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Enhanced Brain Signal Variability in Children with Autism Spectrum Disorder During Early Childhood

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Abstract: Extensive evidence shows that a core neurobiological mechanism of autism spectrum disorder (ASD) involves aberrant neural connectivity. Recent advances in the investigation of brain signal variability have yielded important information about neural network mechanisms. That information has been applied fruitfully to the assessment of aging and mental disorders. Multiscale entropy (MSE) analysis can characterize the complexity inherent in brain signal dynamics over multiple temporal scales in the dynamics of neural networks. For this investigation, we sought to characterize the magnetoencephalography (MEG) signal variability during free watching of videos without sound using MSE in 43 children with ASD and 72 typically developing controls (TD), emphasizing early childhood to older childhood: a critical period of neural network maturation. Results revealed an age-related increase of brain signal variability in a specific timescale in TD children, whereas atypical age-related alteration was observed in the ASD group. Additionally, enhanced brain signal variability was observed in children with ASD, and was confirmed particularly for younger children. In the ASD group, symptom severity was associated region-specifically and timescale-specifically with reduced brain signal variability. These results agree well with a recently reported theory of increased brain signal variability during development and aberrant neural connectivity in ASD, especially during early childhood. Results of this study suggest that MSE analytic method might serve as a useful approach for characterizing neurophysiological mechanisms of typical-developing and its alterations in ASD through the detection of MEG signal variability at multiple timescales. *Hum Brain Mapp 37:1038–1050, 2016.* © 2015 The Authors Human Brain Mapping Published by Wiley Periodicals, Inc.

Key words: autism spectrum disorder; magnetoencephalography; signal variability; multiscale entropy; typical-development; early childhood

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INTRODUCTION

Dynamical brain signal variability is not simply attributable to noise, which rather emerges as a key component of neural systems at multiple hierarchical levels [Faisal et al., 2008; McDonnell and Ward, 2011]. Recent advances in nonlinear complexity analysis over a range of temporal scales have encouraged the investigation of brain signal variability. Those advances have provided important information related to neural network mechanisms [Ghanbari et al., 2013; Misic et al., 2011; Vakorin et al., 2011]. The theory of aberrant neural connectivity lies at the heart of many mental disorders. Therefore, numerous complexity analysis methods have been developed and applied fruitfully to the assessment of aging and mental disorders [reviewed by Stam, 2005; Takahashi, 2013].

Among complexity analyses, multiscale entropy (MSE) is a proposed entropy-based index of physiological complexity. It uses temporal coarse-graining procedures evaluate signals at multiple temporal scales, in recognition of the likelihood that the dynamical complexity of biological signals might operate across a range of temporal scales [Costa et al., 2002, 2005]. Brain activity, a dynamic process with various interactions among widely diverse brain regions over time [reviewed by Sporns et al., 2000; Tononi et al., 1998] and across multiple timescales [Gans et al., 2009], is universally characterized as a scale-free network organization [Barabasi 2009; Ravasz and Barabasi, 2003]. Evaluating a particular pattern of complexity values across the varying timescales facilitates the detection of intrinsic brain signal variability from a purely random system. In that sense, neurophysiologic signals such as magnetoencephalography (MEG) and electroencephalography (EEG) have high temporal resolution. They are therefore rather suitable for identifying brain signal variability across large timescales. As a consequence, application of MSE to M/EEG signals in characterizing the brain signal complexity is expected to add another dimension to already identified neural dynamics of mental disorders [reviewed by Takahashi, 2013].

Autism spectrum disorder (ASD), a heterogeneous neurodevelopmental disorder, is clinically defined by a triad of deficits: impaired social interaction, impaired communication, restricted interests, and repetitive behaviors [APA, 2013]. Appearing during the first 3 years of life, it is a strongly genetically influenced psychiatric disorder of young people [Rutter, 2000]. Recent theoretical and empirical work has indicated that a core neurobiological mechanism that is putatively linked to ASD symptoms involves aberrant neural connectivity [reviewed by Courchesne and Pierce, 2005; Schipul et al., 2011; Wass, 2011], widely taken as "hypo-connectivity" [Belmonte et al., 2004; Minshew and Williams, 2007]. This hypo-connectivity theory has been challenged by recent results of studies suggesting "hyper-connectivity" in ASD individuals [Keown et al., 2013; Kitzbichler et al., 2015; Lynch et al., 2013; Supekar et al., 2013; Uddin et al., 2013a]. Uddin et al. [2013b] introduced the reasonable hypothesis that abnormal ASD developmental patterns shift from intrinsic hyper-connectivity to hypo-connectivity during the pubertal period.

A handful of recent reports have described exploration of abnormal brain signal variability in ASD. Lower EEG complexity was reported in infants with high risk of ASD [Bosl et al., 2011] and in adult subjects with ASD [Catarino et al., 2011]. Contrary to these findings, both lower-complexity and higher-complexity alterations were observed in a region-dependent and timescale-dependent manner under a resting state [Ghanbari et al., 2013], during cognitive tasks [Misic et al., 2014], and during treatment [Okazaki et al., 2015]. Several ideas might be proposed as attempts to reconcile this discrepancy. First, typical development and normal aging must be considered [McIntosh et al., 2008] because emerging evidence has indicated significant shifts in brain signal complexity with aging [reviewed in Garrett et al., 2013]. During life-span development through infancy and childhood, rapid and sweeping transformations in the neural network architecture are observed, such as synaptic pruning, myelination, and structural network changes [Dean et al., 2014b; Huang et al., 2015; Innocenti and Price, 2005; Schuldiner and Yaron, 2015]. These alterations are thought to increase brain signal variability during typical development [Anokhin et al., 2000; Lippe et al., 2009; Vakorin et al., 2011]. Although previous studies examine various age groups ranging from infancy [Bosl et al., 2011] and childhood [Ghanbari et al., 2013; Misic et al., 2014] to adulthood [Catarino et al., 2011], no report in the relevant literature has addressed early-to-late childhood phenomena: a critical period in neural network development [Dean et al., 2014a,b] and a time of frequent emergence of ASD symptoms. Another idea is that the degree of cognitive function in this disorder influences neural connectivity, which might engender alteration of the brain signal variability. A recent study [Kikuchi et al., 2013b] demonstrated that preserved ability in visual reasoning tasks is associated with rightward lateralization of neurophysiological connectivity between the parietal and temporal regions in children with ASD. In fact, an optimal level of signal variability is reportedly necessary to facilitate learning and adaptation to the changing demands of a dynamic environment [Faisal et al., 2008]. For instance, brain signal variability reportedly increases with age while presenting important implications for functional benefits of cognitive processing [McIntosh et al., 2008; Misic et al., 2010], whereas in some brain regions, an increase in signal variability has been associated with cognitive decline [Garrett et al., 2011; Samanez-Larkin et al., 2010] as well as dementia [Mizuno et al., 2010] in older adults. Consequently, studies particularly addressing early childhood with intellectual assessment are expected to offer crucially important information for the exploration of aberrant neural connectivity in ASD.

For this investigation, we sought to characterize the brain signal variability of ASD in view of typical age-

TABLE I. Physical and cognitive characteristics of children

	ASD children ($n = 43$)	TD children ($n = 72$)	P value
Female/male	9/34	21/51	0.39
Age (months)	68.6 (40–92, 10.2)	66.0 (40–110, 16.8)	0.30
Head circumference (cm)	51.1 (47.0–54.5, 1.57)	51.2 (48.0–54.8, 1.39)	0.87
Mental processing composite score	99.4 (60–134, 17.3)	100.7 (63–128, 13.3)	0.66
ADOS score			
Communication score	3.26 (0–8, 1.9)	NA	
Social interaction score	6.70 (2–14, 2.7)	NA	
Total score	9.95 (2–17, 4.5)	NA	

Values represent mean (range, SD).
ADOS, autism diagnostic observational schedule.

related alterations, and strove to ascertain the possible effects of intelligence and disease severity of ASD. To these ends, we developed a custom-made MEG device for young children and recruited typically-developing (TD) children and children with ASD aged 3–9 years, a unique period during which substantial neural connectivity development is expected. The brain signal variability was characterized using MSE analysis during free watching of videos, with intellectual function assessed using the Kaufman Assessment Battery for Children (K-ABC) [Kaufman and Kaufman, 1983].

MATERIALS AND METHODS

Participants

Some information related to this population has been reported previously in the literature [Kikuchi et al., 2013a,b, 2015]. From the Kanazawa University Hospital and prefectural hospitals in Toyama, 43 children diagnosed with ASD with mean age of 68.6 months (40–92, SD: 10.2) and 72 TD age-matched, sex-matched, and intelligence-matched children with mean age of 66.0 months (40–110, SD: 16.8) were recruited (Table I). The clinical group was diagnosed using the Autism Diagnostic Observational Schedule, Generic (ADOS) [Lord et al., 1999], and the Diagnostic Interview for Social and Communication Disorders (DISCO) [Wing et al., 2002] at the time of MEG and K-ABC data acquisition. All children with ASD included in this study fulfilled the diagnosis of childhood autism ($n = 28$), atypical autism ($n = 8$), or Asperger's syndrome ($n = 7$) with DISCO. Actually, ASD children with scores below the ADOS cut-offs were included in the study if they satisfied the criteria for ASD using DISCO. In this study, most ASD children had "high-functioning autism" because we recruited participants who were cooperative and who clearly assented to participation in our experiment. Therefore, eventually, the ASD children with low intellectual ability were few. Additionally, we did not have data from children with mental retardation to control the intellectual ability between the groups. Therefore, ASD children with the mental processing composite (MPC) score of <60 were excluded from this study. All parents agreed to allow their children to participate in the study with full knowledge of the experimental characteristics of the research. Written informed consent was obtained from all parents before the start of the experiment. All protocols of the study conform to Declaration of Helsinki guidelines. All were approved by the Ethics Committee of Kanazawa and Toyama University Hospital.

Assessment of Cognitive Function

Children's cognitive function was assessed by a trained assistant psychologist (Y.Y.) using the Japanese version of the K-ABC, which was designed to evaluate intelligence and achievement of children: 2.5–12.5 years of age. The test, comprising 16 subsets, is summarized into two scales: the MPC, a global measure of the child's cognitive ability in the two dimensions of sequential and simultaneous processing, and the achievement scale. The MPC is regarded as equivalent to an intelligence quotient. We therefore used the MPC as an assessment of child's cognitive function. Each raw score is standardized to a mean of 100 (SD 15). The respective means of the MPC scores of children with ASD and TD were 99.4 (60–134, SD: 17.3) and 100.7 (63–128, SD: 13.3). The groups did not differ in terms of the score (Table I).

MEG Recordings

On a separate day from that of K-ABC measurement, MEG data were recorded using a multichannel superconducting quantum interference device (SQUID) custom-made 151-channel whole-head coaxial gradiometer MEG for children (PQ 1151R; KIT/Yokogawa Electric Corp. Kanazawa, Japan) in a magnetically shielded room (Daido Steel Co. Ltd., Nagoya, Japan). Figure 1 shows the stereographic projection of the MEG sensors onto a planar image. Before recording, three coils were attached at the bilateral mastoid processes and nasion as fiduciary points

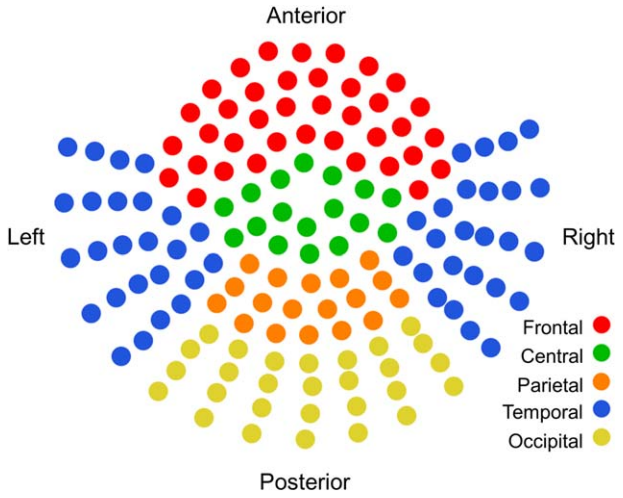

Figure 1.
Stereographic projection of MEG sensors onto a color-coded planar image showing dots corresponding to different brain regions.

to localize the child's head relative to the MEG sensor array. The MEG data were acquired with a sampling rate of 1000 Hz and were filtered with a 200 Hz low-pass filter. During MEG recording, the child lay supine comfortably on a bed with the head inside the MEG system helmet. All children viewed a video program projected onto a screen throughout the recording session to promote a consistent state of alertness and concentration. The sound of the narration was carried binaurally through a tube placed in front of the child. Before recording, children selected a video program according to their preference from a number of video programs that were expected to be attractive for young children. We asked children whether they were content to view the video program. As a practical matter, most of the children selected popular Japanese animations except for two ASD children who selected a video program of a running train. During MEG recording, narration was stopped. One staff member (author Y.Y.) remained in the shielded room to confirm that each child was concentrating on the video program and to encourage participants to maintain a steady body position when necessary.

Offline analysis of the MEG data was performed using a BrainVision Analyzer 2 (Brain Products GmbH, Gilching, Germany) and Matlab (the MathWorks Inc., Natick, MA). The MEG data were resampled at 500 Hz with 1.5–60 Hz bandpass and 60 Hz notch filters. Data were segmented for 5 s (2,500 data points: 5 s × 500 Hz). Artifacts such as eye movements, blinks, muscle activities, and other artifacts were visually identified and were excluded from analyses. The process of eliminating contaminated data was done by an MEG expert who was blinded to the identity of the subjects. A minimum 20 s recording period (i.e., four segments) was accepted for each subject. Finally, the average numbers of segments available per subject were, respectively, 10.7 (4–16, SD: 3.7) for ASD and 11.1 (4–19, SD: 2.7) for TD. For each subject, MSE was calculated on all selected segments separately and was then averaged into a single value as mean MSE.

MSE Analysis

The MSE method uses a coarse-graining procedure to quantify the degree of signal variability in a time series over multiple timescales [Costa et al., 2002, 2005]. Irregularity at each scale was calculated using sample entropy (SampEn), which is well suited to analyzing short and noisy experimental data [Richman et al., 2004; Richman and Moorman, 2000]. For extension to multiple timescales, the original MEG time series $\{x_1, x_2, \ldots, x_N\}$ was coarse-grained using the scale factor (SF) τ, with nonoverlapping windows as shown below.

$$y_j^{(\tau)} = (1/\tau) \sum_{i=(j-1)\tau+1}^{j\tau} xi, \qquad 1 \le j \le N/\tau \tag{1}$$

Then, SampEn was calculated for each series$\{y^{(1)}\}$: SampEn is the negative of the logarithmic conditional probability that two sequences of m consecutive data points which are mutually similar (within given tolerance r) will remain similar at the next point $(m+1)$ in the dataset (N), where N is the time series length. Considering the EEG time series $\{x_1, x_2, \ldots, x_N\}$ as observations of a stochastic variable x, dynamic SampEn is defined as

$$h_{samp}(r, m, N) = -\log_e[C_{m+1}(r)/C_m(r)], \tag{2}$$

where $C_m(r) = \{$number of pairs (i, j) with $|z_i^m - z_j^m| < r$, $i \neq j\}/\{$number of all probable pairs, i.e., $(N - m + 1)(N - m)\}$. Therein, $z = y^{(\tau)}$, and z^m is a vector of m sample time series of $(N - m)$ length, and $|z_i^m - z_j^m|$ denotes the distance between points z_i^m and z_j^m in the space of dimension m, and r is the effective filter for measuring consistency of time series. Various theoretical and clinical applications have demonstrated that $m = 1$ or 2, and $r = 0.1$–0.25 of the standard deviation of the data points provides good statistical validity for SampEn [Lake et al., 2002; Richman et al., 2004]. For these analyses, we used $m = 2$ and $r = 0.2$, which are values that were applied in our previous study [Mizuno et al., 2010; Okazaki et al., 2013, 2015; Takahashi et al., 2009, 2010; Ueno et al., 2015]. For the coarse-grained time series at SF $\tau = 1$, the time series $\{y^{(1)}\}$ was simply identical to the original time series. The SampEn values for low SFs captured short-range temporal irregularity, whereas higher SFs captured long-range temporal irregularity. The MSE calculation was conducted with self-produced software developed using a commercially available software package (Mathematica 8; Wolfram Research, Inc.).

TABLE II. ANCOVA results for MSE analysis between groups (TD vs ASD) for each brain region

	All children 72 TD (21 F, mean age: 66.0 mo (range 40–110, SD 16.8)) vs 43 ASD (9 F, mean age: 68.6 mo (range 40–92, SD 10.2))		Younger children 46 TD (17 F, mean age: 55.2 mo (range 40–70, SD 7.3)) vs 21 ASD (6 F, mean age: 61.1 mo (range 40–70, SD 8.8))		Older children 26 TD (4 F, mean age: 85.1 mo (range 70–110, SD 10.3)) vs 22 ASD (3 F, mean age: 75.9 mo (range, 70–92, SD 5.0))	
	Group effect (F, P, *partial* η^2)	Group × scale factor (F, P, *partial* η^2)	Group effect (F, P, *partial* η^2)	Group × scale factor (F, P, *partial* η^2)	Group effect (F, P, *partial* η^2)	Group × scale factor (F, P, *partial* η^2)
Frontal	2.2, 0.10, 0.025	**5.2, 0.008, 0.045**	6.3, 0.014, 0.093	5.1, 0.010, 0.076	0.07, 0.80, 0.002	0.61, 0.53, 0.014
Central	5.9, 0.017, 0.051	**6.1, 0.004, 0.052**	6.6, 0.013, 0.096	**6.5, 0.0037, 0.094**	0.22, 0.64, 0.005	0.42, 0.64, 0.01
Parietal	**11.2, 0.001, 0.092**	3.6, 0.019, 0.032	**9.4, 0.0032, 0.13**	**5.6, 0.0024, 0.085**	3.5, 0.068, 0.077	0.83, 0.44, 0.019
Temporal	**7.3, 0.008, 0.062**	**7.6, 0.0016, 0.064**	5.7, 0.018, 0.086	**6.0, 0.0069, 0.089**	0.38, 0.057, 0.083	0.90, 0.41, 0.021
Occipital	6.6, 0.012, 0.055	3.5, 0.040, 0.031	4.8, 0.032, 0.072	3.7, 0.032, 0.057	2.1, 0.16, 0.047	1.2, 0.30, 0.027

Scale factor: 1–20. For clarity, $P < 0.01$ are shown in bold.
Abbreviations: ANCOVA, analysis of covariance; ASD, autism spectrum disorder; do, days old; F, females; MSE, multiscale entropy; TD, typical development.

Statistical Analysis

Almost all the SampEn values at each SF for each group were distributed normally (tested using a Shapiro–Wilk test). A repeated measures analysis of covariance (ANCOVA), with group (ASD vs TD) and sex (male vs female) as between-subject factors, SF (τ: 20 scales) as within-subject factors, and age as a covariate was conducted to test for group differences. For significant main effects for group and group-by-SF interactions, independent t tests were used to compare group differences separately for each SF. The Greenhouse–Geisser adjustment was applied to the degrees of freedom for all analyses. Spearman's rank–order correlations were used to evaluate potential associations between MSE values and patient physical and clinical data. We applied the Benjamini–Hochberg false discovery rate (FDR) for group comparisons and correlations for correlation analyses to control multiple comparisons. For *post-hoc* t tests of ANCOVA, 20 SFs and five brain subregions (i.e., 100 p values) were controlled with $q < 0.01$. For sensor-wise group comparisons of MSE values, 151 sensors and 20 SFs (3020 p values) were controlled for each comparison (all children, younger children, and older children) with $q < 0.01$. Similarly, sensor-wise correlations of age and MSE values, 151 sensors and 20 SFs (3020 p values) were controlled respectively for TD group and ASD group with $q < 0.01$. For sensor-wise correlations with ASD symptoms (communication score and social interaction score) and MSE values in the ASD group, 151 sensors (151 p values) for each SF were controlled with $q < 0.05$ because of the weaker statistical power.

RESULTS

MSE Value TD vs ASD

The head size changes considerably during the developmental period in this study. We found significant correlation of the age and head circumference in both the TD group (rho = 0.36, $p = 0.002$) and the ASD group (rho = 0.35, $p = 0.021$). This correlation must affect the distance to the sensors and might act on the MEG signal, especially when working in sensor space analysis. No significant difference of head circumference was found between the TD group and the ASD group (Table I). Furthermore, no significant correlation was found between the MSE value and the head circumference (data not shown), which might indirectly reveal the irrelevance of head-size to MSE result in this study.

For ANCOVA calculations, sensors were divided into five subregions as frontal, central, parietal, temporal, and occipital regions (Fig. 1). No significant interaction or main effect for sex was observed in either brain region. Therefore, we excluded sex for *post hoc* ANCOVA. Table II presents the summary of the ANCOVA on MSE results for group differences. Significant group-by-SF interactions

were observed in frontal, central, and temporal regions (higher MSE values in the ASD group at higher SFs). Significant main effects for group were observed in the parietal and occipital regions (higher MSE values in the ASD group). *Post hoc* analysis identified significant increase at coarse scales in the ASD group, except for the frontal region (Fig. 2A). To clarify the possible group differences across sensors, a sensor-wise group comparison of MSE values is portrayed in the array plot (Fig. 2B) and topography (Fig. 2C). Results revealed similar finding across widespread brain regions. Results showed a significant effect of age on the MSE values. Therefore, we further divided both groups into two age bins as younger and older children. The ASD group had fewer subjects. Therefore, we divided the ASD group with 70 months old as younger (21 ASD children) and older (22 ASD children) subgroups. We similarly divided the TD group with 70 months old as younger (46 TD children) and older (26 TD children) subgroups. As a result of ANCOVA, no significant interaction or main effect for sex was observed in either brain region. Therefore, we excluded sex for *post hoc* ANCOVA. Regarding younger children, significant group-by-SF interactions in central, parietal, and temporal regions (higher MSE values in the ASD group at higher SFs), and the main effect for group in parietal region (higher MSE values in the ASD group) was observed. Older children showed no group-by-SF interaction or main effect for group (Table II). Sensor-wise MSE group differences for all children, younger children, and older children are presented in Figure 2B. Higher MSE values were observed in ASD, notably in younger children, but not for older children. The higher MSE values in the ASD group were observed predominantly across temporo–parieto–occipital regions (Fig. 2C).

Correlations of MSE Values with Demographic/Clinical Variables

In the TD group, MSE values increased significantly with age in widespread brain regions at SFs around 10, although weak association was observed in the ASD group at finer scales in the central region (Fig. 3A–C). Closer inspection of the TD group revealed strong correlation particularly in the parieto–temporo–occipital regions at around SF 10, but not in the fronto–central region (Fig. 3A,B, left panel). In the ASD group, correlation was found only in the central region at finer timescales (Fig. 3A,B, right panel and Fig. 3C, left middle panel). The MPC score did not correlate with the MSE value in either the TD or the ASD group (data not presented). Regarding possible associations between MSE value and disease severity evaluated by ADOS score, slight negative correlation was found between the communication score and MSE values predominantly in the fronto-central regions at larger SFs (Fig. 4A), whereas the social interaction score was not correlated to signal variability (Fig. 4B). These correlations were unchanged even after adjustment for age (data not shown). Furthermore, because a negative correlation was found between the MPC score and communication score ($\text{rho} = -0.34$, $p = 0.028$), we additionally examined the association of the communication score and MSE values adjusting with the MPC score. Even after adjusting with the MPC sore, the negative correlation of MSE value and communication score were unchanged (data not shown). These brain regions (fronto-central region), showing negative correlation, were not overlapping with the region that showed a significant increase of the MSE value in the ASD group (Fig. 4C).

DISCUSSION

For this study, we used MSE analysis to evaluate MEG signal variability in children with ASD and TD children through early childhood to later childhood, which is a critical period of network maturation and which is a period involving the frequent emergence of ASD symptoms. Actually, MSE quantifies the degree of signal irregularity over a range of timescales. Therefore, results revealed age-related increase of brain signal variability in a specific timescale in TD group. This finding agrees well with a recent "increasing the brain signal variability" theory of typical development [Lippe et al., 2009; McIntosh et al., 2008, 2014; Misic et al., 2010; Vakorin et al., 2011]. By contrast, in the ASD group, atypical age-related signal variability alteration was observed. Additionally, enhanced brain signal variability was observed in children with ASD, which was confirmed for younger children, perhaps reflecting an "aberrant neural connectivity" theory in ASD, which reportedly shifts from intrinsic hyper-connectivity to hypo-connectivity across the pubertal period [Uddin et al., 2013b]. Although intellectual function did not affect results in either TD children or children with ASD, the symptom severity, a communication score, was associated region-specifically and timescale-specifically with reduced brain signal variability.

Age-related signal variability alteration is widely studied. It is generally characterized as an inverted u-shaped curve [reviewed in Garrett et al., 2013]. Up to young adulthood, brain signals reportedly increase with age. For example, Meyer-Lindenberg [1996] studied resting-state EEG complexity using the correlation dimension and the Lyapunov coefficient during normal development (54 TD children and 12 adults). The correlation dimension was shown to increase with age. One earlier study of the literature examined EEG dimensional complexity in across 7–17 years TD subjects at rest and during the performance of verbal and spatial cognitive tasks [Anokhin et al., 2000]. The results indicate an overall increase of EEG dimensional complexity with age both in a resting state and during the performance of cognitive tasks, replicating their earlier findings [Anokhin et al., 1996]. Recently, signal complexity studies extending to coarser timescales

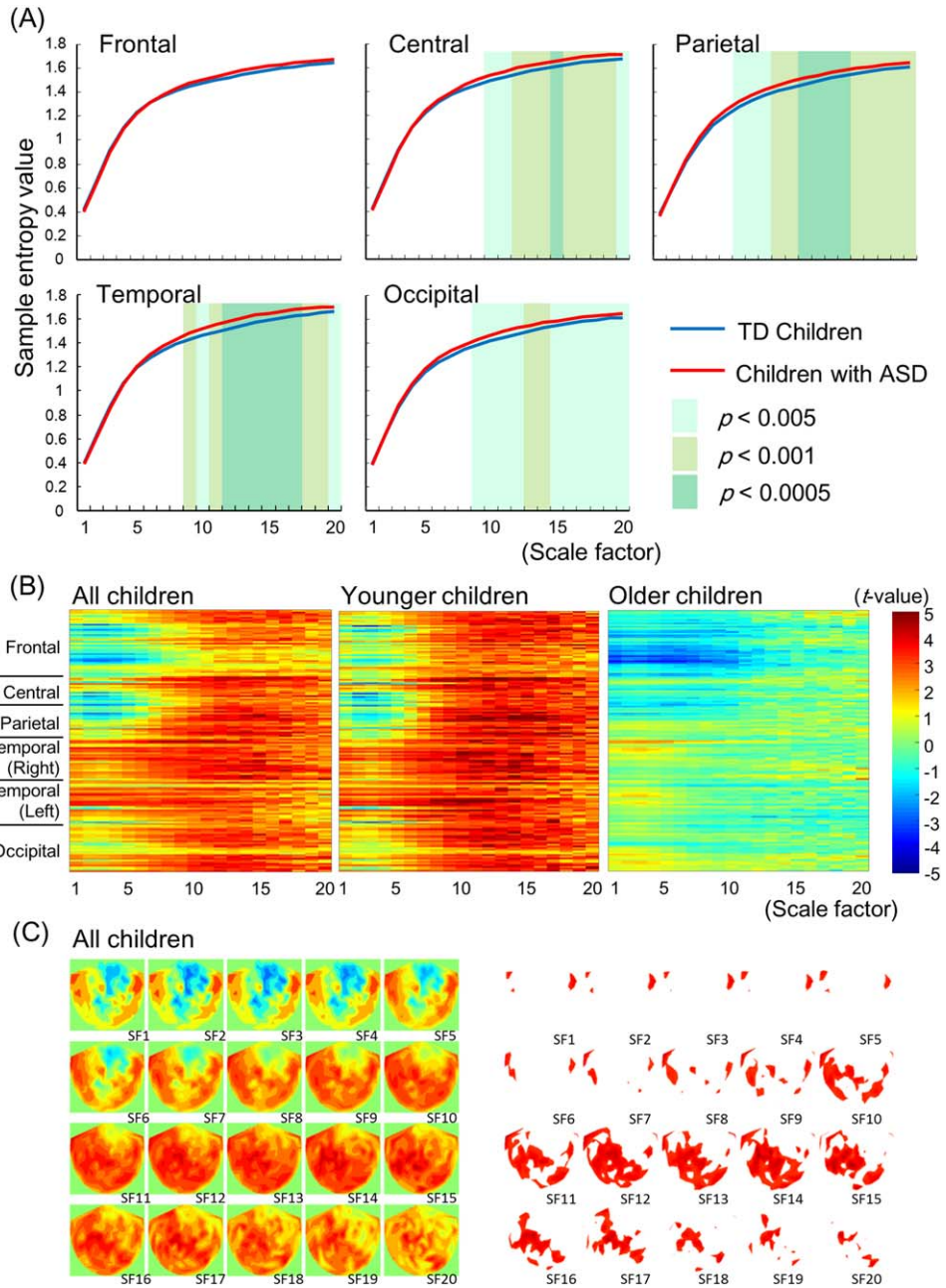

Figure 2.

Group differences of the MSE value. (A) Each panel represents average MSE curves for TD children (blue line) and children with ASD (red line) for each subregion corresponding to Fig. 1. *Post-hoc* comparisons between groups were highlighted with $p < 0.005$ (light-green shaded areas), $p < 0.001$ (green shaded areas), and $p < 0.0005$ (dark-green shaded areas). FDR (controlling for 20 SFs $\times$ five subregions) q values of 0.01 and 0.005, respectively, correspond to p values of 0.0040 and 0.0019. (B) Array plot showing sensor-wise group comparisons of MSE values (*X*-axis, SFs; *Y*-axis, sensors sorted by subregions according to Fig. 1). Values represent t values for each comparison (151 sensors $\times$ 20 SFs). Each panel shows all children, younger children, and older children. T values for FDR (controlling for 20 SFs $\times$ 151 sensors) adjusted $q = 0.01$ correspond to 3.06 ($p = 0.0031$) for all children and 2.97 ($p = 0.0044$) for younger children. T values of 4.0 correspond respectively to $p = 0.00011$ for all children and $p = 0.00018$ for young children. No significant difference was found in older children. (C) Topography of t values of group difference in all children (left). Brain regions that showed lower than FDR adjusted $q = 0.01$ are depicted (right).

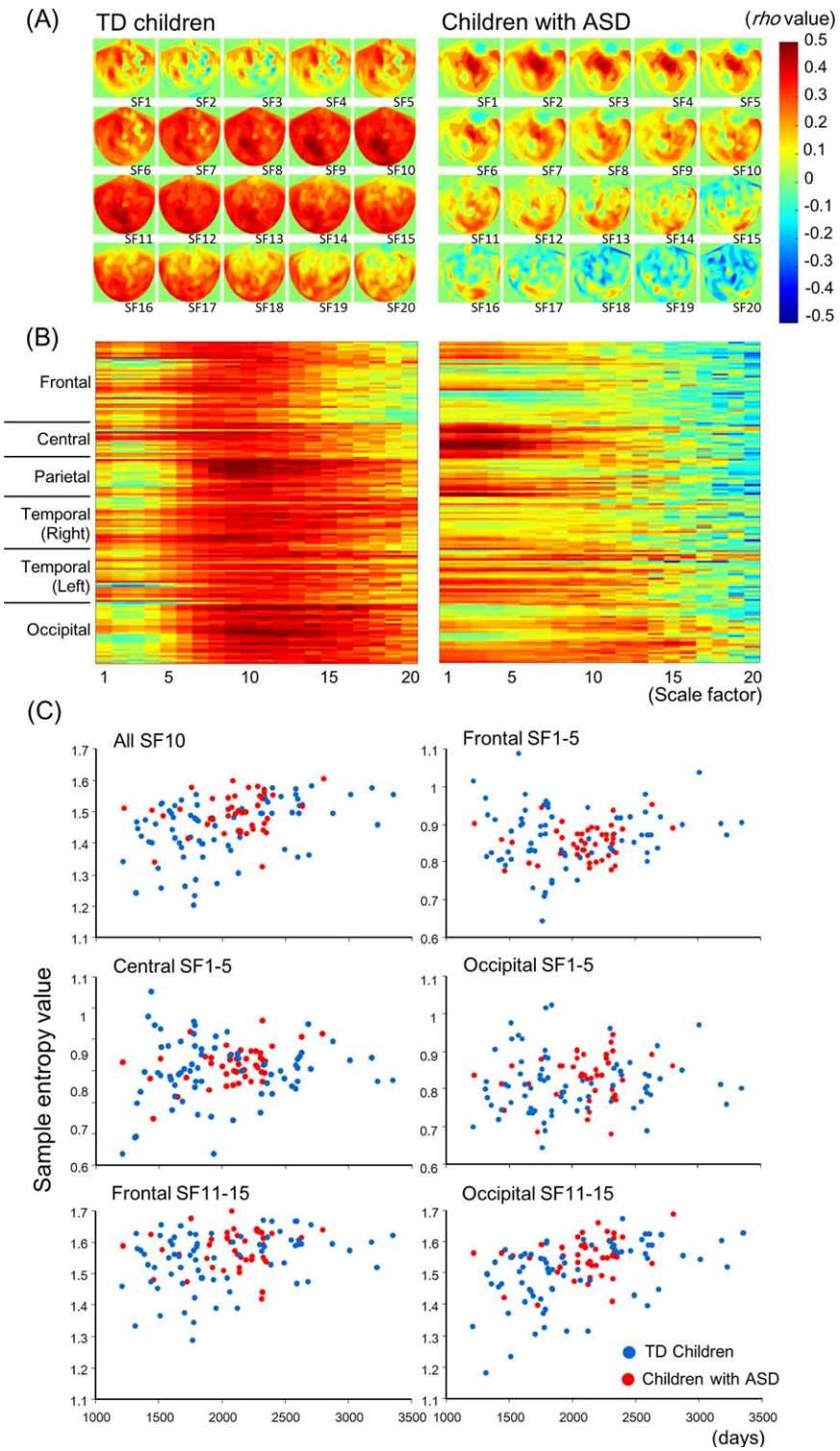

Figure 3.

Associations between age and MSE values. (A) Topography of correlation coefficient values between age and MSE values for TD children (left) and children with ASD (right). Values represent correlation coefficients. Positive values indicate age-related MSE increase (and vice versa). (B) Array plot representing sensor-wise correlations of age vs MSE values (*X*-axis, SFs; *Y*-axis, sensors sorted by subregions according to Fig. 1) for TD children (left) and children with ASD (right). *Rho* value for FDR (controlling for 20 SFs $\times$ 151 sensors) adjusted $q = 0.01$ corresponds to 0.34 ($p = 0.0030$) for TD children. (C) Scatter plots showing age vs average MSE values in TD children and children with ASD: all sensors at SF 10 (top left panel), frontal (top right panel) and central (middle left panel) and occipital (middle right panel) sensors at SF 1–5, and frontal (bottom left panel) and occipital sensors at SF 11–15.

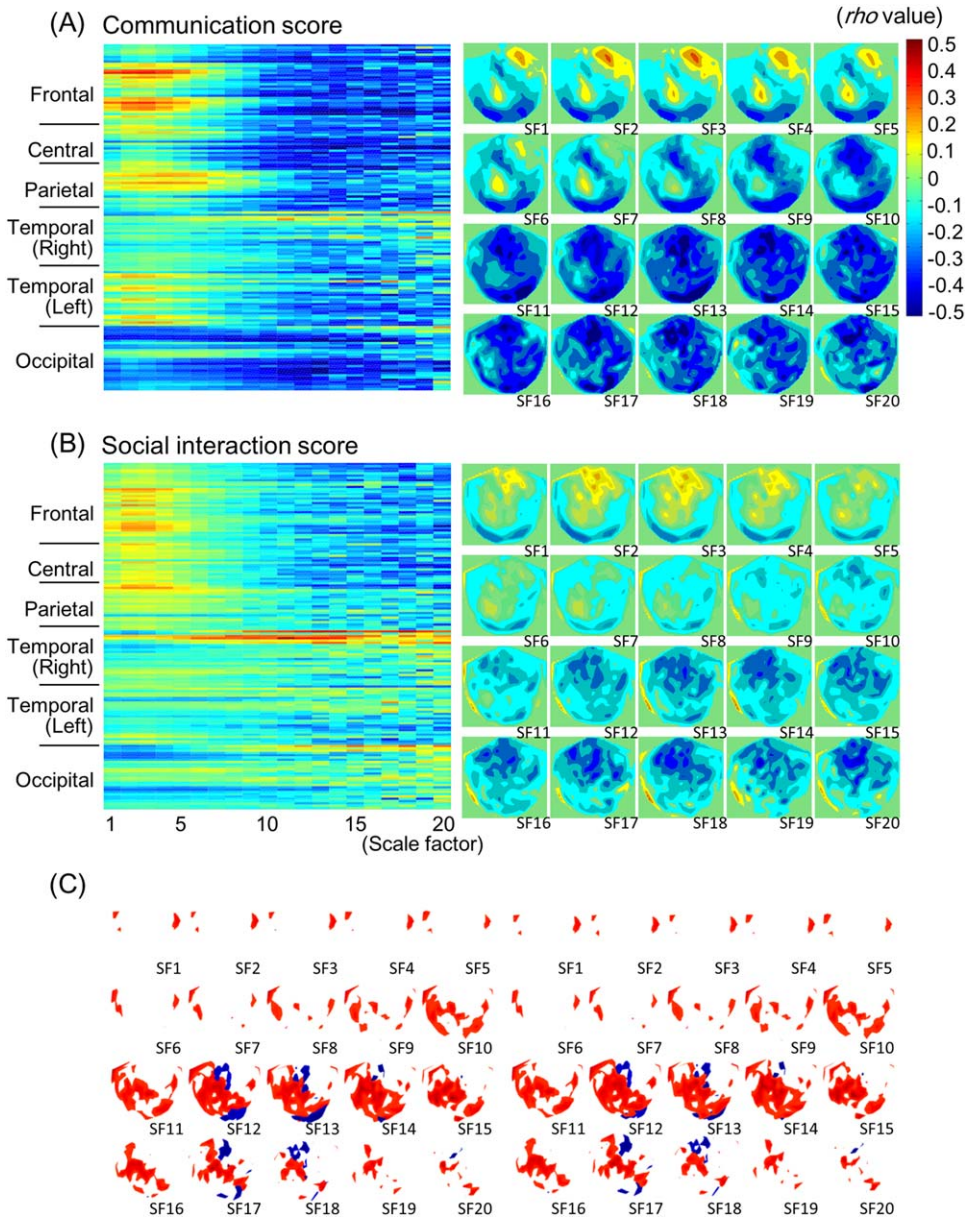

Figure 4.

Association between disease severity and MSE values. (A) Array plot of the sensor-wise correlation coefficient between symptom severity (communication score) and MSE values (*X*-axis, SFs; *Y*-axis, sensors sorted by subregions according to Fig. 1) in children with ASD (left). Topography of correlation coefficient values between symptom severity (communication score). (B) Array plot of the sensor-wise correlation coefficient between symptom severity (social interaction score) and MSE values (*X*-axis, SFs; *Y*-axis, sensors sorted by subregions according to Fig. 1) in children with ASD (left). Topography of correlation coefficient values between symptom severity (social interaction score) and MSE values. Positive values denote severity-related MSE increase (and vice versa). (C) Overlapped topographies of correlation with symptom severity (Fig. 4A, right (depicted by thresholding lower than FDR adjusted $q = 0.05$ controlling for 151 sensors)) and *t* values of group difference in all children (Fig. 2C, right). Superscription of topography of correlation with symptom severity on topography of *t* values of group difference in all children (left), and vice versa (right).

(i.e., MSE) have been conducted. One earlier study by McIntosh et al. [2008] explored EEG signal variability and its relevance to cognitive performance in 8–15-year-old children and 20–33-year-old adults. They found an increase of signal variability with age. This increase was associated with higher cognitive performance. Another study, conducted by Lippe et al. [2009], specifically examined the younger age group of 1–66 months of age. They evaluated EEG signal complexity during visual and auditory tasks. Findings similarly revealed a signal complexity increase with age in response to both stimuli. Findings of these development-related increases in signal variability were investigated complementarily with network connectivity analyses. The results underpinned important implications of functional connectivity [Ghanbari et al., 2013; Misic et al., 2011; Vakorin et al., 2011].

Although the theory of "increasing brain signal variability during development" is a widely accepted hypothesis [reviewed by Garrett et al., 2013], results of brain signal variability in ASD vary among studies. Bosl et al. [2011] examined resting-state EEG complexity by modified MSE in 33 TD infants and 46 infants in families with a history of ASD (high-risk ASD group) across ages of 6–24 months. They found consistently lower EEG complexity in high-risk of ASD group over all electrodes, across all timescales and at all ages, particularly at age 9–12 months, which must be more informative. It is noteworthy that the high risk of the ASD group was classified with high accuracy. Another ASD-related decrease in EEG complexity was reported by Catarino et al. [2011]. They examined EEG complexity using MSE in 15 adult subjects with ASD (mean age of 29.38) and 15 TD controls (mean age of 31.44) during a face and chair matching task. They found significant reduction of EEG complexity in subjects with ASD over temporo-parietal and occipital regions as the timescale increases, although EEG power was not reduced, which indicates the irrelevance of EEG power spectra to complexity values. They also assume that the complexity reduction at a larger temporal scale suggests the existence of a power-law scaling property, which is a characteristic of nonlinearity. Contrary to these findings, Ghanbari et al. [2013] jointly examined MSE and synchronization likelihood to obtain a more detailed characterization of resting-state MEG activity in 26 children with ASD (mean age, 10.1 years) and 22 TD children (mean age, 10.9 years). They found both increased and decreased signal variability occurring both region-specifically and frequency-specifically. It is particularly interesting that group differences between ASD and TD subject in complexity and synchronization appear to be spatially complementary, such that where synchronization was elevated in ASD, complexity was reduced (and vice versa). Additionally, symptom severity, evaluated by social responsiveness scale, was correlated with MEG complexity in both positive and negative directions across frequencies. Another study was conducted by Misic et al. [2014] to assess MEG complexity with MSE in 14 children with ASD (mean age, 10.9 years) and 14 TD children (mean age, 11.2 years) during the performance of cognitive control tasks. Their data-driven multivariate analysis revealed two distributed networks in a timescale-dependent and task-relevant manner. They assumed that ASD involves disrupted temporal organization in these networks for optimal cognitive processing. Although describing only a single case, we also reported region-specific and timescale-specific alterations in EEG signal variability along with successful treatment of obsessive–compulsive symptoms using modified electroconvulsive therapy in a patient with ASD [Okazaki et al., 2015].

A conceptual framework used to describe age-related increase in the signal variability hypothesis can be explained partially by stochastic resonance theory [Wiesenfeld and Moss, 1995]. Stochastic resonance is a phenomenon by which moderate-level unpredictable signal fluctuations can increase the quality of signal transmission or signal detection, which reportedly facilitates information processing in a neural system [reviewed in Faisal et al., 2008; McDonnell and Ward, 2011]. How can our finding of enhanced brain signal variability in ASD be interpreted? A reasonable explanation is that an optimal level of signal fluctuations can contribute to the facilitation of cognitive processing [McDonnell and Abbott, 2009; McDonnell et al., 2007; Moss et al., 2004]. Therefore, a moderate level of signal variability, an inverted U-shaped curve, is beneficial for efficient cognitive processing. For instance, abnormally increased signal variability was reported in mental disorders. Patients with schizophrenia showed higher EEG signal variability at coarser timescales: this was decreased to healthy controlled levels using antipsychotic drugs [Takahashi et al., 2010]. In Alzheimer's disease, less EEG signal variability at finer timescales was observed in more frontal areas, consistent with previous findings. By contrast, higher EEG signal variability at coarser timescales was observed across brain areas in Alzheimer's disease. This increase was positively correlated with cognitive decline [Mizuno et al., 2010]. Consequently, overly high signal variability that might be associated with enhanced functioning observed in children with ASD might engender disabilities in this disorder [reviewed in Mottron et al., 2014]. This notion appears to be applicable to the recent hyper-connectivity hypothesis [Uddin et al., 2013b]. Of particular note is that this hyper-connectivity appears to be more characteristic of young (prepubertal) children with ASD, whereas hypo-connectivity might be more prevalent in adolescents [Uddin et al., 2013b]. It is particularly interesting that this hyper-connectivity observed in child ASD is reportedly associated with higher levels of fluctuations in regional brain signals [Supekar et al., 2013]. The present results related to enhanced signal variability observed particularly in younger children with ASD agree well with this notion. Growing evidence has reported enhanced functioning in ASD without intellectual disability, particularly related to perceptual functions and

their related brain areas such as temporal, parietal, and occipital regions [reviewed by Mottron, 2014; Samson et al., 2012]. It is noteworthy that, in our study, enhanced complexity was observed predominantly in perceptual functioning related brain regions (Fig. 2). Considering that we only recruited children with ASD without intellectual disability, increased brain signal variability might reflect enhanced brain activity in a certain brain region in ASD. Another important finding of this study is that signal variability is associated negatively with symptom severity in children with ASD, which is seemingly contradictive of previously described theories. More detailed insight into our results provides additional features that elucidate this paradoxical finding. The brain region that showed negative correlation with symptom severity in ASD (Fig. 4A) did not correspond to the brain regions where significant group difference was observed (Fig. 4C). Therefore, we might assume that brain regions which showed enhanced complexity and disturbance in communication skill observed in the ASD group might be presented region-specifically and temporal-specifically under different pathological mechanisms. However, the question remains of why intellectual function did not correlate with signal variability, which is inconsistent with earlier findings obtained from several studies [McIntosh et al., 2008; Misic et al., 2010]. This inconsistency might be understood according to the idea of a stochastic resonance theory as described above. The moderate level, not too little or not too much, of signal fluctuations that are appropriate for one's age can support efficient information processing [Li et al., 2006; McDonnell and Abbott, 2009; McDonnell et al., 2007; Moss et al., 2004]. In other words, intellectual function might not associate linearly with signal variability. Our study was a cross-sectional study. The ASD group exhibited smaller age variation than the TD group did, which presents difficulties when investigating age-related alteration. Additional longitudinal follow-up studies including individuals with various ranges ages and intellectual functions are expected to be necessary to clarify these controversial points.

Some other limitations of our study must be considered. We examined MEG data during free viewing of videos without sound, which were selected according to the children's preferences. Diminished entrainability of the ASD brain has been reported for stimuli of certain types [Stroganova et al., 2012; Wilson et al., 2007]. This phenomenon might elicit different spatiotemporal properties of the video stimuli provided during the recording periods. It is also noteworthy that the age-related increase of EEG signal complexity change during early childhood varies with the stimulus [Lippe et al., 2009]. Additionally, we were unable to evaluate the degree to which subjects devoted special attention the video program that they selected. Future studies that use attention-controlled conditions with the baseline period are expected to provide more reliable evidence than the current investigation has yielded. Another technical consideration is that despite the recent advent of cortical source solutions that increase spatial location precision, we conducted original sensor space analysis. This study includes children in early childhood who might have difficulties in correcting MRIs and in keeping their body still without having some attraction such as watching videos. Furthermore, head motion artifacts, which might vary with age, sex and group, must exert a strong effect on the MSE result. We strictly eliminated any contaminated MEG data, such as data obtained when clear head movement occurred, as confirmed by video monitoring or MEG artifacts. Additionally, region-specific and temporal-specific differences in age-related trajectory patterns (Fig. 3C) might indirectly reflect the irrelevance of motion artifact to the MSE results. However, differences in fine head movements could have possibly confounded the study results. Last, studies using MEG-MSE analysis are vulnerable to multiple comparisons because of the many SFs and sensors that are examined, thereby potentially increasing the possibility of type I error. We applied FDR to control multiple comparisons.

CONCLUSION

Although several limitations must be clarified, findings derived from this study underscore the potential usefulness of MSE for exploring age-related variations in MEG signal and its alterations in ASD during early childhood. Results of this study suggest that MSE analytic methods might serve as a useful approach for characterizing neurophysiological mechanisms of typical development and its alterations in ASD through the detection of MEG signal variability at multiple timescales.

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