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The Potential Application of Multiscale Entropy Analysis of Electroencephalography in Children with Neurological and Neuropsychiatric Disorders

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Abstract: Electroencephalography (EEG) is frequently used in functional neurological assessment of children with neurological and neuropsychiatric disorders. Multiscale entropy (MSE) can reveal complexity in both short and long time scales and is more feasible in the analysis of EEG. Entropy-based estimation of EEG complexity is a powerful tool in investigating the underlying disturbances of neural networks of the brain. Most neurological and neuropsychiatric disorders in childhood affect the early stage of brain development. The analysis of EEG complexity may show the influences of different neurological and neuropsychiatric disorders on different regions of the brain during development. This article aims to give a brief summary of current concepts of MSE analysis in pediatric neurological and neuropsychiatric disorders. Studies utilizing MSE or its modifications for investigating neurological and neuropsychiatric disorders in children were reviewed. Abnormal EEG complexity was shown in a variety of childhood neurological and neuropsychiatric diseases, including autism, attention deficit/hyperactivity disorder, Tourette syndrome, and epilepsy in infancy and childhood. MSE has been shown to be a powerful method for analyzing the non-linear anomaly of EEG in childhood neurological diseases. Further studies are needed to show its clinical implications on diagnosis, treatment, and outcome prediction.

Keywords: EEG; multiscale entropy; autism; attention deficit/hyperactivity disorder; Tourette syndrome; epilepsy; neonatal seizure

1. Introduction

Electroencephalography (EEG) is a commonly-used modality to examine children with neurological or neuropsychiatric disorders. It is a safe and non-invasive physiological examination without radiation exposure and is widely used in the evaluation of complex networks and function of the brain. Compared with other time-consuming imaging modalities such as functional magnetic resonance imaging (fMRI), it can be done easily without the need for anesthesia or sedation, even in young infants and neonates.

As a result of the complex networks in the brain, EEG signals carry non-linear temporal and spatial information reflecting the underlying network of neuronal connections, which exhibit a hierarchical and scale-free organization [1,2]. The safety, availability, and powerfulness of EEG make it one of the most important modalities to study the underlying pathophysiology of neurological or

neuropsychiatric disorders in children. Various algorithms based on estimates of the entropy of EEG signals have been developed to investigate the underlying brain connectivity. These estimates, such as approximate entropy (ApEn) and sample entropy (SamEn), quantify the regularity of a time series by calculating the occurrence of similar patterns in a series and have shown meaningful results on the analysis of EEG and other biophysical signals [3,4]. Entropy-based algorithms for EEG analysis have been used in autodetection of seizures and classifying EEG of normal individuals and those having neurological diseases [5–7]. However, these entropy-based algorithms only reflect dynamics in a short temporal range and tend to give a greater value of irregularity on randomly-generated data. Therefore, multiscale entropy (MSE) has been introduced to reflect the complexity, or the "meaningful structural richness", by analyzing the SamEn on a set of coarse-grained time series derived from the original biophysiological signals at different scale factors [8]. This multiscale approach has found that changes of entropy may only be recognized in either larger or smaller time scales in the studies of childhood neuropsychiatric diseases such as autism spectrum disorders (ASD) and Gilles de la Tourette syndrome (GTS), as well as in childhood neurological disorders such as childhood epilepsy syndromes and neonatal seizures (Table 1). The aims of this article are to give a brief summary of the current concept of entropy analysis with a multiscale approach in pediatric neurological and neuropsychiatric disorders.

Table 1. Summary of studies using entropy analysis in pediatric neurological and neuropsychiatric disorders.

Neurologic and Neuropsychiatric Disorders	Study	Subjects	Analysis Methods	Condition	Main Findings
ASD	Bosl et al. (2011) [9]	46 HRA infants; 33 controls	Modified MSE	Resting	The pattern of development of complexity were different in HRA and control infants. The differences were greatest at ages 9–12 months. A model developed using machine learning algorithms showed 80% accuracy to identify HRA infants at 9 months old.
	Catarino et al. (2011) [10]	15 adult diagnosed with ASD; 15 normal control	MSE Power analysis	EEG during face and chair detection task	Reduction of EEG complexity over temporal-parietal and occipital regions in ASD patients during face and chair matching task compared with typical controls was noted using MSE analysis. No differences in EEG power spectra were noted between groups.
	Ghanbari et al. (2015) [11]	26 ASD; 22 age-matched TD	MSE and synchronization likelihood on MEG signals	Resting, eye closed	Reduction of MEG complexity in frontal areas in alpha frequency band and in occipital areas in delta frequency band. Correlation was shown between complexity difference and symptom severity.
	Okazaki et al. (2015) [12]	An adult with ASD receiving electroconvulsive therapy for catatonia symptom	MSE	Waking EEG, before, during and after electroconvulsive therapy	Decreased MSE in smaller scale over frontocentral area and increased MSE in larger scale over the occipital area during and after electroconvulsive therapy. The changes were accompanied by improvement of catatonia and correlated to change in serum brain-derived neurotrophic factor level.
	Takahashi et al. (2016) [13]	43 ASD; 72 TD	MSE	Video-watching	Alteration in typical age-related increase of MEG complexity in ASD. Enhanced MEG complexity in younger children with ASD.
	Simon et al. (2017) [14]	20 younger siblings of ASD	Composite MSE	Video-watching	Composit MSE at high frequency over temporooccipital region was negatively correlate to sensory hyporesponsiveness.
	Bosl et al. (2017) [15]	18 ASD; 26 CAE; 47 control	Modified MSE Recurrence quantification analysis	Resting	ASD showed higher modified MSE in the frontal, occipital, and left temporal areas.
	Tian Liu et al. (2017) [16]	20 ASD; 20 control	MSE	Observation task Imitation task	Lower MSE in ASD group was seen during obsrevation task at bilateral central, occipital, and right temporal areas. Lower MSE in ASD group were seen during imitation task at left central, parietal, occipital, and right temporal areas.

Table 1. *Cont.*

Neurologic and Neuropsychiatric Disorders	Study	Subjects	Analysis Methods	Condition	Main Findings
ADHD	Ke et al. (2014) [17]	14 healthy adults	θ/β MSE	Visual attention, No attention Resting	Greater SamEn and MSE were correlated to the higher level of attention. Accuracy of support vector machine classfication using SamEn or MSE is better than using linear θ/β ratio, and is higher with small scale factor of MSE.
	Li et al. (2016) [18]	13 ADHD; 13 control	MSE	During multi-source interference task	Increased complexity of EEG signals in delta and theta frequency band and decreased omplexity in alpha frequency bands in ADHD.
GTS	Weng et al. (2017) [19]	10 children with GTS; 10 healthy controls	MSE	Resting, eye open	Reduction of complexity in the bilateral central, parietal, occipital, and left temporal regions. Change in the channel F3 was noted only at low frequency but not in high frequency spectra.
Childhood absence epilepsy	Ouyang et al. (2013) [20]	7 CAE	MPE MSE	Inter-ictal Pre-ictal Ictal	Siginificant decrease in EEG complexity during the pre-seizure period and further decrease in complexity during seizure period. EEG records from different state can be classified by linear discriminant analysis with multiscale PE or SamEn.
	Weng et al. (2015) [21]	21 children with CAE	MSE	Inter-ictal Pre-ictal Ictal	Decreased complexity index in ictal than pre-ictal EEG. Greatest change was noted in the frontal and central regions. More significant difference in complexity index was noted using a higher sampling frequency of EEG recording.
	Bosl et al. (2017) [15]	18 ASD; 26 CAE; 47 control	Modified MSE Recurrence quantification analysis	Resting	CAE showed higher modified MSE in frontal, occipital, temporal, and parietal regions.
Neonatal seizure	Zhang et al. (2009) [22]	168 newborns	SamEn	Active sleep Quiet sleep	Increase of SamEn during eurodevelopment from preterm to term (PMA 25–41 weeks). SamEn during active sleep decrease after term (PMA 42–52 weeks) was seen. SamEn fluctuation was greater in preterm infants and diminished during development to term.
	Lu et al. (2015) [23]	9 neonatal seizures without later epilepsy; 14 neonatal seizures with later epilepsy; 9 controls	MSE	Light sleep	EEG complexity significantly decreased over channels C3, C4, and Cz in neonates with seizure and later epilepsy compared with control group. EEG complexity of neonates with seizure without later epilepsy was not different from controls.

ASD: autism spectrum disorders; ADHD: attention-deficit/hyperactivity disorder; CAE: childhood absence epilepsy; EEG: electroencephalography; GTS: Gilles de la Tourette syndrome; HRA: high-risk autism; TD: typically developing controls; MEG: magnetoencephalography; MPE: multiscale permutation entropy; MSE: multiscale entropy; PE: permutation entropy; PMA: postmenstrual age; SamEn: sample entropy.

2. The General Concept of Entropy of EEG

The original concept of entropy is a measure of disorders in thermodynamics [24], which has been applied to analyze various physical signals such as EEG. Entropy is considered to be a method of detection of the system's randomness and predictability. In studies about the depth of anesthesia, entropy is higher when the patient is awake, while it is lower when the patient is in anesthesia [25]. The number of research works about the entropy of EEG in different neurological diseases has increased greatly in the past few years. The research objectives can be classified into two main targets: the discussion of different entropy indexes compared with other physiological indicators [26], and the applications of entropy in various physiological conditions.

The concept of entropy leads to the generation of multiple algorithms. The generation of these algorithms is related to time series and phase space. However, different algorithms may have different advantages and disadvantages [26]. Therefore, the entropy indexes need to be combined with other diagnostic indexes to support the correlation of entropy indexes with the outcome.

Although entropy can be used as an index of patients' physiological conditions, entropy can only have a relative value to evaluate the change of physiological conditions. Therefore, most studies focused on the difference and the correlation of entropy in different conditions. The change of entropy had been used to evaluate neurological recovery in rats under hypothermia treatment [27]. The results indicated that the entropy increases with the treatment time. MSE analysis had also been used to evaluate the conditions in Alzheimer's disease. The healthy controls had large entropy in low-scale factors; in contrast, the patients with Alzheimer's disease had large entropy in high-scale factors [28]. The entropy indexes of schizophrenia patients were higher than those in patients receiving drug treatment [29]. Therefore, the entropy analysis of EEG can be used in different aspects of neurological diseases. In the following sections, we will illustrate some applications of entropy in neurological and neuropsychiatric diseases in children.

3. Definitions and Properties of Entropy Indices Applied on EEG

3.1. Approximate Entropy

The ApEn is an estimation of the Kolmogorov entropy from the probability of occurrence of similar segments of contiguous points in a time series [30,31]. It has the advantage that it can reliably classify deterministic, chaotic, and stochastic signals with a relatively small data size (at least 1000 data points) [32]. The drawbacks of ApEn are that it is a biased estimate due to counting self-matches in the calculation. Sensitivity to data length and lack of consistency against changes of the embedding dimension and tolerance level also limited its application [30].

3.2. Sample Entropy

SamEn is derived from ApEn. It is an unbiased estimate by eliminating self-matching. To avoid the undetermined value ln(0) when no matches are found except a self-match, the total number of segment matches is calculated before taking the logarithm.

While keeping the ability to differentiate different classes of dynamic systems as ApEn, the additional advantage of SamEn is the consistency against the change of the embedded dimension and tolerance level [30]. If one signal has a higher SamEn than another, the relationship remains unchanged when calculating with different embedded dimensions and tolerance levels. It is also less sensitive to the data length. These properties make SamEn more applicable and easier to interpret than ApEn for use in the research of biophysiological signals.

3.3. Permutation Entropy

Permutation entropy (PE) is calculated from the probability distribution of the order of m continuous points in a time series to be one of the m! possible permutations. Due to the simplicity, the permutation entropy has a low computational complexity. It also has the advantage of robustness against noisy data [5].

3.4. Spectral Entropy

The spectral entropy is the Shannon's entropy of the probability distribution function derived from the power spectrum density of the time series [5]. Spectral entropy has been applied successfully in the monitoring of anesthesia depth [33]. The drawback of spectral entropy is that it calculates only the unpredictability of the frequency distribution when a signal is decomposed to sinusoidal waves and cannot explain the unpredictability of the changes in signal value over time [5,34].

3.5. Recurrence Quantification Analysis (RQA) Entropy

RQA is a method for analyzing hidden periodicity based on recurrence plots. Periodicity is identified by plotting points with values close together on a recurrence matrix. It can be extended with additional dimensions, each with a time lag with respect to the original time series. Diagonal lines on

the plot represent recurrent segments of contiguous points in the time series, except the main diagonal line representing self-matching. RQA entropy is the Shannon entropy of the probability distribution of the length of diagonal lines on the recurrence plot [35]. RQA measurements can detect the transition of chaotic states within a time series and is useful for non-stationary data [36].

Other recurrence variables can also be used as the measurement of regularity. For example, the maximal length of diagonal lines (L_{max}) on a recurrence plot, except the main diagonal line is inversely proportional to the Lyapunov exponent, which is also an important index of dynamic chaos [35].

3.6. Multiscale Entropy

One of the problems of using the above entropy indices as a representation of the complexity of a biophysiological signal is that the estimation of entropy often gives a significant value on randomly-generated white noise [8]. In most physiological systems, higher complexity is often expected in a more healthy condition as a representation of physiological responsiveness to the changing environment. An ideal index of the complexity of the biological signal should have the ability to differentiate a signal carrying rich biological information, even though the biological information includes a similar white noise signal such as the electrocardiography of atrial fibrillation [8]. The observation that most biological signals carry information in a wide range of time scales gives rise to the proposal of the multiscale entropy (MSE) method. In the MSE method, a set of course-grained time series was constructed from the original signal's correspondence to a wide range of scale factor τ.

We apply one of the above entropy indices such as SamEn on the coarse-grained series and get a series of entropy calculated at different scale factors. The complexity of different signals can be compared by directly comparing the entropy-scale curves. We can also use Zhang's complexity, which summarizes the scale-dependent entropy by the integral of the entropy across all scales. Studies using multiscale entropy have shown differences of the EEG entropy change between large and small time scales, which may not be found without multiscale analysis [12,19–21]. The result of applying this novel approach in different childhood diseases is reviewed in the following sections.

3.7. Modifications of Multiscale Entropy

Various modifications of MSE have been applied in previous studies [9,14,15,20]. For example, one modification is to use modified sample entropy (mSamEn) by substituting the strict cut-off used to define the similarity of two segments of time series with a sigmoidal function, which improves the relative consistency of parameter selection and the robustness to noise [37]. Composite MSE calculates the average of the entropy obtained from a series of coarse-grained signals with a shift of the time-frame for coarse-graining [38]. The advantage of composite MSE is to improve the stability of the results at a large-scale factor in short time series.

4. Developmental and Neuropsychiatric Disorders

The hierarchical organization of a neuronal network of the human brain changes during development. A study using fMRI to compare brain network properties showed that there are significant differences in the hierarchical organization and interregional connectivity between children and adults [39]. Connectivity analysis using white-matter tracking showed differences in short- and long-range functional connectivity during the process of functional maturation [39]. The alteration in the development of normal brain connectivity may lead to a variety of developmental/neuropsychiatric disorders, such as ASD and attention deficient/hyperactivity disorders (ADHD) [40]. Studies comparing MSE between normally-developing children and children with neuropsychiatric disorders have revealed information with potential diagnostic, therapeutic, or prognostic value [9–11,18,19].

4.1. Tourette Syndrome

GTS is a neuropsychiatric disorder with both motor and vocal tics as its core symptoms [19,41,42], and it may have many comorbidities. Most cases of GTS have onset in childhood, and tics may present

with motor movements or vocalizations, which are repetitive, automatic, rapid, and can be simple or complex in nature [43].

The generation of tics may use motor pathways different from those of voluntary movements, and they may also have interactions with the secondary sensorimotor networks [44]. Defects in inhibitory gamma-aminobutyric acid-ergic (GABAergic) and cholinergic interneurons in the striatum and increased dopaminergic innervation have been proposed to cause tics [45]. Imaging studies also showed structural abnormalities involving the basal ganglion system, especially in the caudate nucleus [46]. Alterations of activity of the cortico-striato-thalamo-cortical circuits have also been noted with fMRI [47] and had been suggested as a reflection of a developmental defect in brain maturation [48]. The entropy of EEG had been applied to investigating the functional connectivity of brains in children with GTS. Resting state EEG complexity based on the change of MSE in children with GTS exhibited significantly lower EEG complexity in bilateral central, parietal, occipital, and left temporal areas in both lower and higher frequency spectra [19]. In contrast, the EEG complexity was only significantly lower in the left frontal area at the lower frequency [19]. The decrease in brain signal complexity may be related to increased functional connectivity in these regions [11]. These findings were compatible with previous studies on functional neuroimaging, which showed functional alterations in the motor, sensory, and associated networks in adults with GTS [44] and dopaminergic dysfunction of occipital cortex in GTS [49]. These findings suggest that MSE is a good indicator for regional changes in brain function.

4.2. Autism Spectrum Disorder

ASD is an important neuropsychiatric disorder in children. It is defined as a wide continuum of neurodevelopmental conditions characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior, interest or activities [50]. Individuals with ASD may express different severity in symptoms, intellectual disability, and function [50]. The high recurrence rate in family and siblings of ASD indicates a strong inherited genetic basis [51]. Neuropathology and neuroimaging studies have shown abnormalities in the frontal lobe, amygdala, and cerebellum with wide heterogeneity [52], which indicate a complicated alteration of brain development and connection.

The investigation of EEG complexity on multiple temporal scales is helpful in disclosing the information of the brain's connectivity in ASD. Boel et al. [9] used a modified MSE (mMSE) method, which utilized an algorithm comparing vector similarity with a sigmoidal function in the calculation of the modified sample entropy (mSamEn) of each coarse-grained time series, to compare the complexity of baseline EEG activity in individuals with high risk of ASD. High risk of ASD was defined by having a sibling with ASD in the family. They found that the mMSE value showed a developmental change over age, reflecting the evolution in brain connectivity with development. The mean mMSE in the control group was significantly higher than the high risk group with the greatest differences of EEG complexity at the age of 9–12 months. A model developed using the machine learning algorithm and mMSE data also showed 80% accuracy in identifying high risk of ASD subjects at nine months old.

Recently, the study of EEG complexity during a visual task showed a reduction of EEG complexity in individuals with ASD over the temporal-parietal and occipital regions, without significant differences in the power spectra [10]. The neuroimaging studies during visuospatial processing also showed differences between ASD and controls in similar regions [53–55]. Decreased EEG complexity in individuals with ASD was also found during observation and imitation tasks over central, parietal, occipital, and right temporal areas. These areas were compatible with the areas activated during imitation tasks in fMRI studies and may indicating a deficit in the "mirror neuron system" in ASD [16,56]. Treatments of ASD-related symptoms may also affect EEG complexity. Electroconvulsive therapy (ECT) for catatonic obsessive-compulsive symptoms had shown an increase in EEG complexity at a higher scale factor over the occipital region, as well as a decrease in the EEG complexity at a lower scale factor over frontocentral areas [12]. The changes in EEG complexity were also correlated with the improvement of catatonic symptoms and an increase of serum brain-derived

neurotropic factor [12]. Although most studies showed decreased EEG complexity in individuals with ASD, an increased EEG complexity at rest has been noted in a study of older individuals with ASD [15], which showed that the EEG complexity of ASD was in between that of the control and individuals with absence seizures.

Diminished or delayed behavior responses to sensory stimuli have been addressed in ASD [57]. A negative correlation between EEG complexity in high frequency over the temporo-occipital region and sensory hyporesponsiveness was noted in younger siblings of ASD toddlers [14]. This indicated that the change in EEG complexity may be a potential indicator of the subclinical abnormality of brain function.

Both the functional connectivity and complexity of magnetoencephalography (MEG) signals also showed that individuals with ASD had lower complexity compared with typically-developed subjects in frontal areas in the delta band and in occipital areas in the alpha band. The difference was correlated with symptom severity in terms of the Social Responsiveness Scale (SRS) scores [11]. Alteration of the typical age-related increase in brain signal variability during normal development in early childhood has also been noted in ASD by MSE analysis of the MEG signal [13]. On the other hand, an enhanced MEG complexity over the temporo-parieto-occipital region in ASD was noted in younger children, which may support the "aberrant neural connectivity" theory in ASD [13]. Therefore, the complexity of both EEG and MEG can be used to investigate the functional deficits of children with ASD.

4.3. Attention-Deficit/Hyperactivity Disorder

ADHD is a disorder characterized by inattention and hyperactive-compulsive behavior. It commonly develops in childhood with heterogeneous genetic alteration and in association with other neurological disorders [58]. Impairment of behavioral inhibition has been proposed as the core deficit in ADHD [59]. Increased activation of the basal ganglia and cerebellum and decreased activation and volume of prefrontal cortex have been noted from functional and structural imaging [60,61].

EEG complexity had also been used to investigate the functional deficits in children with ADHD [18]. In an adult study of EEG complexity during visual tasks, the SamEn and MSE were increased in temporo-occipital regions at a higher attention level, especially at small scale factors, and showed better classification accuracy compared with the θ/β ratio [17]. Accordantly, the individuals with ADHD exhibited increased EEG complexity in the delta and theta frequency bands and decreased EEG complexity in the alpha and beta frequency bands. Functional imaging studies had shown increased short-range functional connectivity density (FCD) in the orbital frontal cortex, ventral striatum, and superior frontal cortex; and decreased long-range FCD in the cerebellum and superior parietal cortex [62]. The different changes in complexity in higher and lower frequency bands may reflect the unequal changes in different connectivity properties.

5. Epilepsy and Seizures in Infancy and Childhood

Epilepsy in infancy and childhood is distinct from epilepsy in adults in many aspects. Many pediatric epilepsy syndromes have their typical age of onset, specific seizure types, characteristic EEG features, relatively predictable prognoses, and responses to treatments. This suggests a unique pathophysiologic change in each stage of brain development in their pathogenesis [63,64]. Recurrent seizures in the early stage of brain development have been shown to produce a long-term influence on the formation of normal functional connections [65]. Therefore, MSE and complexity analysis of EEG may provide a method to investigate the consequences of seizure and epilepsy on a developing brain.

5.1. Childhood Absence Epilepsy

Childhood absence epilepsy (CAE) is a childhood-onset epilepsy syndrome with a high prevalence [66]. The onset age is usually between three and eight years. It is characterized by a brief loss of awareness, accompanied by a pause of ongoing movements, which frequently occurs throughout the day. The typical EEG finding in absence seizure is a 3-Hz generalized spike-and-wave

discharge (GSW). Although it is classified as generalized epilepsy, a variety of hypotheses assume a focal origin of GSW in absence seizure, from centrocephalic origin to cortical focuses [67]. Evidence from EEG-fMRI have shown activation from regions of the cortical or subcortical networks, including the posterior cingulate, precuneus, superior lateral occipital cortex, frontal lobe, and caudate, preceding GSW discharges [68].

A recent study showed that the inter-ictal EEG complexity in children with CAE was significantly higher than the control over the frontal, occipital, temporal, and parietal areas [15]. In contrast, the reduction of EEG complexity in all channels during the seizure was noted in children with CAE [21]. The greatest change was also noted in the frontocentral regions, compatible with the hypothesis of the involvement of the cortico-thalamo-cortical network in the generation of GSW in absence seizure [67].

EEG complexity may also be useful in identifying subtle EEG changes before the onset of a seizure. EEG complex analysis with PE showed a significant decrease of PE during pre-ictal periods (within two seconds before the onset of GSW), but no significant difference was found using SamEn [20]. Both multiscale PE and MSE also show a more significant decrease of complexity during the pre-ictal and ictal period [20]. In a recent study, decreased MSE of EEG in the pre-ictal and ictal period of absence seizures was found more significant with a higher scale factor and a higher sampling frequency [21]. These results indicate that multiscale analysis with higher sampling frequency is more appropriate to detect pre-ictal EEG changes in absence seizures.

5.2. EEG Application in Neonates

Normal neonatal EEG has a huge difference from the EEG of the other age groups. EEG in preterm neonates showed a temporal maturation: delta bursts decrease, while continuity and interhemispheric synchrony increase with the increase of postconceptional age [69]. Transient EEG patterns may occur and disappear at specific stages of maturation [69,70]. Normal term neonates do not exhibit a mature wake and sleep EEG architecture as older infants until a few weeks after birth. The brain maturation can be evaluated by visual analysis of these EEG patterns. Changes in EEG pattern may also be associated with the neurodevelopmental outcome of preterm neonates [69]. Because MSE and EEG complexity is closely related to functional brain connectivity, the changes of EEG complexity in neonates may be associated with subsequent neurodevelopment and the risk of neurological diseases.

The incidence of seizures in neonates from population-based studies is 1–2 per 1000 live births, which is higher than any other age group. The high incidence of seizures in the neonatal period is contributed to by intrinsic factors, including the neuronal hyperexcitability, active synaptogenesis, the paradoxical depolarization effect of GABA receptors, as well as external exposures, such as hypoxic-ischemic encephalopathy, metabolic disturbance, intracerebral hemorrhage, central nervous system infection, and inborn errors of metabolism [71]. There is still a lack of consensus on the proper management and duration of the treatment of neonatal seizures. Clinical and animal studies have shown that neonatal seizures may affect early brain development, leading to metabolic alteration in term neonates with hypoxic-ischemic encephalopathy (HIE) [72,73]. Seizure has also been associated with unfavorable neurologic outcomes in HIE [74]. The change of EEG had also been found to be associated with the neurologic outcome of neonates with seizures. Neonates with inter-ictal epileptiform discharges and abnormal EEG background activities were shown to have a poor prognosis [71].

The EEG complexity tends to increase with neurodevelopment and brain maturation as indicated by post-menstrual age and the birth status. Lower mean SamEn and higher fluctuation were noted in preterm neonates from the postmenstrual age of 25 weeks. The increase of mean SamEn and the diminishing of fluctuation continue until term as a result of increased EEG background continuity [22]. Entropy measures such as Shannon entropy have also been incorporated with other EEG features for automatic classification of EEG between healthy and sick neonates [75].

A previous study has used a variety of EEG features for the detection of neonatal seizure [76]. The two entropy-based features with the highest performance on receiver operating characteristic

(ROC) analysis were Shannon entropy and singular value decomposition entropy. Both showed decreased EEG complexity during a neonatal seizure. Another study showed that decreased MSE of EEG and EEG complexity in neonates with seizure were associated with the development of later epilepsy [23]. The decrease of EEG complexity was most significant over bilateral central and mid-central areas in patients with later epilepsy compared with normal controls. Because neonates with later epilepsy had a higher incidence of developmental delay, the lower EEG complexity in bilateral central and mid-central areas may have arisen from the mixed effects of underlying etiologies and brain immaturity, possible anti-epileptic drug use, and prolonged seizure-related injuries.

Amplitude-integrated EEG (aEEG) is a method of continuous EEG monitoring widely used in the neonatal intensive care unit. The signal of aEEG is derived from a single bipolar channel of EEG with semilogarithmic amplitude compression and time compression. A previous study of aEEG showed increased ApEn in preterm and term neonates with HIE or epilepsy compared to normal term neonates [77], which was not in accordance with the assumption of decreased complexity in a damaged brain. The clinical significance of the inconsistent results remains unclear, but it indicated that the entropy of aEEG may be useful in identifying the abnormality of neonatal brain function. Whether the investigation of the changes of aEEG using the MSE approach may get more consistent results remains to be clarified.

6. Future Applications

Previous studies have indicated that MSE can be a powerful tool in understanding underlying disturbances of neural networks in a variety of pediatric neurological and neuropsychiatric disorders. Although many correlations of disease status and MSE changes were pointed out in previous studies, the implications of these on clinical diagnosis, treatment, and outcome prediction still need to be determined. Both linear and non-linear methods, including inter-hemisphere functional coupling, spectral analysis, and fractal dimension, had shown abnormality in adults with intellectual disability due to diseases such as Down syndrome [78–80]. Current studies mainly focus on the application of automatic EEG analysis on disease diagnosis, but the prediction of prognosis and treatment response by subtle entropy changes that cannot be identified by visual analysis may also have great clinical implications and should be studied further. There are still some limitations on the MSE. The reduced length of the coarse-grained series as the scale factor increases has limited its use on short time series with larger-scale factors. Furthermore, coarse graining may destroy the intrinsic dynamical scales defined by the signal-generating system. Fortunately, Huang et al. [78] proposed employing a data-driven method of empirical mode decomposition (EMD) to generate intrinsic multiple scales from the input data to be used for the subsequent MSE analysis [79]. The advantage of this EMD-based MSE method is that it operates locally, is based on the extrema of the input signal, and produces well-defined narrowband scales intrinsic to the input data. Furthermore, the limitation of a sufficient input data length due to the coarse graining process is alleviated, since EMD generates temporal data scales of the same length as that of the input signal. Another advantage of using EMD is that the standard MSE cannot deal with non-stationary signals. If a signal contains one or more pronounced trends, SamEn cannot be shown to have significant difference because trends tend to dominate other interesting features. Fortunately, EMD naturally captures a trend in the input data in the residue of the last extracted component, which can be removed so that MSE can calculate each intrinsic mode function for the small changes of these non-stationary signals [80]. The current MSE algorithm has not counted the interactions of EEG signals at different brain locations. Future studies may consider using modifications or improvements in algorithms, such as the composite MSE [38] and the multivariate MSE [81], which may provide more robust entropy estimates or reveal information from the interaction between different locations with a simultaneous analysis of the multichannel signal.

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