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RESEARCH ARTICLE

Estimating brain effective connectivity from EEG signals of patients with autism disorder and healthy individuals by reducing volume conduction effect

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Abstract

Studying brain connectivity has shed light on understanding brain functions. Electroencephalogram signals recorded from the scalp surface comprise inter-dependent multi-channel signals each of which is a linear combination of simultaneously active brain sources as well as adjacent non-brain sources whose activity is widely volume conducted to the scalp through overlapping patterns. Evaluation of brain connectivity based on multivariate autoregressive (MVAR) model identification from neurological time series can be a proper tool for brain signal analysis. However, the MVAR model only considers the lagged influences between time series while ignoring the instantaneous effects (zero-lagged interactions) among simultaneously recorded neurological signals. Hence predicting instant interactions may result in fake connectivity, which may lead to misinterpreting in results. In this study, we aim to find instantaneous effects from coefficients of the MVAR model acquired using an ADALINE neural network and investigate the efficiency of the proposed algorithm by applying it to a simulated signal. We show that our coefficients are estimated accurately from channels of the simulated signal. Moreover, we apply the proposed method on a dataset of a group of 18 healthy children and 10 children with autism by comparing their effective connectivity estimated by direct directed transfer function method using new and old coefficients. Finally, to show the efficiency of the algorithm we exploit the support vector machine method for classifying the dataset. We show that there is a significant improvement in the results obtained from the proposed method.

Keywords Autism · Effective connectivity · eMVAR · ADALINE neural network · Volume conduction · EEG

Introduction

The brain is one of the most developed systems in the body on which a plethora of different studies have been performed to identify its structure and functionality. Network studies of brain connectivity have discovered attributes that promote the segregation and integration of information flow. Anatomical and functional segregation in the brain refers to localizationism, the existence of specialized interconnected neurons and brain areas, while functional integration refers to the combination of specialized information from distributed brain regions. The balance between segregation and integration is essential for neural systems to have flexible cognition and behavior, misconduct to this ability is a common feature of several neuropsychiatric disorders. (Sporns and Tononi 2007; Sporns 2013; Lord 2017).

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Studying brain connectivity and dynamics provides an important tool for understanding brain networks through different brain states, and their potential association with various behavior. In general, brain connectivity is divided into three categories: (1) Structural connectivity refers to the neural fiber network and the structural integrity of tracts connecting different brain areas, (2) Functional connectivity contains statistical dependencies of the undirected brain activity across various regions, and 3. Effective connectivity includes causal and directed connectivity of brain activity. Investigating the connection between the activity of different brain regions using effective and functional connectivity is a challenging and developing topic in neuroscience which give researchers the ability to obtain broad knowledge and information regarding brain activity and provides better predicting, diagnostic or therapeutic approaches for neurological disorders like Autism, Alzheimer, Parkinson, schizophrenia, and epilepsy. Although different approaches are used to assess brain connectivity, we will focus on analyses of directed functional connectivity (i.e., effective connectivity). This category of connectivity can be computed using several methods including: directly from signals, i.e., data-driven, like Granger Causality (GC), or based on a model specifying the causal links, i.e., model-based, like dynamic causal modeling (DCM) and structural equation modeling (SEM) (Sakkalis 2011; Friston 2011; He 2019).

Granger causality (GC) is a method based on the statistical concept of causality where $y_j(n)$ causes $y_i(n)$ if the past information of $y_j(n)$ can improve the prediction $y_i(n)$, which is used for connectivity estimation. Analyzing neurophysiological signals using MVAR models based on the Granger causality concept (Granger 1969) is very popular and practical. Using this methodology, we can model the interaction between EEG channels as linear differential equations in which the direction can define the inter-channel (directed or undirected) information flow (Astolfi 2008). Directed transfer function (DTF) (Kaminski 1991), direct directed transfer function (dDTF) (Korzeniewska 2003), partial directed coherence (PDC) (Baccalá 2001) and generalized PDC (GPDC) (Baccalá 2007) techniques are popular connectivity measures derived from MVAR models. A controversial issue in MVAR-based causality analysis is that the model only reports the lagged effects, i.e., previous influences of a time series on another set, while instantaneous effects, considered as the volume conduction, are not described with any coefficient in the model.

Volume conduction (VC) arises from the distribution of electrical fields for EEG and magnetic fields for MEG data. In essence, instead of exclusively measuring the neighboring brain regions, each channel includes linear combinations of simultaneous activity of the brain and non-brain electrical resources whose activity is widely volume conducted to the scalp through overlapping patterns (Nunez 1997). Acquired signals from electrodes may demonstrate spurious effective and functional connectivity due to volume conduction even among non-interactive brain sources (Brunner 2016; Van de Steen 2019). Several methods have been proposed for removing the effect of volume conduction in estimating brain connectivity using signals collected from multi-channel EEG recordings. Multiple studies have proposed investigating brain connectivity in source space which includes assessing underlying nerve sources from head EEG signals (Gómez-Herrero 2008; Schoffelen 2009; Haufe 2013). Nonetheless, neural source determination from EEG signals is an ill-posed inverse problem that does not have any unique solution without initial knowledge or strong statistical assumptions so the accurate estimation of the connectivity network is not guaranteed (Baillet 2001). Moreover, the inverse problem does not remove the mixing effects completely and hence spatial leakage will still be present in the source space especially for those that are close to each other (Van de Steen 2019).

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders that influences the normal process of brain development which may affect social skills and communication. Individuals suffering from ASD have difficulties in social interactions, as well as verbal and nonverbal communications. Moreover, they may have limited interests and repetitive behaviors on certain occasions. One of the most effective biomarkers for investigating this disorder is brain connectivity. To be specific, functional and effective connectivity are powerful in gaining qualitatively different results which are significant in giving us intuition about how the brain connections are changed in autism (O'Rielly 2017; Vissers 2012; Wass 2011; Coben 2013; Maximo 2014; Ghahari 2020). Previous studies on brain connectivity in ASD individuals demonstrate various results, which is due to the different imaging modalities, measurement techniques, paradigms, participant characteristics, definitions, and theoretical models for (re)constructing brain networks to test a given hypothesis. Although in many studies, functional Magnetic Resonance Imaging (fMRI) has been used for investigating connectivity, nonetheless, due to rich temporal dynamics, Electroencephalogram (EEG) or Magnetoencephalogram (MEG) are preferred. Both fMRI and MEG are so sensitive to motion artifacts and mostly impractical for children with repetitive and stereotyped behavior (Mohammad-Rezazadeh 2016). Initial findings in autism using MRI analysis propose the hypothesis of overall deficiency in connection in the neural network based on reduction in blood oxygenation level-dependent (BOLD) signal correlations

among several cortical regions in adults with ASDs during comprehension-related experiences (Just 2004). Nonetheless, many other studies claimed more complex patterns, a mixture of hypo- and hyper connectivity, caused due to the distance between the brain regions. (For review, refer to Hull 2017; O'Rielly 2017; Vissers 2012; Mash 2017; Rane 2015).

While, based on previous works, ASDs are claimed to be characterized by reduction in long-range connectivity especially between frontal lobe and other brain regions; however, in some studies, predominantly supported by structural and functional MRI (Visser 2012; Wass 2011; Müller 2011), increase in short-range connectivity, local connectivity, has also been reported (Belmonte 2004; Courchesne 2005).

On the other hand, in EEG/MEG literature, both local hypo and hyper-connectivity are shown through coherence analyses. Many studies reported reduced long-range coherence patterns in resting-state EEG of ASD subjects, yet significantly weaker connectivity between the frontal lobe and other cortical regions (Murias 2007; Coben 2008; Barttfeld 2011). Specifically, Duffy (2012) showed that within the beta band, there is weaker connectivity in left frontal–temporal, frontoparietal, and occipitofrontal regions which are similar to what has been resulted from multiple fMRI studies in resting state (Koshina 2008; Just 2004; Sato 2012). To put all these findings into perspective, weakened long-range connectivity between the frontal lobe and other cortical regions is suggested. This is not a surprising pattern for ASDs, because the frontal lobe plays an important role in verbal, cognitive, social, and interactive functions (Courchesne 2005). Findings on short-range connectivity in EEG/MEG literature are inconsistent. Both intrahemispheric and interhemispheric interactions have been shown to be decreased in delta and theta bands in children with autism compared to healthy children (Coben 2008), while weaker connectivity between frontal and other cortical regions has been reported in both the delta frequency band (Barttfeld 2011) and alpha frequency band in Murias (2007). On the contrary, in the delta frequency band, increased short-range connections have been found in left frontal (Barttfeld 2011), and within frontal in the theta band (Murias 2007) in ASD individuals compared to healthy subjects.

The hypothesis of long-range versus short-range connectivity remains elusive, especially in EEG/MEG, but confirm that in people with ASD, brain regions connect in a different way than they do in healthy people and it is characterized by abnormal patterns of brain connectivity. These methods have great amounts of time separability, in millisecond scale, however, due to the lack of spatial resolution for recognizing the sources close together and also, the effect of volume conduction on the signals recorded from close electrodes (Srinivasan 2007) findings on short range connection patterns resulted from EEG studies are not consistent enough. In previous studies on these modalities, the long-range underconnectivity approach has been well proven, but local over connectivity results are inconsistent and should be investigated more in detail (Mash 2017; O'Reilly 2017).

In this study, we aim to present a framework to reduce the zero-lagged causality (i.e., volume conduction effects) based on MVAR models. We apply our method to a theoretical simulated example and compare their estimated coefficients before and after including the zero-lagged term. Then, we present an application of the framework to a resting state EEG dataset that entail utilization of both coefficients and investigation of different aspects of causal information transfer based on dDTF. Finally, we classify our dataset into two group of typically developed individuals and children with autism.

Method

Multivariate Autoregressive models are a proper tool for studying physiological time series like EEG.

$$Y(n) = \sum_{k=1}^{p} A(k)Y(n-k) + U(n) \tag{1}$$

where $A(k)$ describes the lagged interactions among observed time series and $p = 1, \ldots P$ is the model order, defining the maximum lag used for measuring the interactions. The input $U(n)$, is assumed to be composed of white and uncorrelated noise. Since MVAR is strictly a causal model, it only reports the lagged effects, namely previous influences of a time series on another set, while instantaneous effects which are considered as the volume conduction (effect of $y_j(n)$ on $y_i(n)$are not described with any coefficient in the model. The problem here is any zero-lag correlations in Y_k cannot be described by the MVAR model because $A(k)$ is defined only for positive lags ($k = 0$ is not considered in the Eq. 1) As a result of ignoring instantaneous interactions in the model, spurious connectivity is produced in the model which may cause misinterpretation in the results (Lutkepohl 1993; Faes 2010). To encounter this issue Faes and Nollo (2010) suggested exploiting an extended version of MVAR which includes instantaneous interactions. Equations 2 demonstrates the extended MVAR (eMVAR) model.

$$Y(n) = \sum_{k=0}^{p} B(k)Y(n-k) + W(n) \tag{2}$$

where $Y(n) = [y_1(n), \ldots, y_M(n)]^T$ is the observed time series, p the model order,, $B(k)$ are $M \times M$ coefficients matrices in

which $b_{ij}(k)$ presents the dependence of $y_j(n-k)$ on$y_i(n)$; (i, j = 1,…,M; k = 0, 1,…,p) and W=$[W_1,\ldots,W_M]^T$ is an innovative term that is composed of white and independent scalar processes. As it is shown, in contrast with (1), in (2) k takes the value 0 as well, which cause the model to account the instantaneous effect from $y_j(n)$ to $y_i(n)$ in the form of the coefficients $b_{ij}(0)$ of the matrix $B(0)$. Below we can see the relationship between these two models:

$$\begin{aligned} Y(n) &= \sum_{k=1}^{p} LB(k)Y(n-k) + LW(n) \\ A(k) &= LB(k) \quad k \geq 1 \\ U(n) &= LW(n) \\ \mathrm{L} &= \mathrm{I} - \mathrm{B}(0)^{-1} \end{aligned} \tag{3}$$

where I is the $M \times M$ identity matrix, L results from Cholesky decomposition method applied to the covariance of $U(n)$ and $B(0)$ is estimated using L such that, $B(0) = I - L^{-1}$. We should take this into consideration that, when $B(0)$ = 0, instantaneous causality is missing and remained causality is equal to the lagged causality while, when $B(0)$ is not only extended causality differs from lagged causality, but also lagged causality estimated from Eq. (3) differs from lagged causality estimated from the model (1) because the inclusion of instantaneous effects in the MVAR model changes also the values of the lagged effects ($B_k \neq A_k$ for $k > 0$) (Faes 2010,2013).

In this study, a novel method is proposed for estimating the $B(0)$ term describing the volume conduction effect. Since MVAR is a linear model, we exploit the Adaptive Linear Neural Network (ADALINE) due to having a linear transfer function aiming to reduce the dependency between the channels. To obtain the instantaneous effects, we set the input and output of the ADALINE the same and equal to the EEG signal and for attaining the instantaneous effects of volume conduction, weights in each row (channel) of the input which was linked to the corresponding channel in the output was set to zero ($w_{i,j} = 0\, for\, i = j$). Then we tried to find the remaining weights which were actually the inter-channel influences. The bias was set to zero. The resulting matrix which is a square matrix with diagonal elements equal to zero is, in fact, the $B0$ volume conduction matrix which shows the instantaneous effect. Now in practice after estimating $A(k)$ from the strictly causal MVAR model (1) we should solve the instantaneous model by ADALINE network to estimate $B(0)$ then using the following equation, we can calculate the $B(k)$ coefficients which describes only the lagged interactions:

$$Y(n) = \sum_{k=1}^{p} \mathrm{L}^{-1}A(k)Y(n-k) + W(n) \tag{4}$$

$$B(k) = \mathrm{L}^{-1}A(k) = [\mathrm{I} - \mathrm{B}(0)]A(k) \tag{5}$$

By removing $B(0)$ from AR coefficients of the observed time series from $Y(n)$ channels, we aim to reduce the dependency between the channels resulting in improving the prediction of sources parameters via the sensor level. We can implement this procedure to connectivity measures based on multivariate autoregressive (MVAR) modeling. Here in this study, we estimate and compare the effective connectivity via the dDTF method using both $A(k)$ and $B(k)$.

DTF determines the interrelations between two signals with respect to all other existing signals in a system. As it is shown on Eq. 6. it is defined using the transfer matrix, H_{ij}, and represents the connection between the jth input and the ith output of the system (Kaminski 2014):

$$\gamma_{ij}^2(f) = \frac{\left|H_{ij}(f)\right|^2}{\sqrt{\sum_{m=1}^{M}|H_{im}(f)|^2}} \tag{6}$$

where $H(f) = [I - A(f)]^{-1} = \overline{A}(f)^{-1}$ is a $M \times M$ transfer matrix. However, DTF demonstrates both direct and indirect activity propagation within the whole system, hence to obtain, only direct propagations, dDTF was proposed. To remove the dependence of the denominator of DTF on the frequency and allowing more interpretable comparison of information flow at different frequencies, full frequency Directed Transfer Function (ffDTF) was defined (Korzeniewska 2003).

$$\eta_{ij}^2(f) = \frac{\left|H_{ij}(f)\right|^2}{\sum_f \sum_{k=1}^{M}|H_{ik}(f)|^2} \tag{7}$$

Partial coherence (pCoh) is also given by a formula on Eq. 8, in which $S(f)$ is the Spectral matrix (Bendat and Piersol 1986):

$$\begin{aligned} pcoh &= \frac{\widehat{S_{ij}}(f)}{\sqrt{\widehat{S_{ii}}(f)\widehat{S_{jj}}(f)}} \\ \hat{S}(f) &= S(f)^{-1} \end{aligned} \tag{8}$$

Finally, dDTF is obtained from multiplying ffDTF by pCoh (Korzeniewska 2003):

$$\delta_{ij}^2(f) = \eta_{ij}^2(f)P_{ij}^2(f) \tag{9}$$

Figure 1, demonstrates the flowchart of the algorithm procedure.

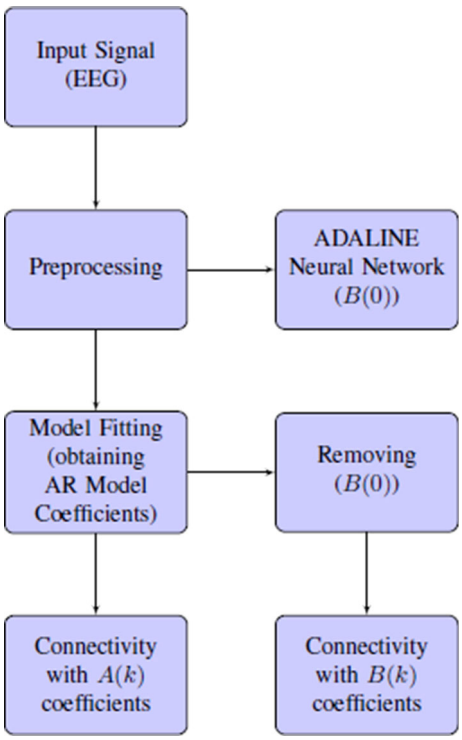

Fig. 1 The flowchart of the algorithm procedure

Results

Theoretical simulation

In this section to provide better observation and understanding of the proposed method we describe the analysis of AR coefficient for a simple theoretical example to show how the instantaneous effect impacts the measurements in the sensor space. Then, we investigate two non-interacting sources with a simulated signal of length 10,000 presented below in Eqs. (10) and (11) in which, the time series X represent the source signals. The coefficient matrix is the AR coefficient and the δ values are uncorrelated white noise. Y represents the sensor signals produced by channels in which the volume conduction effect is multiplied and the model order p is set to 2.

$$X = \begin{cases} x_1(n) = 0.9x_1(n-1) - 0.5x_1(n-2) + \delta_1(n) \\ x_2(n) = 0.7x_2(n-1) - 0.3x_2(n-2) + \delta_2(n) \end{cases} \tag{10}$$

$$Y = \begin{cases} y_1(n) = 0.9x_1(n) - 0.3x_2(n) \\ y_2(n) = 0.2x_1(n) + 0.7x_2(n) \end{cases} \tag{11}$$

In this order to demonstrating the efficiency of our method, we estimated the AR coefficients both from sources ($X(t)$) and from channels ($Y(t)$) based on Vieira Morf, that represent the best estimation of coefficient, to compare the results before and after including the zero-lag term. Then, by estimating instantaneous effects (B0) using ADALINE network and subtracting them from pre-obtained coefficients ($A(k)$), new coefficients ($B(k)$) would be determined. The results are shown in Tables 1 and 2. We implemented the method ten times, with different random initialization, and the results are shown by "mean ± standard deviation" of the estimations.

Table 1 contains the source-estimated coefficients of both time series when there is no mixing effect. Our proposed method has no significant effect on coefficients, and both measurements show almost the same well-estimated results. Table 2 illustrates the results when zero-lagged terms are included, the mixing matrix multiplied in Y time series, mapping signals from sources to channels. As it is observable this instantaneous term alters the estimation of the coefficients and lead to spurious connectivity between two non-interacting sources. Using our proposed framework, we tried to reduce zero-lagged effects from AR coefficients acquired from mixed time series to mitigate the dependency between them. The coefficients are zero in both directions between the two sources x_1 and x_2 ($A_{12} = A_{21} = 0$) while, the estimated values are larger than zero between the two sensors y_1 and y_2, exploiting new method moves this bidirectional interaction towards zero. Also, the small value of SDs for both methods emphasize appropriate repeatability of results.

After assessing the coefficients, we applied Frequency Response Analysis (FRA) to graphing the dynamic response of our results to see exactly how the magnitude and phase response changes over a range of different frequencies. We used frequency peak to compare the discrepancy between the frequency responses of both sensor-estimated coefficients with the originals to provide an initial assessment of the similarity. Figure 2, demonstrate the comparison of FRA, as it has shown frequency peak of our proposed method is closer to the frequency peak of the original coefficients and provide a more reliable estimation.

Dataset

In this study we use a dataset of children with ASD, recorded by Dr. Coben and his team at Integrated Neuroscience Services (INS). The dataset contains EEG signals from 10 children suffering from autism and 18 typically developed (TD) children. EEG was recorded with 19 electrodes according to the 10–20 standard with sampling rate of 128 HZ in eyes-open resting state while individuals are asked to try to keep their eyes on a cross sign on the screen in front of them.

To reduce the computational load, we selected 9 separate channels from different regions of the brain including:

Table 1 Original and estimated source coefficients (from *X* time series) for the simulated model by proposed method for lag = 1, 2

Source coefficients	Originals Lag = 1	Estimated A(k)	Estimated B(k)	Originals Lag = 2	Estimated A(k)	Estimated B(k)
1 → 2	0.9	0.8990 ± 0.0077	0.8993 ± 0.0079	− 0.5	− 0. 5012 ± 0.0075	− 0.5011 ± 0.0079
2 → 1	0	0.0026 ± 0.0073	− 0.0031 ± 0.0191	0	0.0023 ± 0.0061	0.0036 ± 0.0074
1 → 2	0	− 0.0040 ± 0.0072	− 0.0060 ± 0.0120	0	0.0010 ± 0.0067	0.0013 ± 0.0126
2 → 2	0.7	0.6981 ± 0.0099	0.6980 ± 0.0103	− 0.3	− 0.2970 ± 0.0067	− 0.2973 ± 0.0065

Results of estimated coefficients are shown by mean ± standard deviation

Table 2 Original and estimated sensor coefficients (from *Y* time series) for the simulated model by proposed method for lag = 1, 2

Sensor coefficients	Originals Lag = 1	Estimated A(k)	Estimated B(k)	Originals Lag = 2	Estimated A(k)	Estimated B(k)
1 → 1	0.9	0.8819 ± 0.0073	0.8830 ± 0.0071	− 0.5	− 0. 4826 ± 0.0084	− 0.4854 ± 0.0048
2 → 1	0	0.0760 ± 0.0102	0.0116 ± 0.0259	0	− 0.0765 ± 0.0080	− 0.0487 ± 0.0114
1 → 2	0	0.0390 ± 0.0057	− 0.0007 ± 0.0108	0	0. 0409 ± 0.0050	− 0.0188 ± 0.0066
2 → 2	0.7	0.7144 ± 0.0090	0.7070 ± 0.0075	− 0.3	− 0.3141 ± 0.0059	− 0.3095 ± 0.0050

Results of estimated coefficients are shown by mean ± standard deviation

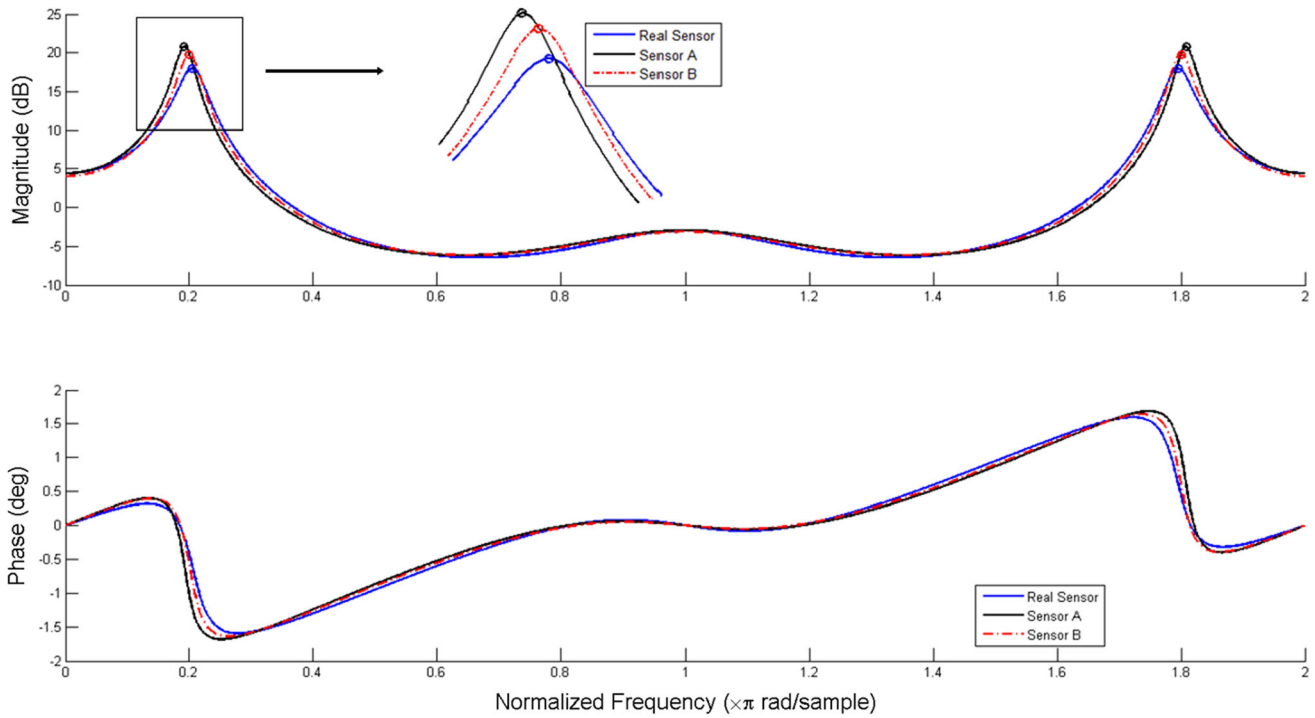

Fig. 2 Comparison of FRAs calculated from both estimated coefficients ($A(k)$ and $B(k)$) and original coefficients

(F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). As for data processing, we used EEGLAB toolbox in MATLAB (Delorme 2004). A high-pass filter with a cut-off frequency of 1 HZ is applied to the data for baseline drift removal. Then the data is cleaned by the ASR plugin and to attenuate the power line noise (60 Hz), the Cleanline plugin was used. Then the Independent Component Analysis (ICA) is used to remove the EOG and EMG artifacts. MVAR model is fitted using Vieira Morf algorithm. Akaike Information Criterion (AIC) was also used for model order selection. We focused on computation of effective connectivity, direct Directed Transfer Function (dDTF) was computed from both

$A(k)$ and $B(k)$ coefficients. Then, statistical significance of estimated interactions was assessed based on the surrogate data test by generating phase randomization (p-value < 0.05).

Group analysis

For group analysis, to compare the connectivity discrepancy between two groups, average is taken from all subjects with autism and healthy individuals. Here as an exemplification, effective connectivity of three bands of frequency (Delta, Theta and alpha) with both $A(k)$ and $B(k)$ coefficients for two groups are illustrated in Figs. 3 and 4, respectively, in which $A(k)$ coefficients are estimated by strictly causal MVAR modeling and B(k) coefficients are lagged coefficients for which the instantaneous effect, $B(0)$, is removed from the MVAR model estimating ($A(k)$). We used BrainNet Viewer software for visualizations (Xia 2013).

In Figs. 3 and 4, brain regions are approximately determined according to Kabdebon (2014), and to be more observable and differentiable between two cases, the thickness of the arrows corresponds to the intensity of information flow. In Fig. 3, the effective connectivity of children with autism using both $A(k)$ and $B(k)$ are demonstrated. For children with autism, interactions based on both coefficients have almost the same pattern, overall connectivity decreased from Delta to Alpha band of frequency. The intensity of connectivity in individuals with autism is more concentrated in right lobe; they are mostly directed from frontal lobe toward posterior (occipital, temporal and parietal). While, long-range intra-hemispheric connections in both coefficients are decreased specially in left hemisphere, connectivity is increased in frontal lobe in $A(k)$. Interactions with $A(k)$ coefficients is significantly lower than their connectivity with $B(k)$ coefficients in alpha band.

Figure 4, illustrate the effective connectivity of typically developed individuals using both $A(k)$ and $B(k)$. They have almost the same pattern in each column, overall connectivity decreased from Delta to Alpha band of frequency. Connectivity based on $A(k)$ coefficients are significantly low, their values are close to zero. Nevertheless, with $B(k)$ coefficients connections are spread out all across the head and show a symmetry connection. Overall connectivity values in healthy children are weaker than their autistic counterpart.

Classification

To investigate and evaluate extracted connectivity using dDTF for both $A(k)$ and $B(k)$ coefficients (volume conduction is removed in $B(k)$ using proposed method), we applied support vector machine (SVM) with RBF kernel function. Due to lacking enough subjects, we exploited Leave One Out (LOO) approach for splitting train and test dataset. Connectivity between channels and frequency have been considered as features for classifier. Below in Table 3, accuracy, sensitivity, specificity and precision are calculated for both $A(k)$ and $B(k)$ through confusion matrix. we had improvement in dDTF classification with 96% accuracy using $B(k)$ coefficients.

Discussion

Previous works on effective connectivity in autism have mostly been relying on either model-based method, say dynamic causal modeling (DCM), and structural equation modeling (SEM)), or task-based methods (Wicker et al. 2008; Grezes et al. 2009; Sato et al. 2012; Shih et al. 2010). However, these kinds of methods mainly rely on a prior specification of the connectivity linkages meaning the structural graph must be known in advance (Sakkalis 2011). Moreover, without having fundamental knowledge of functional differences between individuals with ASD at rest state, task-dependent changes in brain function are difficult to describe (Wang 2013). In this study we used MVAR based connectivity analysis on resting state EEG data. MVAR based measures are data-driven techniques that do not assume any specific underlying model or prior knowledge but are influenced by volume conduction and their straight application to sensor EEG data can lead to the detection of spurious connections. Although in several works which have suggested studying at source space, some researchers have tried to reduce the undesired influence of VC effects on the estimated connectivity networks by solving the EEG/MEG inverse problem and estimating the connectivity among the estimated brain sources; however, due to the ill-posed nature of the EEG/MEG inverse problem, the accurate estimation of the connectivity network is not guaranteed. Mixing effects caused by volume conduction can also occur in the source space (Van de Steen 2019). Results derived from MVAR model coefficients do not include zero-phase terms as a result of which, neglecting instantaneous effects by the model can affect the correlation structure of the model residuals, which are normally assumed to be uncorrelated and also the lagged dependencies (Lutkepohl 1993). For overcoming this issues eMVAR modeling was proposed (Faes 2010). The

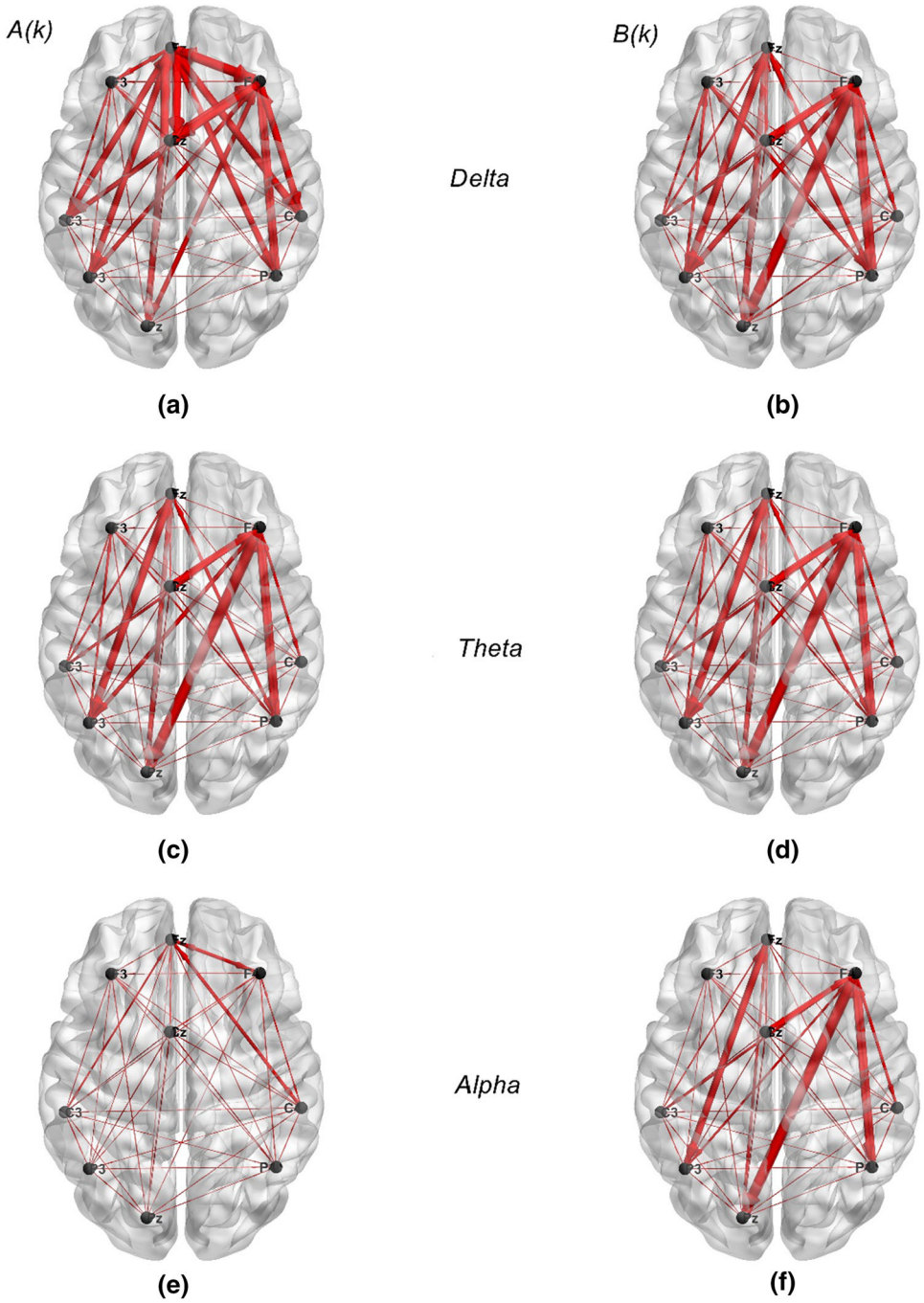

Fig. 3 Effective connectivity representation of band frequencies (Delta, Theta, Alpha) with ***A(k)***, right column, and ***B(k)***, left column, coefficients of ASDs (thickness of the arrows corresponds to the intensity of information flow)

basic problem in eMVAR method is that the instantaneous model may suffer from lack of identifiability, being related to the zero-lag covariance structure of the observed data. In the other words, there may be several combinations of L (or, equivalently, B (0)) and $W(n)$ which result in the same $U(n)$, and thus describe the observed data $Y(n)$ equally well. The easiest way to solve this ambiguity is to impose a priori the structure of instantaneous causation, i.e., to set the direction (though not the strength) of the instantaneous transfer paths. Nevertheless, if similar prior knowledge is not available, as happens e.g., in the analysis of EEG data, other ways have to be followed to overcome problem of identifiability of the extended model (Faes 2013). To get the better of this, we proposed a novel method to estimate zero lag effects using ADALINE that only needs to fit the time series in this network. We showed that we can improve the connectivity results by reducing the channel dependencies and undesired effects of instantaneous correlations between time series.

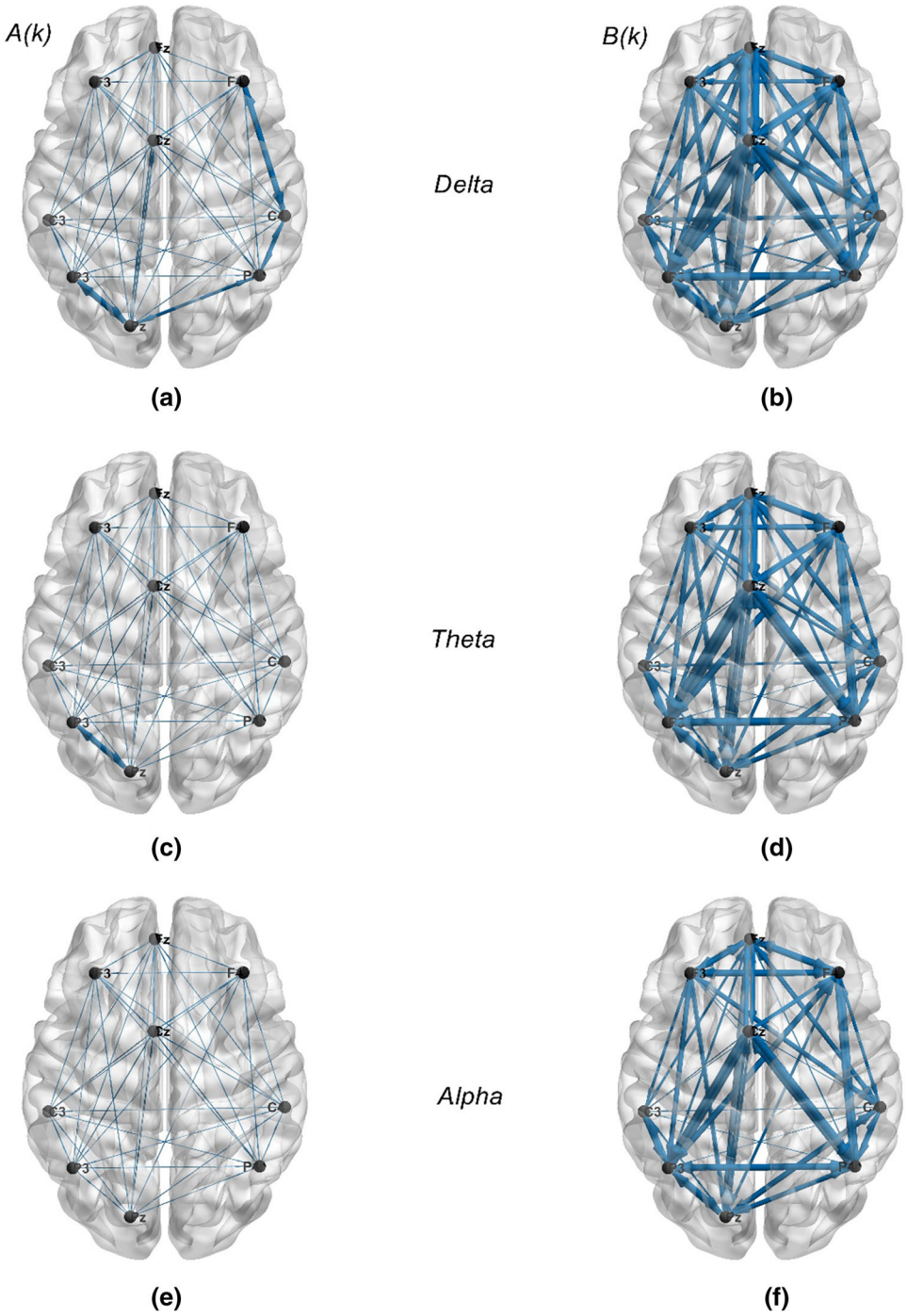

Fig. 4 Effective connectivity representation of band frequencies (Delta, Theta, Alpha) with ***A(k)***, right column, and ***B(k)***, left column, coefficients of TDs (thickness of the arrows corresponds to the intensity of information flow)

Table 3 Classification results for $A(k)$ and $B(k)$ coefficients (%)

dDTF	Accuracy	Sensitivity	Specificity	Precision
A(k)	88	80	94	88.8
B(k)	96	90	100	100

Evaluating effective connectivity in both TD and ASD groups in the resting state shows a weaker left frontal to temporal-parietal-occipital connectivity in children with ASD cases compared to control subjects. This finding is aligned with results from several fMRI studies (Just 2004; Koshino 2008; Sato 2012) and EEG study (Duffy 2012) in resting state and converge to suggest weakened long range connectivity between the frontal lobe and other cortical regions. Weaker frontal connectivity based on

$B(k)$ coefficients is correspondent with (Coben et al. 2008; Dawson et al. 1995), also intra-hemispheric connections in children with autism compared to healthy individuals reduced which is compatible with (Coben 2008; Elhabashy 2015; Lushchekina 2016).

In conclusion, evaluating effective connectivity indicates that ASD is a disorder characterized by abnormal patterns of brain interaction. the proposed method for the assessment of causality has been shown to be useful in practical analysis, for counteracting the problems arising from the presence of instantaneous effects in multiple interacting time series. Our results are compatible with previous studies indicating that brain activity in frontal, is poorly coordinated in individuals with ASD compared to healthy subjects. The way we used our proposed method and how it affects the results is shown and described under the simulation section. Moreover, for performance evaluation, we can see that our proposed method achieves 96% accuracy in SVM classification.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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