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Review

Event related potential analysis techniques for autism spectrum disorders: A review

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ABSTRACT

Autism Spectrum Disorders (ASD) comprise all pervasive neurodevelopmental diseases marked by deficits in social and communication skills, delayed cognitive development, restricted and repetitive behaviors. The core symptoms begin in early childhood, may continue life-long resulting in poor performance in adult stage. Event-related potential (ERP) is basically a time-locked electroencephalogram signal elicited by various stimuli, related to sensory and cognitive processes. The various ERP based techniques used for the study of ASD are considered in this review. ERP based study offers the advantage of being a non-invasive technique to measure the brain activity precisely. The techniques are categorized into three based on the processing domain: time, frequency and time-frequency. Power spectral density, coherence, phase synchrony, multiscale entropy, modified multiscale entropy, sum of signed differences, synchrostates and variance are some of the measures that have been widely used to study the abnormalities in frequency bands and brain connectivity. Various signal processing techniques such as Fast Fourier Transform, Discrete Fourier Transform, Short-Time Fourier Transform, Principal Component Analysis, Wavelet Transform, Directed Transfer Function etc. have been used to analyze the recorded signals so as to unravel the distinctive event-related potential patterns in individuals with ASD. The review concludes that ERP proves to be an efficient tool in detecting the brain abnormalities and connectivity issues, indicating the heterogeneity of ASD. Many advanced techniques are utilized to decipher the underlying neural circuitry so as to aid in therapeutic interventions for improving the core areas of deficits.

1. Introduction

Autism Spectrum Disorders (ASD) refer to a spectrum of neurodevelopmental disorders characterized by stereotypic behaviors, limited interests and activities, deficiency in verbal and non-verbal communication, social skills and marked by unique differences and strengths (Fakhoury, 2015). Hypo-or hyper-reactivity to sensory input is also a frequently noted symptom of ASD (American Psychiatric Association, 2013). As per the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), ASDs are composed of four distinct disorders which include autistic disorder, childhood disintegrative disorder, Asperger syndrome (AS) and pervasive developmental disorder-not otherwise specified (PDD-NOS). But DSM-5 removed the diagnostic subcategories for AS and PDD-NOS and instead included the severity levels of ASD as Level 1, Level 2 and Level 3 based on the support required (American Psychiatric Association, 2013). Autism was first reported by Kanner (Kanner, 1943). The ASD is diagnosed by the age of 3 years (Mandell et al., 2010). Some of the comorbid conditions in ASD include attention deficit/hyperactivity disorder (AD/HD), epilepsy, gastrointestinal symptoms, toileting, sleep disorders and feeding problems (Mannion and Leader, 2013).

According to the World Health Organization (WHO), the global prevalence of autism is reported to be 1 in.160 children. The Centers for Disease Control and Prevention (CDC) in USA reported a prevalence rate of 1 in.68 children (Autism and Developmental Disabilities Monitoring Network, 2016). Only few studies have been reported on the prevalence of ASD in developing countries, including India. Recent studies reveal that there is a higher diagnosis rate in males than in females (Halladay et al., 2015) with a prevalence ratio of 4:1(Poovathinal et al., 2016). The survey conducted in few states of northern part of India reveals the prevalence rate to be 1 in.66. In India, only few attempts have been made to explore the genetic substrates and effective treatment methods for ASD (Vijay Sagar, 2011). The prevalence rate in different parts of the world provides an alarming picture regarding ASD and catches much of the attention in research.

With rapid technological advances, various electrophysiological and neuroimaging techniques such as Electroencephalography (EEG), Event-related potential (ERP), Magnetoencephalography (MEG),

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Diffusion Tensor Imaging (DTI) and Magnetic Resonance Imaging (MRI) have evolved to analyze the intricacies involved in autistic brain. Out of the numerous techniques, this review primarily focuses on ERP methods that were used to explore the brain pattern in ASD. ERP represents electrical activity of the brain in response to a particular stimuli or event. ERP can be evoked by sensory, cognitive or motor events (Sur and Sinha, 2009). The components of ERP signal indicate early sensory perception, memory updating, attention, error monitoring, and other cognitive activities (Sokhadze et al., 2017). Since ERP signals are obtained by grand averaging of several epochs of similar types, signal-to-noise ratio is improved (Mumtaz et al., 2015). Since altered sensory perception has been one of the clinical descriptions of ASD (Thye et al., 2017), ERP gains significance as a promising diagnostic tool. In this paper, we present an overview of the ERP based analysis techniques utilized in ASD studies in order to understand its merits and pitfalls.

2. Methodologies

Various techniques have been used for the analysis of ERP signals based on three different domains viz. time, frequency and time-frequency. Feature indicates a distinguishing property embedded in a signal and feature extraction process attains significance in the context of preserving vital information about a signal (Al-Fahoum and Al-Fraihat, 2014). The process of classifying these extracted features aids the clinicians in the proper diagnosis of ASD. Feature extraction and the use of classifiers in these domains of analysis are dealt in the successive sections. Table 1 summarizes the various methodologies employed for ERP analysis in ASD. The details of the subjects participated in the various studies are being included in the tabular column.

2.1. Time domain analysis

ERP signals possess very good temporal resolution (Jeste and Nelson, 2009) and hence can be effectively analyzed in time domain. Independent Component Analysis (ICA) is a time-domain linear transformation technique in which the problem is to find a function f which can convert an m-dimensional random variable x into the n-dimensional transform: $s = (s_1, s_2, ...s_n)^T$ by the relation

$$s = f(x) \tag{1}$$

This technique aids in the development of a linear transformation which facilitates subsequent data analysis and is also computationally efficient. ICA finds numerous applications including blind separation of EEG signals, feature extraction etc.

Principal Component Analysis (PCA) is a frequently used method to identify the patterns in data and express it in a form that highlights their differences and similarities. PCA also facilitates dimensionality reduction of huge data. PCA computes those components s_i with maximum possible variance obtained from n linearly transformed components by the relation (Hyvarinen, 1999)

$$s_i = w_i^T x \tag{2}$$

where w_i are the eigen vectors corresponding to the highest eigen values of the covariance matrix

$$C = E[xx^T] \tag{3}$$

2.1.1. Time domain measures

Time domain measures play a significant role in deciphering the underlying neural circuitry in ASD. In this section, several time domain measures that are employed in ASD studies are explained. Sum of signed differences (SSD) indicate the difference between the average standard response and the average deviant response and minimizes the effect of noise (Eldridge et al., 2014). The variance represents the variation of typical response over a particular time period. Sample entropy (S_E) quantifies the degree of randomness of a time-series. It also gives an indication that two sequences with matching data points for the first two values will also match for the succeeding point (Costa et al., 2005). The multiscale entropy (MSE) method gives a measure of the complexity of a time-series by computing S_E over different time scales through coarse-graining procedure (Costa et al., 2002). Consider an EEG time-series $\{x_1, x_2, ...x_i, ...x_N\}$ which is divided into non-overlapping windows of length τ seconds. The data points inside each window is averaged to obtain each element of the coarse-grained time series as per the equation (Costa et al., 2005)

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \ 1 \le j \le \frac{N}{\tau} \tag{4}$$

Then sample entropy is calculated for each coarse-grained time series $y_j^{(\tau)}$ and plotted as a function of τ. This whole procedure is termed as MSE method. The modified multiscale entropy (mMSE) is the set of modified sample entropy values (mSE) computed at each of the coarse-grained scales ranging from 1 to 20 (Bosl et al., 2011). The mSE is a modified version of sample entropy which is based on nonlinear sigmoid function and is more robust to noise (Xie et al., 2008).

The phase lag index (PLI) is a major functional connectivity measure that quantifies the extent to which the phase leads or lags between signals from different brain regions. The weighted phase lag index (WPLI) is an extension of PLI that estimates the consistent 90° (or 270°) phase lagging of one EEG signal from another (Lau et al., 2012). The problem of sample-size bias can be minimized by further modifying WPLI. The debiased WPLI-square estimator (dbWPLI) can be computed as a weighted statistic by (Vinck et al., 2011)

$$\hat{\Omega}^w = \frac{\sum_{j=1}^{N} \sum_{j=k+1} W_{j,k} d(X_j, X_k)}{N(N-1)\overline{W}} \tag{5}$$

$$d(U, V) \equiv \mathrm{sgn}(\Im\{U\}) \mathrm{sgn}(\Im\{V\}) \tag{6}$$

where $W_{j,k} \equiv |\Im[X_j]\Im\{X_k\}|$ is the weight, $\overline{W}$ is the average weight, d is the function defined on two complex-valued random variables U and V.

Transfer entropy (TE), being an alternative connectivity measure, quantifies the direction of information transfer between two channels. Transfer entropy (Vicente et al., 2011) between two time series x_t and y_t is written as

$$TE(X \to Y) = \sum_{y_{t+u}, \mathbf{y}_t^{d_y}, \mathbf{x}_t^{d_x}} p\left(y_{t+u}, \mathbf{y}_t^{d_y}, \mathbf{X}_t^{d_x}\right) \log \frac{p\left(y_{t+u} | \mathbf{y}_t^{d_y}, \mathbf{X}_t^{d_x}\right)}{p\left(y_{t+u} | \mathbf{y}_t^{d_y}\right)} \tag{7}$$

where t is the discrete time index,

u is the prediction time interval,

$y_t^{d_y}$, $x_t^{d_x}$ are d_x– and d_y– dimensional delay vectors.

TE has been modified to satisfy the self-prediction optimality requirement to form TE_{SPO} (Khadem et al., 2016).

$$TE_{SPO}(X \to Y, u) = I(Y_t, \underline{X}_{t-u} | \underline{Y}_{t-1}) \tag{8}$$

where u is the information transfer delay from X to Y

I is the conditional mutual information

$\underline{X}_t$ and $\underline{Y}_t$ are the vectors that represent the past-present states of X and Y respectively.

To remove the effects of zero-lag channel dependencies, TE was enhanced to form modified transfer entropy (MTE). MTE can also be defined with self-prediction optimality (Khadem et al., 2016) as given by

$$MTE_{SPO}(X \to Y, u) = I(Y_t, \underline{X}_{t-u} | \underline{Y}_{t-1}, X_t) \tag{9}$$

2.1.2. ASD studies based on time domain measures

Out of the several ERP components, the main components that are actively studied in the context of ASD are: P300, P50, P400, P100, N100, N170, Nc, N300 and mismatch negativity (MMN). This section deals with the major studies conducted on each component and the