function of distance between electrodes fell off more rapidly in AD subjects than in normals. The reduced CMI in AD patients was more apparent for the interhemispheric and distant transmission of information than for local transmission. Local information transmission in the frontal and antero-temporal regions of the brains of AD subjects, however, was also reduced. These results suggest that the cognitive deficits in AD may be associated with a deficiency in transmission of information across brain regions.

The significantly reduced transmission of information between pairs of distant electrodes supports the existence of a functional impairment in the long cortico-cortical fiber pathways in AD subjects (Locatelli et al., 1998). AD is thought to be a syndrome of neocortical disconnection, in which profound cognitive losses results from the disrupted structural and functional integrity of long corticocortical tracts (Leuchter et al., 1992). Senile plaques and neurofibrillary tangles of AD prominently involve the origins and terminations of long cortico-cortical association fibers in the brain (Pearson et al., 1985; Rogers and Morrison, 1985; Esiri et al., 1986; Lewis et al., 1987). Lewis et al. (1987) showed that anatomical disconnections in AD occur at the cortical level and are associated with the death of pyramidal neurons, the cells that primarily give rise to cortico-cortical axonal projections. Previous studies of EEG coherence in AD subjects have demonstrated a significant decrease in alpha coherence. (Leuchter et al., 1987, 1992; Besthorn et al., 1994; Dunkin et al., 1994; Locatelli et al., 1998). Our findings may reflect the effects of neuronal loss, particularly the loss of long corticocortical fibers to produce a functional disconnection of the neocortex.

Table 2
Correlations between MMSE and CMIs[a]

	Local anterior		Local posterior		Distant		Interhemispheric
	Right	Left	Right	Left	Right	Left	
Correlation with MMSE	0.21*	0.23*	0.11	0.14	0.41**	0.35**	0.48**

[a] Coefficients are Spearman rank order correlations. *$P < 0.05$; **$P < 0.01$.

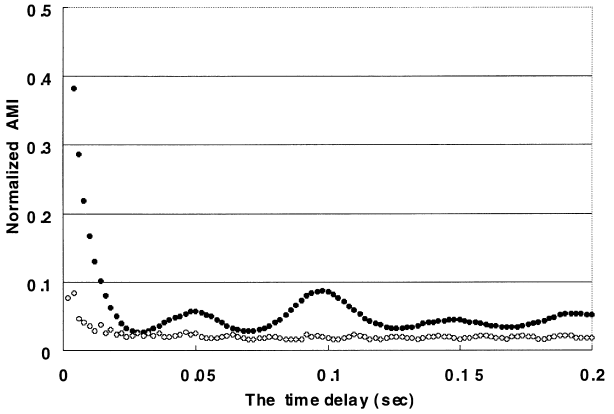

Fig. 4. The typical profiles of the normalized AMIs dividing by I(0) for the EEGs (4000 data points) in an AD patient (●) and a normal subject (○).

We should note that CMI does not directly estimate axonal connection or cortico-cortical communication. Information transmission quantified by CMI should be understood only in a statistical sense to mean that one can obtain information about the time series at one site from the time series at another site. CMI analysis does not provide the actual mechanism or pathways by which that statistical relation is established. Therefore, an impairment of long cortico-cortical fibers may not be the sole cause of or only explanation for the reduced CMI in AD patients. Reduced CMI, for example, could also be caused by the dissociation between cortical and subcortical structures in AD subjects or by the degeneration of subcortical structures such as the thalamus (Masliah et al., 1989; Braak and Braak, 1991; Xuereb et al., 1991), which is involved in the regulation of the neocortical rhythmicity and EEG alpha activity.

Table 3
Mean and standard deviations of the rates of decrease of the AMI for all the subjects in all channels[a]

Lead position	Normal controls	Alzheimer's disease
F7***	−37.55 ± 15.21	−19.93 ± 9.45
F3***	−41.32 ± 13.65	−17.85 ± 9.23
F4**	−37.72 ± 15.34	−15.57 ± 11.34
F8**	−45.33 ± 17.26	−19.38 ± 11.49
Fp1**	−38.43 ± 16.23	−15.45 ± 10.18
Fp2***	−43.84 ± 16.38	−16.54 ± 9.76
C3***	−38.12 ± 12.76	−16.20 ± 8.34
C4***	−37.29 ± 13.54	−16.43 ± 8.65
T3***	−39.85 ± 11.36	−15.76 ± 8.54
T4***	−32.45 ± 11.87	−14.54 ± 9.65
T5***	−31.99 ± 10.48	−14.37 ± 8.43
T6***	−34.26 ± 10.76	−15.23 ± 8.78
P3**	−41.65 ± 15.54	−17.97 ± 9.65
P4**	−42.93 ± 17.76	−18.96 ± 8.65
O1*	−29.45 ± 12.37	−14.29 ± 8.97
O2	−28.58 ± 13.65	−15.48 ± 8.54

[a] *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (two-tailed t test).

Table 4
Correlation between the rate of decline of the AMI and the MMSE scores[a]

Lead position	MMSE
F7	0.37*
F3	0.46*
F4	0.46*
F8	0.38*
Fp1	0.47*
Fp2	0.49*
C3	0.36*
C4	0.38*
T3	0.49*
T4	0.48*
T5	0.49*
T6	0.47*
P3	0.39*
P4	0.38*
O1	0.32*
O2	0.08

[a] These correlations suggest that a slower rate of decline of the AMI is associated with more severe dementia in the AD subjects. Coefficients are Spearman rank order correlation. *$P < 0.01$.

The reduced information transmission between pairs of interhemispheric electrodes in AD patients agrees with the results of an EEG coherence analysis of AD patients reported by Locatelli et al. (1998). They calculated EEG coherence in a small group of AD patients with mild to moderate degrees of dementia and found a significant decrease in alpha interhemispheric coherence, particularly in posterior regions. Using EEG coherence analyses in normal subjects, Thatcher et al. (1986) showed that interhemispheric coherence between F3 and F4 strongly depends on the coherence values over parieto-occipital electrodes, suggesting that coherence in medial frontal regions is highly influenced by long association connections with posterior brain regions. Locatelli et al. (1998) reported that this association was not bi-directional, as posterior interhemispheric coherence did not co-vary with frontal interhemispheric coherence. These findings suggest that the decrease in interhemispheric information transmission in the posterior region is mainly due to the loss of connections between the two hemispheres, presumably through the corpus callosum in AD subjects.

The decreased local CMIs in AD patients was more pronounced in the present study over frontal and anterotemporal brain regions. Besthorn et al. (1994) also reported decreased EEG coherence over the frontal and central brain regions of AD patients using a measure of spatially averaged coherence. In contrast, Locatelli et al. (1998) reported a significant decrease in local coherence in AD subjects over left temporo-parieto-occipital regions. These discrepancies may be due to differences in patient populations, such as in the severity of the dementia. Locatelli et al. (1998), for instance, examined EEG coherence in the early stages of AD, while Besthorn et al. (1994) studied patients with severe dementias, similar to ours.

EEG coherence and CMI both quantify information transmission among different areas of the brain. EEG coherence measures the normalized cross-power spectrum per frequency of two EEG signals recorded simultaneously at different scalp sites. EEG coherence therefore measures only the linear dependencies in the electrical potentials across those sites. CMI analyses, in contrast, takes into account both the linear and nonlinear dependencies of information transmission among those same brain regions. Because neural dynamics almost certainly includes many highly nonlinear processes (Freeman, 1992), coherence analyses could yield the erroneous conclusion that no information is transmitted across brain regions when in fact activity in those regions is highly inter-dependent. We therefore suggest that CMI analysis may be helpful in understanding and quantifying the nonlinear transmission of information within the brain.

We should nevertheless note that, because CMI measures both linear and nonlinear dependence between two time series, we would need to compare CMI estimates with coherence estimates in the EEGs of the same subjects if we wanted to quantify specifically only the non-linear dependence of electrical potentials across brain regions. The similarity of our results with those of coherence analyses in AD subjects may be a consequence of abnormalities in linear rather than nonlinear information transmission in the brains of AD subjects.

4.2. AMI analysis

We found that throughout the cerebrum of AD patients, AMI decreased significantly more slowly with time delay than it did in age-matched normal controls. Because the rate of decline in AMI is positively correlated with entropy (Pompe, 1993; Palus, 1994, 1996), the slower decline in AMI in the EEGs of AD subjects suggests that their EEG activity is less complex than the EEG activity of the normal controls. If we consider the brain to be a non-linear dynamical system, a slower decline in AMI for the AD patients implies that the underlying neural dynamics that produce the electrical potentials of their EEGs are also less complex.

These findings agree with results from previous nonlinear dynamical analyses of the EEG in AD patients. Several studies estimated the correlation dimension (D2) and/or the first positive Lyapunov exponent (L1) of the EEG data in AD patients (Pritchard et al., 1991, 1993, 1994; Besthorn et al., 1995; Stam et al., 1996; Jeong et al., 1998, 2001; Jelles et al., 1999). AD patients had significantly lower values of the D2 and L1 than age-matched normal subjects, indicating that the dynamic processes underlying the EEG record are less complex for AD patients than for normal subjects. Similarly, spectral analysis of the EEG presented an increased power of the lower frequency bands and a decrease in high frequencies in AD patients (Coben et al., 1985, 1990; Penttilä et al., 1985; Hooijer et al., 1990; Soininen et al., 1991; Schreiter-Gasser et al., 1993). A positive linear relationship between slowing of the average EEG frequency and the degree of cognitive impairment has been reported (Coben et al., 1985), suggesting that the slower and less complex temporal characteristics of the EEG may have their origin in deficient information processing within the AD-injured brain. The MI abnormalities noted in AD patients in this study presumably reflect the loss of neurons or synapses that then contribute to less complex dynamical processing within the neural networks of their brains.

Nonlinear dynamical analysis of the EEG has been found useful for detecting relative changes between different brain states, that cannot be detected using conventional analytic techniques. However, estimating the non-linear dynamical complexity of physiological data using such measures as D2 and L1 is problematic. One of the practical difficulties of these measures is that they require a large number of data points. The number of data points necessary to parameterize chaotic systems using measures such as these, in fact, increases exponentially with the number of variables that are needed to specify the dynamics of the system (Eckmann and Ruelle, 1992). A second difficulty of these measure is that they require stationarity in the time series that are being analyzed, and this criterion is in practice hard to satisfy strictly, especially when working with biological time series. A third difficulty is that classical algorithms for calculating nonlinear measures of complexity from experimental data require a very large number of computations in the embedding process (Kantz and Schreiber, 1997). Finally, no universally applicable criteria are available to determine the appropriate input parameters, such as the embedding dimension, the evolution time, and the radial separation, that are necessary to estimate D2 and L1. The absolute values of the nonlinear measures obtained thus often depend on the particular algorithms used for the analyses.

Compared with the use of these nonlinear dynamical measures of complexity, the rate of decline of AMI as a statistical measure related to entropy, therefore has several practical and computational advantages. First, estimation of AMI does not require a large number of data points fewer than 2000 data points are sufficient for obtaining a stable AMI function. Second, the computation of the AMI is fast (several seconds at most), because the computationally complex embedding procedure is not needed to estimate its values. Third, the only input parameter for the AMI is the sampling frequency of the time series. These advantages support the proposal that the behavior of the AMI may be particularly useful for measuring the complexity of physiological data such as the EEG. Its utility as an analytic and diagnostic tool in appropriate clinical settings should be explored. It is possible, for example, that examining the associations of MI measures with cognitive variables and comparing information transmission in AD with other types of dementia may prove helpful in their early different diagnosis and in monitoring disease progression.

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