Cognitive and neuropsychiatric correlates of EEG dynamic complexity in patients with Alzheimer's disease

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A B S T R A C T
This study assessed the utility of multiscale entropy (MSE), a complexity analysis of biological signals, to identify changes in dynamics of surface electroencephalogram (EEG) in patients with Alzheimer’s disease (AD) that was correlated to cognitive and behavioral dysfunction. A total of 108 AD patients were recruited and their digital EEG recordings were analyzed using MSE methods. We investigate the appropriate parameters and time scale factors for MSE calculation from EEG signals. We then assessed the within-subject consistency of MSE measures in different EEG epochs and correlations of MSE measures to cognitive and neuropsychiatric symptoms of AD patients. Increased severity of AD was associated with decreased MSE complexity as measured by short-time scales, and with increased MSE complexity as measured by long-time scales. MSE complexity in EEGs of the temporal and occipitoparietal electrodes correlated significantly with cognitive function. MSE complexity of EEGs in various brain areas was also correlated to subdomains of neuropsychiatric symptoms. MSE analysis revealed abnormal EEG complexity across short- and long-time scales that were correlated to cognitive and neuropsychiatric assessments. The MSE-based EEG complexity analysis may provide a simple and cost-effective method to quantify the severity of cognitive and neuropsychiatric symptoms in AD patients.

1. Introduction

Alzheimer’s disease (AD) is the most common form of dementia in the elderly population. The number of AD patients worldwide was estimated at 26.6 million in 2006, and is steadily increasing (Brookmeyer et al., 2007). In Taiwan, the prevalence of dementia is estimated to be between 1.7% and 4.3% in adults aged 65 years and older (Fuh and Wang, 2008). Currently, AD is diagnosed as possible or probable if a patient has insidious onset, clear-cut history of worsening of cognition by report or by observation, and cognitive deficit either in amnestic or non-amnestic domains, and the symptoms are severe enough to interfere with the patient’s normal daily functioning. However, increasing interest is being directed to developing an objective biomarker that could be used for both AD diagnosis and the assessment of symptom severity. The National Institute on Aging and Alzheimer’s Association has proposed a biomarker in the clinical diagnosis criteria for AD, such as brain amyloid-beta protein deposition or elevated tau protein in cerebrospinal fluid (McKhann et al., 2011).

Enhanced quantitative assessments of AD could therefore offer substantial clinical utility, including the potential to provide a biomarker for AD diagnosis. Such assessments would be especially valuable if they were simple and inexpensive to conduct, as is electro-encephalogram (EEG) monitoring. Previous researchers observed that AD patients exhibit slowing of EEG waves, reduced complexity in EEG signals, and perturbations in EEG synchrony (Dauwels et al., 2011). Briefly, numerous literatures had demonstrated that AD and Mild Cognitive Impairment (MCI) were associated with an increase of power in low frequencies (i.e., delta and theta bands), and a decrease of power in higher frequencies (alpha and beta bands). Studies based on complexity analysis, such as the entropy method, generally showed that AD and MCI had reduced complexity compared to controls. Furthermore, the synchrony (i.e., statistical dependency between two signals, such as Pearson’s correlation or coherence) of resting-state EEG signals of different brain regions may be reduced in MCI and AD, compared to controls. However, inconsistency of...
findings in either complexity- or synchrony-based analysis was still recognized and warrants further investigation.

Within the past decade a complexity analysis called the multiscale entropy (MSE) method was developed, and has been shown to effectively quantify the complex dynamics of biological signals (Costa et al., 2002). MSE has been applied to the analysis of heart rate time series (Norris et al., 2008a, 2008b), electromyogram (Istenic et al., 2010), human gait (Costa et al., 2003b) and posture sway (Costa et al., 2007), and EEG (Catarino et al., 2011; Escudero et al., 2006; Mizuno et al., 2010; Park et al., 2007; Protzner et al., 2011; Takahashi et al., 2010). Three separate studies evaluating the use of MSE in AD patients consistently observed abnormal EEG complexity across various time scales (Escudero et al., 2006; Mizuno et al., 2010; Park et al., 2007). However, the relatively small samples and the inconsistent use of parameters for MSE calculation used in these studies lead to difficulties in interpreting the possible association between MSE and AD severity. Further research based on larger groups of AD patients is necessary to investigate appropriate parameters for MSE calculation, and to identify the cognitive and neuropsychiatric correlates of EEG complexity in this population.

The present study hypothesized that the complexity of surface EEG activity is associated with the cognitive and neuropsychiatric characteristics of AD patients. Our aims were twofold: (1) to investigate appropriate parameters and time-scale factors for MSE calculation using EEG signals; and (2) to identify the source of surface EEG that could potentially predict cognitive and behavioral dysfunction based on MSE complexity measures. We retrospectively analyzed the data for 108 AD patients consistently observed abnormal EEG complexity across various time scales (Escudero et al., 2006; Mizuno et al., 2010; Park et al., 2007). However, the relatively small samples and the inconsistent use of parameters for MSE calculation used in these studies lead to difficulties in interpreting the possible association between MSE and AD severity. Further research based on larger groups of AD patients is necessary to investigate appropriate parameters for MSE calculation, and to identify the cognitive and neuropsychiatric correlates of EEG complexity in this population.

The study group comprised 108 patients with AD (59 women, 49 men) and with a mean age of 78.0 years (SD: 8.6), who were recruited from the Dementia Clinic at the Neurological Institute, Taipei Veterans General Hospital in Taiwan. The diagnosis for AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and the Stroke/Alzheimer’s Disease and Related Disorders Association (McKhann et al., 1984). All patients had received neurological examinations, laboratory tests, EEG monitoring, and neuropsychiatric evaluation during the diagnostic process. Our study was approved by the Institutional Review Board of Taipei Veterans General Hospital to conduct retrospective analysis of the patients’ clinical and EEG data. We excluded patients who had other conditions that caused secondary dementia, such as vascular dementia, Parkinson’s disease, hypothyroidism, vitamin B12 deficiency, syphilis, and prior history of major psychiatric illness (e.g., major depression, bipolar disorder, or schizophrenia).

The severity of dementia was assessed by the Clinical Dementia Rating (CDR) scale (Morris, 1993). Patients were categorized as having AD that was very mild (CDR = 0.5; N = 15), mild (CDR = 1; N = 69), or moderate to severe (CDR ≥ 2; N = 24). Cognitive functioning was evaluated using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), a verbal category fluency test, and the Wechsler forward-and-backward digit span tasks. Behavioral and psychological symptoms of AD were evaluated with the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). The NPI provides quantitative assessment over 12 domains, namely, delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, dis-inhibition, irritability/lability, apathy, aberrant motor activity, appetite, and night-time behavior disturbances.

To determine the appropriate parameters and time-scale factors used in MSE complexity analysis, we compiled a test dataset; this involved recruiting 15 AD patients (7 women, 8 men) with a mean age of 72.5 years (SD: 11.6) and a control group of 15 healthy participants (9 women, 6 men) with a mean age of 69.5 years (SD: 9.5) who were age-matched with the AD patients. All AD patients had a CDR ≥ 2. All healthy controls were cognitively normal and symptom-free, and they were free of neurological disease or psychiatric illness.

2.2. EEG recordings

All participants had received routine EEG recording (Nicolet EEG, Natus Medical, Incorporated, San Carlos, CA, USA) in the EEG examination room at the Neurological Institute of Taipei Veterans General Hospital. The EEG recording protocol began with a 5-min habituation to the examining environment, followed by 3 sessions of 10 to 20 s with the eyes closed and then open, and a session of photo stimulus. Recordings were in accord with the international 10–20 system with linked ear reference, 256 Hz sampling rate, high pass filter of 0.05 Hz, low pass filter of 70 Hz, notch filter of 60 Hz, and impedance below 3 kΩ. We recorded 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). The signals from these 19 electrodes were referenced to linked earlobe electrodes. Vigilance was monitored by the EEG technician, who alerted patients when signs of drowsiness appeared in the tracings. Vertical eyeball movement was detected from electrodes placed above and below the right eye, with the horizontal analog detected from electrodes placed at the left outer canthus. The EEG signals were exported in European Data Format and were processed using MATLAB software (Mathworks Inc., Sherborn, MA). Absolute EEG power analysis was calculated using the Fourier transform with Hanning window. Power spectrum density was classified by 4 frequency bands defined as beta (13–40 Hz), alpha (8–13 Hz), theta (4–8 Hz), and delta (<4 Hz). EEG band power was log-transformed before subsequent analyses.

Fig. 1 shows the flow chart for EEG processing. Briefly, EEG signals were visually inspected to manually extract 10 s of artifact-free EEG signals from each eyes-closed session; thus, each participant had 3 epochs of 10 s each for EEG signals from each electrode. These 3 EEG epochs were used to test the within-subject consistency of MSE assessment, and to determine appropriate parameters of MSE calculations. Other preprocessing steps, such as data reconstruction, were not conducted because such processing may introduce distortions into the data, which could affect MSE calculation (Takahashi et al., 2010).

2.3. Multiscale entropy (MSE) analysis

MSE analysis was developed as a biologically meaningful measure of complexity (Costa et al., 2002, 2005). Complexity is typically assessed using entropy-based methods, by quantifying the regularity or orderliness of a time series (Pincus, 1991; Richman and Moorman, 2000; Rosso et al., 2002). Entropy increases with the degree of irregularity, reaching its maximum in completely random systems. Physiologic output usually exhibits a higher degree of entropy under healthy conditions.
than in a pathological state (Goldberger et al., 2002). However, certain pathological conditions are associated with a high degree of entropy, such as heart rate rhythm in atrial fibrillation, which may result in contradictory or inconsistent results (Costa et al., 2003a). Therefore, MSE has been proposed as a method for assessing sample entropy (Richman and Moorman, 2000) by measuring the entropy over multiple time scales inherent in a time series (Costa et al., 2002).

The procedures involved in calculating MSE have been well reviewed (Costa et al., 2005) and can be summarized in the following 3 steps: (1) construction of a coarse-grained time series according to a scale factor; (2) quantification of the sample entropy of each coarse-grained time series; and (3) examination of the sample entropy profile over a range of scales. The length of each coarse-grained time series is equal to the length of the original time series divided by the scale factor. For Scale 1, the time series is simply the original time series. Sample entropy is defined by the negative natural logarithm of the conditional probability that a dataset of m points (pattern length), also repeats itself for m + 1 points, without allowing self-matches (Richman and Moorman, 2000).

2.4. Selection of appropriate parameters for MSE analysis of EEG signals

MSE analysis involves 2 issues: (1) selection of parameters (r and m) for sample entropy calculation; and (2) range of scale factors being examined. The original development of MSE was applied mainly to heart rate time series, with the parameters commonly being set as m = 2 and r = 0.15 (Cheng et al., 2009; Costa et al., 2002; Norris et al., 2008a; Yang et al., 2011). However, studies on MSE signals have examined the use of several other parameters, such as m = 1 and r = 0.25 (Escudero et al., 2006), m = 2 and r = 0.15 (Catarino et al., 2011), m = 2 and r = 0.20 (Mizuno et al., 2010; Takahashi et al., 2009, 2010), and m = 2 and r = 0.50 (Protzner et al., 2011).

Although m and r are critical in entropy estimation, no guidelines exist for optimizing their values in EEG studies. In the present analysis, we used an empirical approach based on comparisons between healthy controls (N = 15) and a subgroup of moderate to severe AD patients (N = 15) to determine the appropriate parameters and scale factors for calculating MSE. First, MSE was calculated for each EEG channel based on parameters of m = 1 to 2, and r = 0.05 to 0.80. The average sample entropy over all scale factors from 1 to 20 was computed to yield a single MSE measure (Norris et al., 2008b; Yang et al., 2011). The MSE derived from 3 epochs was further averaged to represent an overall MSE measure per patient in each EEG channel. Student’s t-test was used to assess the differences in MSE between the AD patients and controls, and the average absolute t value across all EEG channels was used as an indicator of statistical power for differentiating between the 2 groups under certain MSE parameters. Second, we evaluated the profile of the MSE curve (i.e., sample entropy of various scale factors) for the AD and control groups to determine the appropriate scale factors for calculating MSE in subsequent analyses.

2.5. Statistical analysis

SPSS for Windows Version 15.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. After determining the appropriate MSE parameters and scale factors, we tested the within-subject consistency of MSE measures among different EEG epochs using two-way repeated measure analysis of variance (ANOVA) with Huynh–Feldt corrections for sphericity statistics. We then averaged the MSE measures derived from 3 EEG epochs and used this mean MSE for subsequent analysis.

One-way ANOVA was used to evaluate between-group differences for demographic, clinical, and MSE measures between the control group and the entire AD sample, and the post hoc least-significant difference test was used for paired-group comparisons. To simplify the presentation of data, MSE measures were averaged and categorized according to the positions of EEG electrodes, namely, frontal (F7, FP1, FPZ, F8), frontal-central (F3, Fz, F4, C3, Cz, C4), temporal (T3, T4, T5, T6), and occipitoparietal (O1, O2, P3, Pz, P4) (Bjork et al., 2009). The Jonckheere–Terpstra (nonparametric) test was used to detect trends in MSE data across the control and 3 AD groups.

The relationship between the MSE of EEG signals and cognitive measures was studied using partial correlation analysis, controlling for age and education. The correlation between MSE and neuropsychiatric

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>ANOVA p*</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.9 ± 9.5</td>
<td>77.7 ± 10.3</td>
<td>78.0 ± 6.7</td>
<td>78.2 ± 11.9</td>
<td>0.984</td>
<td></td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>6 (40.0)</td>
<td>8 (53.3)</td>
<td>27 (39.1)</td>
<td>14 (48.3)</td>
<td>0.213</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.1 ± 8.8</td>
<td>10.8 ± 4.6</td>
<td>7.9 ± 5.0</td>
<td>7.7 ± 5.8</td>
<td>0.122</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1.2 ± 0.9</td>
<td>2.3 ± 2.2</td>
<td>2.2 ± 2.1</td>
<td>1.070</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>28.7 ± 1.0</td>
<td>24.2 ± 4.2</td>
<td>19.0 ± 5.2</td>
<td>11.5 ± 4.6</td>
<td>&lt;0.001</td>
<td>2 &gt; 3 &gt; 4</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>11.9 ± 5.2</td>
<td>9.2 ± 3.3</td>
<td>9.2 ± 3.3</td>
<td>3.9 ± 2.4</td>
<td>&lt;0.001</td>
<td>2 &gt; 3 &gt; 4</td>
</tr>
<tr>
<td>Digit forward</td>
<td>8.4 ± 3.1</td>
<td>8.7 ± 2.4</td>
<td>6.4 ± 3.2</td>
<td>3.9 ± 2.4</td>
<td>&lt;0.003</td>
<td>3 &gt; 4</td>
</tr>
<tr>
<td>Digit backward</td>
<td>5.5 ± 2.5</td>
<td>3.9 ± 2.1</td>
<td>2.5 ± 1.7</td>
<td>1.070</td>
<td>&lt;0.001</td>
<td>2 &gt; 3 &gt; 4</td>
</tr>
<tr>
<td>Neuropsychiatric inventory (NPI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>2.8 ± 3.2</td>
<td>14.4 ± 15.3</td>
<td>27.0 ± 23.0</td>
<td>27.0 ± 23.0</td>
<td>&lt;0.001</td>
<td>2 &gt; 3 &gt; 4</td>
</tr>
<tr>
<td>Delusion</td>
<td>0.2 ± 0.8</td>
<td>0.9 ± 1.9</td>
<td>1.1 ± 1.9</td>
<td>0.258</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>0.1 ± 0.3</td>
<td>0.4 ± 1.3</td>
<td>1.0 ± 1.8</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation/agression</td>
<td>0.4 ± 1.1</td>
<td>1.2 ± 2.0</td>
<td>1.5 ± 3.1</td>
<td>0.283</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphoria/depression</td>
<td>0.1 ± 0.3</td>
<td>1.6 ± 2.5</td>
<td>2.3 ± 3.6</td>
<td>0.041</td>
<td></td>
<td>2 &gt; 4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.2 ± 0.8</td>
<td>1.2 ± 2.3</td>
<td>3.5 ± 4.6</td>
<td></td>
<td>&lt;0.001</td>
<td>2 &gt; 4; 3 &gt; 4</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0</td>
<td>0.2 ± 0.7</td>
<td>0.3 ± 0.5</td>
<td>0.451</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>0.2 ± 0.6</td>
<td>1.7 ± 2.7</td>
<td>3.9 ± 4.8</td>
<td></td>
<td>&lt;0.001</td>
<td>2 &gt; 4; 3 &gt; 4</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.2 ± 0.4</td>
<td>0.9 ± 2.0</td>
<td>0.9 ± 2.5</td>
<td></td>
<td>0.473</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>0.5 ± 0.7</td>
<td>1.5 ± 2.8</td>
<td>1.8 ± 2.8</td>
<td>0.322</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>0</td>
<td>1.0 ± 2.1</td>
<td>3.4 ± 4.1</td>
<td></td>
<td>&lt;0.001</td>
<td>2 &gt; 4; 3 &gt; 4</td>
</tr>
<tr>
<td>Sleep change</td>
<td>0.5 ± 1.2</td>
<td>1.8 ± 2.7</td>
<td>4.1 ± 4.6</td>
<td></td>
<td>&lt;0.001</td>
<td>2 &gt; 4; 3 &gt; 4</td>
</tr>
<tr>
<td>Appetite change</td>
<td>0.4 ± 1.1</td>
<td>2.1 ± 3.4</td>
<td>3.3 ± 3.9</td>
<td></td>
<td>0.036</td>
<td>2 &gt; 4</td>
</tr>
</tbody>
</table>

MSE: Mini-Mental State Examination.

* P-value < 0.01.
measures was similarly controlled for age, education, and cognitive scores (MMSE) to exclude the effect of cognitive functioning on behavioral assessments. Statistical significance required a $P$-value of less than .01, stricter than the usual .05. The correlation profiles were visualized topographically using EEGLAB (Delorme and Makeig, 2004) implemented in MATLAB software.

3. Results

3.1. Participants

Demographic and clinical data are presented in Table 1. The 4 participant groups (1 control and 3 AD groups representing differing levels of disease severity) did not differ significantly in age, sex, and education. The AD groups did not differ from each other in the duration of illness. As expected, cognitive functioning worsened with increasing severity of CDR ratings. For behavioral assessment using NPI, moderate to severe AD patients (CDR $\geq 2$) showed greater behavioral problems than patients with very mild or mild AD in the domains of depression, anxiety, apathy, aberrant behavior, sleep, and appetite changes. Fig. 2 illustrated the raw EEG signals and associated power spectrum and MSE profile from a healthy comparison subject and AD patients.

3.2. Determining appropriate parameters for MSE calculation

The first step was to determine the appropriate similarity factor ($r$) and pattern length ($m$) for MSE calculation. Fig. 3 shows that the power to differentiate EEG complexity between the control and AD groups was relatively high in the range of $r = 0.05$ to $r = 0.35$. For practical purposes we chose appropriate parameters of $m = 2$ and $r = 0.15$ (i.e., the highest mean t-value in Fig. 3) and proceeded to analyze all data based on these parameters.

The second step was to determine appropriate scale factors for MSE calculation. Fig. 4 shows that the profiles of the MSE curve differed between the control group and patients with moderate to severe AD for short- and long-time scale factors. Compared with the control group,
these AD patients had significantly lower MSE on the short-time scales, generally for scale factors 1 to 6 in most electrodes (14/19 electrodes). In contrast, the AD patients had significantly higher MSE on the long-time scales, generally between scale factors 16 and 20 in posterior electrodes (11/19 electrodes). We summarized the results by calculating 2 MSE measures, defined as MSE-short and MSE-long, which were obtained by averaging the sample entropy over scale factors 1 to 6 and 16 to 20, respectively.

3.3. Within-subject variability of MSE measures between 3 EEG epochs

Repeated measures analysis using two-way ANOVA was conducted separately to test the within-subject variability of MSE-short and MSE-long measures. Significant within-subject variation was found for MSE-short in the frontal electrode FP2 (F = 3.56; P = .03), and significant within-subject variation was found for MSE-long in FP1 (F = 4.00; P = .02) and FP2 (F = 4.35; P = .01). Neither MSE-short nor MSE-long showed significant variations within subjects among the 3 EEG epochs for other EEG channels.
3.4. Comparison of MSE between control and AD groups

Table 2 shows the comparison of MSE-short and MSE-long values among the control and 3 AD groups, respectively. A significant trend was noted for both the control and AD groups, in which increasing severity of CDR was associated with decreasing MSE-short and increasing MSE-long in the frontal-central, temporal, and occipitoparietal regions (Jonckheere trend test; all \( P < .01 \)). Significant between-group differences were also found for both MSE-short and MSE-long in these 3 regions (all \( P < .01 \)). Post hoc comparisons indicated that patients with moderate to severe AD displayed the lowest MSE-short and the highest MSE-long in the occipital-parietal regions, followed by the mild AD and then the very mild AD groups. The MSE results did not differ between the control and very mild AD groups.

Fig. 5 shows the comparison for the MSE curve between the 4 groups across a scale of 1 to 20. We used the MSE data averaged from 5 occipitoparietal EEG channels (O1, O2, P3, Pz, P4). Compared to the controls, patients with AD showed opposite MSE profiles before and after scale factor 9. Before scale factor 9, MSE showed a dose effect among the 3 AD groups (\( P < .01 \) for trend test at scale 1 to 6), but MSE did not differ between the control and very mild AD groups. After scale factor 9, the MSE for patients with moderate to severe AD was significantly higher than that of controls or the other 2 AD groups (scale 11 to 20; \( P < .01 \)).

3.5. Correlation between MSE and cognitive assessment

Fig. 6 shows the partial correlation between assessment of cognitive functions and MSE of each EEG channel, controlling for age and education.

In the temporal and occipitoparietal regions, MSE-short was significantly correlated to MMSE (T5: \( r = 0.41 \); T6: \( r = 0.44 \); P3: \( r = 0.43 \); P4: \( r = 0.40 \); O1: \( r = 0.40 \); O2: \( r = 0.42 \)), verbal fluency (T5: \( r = 0.27 \); T6: \( r = 0.36 \); P3: \( r = 0.34 \); P4: \( r = 0.32 \); O1: \( r = 0.32 \); O2: \( r = 0.31 \)), and the digit-forward test (P3: \( r = 0.34 \); P4: \( r = 0.32 \); O1: \( r = 0.32 \); O2: \( r = 0.31 \) (all \( P < .01 \)). The MSE-short value correlated with the digit-backward task results at certain temporal and central electrodes (C3: \( r = 0.30 \); C4: \( r = 0.33 \); T5: \( r = 0.35 \)).

Similarly, in the temporal or occipitoparietal regions, MSE-long was correlated to MMSE (T5: \( r = 0.40 \); P4: \( r = 0.37 \); O1: \( r = 0.36 \); O2: \( r = 0.36 \), to verbal fluency (O1: \( r = 0.38 \); O2: \( r = 0.36 \), to sleep change (T6: \( r = 0.35 \); P4: \( r = 0.32 \)). The MSE-long values did not correlate significantly with digit-forward or –backward task results.

3.6. Correlation of MSE with neuropsychiatric assessment

Fig. 7 shows the partial correlation between assessment of neuropsychiatric symptoms and MSE of each EEG channel, controlling for age, education, and MMSE. The strongest correlation was found between sleep changes and MSE-long at O1 (\( r = 0.32 \); \( P < .01 \)). Other correlations between MSE and NPI symptoms attained a trend level of significance (\( P < .05 \)). MSE-short was correlated to NPI (P3: \( r = 0.22 \); O2: \( r = 0.24 \)), and sleep change (T6: \( r = 0.23 \); T3: \( r = 0.20 \); P4: \( r = 0.20 \); O2: \( r = 0.21 \)), and disinhibition (FP1: \( r = 0.24 \); F7: \( r = 0.23 \); P3: \( r = 0.25 \)). MSE-long was correlated to NPI (O1: \( r = 0.26 \); T5: \( r = 0.24 \) and the subdomains of apathy (T5: \( r = 0.29 \); T6: \( r = 0.20 \); P3: \( r = 0.23 \); P4: \( r = 0.24 \); O1: \( r = 0.23 \); O2: \( r = 0.23 \), sleep (T3: \( r = 0.23 \), T4: \( r = 0.20 \); T5: \( r = 0.25 \); T6: \( r = 0.22 \); P4: \( r = 0.27 \); O1: \( r = 0.32 \); O2: \( r = 0.26 \), and disinhibition (FP1: \( r = 0.24 \); F7: \( r = 0.21 \); P3: \( r = 0.23 \); P3: \( r = 0.24 \)).

3.7. Correlation of EEG band power with MSE

Fig. S1 shows the paired-electrode correlation between MSE and four EEG band powers for the 4 groups. For MSE-short, in most regions the negative correlation with theta power was higher for all AD groups (\( r = 0.5 \)), compared with the control (\( r = 0.1 \)). The positive correlation between MSE-short and beta power was dominant in the temporal and parietal regions in patients with mild and moderate to severe AD (\( r = 0.4 \)). In contrast, MSE-long showed an increased negative correlation with beta power in most brain regions in all AD groups (\( r = 0.3 \) to \( r = 0.4 \)), compared with the control (\( r = 0.1 \)). A positive correlation between MSE-long and theta power dominated in the occipital regions (\( r = 0.5 \)) of patients with mild and moderate to severe AD.
4. Discussion

The within-subject consistency results suggested that MSE measures were reliable among different EEG epochs. The key findings were as follows: (1) compared with controls, AD patients showed a decreased MSE complexity in short-time scales and increased MSE complexity in long-time scales; (2) MSE-short and MSE-long were correlated with beta and theta power in different brain regions, respectively; (3) MSE complexity of EEG in temporal and occipitoparietal electrodes was correlated with scores for cognitive functioning, such as MMSE, verbal fluency, and digit span tasks; and (4) MSE complexity in various surface brain regions was correlated with neuropsychiatric symptoms.

The entropy-based quantification of the complexity of biological signals has gained increasing interest in recent years. Our empirical determination of the best parameters for calculating sample entropy in EEG analysis (m = 2; r = 0.15) was consistent with a prior theoretical validation of sample entropy (Richman and Moorman, 2000). We repeated the MSE analysis using parameters employed in previous research (Escudero et al., 2006; Mizuno et al., 2010; Protzner et al., 2011) and found that our selected parameters were optimal for ANOVA and for calculating correlation statistics (data not shown). Although no guidelines existed previously for the selection of parameters for MSE calculation, our parameters (m = 2; r = 0.15) were identical to those used in calculating other types of biological signals (Costa et al., 2002, 2005). This parameter may prove to be generic for studies of complex dynamics in neurophysiologic time series.

Our finding of abnormal MSE complexity across different temporal scales in AD patients was consistent with the results of prior studies (Escudero et al., 2006; Mizuno et al., 2010). We further determined an appropriate range of scale factors, namely MSE-short (scales 1 to 6) and MSE-long (scales 16 to 20), to differentiate between the AD and control groups and to correlate MSE with AD severity. The physiological nature of MSE-short and MSE-long remains unclear, but we speculate that the discrepancy of MSE profile in short and long time scales was due to different pathophysiologic mechanisms toward random or random process. The MSE curve profile indicates the entropy (i.e., degree of randomness) in each time scale. In the loss of physiological hypothesis proposed by Costa et al. (2002) and Goldberger et al. (2002), both regular and random processes are not “complex” and may be considered as a pathologic process in the aging or illness. Therefore, the lower MSE seen in short time scale in AD patients may represent a process of brain activity toward regular, while higher MSE seen in long time scale in AD patients may indicate a different process of brain activity toward random or non-stationary. This speculation can explain the results of different correlation profiles between MSE-short and long and clinical variables. The negative correlation between MSE-short and NPI scores suggests that more regular EEG activity is associated with higher degree of severity in certain NPI domains, and the positive correlation between MSE-long and NPI scores suggests that more random EEG activity is associated with the higher severity of symptoms. Both results of MSE-short and MSE-long are consistent with the loss of physiologic complexity hypothesis proposed by prior literatures (Costa et al., 2002; Goldberger et al., 2002; Peng et al., 2009; Yang and Tsai, 2013).

However, different types of biological signals may display different MSE profiles in healthy versus disease groups. One study that applied MSE to heart rate time series in a sample of heart failure patients showed that an average MSE between scale 6 and 20 had the strongest predictive power of survival (Ho et al., 2011). Another MSE analysis of EEGs in schizophrenic patients found that the MSE profile differed between healthy and psychotic patients (Takahashi et al., 2010). Such differences may be influenced by the pathophysiological nature of an illness. Further investigation of the biological correlates of MSE analysis is warranted.

Prior literatures have shown that certain EEG markers (such as frequency measures) may be correlated to decreased performance in various cognitive domains in AD or MCI patients (for review see Dauwels et al., 2011). Our results suggested that in the occipitoparietal EEG electrodes, both MSE-short and MSE-long were strongly correlated with MMSE and verbal fluency. This finding was congruent with earlier observations that quantitative EEG changes in the posterior brain regions were associated with cognitive decline in AD patients (Claus et al., 1998; Jelic et al., 2000; Prichep et al., 1994). Moreover, we found that MSE-short was exclusively correlated with digit-forward and -backward ability in the occipital–parietal and temporal/central regions, respectively. Digit-forward tasks assess the patient’s attention and concentration, and digit-backward tasks additionally involve the executive working memory (Baddeley, 1992). Thus, EEG dynamic complexity on a short-time scale may differentiate functional decline associated with specific brain regions in AD patients.

Identifying the neuropsychiatric correlates of EEG complexity may provide insight into how brain activity in specific regions relates to behavioral and psychological symptoms of dementia (BPSD). This study found that groups of symptom domains on the NPI were associated with EEG complexity in various brain regions. For example, disinhibition was correlated to frontal EEG complexity; depression and anxiety were correlated to temporal and parietal EEG complexity; and apathy,
Fig. 7. Topography of the correlation profiles between neuropsychiatric assessments and MSE-short (upper panel) and MSE-long (lower panel), respectively.
aberrant behavior, and sleep changes were correlated to occipitoparietal EEG complexity. These findings support the notion that various BPSD can be clustered into mood, psychomotor, or instinctual factors (Fuh and Cummings, 2009; Petrovic et al., 2007). The findings may also have implications for the use of EEG complexity analysis as a simple clinical tool to assess the severity of neuropsychiatric symptoms in AD patients. Few studies have investigated the nonlinear properties of EEGs in patients with AD. Conventional EEG power analysis in these patients generally shows a slowing EEG pattern with increased delta band power and decreased alpha activity (Claus et al., 1998; Kowalski et al., 2001; Schreiter-Gasser et al., 1994; van der Hiele et al., 2007). One study reported that MSE on both the short- and long-time scales was correlated to fast and slow EEG oscillations, and demonstrated this association for the frontal-central position (F2) (Mizuno et al., 2010). The current study further validated parameters for MSE calculation in EEG signals, and defined the short- and long MSE index based on MSE curve profile, and clarified that MSE on short- and long-time scales was associated with neuropsychiatric symptoms and various EEG band powers at specific surface brain regions, and that topographic patterns of these associations were related to AD severity (Fig S1). In addition, the MSE curve for short-time scales was able to better differentiate between patients with differing levels of severity of AD, compared with the long-term scales (Fig S5). Overall, these findings may support the hypothesis that in AD patients, EEG dynamic activity on short- and long-time scales could be modulated by various pathophysiological mechanisms.

The strengths of this study included the use of a large cohort of AD patients, an evaluation of the method of MSE calculation, and comprehensive assessments of cognitive and neuropsychiatric functioning. Nonetheless, the study was subject to certain limitations. First, the study design was cross-sectional, whereas a longitudinal design would better assess the power of EEG complexity in predicting cognitive and behavioral decline in AD patients. Second, although our findings indicated that MSE could detect differences in EEG dynamics at differing levels of severity of AD (moderate to severe, mild, and very mild), it could not distinguish between the control group and patients with very mild AD. However, further refinement may enable the use of MSE to detect very mild AD. Additionally, a more sophisticated neurophysiologic recording, such as magneto-encephalography, may be useful to detect functional changes associated with AD prior to the onset of cognitive and behavioral symptoms (Zamrini et al., 2011).

In summary, quantification of MSE complexity in EEG signals may provide a simple dynamic marker for assessing the cognitive and neuropsychiatric severity of AD. A portable EEG monitoring device may be developed, such as for those using dry EEG electrodes, to monitor brain activity in surface brain regions and to provide clinical information for the objective assessment of neuropsychiatric symptoms in AD patients. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2013.07.022.

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