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Complexity of spontaneous BOLD activity in default mode network is correlated with cognitive function in normal male elderly: a multiscale entropy analysis

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Abstract

The nonlinear properties of spontaneous fluctuations in blood oxygen level-dependent (BOLD) signals remain unexplored. We test the hypothesis that complexity of BOLD activity is reduced with aging and is correlated with cognitive performance in the elderly. A total of 99 normal older and 56 younger male subjects were included. Cognitive function was assessed using Cognitive Abilities Screening Instrument and Wechsler Digit Span Task. We employed a complexity measure, multiscale entropy (MSE) analysis, and investigated appropriate parameters for MSE calculation from relatively short BOLD signals. We then compared the complexity of BOLD signals between the younger and older groups, and examined the correlation between cognitive test scores and complexity of BOLD signals in various brain regions. Compared with the younger group, older subjects had the most significant reductions in MSE of BOLD signals in posterior cingulate gyrus and hippocampal cortex. For older subjects, MSE of BOLD signals from default mode network areas, including hippocampal cortex, cingulate cortex, superior and middle frontal gyrus, and middle temporal gyrus, were found to be positively correlated with major cognitive functions, such as attention, orientation, short-term memory, mental manipulation, and language. MSE from subcortical regions, such as amygdala and putamen, were found to be positively correlated with abstract thinking and list-generating fluency, respectively. Our findings confirmed the hypothesis that complexity of BOLD activity was correlated with aging and cognitive performance based on MSE analysis, and may provide insights on how dynamics of spontaneous brain activity relates to aging and cognitive function in specific brain regions.

Keywords: Aging; Blood oxygen level-dependent; Cognitive function; Complexity; Multiscale entropy

1. Introduction

Analysis of spontaneous blood oxygen level-dependent (BOLD) signals in functional magnetic resonance imaging (fMRI) has been implemented mainly in research on functional brain connectivity by examining interregional correlations in BOLD activity (Biswal et al., 1997; Friston et al., 2003), while

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the temporal properties of BOLD signals remain largely unexplored. The observation that spontaneous BOLD activity in the resting human brain is not random noise (Fox et al., 2007; Zarahn et al., 1997), but specifically organized, has shed new insight into neuroscientific research (Garrett et al., 2010).

Analysis of variability in BOLD signals has been proposed as a significant indicator of aging, in which BOLD activity in older brains is less variable than that in younger brains (Garrett et al., 2010, 2011). A lack of variability in brain activity may be implicated in age-related neural processing deficits and a concomitant decline in cognitive function, warranting comprehensive investigation to identify the correlation between the dynamic processes associated with BOLD activity and cognitive function among the elderly.

The finding of a reduction in the variability of BOLD signals with aging is analogous to the generic notion that a loss of physiologic complexity is correlated with the aging process. It has long been observed that physiologic output (e.g., heart rate) under healthy conditions typically exhibits multiscale variability, long-range correlation, and nonlinearity (Buchman, 2002; Goldberger et al., 2002a). Increased complexity in physiologic output has been proposed to be correlated with healthy conditions whereas aging and pathological conditions often show a reduction in the complexity of physiologic output (Costa et al., 2002, 2005; Goldberger et al., 2002a, 2002b; Lipsitz and Goldberger, 1992). This complexity may arise from the interaction among structural or functional units and feedback loops operating over a wide range of temporal and spatial scales, enabling the organism to adapt to the events of everyday life (Costa et al., 2002, 2005; Goldberger et al., 2002b; Lipsitz and Goldberger, 1992; Peng et al., 2009).

In this study, we therefore hypothesized that (1) complexity of spontaneous BOLD activity is reduced in the older group, compared with the younger group, and (2) cognitive performance among the elderly is correlated positively to the complexity of spontaneous BOLD activity. In addition, because spontaneous BOLD activity was represented mostly in the default mode network (DMN) brain areas (Greicius et al., 2003), we also expected that the correlation between cognitive performance and complexity of spontaneous BOLD activity may exist mainly in DMN areas. We applied a well developed complexity measure—multiscale entropy (MSE) analysis (Costa et al., 2002), capable of quantifying the complexity of dynamic processes across multiple time scales, to analyze BOLD time series data.

Complexity is typically assessed using entropy-based methods by quantifying the regularity (orderliness) of a time series (Costa et al., 2002; Pincus, 1991; Richman and Moorman, 2000; Rosso et al., 2002). Entropy increases with the degree of irregularity, reaching its maximum in completely random systems. However, the conventional entropy-based approach could yield contradictory results in which a high degree of entropy is also observed in pathological conditions, such as heart rate rhythm in atrial fibrillation (Costa et al., 2003a).

MSE analysis was therefore developed as a biologically meaningful measure of complexity (Costa et al., 2002, 2005) by quantifying sample entropy (Richman and Moorman, 2000) over multiple time scales inherent in a time series. MSE has been applied to the analysis of heart rate time series (Norris et al., 2008a, 2008b; Yang el al., 2011), electromyogram (Istenic et al., 2010), human gait (Costa et al., 2003b), posture sway (Costa et al., 2007; Manor et al., 2010), and electroencephalogram (EEG) (Catarino et al., 2011; Escudero et al., 2006; Mizuno et al., 2010; Park et al., 2007; Protzner et al., 2010; Takahashi et al., 2010).

Because no prior study has applied MSE to quantify the complexity of BOLD time series, we also sought to determine appropriate parameters for calculating MSE in BOLD data. Our aims were therefore 3-fold: (1) to empirically investigate the appropriate parameters and time scale factors for MSE analysis of BOLD signals; (2) to compare MSE of BOLD signals between the younger and older group; and (3) to identify brain areas that could be potentially correlated with cognitive function in the older people based on analysis of the complexity of spontaneous brain activity. To this end, we conducted a resting fMRI experiment on a cohort of cognitively normal Han Chinese younger and older males.

2. Methods

2.1. Participants

This study included 99 elderly Han Chinese male subjects recruited from the community and a public veterans housing complex in northern Taiwan (aged 80.6 ± 5.4 years; education: 5.4 ± 5.1 years). For comparison, 56 normal younger male subjects (aged 27.5 ± 4.1 years; education: 18.6 ± 2.7 years) were recruited from the community. The study was conducted in accordance with the Declaration of Helsinki, receiving approval from the local Institutional Review Board. Informed consent was obtained from all subjects prior to commencement of the study. Each subject was evaluated by a trained research assistant using the Mini-International Neuropsychiatric Interview to exclude the presence of Axis I psychiatric disorders (Sheehan et al., 1998). For younger subjects, cognitive function was assessed by Mini Mental State Examination (Folstein et al., 1975) and the Wechsler Digit Span Task (Wechsler, 1997). For older subjects, cognitive function was assessed using the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982), the Chinese version of Cognitive Abilities Screening Instrument C-2.0 (CASI) (Teng et al., 1994), and the Wechsler Digit Span Task (Wechsler, 1997). The CASI is a 100-point cognitive test providing quantitative assessment in 9 domains of cognitive function, including long-term memory, short-term memory, attention, mental manipulation, orientation, abstraction and judgment, language, visual construction, and list-generating fluency. For comparison with younger subjects, CASI subscores were also trans-

Table 1
Demographic and cognitive characteristics of the subjects

Characteristics	Younger group (n = 56)	Older group (n = 99)	p
Age, years	27.5 ± 4.1	80.6 ± 5.4	<0.001
Sex, male	56 (100%)	99 (100%)	1.000
Education, years	18.6 ± 2.7	5.4 ± 5.1	<0.001
Handedness, right	52 (93%)	97 (98%)	0.277
Geriatric Depression Scale (0–15)	—	1.6 ± 2.4	—
Wechsler Digit Span Task, forward	15.3 ± 1.1	12.1 ± 2.9	<0.001
Wechsler Digit Span Task, backward	11.5 ± 2.6	3.7 ± 2.8	<0.001
MMSE	29.0 ± 1.3	26.3 ± 2.7	<0.001
CASI (0–100)	—	87.1 ± 9.3	—
Long-term memory (0–10)	—	5.4 ± 5.1	—
Short-term memory (0–12)	—	10.6 ± 1.6	—
Attention (0–8)	—	6.5 ± 1.2	—
Mental manipulation (0–10)	—	6.9 ± 2.6	—
Orientation (0–18)	—	17.6 ± 1.4	—
Abstract thinking (0–12)	—	9.2 ± 2.2	—
Language (0–10)	—	9.4 ± 1.1	—
Drawing (0–10)	—	8.6 ± 1.9	—
List-generating fluency (0–10)	—	8.7 ± 1.9	—

All subjects were evaluated by a trained research assistant using the Mini-International Neuropsychiatric Interview to exclude the presence of Axis I psychiatric disorders (Sheehan et al., 1998). The presence of dementia was excluded by a CDR ≥ 0.5 (Hughes et al., 1982), and geriatric depression by Geriatric Depression Scale > 6 (Sheikh and Yesavage, 1986). Categorical data are given as n (%).
Key: CASI, Cognitive Abilities Screening Instrument; MMSE, Mini-Mental State Examination.

formed to the Mini Mental State Examination scores (Teng et al., 1994). The cognitive tests were performed on the day or within a week of fMRI scanning.

Older subjects with CASI < 50 (Liu et al., 1994) or CDR ≥ 0.5 (Hughes et al., 1982) were further interviewed by a senior psychiatrist to verify the diagnosis of dementia. Overall exclusion criteria for all subjects consisted of the following: (1) presence of dementia (i.e., CDR ≥ 0.5); (2) presence of Axis I disorders of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (e.g., schizophrenia, bipolar disorders, or unipolar depression); (3) history of neurological conditions (i.e., head injury, stroke, or Parkinson's disease); (4) illiteracy; and (5) female sex. The purpose of including only male subjects was to minimize the confounding effect of sex in cognitive function (Tsai et al., 2010). The study sample represents a group of robust, nondemented, younger and older subjects with normal function in their daily activity. Table 1 summarizes the demographic and clinical characteristics of the subjects.

2.2. fMRI scanning and data processing

All fMRI scanning was performed at National Yang-Ming University on a 3.0 T Siemens MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) equipped with a 12-channel head coil. All fMRI experiments were scheduled in the morning. During the experiment the scanner room was darkened and the subjects were instructed to relax with their eyes closed, without falling asleep. After the resting experiment, the technician routinely asked the subjects if they fell asleep during the resting scan session, and the subjects were rescanned if they believed they fell asleep during the resting scan. T2*-weighted images with BOLD contrast were measured using a gradient echo-planar imaging (EPI) sequence (repetition time [TR] = 2500 ms, echo time = 27 ms, field of view = 200 mm, flip angle = 77°, matrix size = 64 × 64, voxel size = 3.44 mm × 3.44 mm × 3.40 mm). For each run, a total of 200 EPI volume images were acquired along the AC–PC (AC = anterior commissure, PC = posterior commissure) plane. High-resolution structural magnetic resonance images were acquired with 3-D magnetization-prepared rapid gradient echo sequence (repetition time, TR = 2530 ms, echo time, TE = 3.5 ms, inversion time, TI = 1100 ms, field of view = 256 mm, flip angle = 7°). For each subject, the whole fMRI scanning lasted approximately 15 minutes.

Resting functional image data were preprocessed and analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) and the Resting-State fMRI Data Analysis Toolkit (www.restfmri.net) (Yen and Zhang, 2010) implemented in MATLAB Version 7.7 (MathWorks, Inc., Sherborn, MA, USA). Images were slice-timing corrected, realigned, and normalized into the standard stereotaxic space of the Montreal Neurological Institute EPI template and resampled to a 3-mm cubic voxel (Liu et al., 2008; Wang et al., 2006). Covariates of BOLD time series were regressed out before complexity analysis, including the time courses of head motion (3 for translation and 3 for rotation), mean time course of the entire brain (or global trend), white matter, and cerebrospinal fluid. All subjects included in this study exhibited a maximum displacement of less than 1.5 mm at each axis and an angular motion of less than 1.5° for each axis.

The registered fMRI data were segmented into 90 regions (45 for each hemisphere) using the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002). For each subject, a representative BOLD time series of each AAL brain region was obtained by averaging the BOLD time series of all voxels within a given region. The first 5 data points (12.5 seconds) in any BOLD time series were discarded because of the instability of initial magnetic resonance image scanning, leaving 195 data points in the final data. Temporal low-pass filtering (< 0.08 Hz) was performed to reduce the influence of high-frequency noise from physiologic confounders.

2.3. Multiscale entropy

The procedures involved in the calculation of MSE have been well reviewed (Costa et al., 2005) and can be summarized in the following 3 steps: (1) construction of coarse-grained time series according to different scale factors; (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 length N, having repeated itself within a tolerance r (similarity factor) for m points (pattern length), will also repeat itself for m + 1 points, without allowing self-matches (Richman and Moorman, 2000).

Because no rigorous guideline exists for choosing the parameters to calculate sample entropy, prior studies on biomedical signals using sample entropy have shown inconsistent selection of parameters. For example, studies of heart rate typically employed m = 2 and r = 0.15 (Costa et al., 2002; Norris et al., 2009; Yang et al., 2011), whereas studies of EEG used various parameters, including 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., 2010). Furthermore, BOLD time series are usually short (100–200 time points), and coarse-grained procedure in MSE with large scale factor may result in short data length and subsequently unreliable sample entropy estimation. Prior studies suggested that data lengths of 10^m to 20^m (m: pattern length) should be sufficient to estimate approximate entropy (Pincus and Goldberger, 1994) or sample entropy (Richman and Moorman, 2000). Therefore, estimation of sample entropy in short BOLD time series data may be sufficient for m = 1 (requires at least 10–20 time points) but barely for m = 2 (requires at least 100–400 time points).

Because of the aforementioned considerations, we sought to empirically investigate the appropriate parameters and scale factors in MSE calculation, based on comparisons between 2 manually selected subsets of age- and education-matched older subjects with low and high cognitive score (n = 10 each; age: 81.6 ± 2.4 vs. 81.5 ± 4.0 years, t = 0.068, p = 0.947; education: 9.3 ± 3.7 vs. 9.7 ± 3.7 years, t = −0.243, p = 0.811; CASI: 81.2 ± 6.7 vs. 96.5 ± 2.2, t = −6.872, p < 0.001). First, MSE was calculated for each BOLD time series based on parameters of m = 1 to 2, r = 0.05 to 0.50 and scale factor = 1 to 5. For scale 5, the data length was 39 points. Student t test was used to assess the differences in sample entropy across scale 1 to 5 in each AAL region between the subjects of low and high cognitive score. The procedure was then repeated for all combinations of parameters. The number of AAL regions with a significant difference (p < 0.05, 2-tailed) in sample entropy between groups was counted and used as an indicator of power for differentiating the 2 groups under certain MSE parameters.

2.4. Statistical analysis

SPSS for Windows Version 15.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. With the appropriate parameters for calculating MSE in BOLD signals being determined, Student t test was used to assess the difference in MSE of BOLD signals between the younger and older groups. For the older group, the correlation between age, education and MSE of BOLD signals was studied using Pearson's correlation, and the relationship between cognitive tests and the MSE in each brain region was studied using Pearson's correlation or partial correlation analysis, controlling for age or education, if these 2 covariates were found to be correlated with MSE measures. We did not test the correlation between cognitive scores and MSE of BOLD activity in the younger group, because of the ceiling effect of cognitive tests in the younger age (Damoiseaux et al., 2008). Skewness was used to evaluate the asymmetry in the distribution of cognitive test scores before conducting partial correlation analysis. Skewed distribution (absolute value of skewness > 1) was transformed using the Box-Cox method to produce normal distribution. In addition, Pearson's correlation was also used to evaluate the relationship between MSE and SD of BOLD signals in each AAL region. For multiple comparison issues, a stricter significance level of p value less than 0.01 (2-tailed) was required for statistical significance in all correlation analyses and comparisons between younger and older groups.

3. Results

3.1. Determining appropriate parameters for MSE calculation in BOLD signals

Fig. 1 shows the number of AAL brain regions with a significant difference in sample entropy between groups of subjects with low and high cognitive score. The comparison was made by calculating MSE using a wide range of parameters. Generally, MSE calculation with pattern length m = 1 yielded higher number of significant AAL regions than that with m = 2. For results obtained with m = 1, the peak number of significant AAL regions occurred at similarity factor r = 0.25 for scale 2, r = 0.3 for scale 3, r = 0.4 for scale 4, and r = 0.45 for scale 5. When comparison was made using averaged sample entropy across all scales, the number of significant AAL regions was relatively high at m = 1 and r = 0.2–0.5 (bottom right panel in Fig. 1). Based on these findings, we therefore chose m = 1 and r = 0.35 as the provisional parameters.

Fig. 2a shows the MSE curve across scale 1 to 5 between groups of subjects with low and high cognitive score in right posterior cingulate gyrus, and Supplementary Table 1 shows the detailed list of significant AAL regions using the chosen parameters in each scale. Predominantly, subjects with low cognitive score had a lower complexity in most identified AAL brain regions (26 out of 33 regions in Supplementary Table 1) than those with high cognitive scores, except for 7 regions in portions of limbic, occipital, and temporal lobes. For practical purposes, we summarized the results by averaging the sample entropy over scale factors 1 to 5, and applied this single MSE measure to subsequent analysis of the correlation between

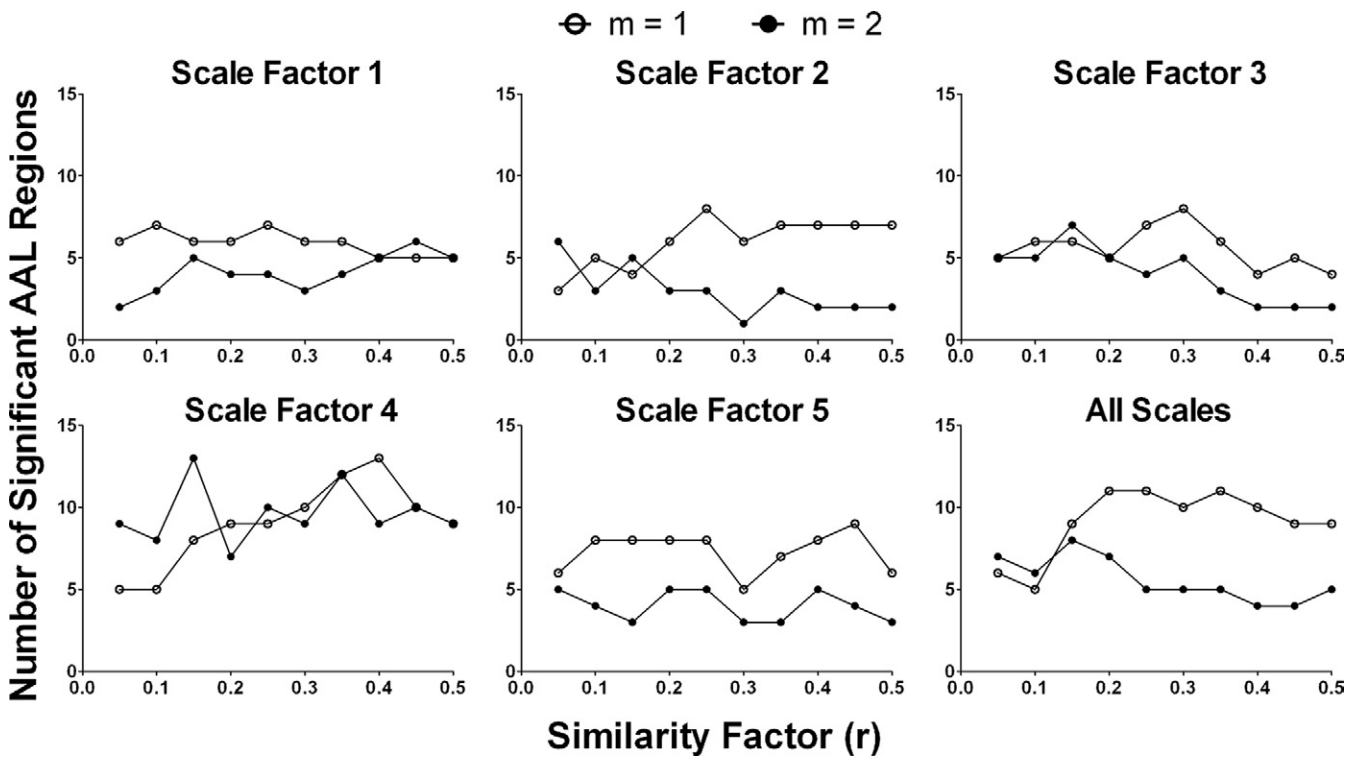

Fig. 1. Number of automated anatomical labeling (AAL) brain regions with significant difference in sample entropy between groups of older subjects with low and high cognitive score ($n = 10$ each). The test was performed for all combinations of parameters of pattern length m = 1 (hollow circle), m = 2 (black circle), similarity factor r = 0.05 to 0.50, and scale factor 1 to 5. For all scales (right lower panel), the sample entropy across scale 1 to 5 was averaged to test the difference between 2 groups. The significance level for the difference of sample entropy between groups was $p < 0.05$ (2-tailed).

BOLD complexity and cognitive functions. The approach of averaging sample entropy over multiple scales has been adopted in prior MSE studies (Cheng et al., 2009; Mizuno et al., 2010; Norris et al., 2009; Yang et al., 2011).

3.2. Comparison of MSE of BOLD signals between the younger and older group

Table 2 shows the comparison of MSE of BOLD signals in 90 AAL regions of the brain between the younger and

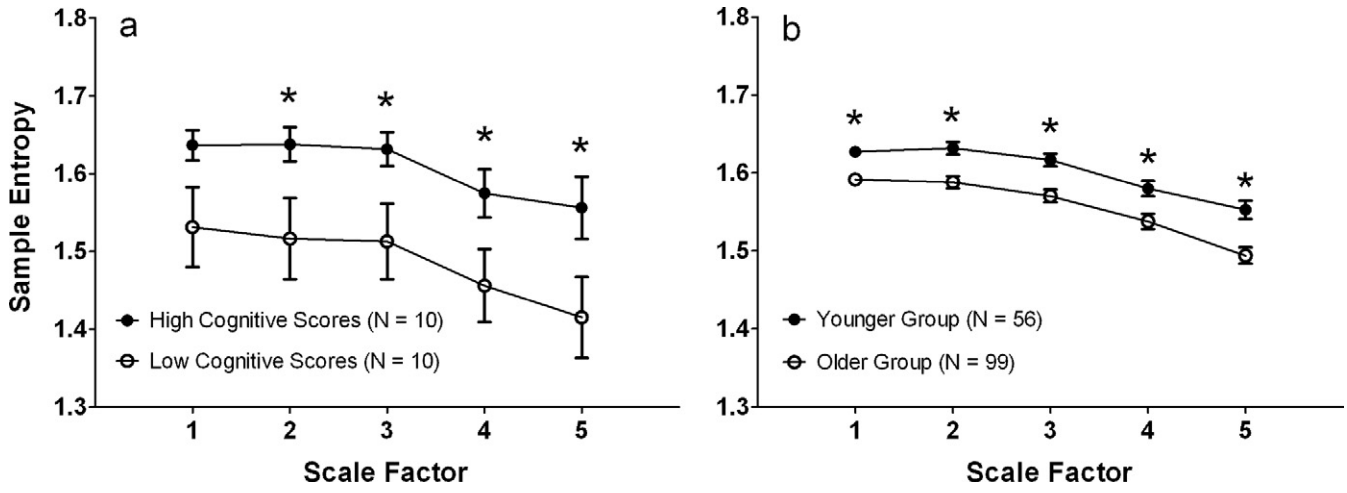

Fig. 2. Multiscale entropy (MSE) curve across scale factor 1 to 5 in right posterior cingulate gyrus for (a) older subjects of low and high cognitive score, and (b) younger and older subjects. Sample entropy was calculated using pattern length m = 1 and similarity factor r = 0.35. The error bar represents the standard error of MSE within the group. * Significant group difference at $p < 0.05$, 2-tailed.

Table 2
Comparison of multiscale entropy of BOLD time series in 90 AAL regions of the brain between the younger and older group

AAL regions[a]	Younger group (n = 56)	Older group (n = 99)	t	p
Frontal lobe				
Olfactory cortex, left	1.586 ± 0.057	1.556 ± 0.058	3.081	0.003
Limbic lobe				
Posterior cingulate gyrus, right	1.602 ± 0.055	1.561 ± 0.065	3.981	<0.001
Hippocampus, right	1.590 ± 0.057	1.558 ± 0.075	2.812	0.006
Parahippocampal gyrus, right	1.600 ± 0.058	1.554 ± 0.078	3.784	<0.001
Occipital lobe				
Superior occipital gyrus, left	1.591 ± 0.064	1.553 ± 0.078	3.134	0.002
Subcortical region				
Caudate, left	1.590 ± 0.052	1.562 ± 0.067	2.686	0.008
Thalamus, left	1.597 ± 0.047	1.571 ± 0.068	2.620	0.010

* Only brain regions with significant statistical test were shown.
Key: AAL, automated anatomical labeling; BOLD, blood oxygen level-dependent.

older group. Compared with the younger group, the older subjects had significantly reduced MSE of BOLD signals in left olfactory cortex ($p = 0.003$), right posterior cingulate gyrus ($p < 0.001$), right hippocampus ($p = 0.006$), right parahippocampal gyrus ($p < 0.001$), left superior occipital gyrus ($p = 0.002$), left caudate ($p = 0.008$), and left thalamus (at trend significance $p = 0.010$). For older subjects, no brain region was found to have significantly increased MSE of BOLD signals than the younger subjects. Fig. 2b shows the MSE curve across scale 1 to 5 between the younger and older group in right posterior cingulate gyrus.

3.3. Correlation of age and education with MSE of BOLD signal

Supplementary Table 2 shows the Pearson's correlation between age, education, and MSE of BOLD signals in the younger and older group. For the younger group, no significant correlation was found between the complexity of BOLD signals and age or education. For the older group, age was negatively correlated with the complexity of BOLD signals at the right pallidum ($r = -0.305$, $p = 0.002$), right angular gyrus ($r = -0.272$, $p = 0.006$), and amygdala ($r = -0.260$, $p = 0.009$). The correlation analysis between

Table 3
Correlations between CASI scores and multiscale entropy of BOLD time series in 90 AAL regions of the brain in the older group

AAL regions	Correlated cognitive domain	r	p
Frontal lobe			
Superior frontal gyrus, left	Short-term memory	0.329	0.001
Superior frontal gyrus, right	Short-term memory	0.258	0.010
Middle frontal gyrus, right	Short-term memory	0.310	0.002
Inferior frontal gyrus, triangular, left	Short-term memory	0.284	0.004
Limbic lobe			
Anterior cingulate gyrus, right	Attention	0.294	0.003
	Orientation	0.296	0.003
Posterior cingulate gyrus, right	CASI—total score	0.293	0.003
	Mental manipulation	0.271	0.007
	Language	0.267	0.007
Hippocampus, left	Attention	0.360	<0.001
Hippocampus, right	CASI—total score	0.276	0.006
	Short-term memory	0.272	0.007
Parahippocampal gyrus, left	Short-term memory	0.366	<0.001
Subcortical region			
Amygdala, left	Abstract thinking	0.278	0.006[a]
Caudate nucleus, left	Short-term memory	0.287	0.004
Putamen, left	List-generating fluency	0.285	0.004
Thalamus, left	Short-term memory	0.285	0.004
Temporal lobe			
Superior temporal pole, left	Long-term memory	−0.281	0.005
Middle temporal gyrus, right	Short-term memory	0.343	0.001
Inferior temporal gyrus, left	Short-term memory	0.297	0.003

Key: AAL, automated anatomical labeling; BOLD, blood oxygen level-dependent; CASI, cognitive abilities screening instrument.
[a] Partial correlation controlled for age; other correlations were computed using Pearson's correlation without controlling for age or education.

Fig. 3. Scatter plots between cognitive scores and multiscale entropy (MSE) of blood oxygen level-dependent (BOLD) signals in the older group: (a) cognitive ability screening instrument (CASI) versus MSE in right posterior cingulate gyrus, (b) short-term memory versus MSE in left parahippocampal gyrus, (c) attention versus MSE in left hippocampus, and (d) orientation versus MSE in right anterior cingulate gyrus, (e) long-term memory versus MSE in left superior temporal pole, (f) abstract thinking versus MSE in left amygdala (controlled for age), (g) mental manipulation versus MSE in right posterior cingulate gyrus, (h) language versus MSE in right posterior cingulate gyrus.

education and MSE did not yield significant results. Therefore, subsequent correlation analyses between MSE and cognitive tests scores were controlled for age only in these 3 regions.

3.4. Correlation of cognitive tests with MSE of BOLD signal in the older group

Table 3 shows the correlation between CASI and subscores and MSE of BOLD time series in 90 AAL regions of the brain. Cognitive scores were positively correlated with MSE in most identified brain regions, except that long-term memory was correlated negatively with MSE in left superior temporal pole ($r = -0.281$, $p = 0.005$). MSE values from DMN areas in limbic lobe, including anterior cingulate gyrus, posterior cingulate gyrus, hippocampus, and parahippocampal gyrus, were found to have the largest number of correlations with various cognitive domains. For example, MSE in right anterior cingulate gyrus was positively correlated with attention and orientation ($r = 0.294$, $p = 0.003$; $r = 0.296$, $p = 0.003$, respectively). MSE in right posterior cingulate gyrus was positively correlated with total CASI score ($r = 0.293$, $p = 0.003$), mental manipulation ($r = 0.271$, $p = 0.007$), and language ($r = 0.267$, $p = 0.007$). MSE in left hippocampus was positively correlated with attention ($r = 0.360$, $p < 0.001$), and right hippocampus was positively correlated with CASI ($r = 0.276$, $p = 0.006$) and short-term memory ($r = 0.272$, $p = 0.007$). MSE in left parahippocampal gyrus was positively correlated with short-term memory ($r = 0.366$, $p < 0.001$). Other subcortical brain regions were correlated differently with various cognitive domains. MSE in amygdala was positively correlated with abstract thinking ($r = 0.278$, $p = 0.006$, controlled for age). MSE in putamen was positively correlated with list-generating fluency ($r = 0.285$, $p = 0.004$).

MSE in Digit Forward task was positively correlated with posterior cingulate gyrus at trend significance ($r = 0.214$, $p = 0.034$), and Digit Backward task and drawing component of CASI were not correlated with MSE in any brain region. Fig. 3 shows the scatter plots between major cognitive domains and MSE of BOLD signals in the most significantly correlated brain regions.

3.5. Correlation between MSE and standard deviation of BOLD signal

Supplementary Table 3 shows the Pearson's correlation between MSE and SD of BOLD signals. MSE was correlated negatively to SD of BOLD signals. For the younger group, significant correlation was found only in 1 AAL brain region (superior occipital lobe: $r = -0.371$, $p = 0.005$). For the older group, significant correlations (r approximatey $= -0.25$ to -0.4) were found in 18 out of 90 AAL brain regions, with the highest number of correlated areas in frontal lobe ($n = 12$), followed by

limbic lobe ($n = 3$), temporal lobe ($n = 2$), and occipital lobe ($n = 1$).

Supplementary Table 4 shows the comparison of SD of BOLD signals between the younger and older group. To simplify the presentation and to compare with MSE findings, only brain regions identified in Table 2 were shown. SD of MSE did not differ between younger and older groups in posterior cingulate gyrus ($p = 0.568$) and hippocampus (0.437), and only had trend significance of difference in parahippocampal gyrus ($p = 0.023$). Notably, older subjects had significantly higher SD than younger subjects in the most frontal, parietal, temporal, and occipital brain regions ($p < 0.01$, data not shown).

4. Discussion

There is a high degree of heterogeneity in the cognitive changes that occur with aging (Wilson et al., 2002). Delineating the correlations between cognitive function and structural and functional properties in brain imaging can reveal important insights into the neurobiology of aging. A great deal of previous work has been conducted on the correlation between the structure of the brain and cognitive performance among healthy elderly subjects (Kaup et al., 2011). Most structural studies have found a positive relationship between cognitive performance and the size of various regions of the brain (Craik and Salthouse, 2008; Dickerson et al., 2004; Raz et al., 1998). However, the brain size/cognitive performance model may be over simplified and unable to capture the dynamics of brain activity. Thus, the analysis of temporal dynamics in spontaneous brain activity could complement structural studies on cognitive aging.

We employed MSE analysis to quantify the complexity of BOLD activity at rest, discovering that the complexity of spontaneous BOLD signals is reduced with aging, and the complexity of BOLD signals in major DMN brain areas, such as hippocampus, cingulate cortex, superior and middle frontal gyrus, and middle temporal gyrus, is significantly correlated with various cognitive domains in normal elderly subjects. Our results support the hypothesis that a decrease in the complexity of spontaneous brain activity is correlated with aging, and most importantly, such reduced complexity of spontaneous brain activity in the elderly is correlated with diminished cognitive performance. To our knowledge, this is the first study to investigate the complexity in spontaneous BOLD signal activity in the aging cohort and its cognitive correlates for the elderly.

4.1. Implications of BOLD complexity in cognitive decline

Our results of correlation between complexity of BOLD activity and cognitive function scores suggest that spontaneous brain activities may play important roles in age-associated cognitive decline. For example, short-term memory is one of the most important cognitive functions involved in aging (Caird, 1966) and was found to have the highest number of correlations with MSE in various brain regions, not only in hippocampus and parahippocampal gyrus, but also in frontal lobes, caudate nucleus, thalamus, as well as middle and inferior temporal gyrus.

Most regions of the brain identified in the present study, such as superior and middle frontal cortex, hippocampus, cingulate cortex, and inferior and middle temporal cortex, are within DMN, which is characterized by the coactivation of certain cortical regions in a distributed network during the resting state of the brain (Raichle and Snyder, 2007). However, the role of DMN activity in cognitive function decline is not fully understood (Mevel et al., 2011). Although BOLD activity in the DMN has been shown to be attenuated during a cognitively demanding task (Raichle and Snyder, 2007), previous task-based studies suggested that DMN activity is closely related to the important cognitive functions (Mevel et al., 2011). For example, activity in posterior cingulate cortex is reported during tasks that implicate the autobiographical episodic memory and self-referential processes (Buckner and Carroll, 2007; Ries et al., 2006; Schneider et al., 2008), the medial frontal cortex is associated with social cognitive processes (Amodio and Frith, 2006), and the medial temporal lobe is mainly involved in episodic memory (Milner, 2005; Viard et al., 2007).

Other brain areas in subcortical regions, such as amygdala and putamen, were found to be correlated with abstract thinking and list-generating fluency, respectively. Subcortical nuclei are essential for cognitive function (Alexander et al., 1986; Middleton and Strick, 2000) and are widely connected to cortical areas (Bressler and Kelso, 2001). In the context of disconnection hypothesis (Friston, 1996), cognitive decline correlated with the reduction of complexity in subcortical regions may implicate reduced information transfer between cortical and subcortical regions, either in the form of reduced functional connectivity or impaired anatomical connectivity (Schmahmann and Pandya, 2008), and may warrant future investigation with combining the use of structural and fMRI techniques, such as diffusion tensor imaging.

4.2. Implications of BOLD complexity in the aging

This study found that MSE of BOLD activity in the older subjects was reduced in the olfactory cortex, posterior cingulate cortex, hippocampal cortex, superior occipital gyrus, caudate, and thalamus, when compared with younger subjects. The most significant reduction in MSE of BOLD activity in the older group was found in posterior cingulate gyrus (Table 2), which is consistent with the findings of the correlation between cognitive scores and MSE of BOLD activity in the older group. Prior studies of functional connectivity in normal aging found that older subjects exhibited significantly lower magnitude of DMN coactivation in the posterior cingulate cortex (Damoiseaux et al., 2008; Koch et al., 2010), and observed reduced network efficiency in older people in frontal, temporal, limbic, and subcortical brain regions (Achard and Bullmore, 2007). The association between altered functional connectivity and

reduced complexity of BOLD activity is not trivial. However, our findings may be in line with previous connectivity-based studies, and we hypothesize that the aging process may be correlated to with reduced network complexity and integration (Fox et al., 2006; Friston, 1996; Garrett et al., 2010; Nir et al., 2008).

4.3. Methodological concerns

Analysis of the complexity related to neurophysiologic signals has generated considerable interests in recent years. Alteration in MSE complexity in surface EEG has been found to be correlated with a cognitive decline in aging (Takahashi et al., 2009), Alzheimer's disease (Escudero et al., 2006; Mizuno et al., 2010), schizophrenia (Takahashi et al., 2010), and autism (Catarino et al., 2011). Our analysis of complexity was based on resting state BOLD activity, providing direct evidence of dynamic changes in intrinsic brain activity. Intriguingly, the MSE curve profile (Fig. 2) in this study shows a decreased MSE with increased scale factors and does not match the typical MSE curves seen in other studies (Catarino et al., 2011; Costa et al., 2005; Takahashi et al., 2010). For example, MSE curve profile for EEG signals has been shown to increase with small-scale factors and decrease with large scale factors (Takahashi et al., 2010). The different profile of MSE curve in the current study may be due to the limitation of fMRI technique in that the sampling rate of BOLD signals is usually low (i.e., 0.4 Hz in this study). Such low sampling rates could resemble the results for large-scale factors in EEG signals seen in prior MSE studies, thus exhibiting decreased MSE with increased scale factors in the BOLD signals.

It is noteworthy that complexity measure is not equivalent to variability measure (Goldberger et al., 2002b), such as SD, and we found a relatively low number of AAL brain regions that had significant correlations between SD and MSE of BOLD signals (Supplementary Table 3). Importantly, we found that SD was negatively correlated with MSE of BOLD signals (Supplementary Table 3), and was increased in older subjects, compared with the younger people (Supplementary Table 4). These results are inconsistent with previous findings of decreased SD of BOLD signals with age (Garrett et al., 2010) and was correlated with reduced task performance (Garrett et al., 2011). Despite the difficulty of translating variability to the complexity (Goldberger et al., 2002b), the discrepancy may be because of the different paradigms used, in that our study used resting state BOLD signals for its analysis, whereas Garrett et al. (2010, 2011) examined task-based BOLD signals. The relationship between MSE and SD may be further explored in future studies. Nevertheless, the complexity measure based on MSE analysis may reveal nonlinear aspects of brain activity that are complementary to conventional variability statistics.

4.4. Limitations

Several limitations should be considered in interpreting these data. First, the length of the BOLD time series comprised only 195 data points; therefore, the estimation of MSE may be biased at large-scale factors. This issue has been demonstrated in a prior study in which sample entropy calculation was deviated from the theory as much as 35% for data of 15 points (Richman and Moorman, 2000). However, such limitation may be compensated by the use of small pattern length ($m = 1$) and relatively large similarity factor ($r = 0.35$) (Richman and Moorman, 2000) to accommodate the short and noisy BOLD data. Second, presence of brain atrophy in the elderly may confound the BOLD complexity calculation, particularly in the frontal regions (Price et al., 2006). Third, we used a relatively low sampling rate (TR = 2.5 seconds) for multislice acquisitions. Although a low pass filter was applied in this study, we cannot entirely exclude the influence from respiration and cardiovascular hemodynamics at this sampling rate (Lowe et al., 1998). Fourth, this study examined only male subjects, and the findings may not be extended to females. Certain ceiling effects of cognitive function might exist even in normal older people, such as orientation, long-term memory, and language (Fig. 3), and the correlation between MSE of BOLD activity and these cognitive domains may be biased. In addition, the cross-sectional nature of the study may limit the predictive power in identifying regions of the brain related to long-term changes in cognitive performance. A prospective follow-up of cognitive function may prove valuable.

4.5. Conclusions

The physiologic nature of complexity in spontaneous BOLD signals, although elusive, may be linked to the metabolic aspect of neuronal activity. Most regions of the brain identified in this study present a positive correlation between the complexity of BOLD signals and cognitive performance. Furthermore, these identified brain regions, such as hippocampus and cingulate cortex, are found to have a high degree of functional connectivity not only within DMN but also global brain regions (Buckner et al., 2005; Cole et al., 2010; Sheline et al., 2010). From a systemic point of view, a higher degree of complexity in the output of a system requires more intercomponent connections to maintain dynamic processes at various time scales (Lipsitz and Goldberger, 1992; Peng et al., 2009; Vaillancourt and Newell, 2002). In future studies, complexity analysis of spontaneous brain activity in relation to functional connectivity may provide insights on how dynamics of spontaneous brain activity relates to aging and cognitive function in specific brain regions.

Disclosure statement

The authors have no conflicts of interest.

The study was conducted in accordance with the Decla-

ration of Helsinki, with approval from the local Institutional Review Board. Informed consent was obtained from all subjects before commencement of the study.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.05.004.

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