Down syndrome's brain dynamics: analysis of fractality in resting state

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Abstract To the best knowledge of the authors there is no study on nonlinear brain dynamics of down syndrome (DS) patients, whereas brain is a highly complex and nonlinear system. In this study, fractal dimension of EEG, as a key characteristic of brain dynamics, showing irregularity and complexity of brain dynamics, was used for evaluation of the dynamical changes in the DS brain. The results showed higher fractality of the DS brain in almost all regions compared to the normal brain, which indicates less centrality and higher irregular or random functioning of the DS brain regions. Also, laterality analysis of the frontal lobe showed that the normal brain had a right frontal laterality of complexity whereas the DS brain had an inverse pattern (left frontal laterality). Furthermore, the high accuracy of 95.8 % obtained by enhanced probabilistic neural network classifier showed the potential of nonlinear dynamic analysis of the brain for diagnosis of DS patients. Moreover, the results showed that the higher EEG fractality in DS is associated with the higher fractality in the low frequencies (delta and theta), in broad regions of

the brain, and the high frequencies (beta and gamma), majorly in the frontal regions.

Keywords Down syndrome · EEG · Fractal dimension

Introduction

Down syndrome (DS) is a common genetic disorder, with an extra copy of chromosome 21, which causes lifelong mental retardation and developmental delays especially in learning and language (Nadel 2003). Many neuroimaging studies have been carried out to understand differences of the DS and normal brains, from the EEG-based study of Kreezer in 1936 until now (Schmid et al. 1992).

MRI volumetric analyses show that total brain volume, total gray matter, and total white matter volumes of DS subjects are considerably smaller than normal subjects (Pinter et al. 2001). Slow wave brain is the major characteristic of the DS brain activity detected by EEG (Babiloni et al. 2009). Slow wave brain means higher activity of the brain in low frequencies (delta) and lower activity in high frequencies (alpha and beta). Moreover, there is an inverse relationship between alpha activity and age in DS patients (Sannita et al. 1993). All of the afore-mentioned results of spectrum and coherence analyses of the EEG come from regarding the brain as a simple linear system. Whereas regarding the brain as a highly complex and nonlinear system (Ahmadlou and Adeli 2011a, b, 2012; Ahmadlou et al. 2013; Hu and Liang 2011; Kiebel et al. 2008; Wang et al. 2010) makes one wonder about what happens in the nonlinear dynamics and complexity of the DS brain. The high temporal resolution of EEG has made it a powerful tool for nonlinear analysis of brain dynamics (Ahmadlou et al. 2012d, e; Nakatani et al. 2011; Schinkel et al. 2007;

Sahel Hemmati and Mehran Ahmadlou had equal contribution in this research and both should be considered as the first author.

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Vialatte et al. 2009). In this study, fractal dimension (FD) of the EEG, as a key characteristic of brain dynamics (Ahmadlou et al. 2012b; Gao et al. 2011), is used for evaluation of the dynamical changes in the DS brain.

Fractal dimension (FD) quantifies the self-similarity in a time series. This refers to the number of times similar patterns in a time series are repeated in different temporal scales. FD of a brain signal shows how much regularly or irregularly the brain works (such as a periodic or a random system, respectively) and how much complex it is (the range between random and periodic). The higher the FD, the higher the brain complexity. However, very high variations of FD as compared to FD of normal EEGs show a brain disease/disorder. As a key characteristic of brain dynamics, FD is increasingly being studied to understand the dynamics of many neurological and cognitive/behavioral disorders such as Alzheimer's disease (Ahmadlou et al. 2010b, 2011), autism (Ahmadlou et al. 2010a; Catarino et al. 2011), major depressive disorder (MDD) (Ahmadlou et al. 2012c), and attention deficit/hyperactivity disorder (ADHD) (Fernández et al. 2009; Sohn et al. 2010). In some cases such as epilepsy the FD is decreased (Adeli et al. 2007) and in some cases such as MDD it is increased (Ahmadlou et al. 2012c).

In this study, we have determined how the brain dynamics vary in DS. There are many algorithms for measuring FD. Katz's Fractal Dimension (KFD) algorithm (Katz 1988) is one of the most common FD algorithms. Esteller et al. (2001) compared the KFD with another common FD algorithm, the Higuchi's FD (Higuchi 1988). They showed the KFD is more robust to noise in comparison with the Higuchi's FD, which makes it more effective for detecting the beginning of the ictal period and measuring FD of natural signals. Recently Ahmadlou et al. (2010a, 2011) showed KFD has impressive ability in prediction of Alzheimer's disease and diagnosis of autism. Hence in this study in order to measure the fractality of the EEGs in DS subjects, the KFD algorithm was used. Moreover, the FD differences between the DS and normal groups are investigated in different EEG subbands to find out which frequency bands are responsible for the deficient brain fractality in DS.

Methods

Participants

A number of 42 right-handed children and adolescents, including 20 DS and 22 healthy subjects, participated in this study. The healthy participants were recruited from Tehran citizens who were informed about the study by posters hung around the city, and the genetically confirmed

DS participants were recruited from the DS Association Center in Tehran, who participated voluntarily. The healthy group included 10 females and 12 males, aged from 5 to 15 years, and the DS group included 7 females and 13 males, aged from 4 to 14 years. The healthy participants included in the study had no history of neurological/psychological disorders, brain injuries or seizures. The parents of all participants signed a written informed consent prior to participation. Nonverbal intelligence quotient (IQ) and handedness of all participants were scored by the Raven Progressive Matrices and the Edinburgh Handedness Questionnaire (ranging from 0 to 100 for right-handedness), respectively. Birth weight was asked and the head circumference determined by an examiner. Table 1 represents the mean age, nonverbal IQ score, handedness score, birth weight, and head circumference for the two groups. Also, the *F* values and *p* values, determined by one-way analysis of variance (ANOVA), show no statistically significant difference in age, birth weight, and handedness between the normal and DS groups, and as expected, the groups are significantly different in terms of nonverbal IQ and head circumference.

Psychophysiological recording

EEGs were recorded using a 19-channel PC-based system. Using an electrocap the Ag–AgCl electrodes were placed at 19 scalp locations (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz) according to the international 10–20 system, referenced against averaged earlobes with the ground electrode on Fpz (see

Table 1 Statistical description of the participants' characteristics (age, nonverbal IQ, handedness, birth weight, and head circumference)

	Mean	SD	<i>F</i>	<i>p</i> value
Age (years)				
Normal	9.5962	2.50607	3.271	0.078
DS	8.1053	3.01652		
Nonverbal IQ				
Normal	110.8889	16.69762	218.41	0.000*
DS	55.25	5.75		
Handedness				
Normal	94.1789	12.38851	4.153	0.050
DS	62.8472	65.84826		
Birth weight (g)				
Normal	3,186.1111	532.69723	1.266	0.269
DS	2,925.2941	816.89288		
Head circumference (cm)				
Normal	53.8947	1.67148	71.937	0.000*
DS	49.1778	1.71106		

* Correlation is significant at the 0.001 level (2-tailed)

Fig. 1). The electrode-scalp resistance was kept below 10 k Ω . The vertical-horizontal EOG was registered on the right eye. With the subjects in a relaxed state and eyes closed, sitting on a comfortable fixed chair in a quiet room, continuous EEGs were recorded for 240 s with a sampling rate of 250 Hz (60,000 data points), filtered by a band-pass of 0.1–100 Hz, and digitized in 16 digits. An interval of 15,000 data points (1 minute) of each participant's EEG, judged to be free of eye blinking and electro-oculographic artifacts, where the absolute amplitude of EOG was <70 μ V and free of movement artifacts, was selected from each EEG to be included in the study, based on visual inspection. Figure 2 shows EEG power spectrum at representative frontal, central, and parietal midline electrodes (Fz, Cz, and Pz) for the normal group (represented in a, c, and e, respectively, at the left side, depicted by black lines) and the DS group (represented in b, d, and f, respectively, at the right side, depicted by gray lines).

EEG analysis

The EEGs were digitally filtered in 1–70 Hz by a Butterworth band-pass filter. Also a 50 Hz notch filter was applied to remove the electricity line interference. Then the fractality and complexity of the EEGs were computed using the KFD algorithm. In this algorithm, conceptually, variation of distances of successive points is considered as irregularity and fractality in the time series. Consider $\mathbf{x} = [x_1, \dots, x_N]$ as an EEG with N sample times, where x_i indicates the i th sample of $\mathbf{x}$. The KFD values were

computed for the EEG of each channel of each subject using the following guideline (Katz 1988):

- I. For $j = 1, \dots, N$ find the maximum value of $|x_1 - x_j|$ and call it d .
- II. Compute L as the total length of the time series $\mathbf{x}$ and a as the average distance between successive points of $\mathbf{x}$:

$$L = \sum_{i=2}^N |x_i - x_{i-1}| \quad (1)$$

$$a = \frac{L}{N-1} \quad (2)$$

Compute KFD according to:

$$KFD = \frac{\ln(\frac{L}{a})}{\ln(\frac{d}{a})} \quad (3)$$

Following Esteller et al. (2001) the KFD was computed using a sliding window approach. A sliding window of 1.2 s was used to promote stationarity (i.e. considering the EEG sampling rate of 250 Hz, the sliding window was 300 points) with 50 % overlap.

Finally, as different frequencies of EEG have different roles in brain functions (Klimesch and Arora 2012; Ozaki et al. 2012), to reveal the effect of frequency bands on the between-group differences of the EEG KFDs, EEGs were decomposed to the conventional EEG bands, gamma (30–70 Hz), beta (13–30 Hz), alpha (8–13 Hz), theta (4–8 Hz), and delta (0.1–4 Hz). Then the KFDs of the EEG subbands were computed as well.

Statistical analyses and classification

Normality of the KFD distribution at each channel was assessed by the Kolmogorov–Smirnov test (using SPSS 20.0 for Windows). One-way ANOVA was used to analyze the group differences in KFD between male and female groups at each channel (using SPSS 20.0 for Windows). There were 19 electrode loci to distinguish females from males based on KFD. Therefore, considering a family-wise alpha of 0.05, after Bonferroni correction, a per-comparison alpha of $1 - 0.95^{1/19} = 0.0027$ was obtained as the significance p value. The correlation of age, nonverbal IQ, and handedness of the participants with the obtained FDs was evaluated with Pearson's coefficient of correlation. Also asymmetry of KFDs of the frontal lobe, as the main lobe responsible for IQ and mental retardation, was analyzed using ANOVA. In order to show repeatability of the approach, the EEGs were subdivided to two intervals of 7,500 data points and the ability of the KFD in discriminating the two groups was analyzed by repeated measures multivariate analysis of variance (ANOVA). As such we

Fig. 1 Circles with the double edges show the loci with the FDs significantly different in the DS and normal groups (p value < 0.0027)

Fig. 2 EEG power spectrum at representative frontal, central and parietal midline electrodes for the normal group (represented in a, c, and e, respectively, at the *left side*, depicted by *black lines*) and the DS group (represented in b, d, and f, respectively, at the *right side*, depicted by *gray lines*)

considered the interval, channel, and interval $\times$ channel as within-subjects factors and the group (normal and DS) as between-subjects factor.

Furthermore, machine classification was applied to differentiate the discriminative fractality of the brain activity between the DS and normal groups, using enhanced probabilistic neural network (EPNN) (Ahmadlou and Adeli 2010b). Repeated random sub-sampling cross-validation method was used for evaluation of the classification accuracy (Ahmadlou and Adeli 2010a). As such, about 70 % of the data (data of 30 subjects) were randomly selected and used for training and the remaining data (data of 12 subjects) were used for testing. This random selection was repeated 100 times and the average value was considered as the final accuracy for distinguishing the two groups.

Moreover, to find that the differences of the EEG fractality between the groups is affected by fractality of which frequency subband, the ANOVA analysis was carried out to show the between-group differences of the KFDs in each EEG subband.

Results

Table 2 shows the mean and standard deviation of the KFD values of each EEG channel for DS and normal participants as well as the associated p values and F values obtained by one-way ANOVA in distinguishing the two groups. As can be observed, in all loci, except the occipital loci (O1 and O2), p values discriminating the DS and normal groups were less than 0.05. Also, considering that the threshold of significance obtained by Bonferonni correction is 0.0027, Table 2 shows that the KFDs of Fp1, Fp2, F7, F8, F3, T3, and P4 were significantly different between the two groups.

Based on KFDs of the most discriminative loci (Fp1, Fp2, F7, F8, F3, T3, and P4) as the inputs, the classification was performed. An accuracy of 95.8 % was obtained for discriminating the normal and DS subjects, with a specificity of 92.7 % and a sensitivity of 99.2 %. Figure 3 shows the average values of KFD obtained in each group of subjects for all loci. All values in the DS group were greater than those in the normal group. Moreover, lateralization analysis of the frontal loci (Fp1–Fp2, F3–F4, and F7–F8) showed significant difference in the F3–F4 and F7–F8 laterality with p values of 0.010 and 0.028, respectively. As Fig. 2 shows, the normal brain has a right laterality of KFD in frontal lobe (KFDs of F3 and F7 are less than KFDs of F4 and F8), whereas the DS brain has a left laterality of KFD in frontal lobe (KFDs of F3 and F7 are greater than KFDs of F4 and F8).

The repeated measures ANOVA was carried out for the repeatability of the approach. The significant between-subjects p value of 0.000 and the insignificant within-subjects p value of 0.883 ($F = 0.022$) and 0.829 ($F = 0.684$) for the interval factors of interval and interval $\times$ channel were obtained respectively; while the channel factor showed a significant difference (p value = 0.000). Figure 4 shows the average values of KFD obtained in each group of the subjects in the intervals 1 and 2.

Then the frequency analysis of FD differences was carried out. Figure 5 shows the averaged KFD values of in each channel for the DS and normal groups at all EEG subbands. Compared to the normal group, the DS group shows an increased KFD overall the brain in all EEG subbands, except alpha subband. p values of the KFDs in all EEG subbands in distinguishing the two groups are presented in the Table 2. It shows that the between-group differences of the KFDs are associated with the delta in all

Table 2 Mean and standard deviation of KFDs of the EEG loci in each group (normal and DS) as well as *p* values and *F*s of the ANOVA in distinguishing the two groups

	KFD of EEG				Delta	Theta	Alpha	Beta	Gamma
	Mean	SD	<i>F</i>	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value
Fp1									
Normal	1.1586	0.02757	37.097	0.000***	0.000***	0.000***	0.030*	0.000***	0.000***
DS	1.2853	0.10145							
Fp2									
Normal	1.1566	0.02525	40.253	0.000***	0.000***	0.000***	0.025*	0.000***	0.000***
DS	1.2940	0.10687							
F7									
Normal	1.1574	0.02770	17.680	0.000***	0.000***	0.001**	0.052	0.005**	0.001**
DS	1.2949	0.16424							
F3									
Normal	1.1663	0.02994	12.540	0.001**	0.000***	0.002**	0.098	0.010*	0.008**
DS	1.2726	0.14973							
Fz									
Normal	1.1828	0.03116	8.081	0.007**	0.000***	0.013*	0.958	0.006**	0.020*
DS	1.2392	0.09469							
F4									
Normal	1.1808	0.02850	8.900	0.005**	0.000***	0.002**	0.823	0.009**	0.026*
DS	1.2347	0.08620							
F8									
Normal	1.1694	0.03386	16.585	0.000***	0.000***	0.000***	0.059	0.001**	0.003**
DS	1.2519	0.09583							
T3									
Normal	1.1690	0.04501	14.847	0.001**	0.000***	0.001**	0.054	0.000***	0.005**
DS	1.2658	0.11718							
C3									
Normal	1.1698	0.03293	8.305	0.006**	0.002**	0.011*	0.178	0.003**	0.030*
DS	1.2833	0.19791							
Cz									
Normal	1.1716	0.02740	8.498	0.006**	0.000***	0.003**	0.378	0.010*	0.029*
DS	1.2557	0.14417							
C4									
Normal	1.1713	0.02852	10.238	0.003**	0.000***	0.001**	0.763	0.012*	0.016*
DS	1.2316	0.09053							
T4									
Normal	1.1749	0.04322	8.958	0.005**	0.000***	0.001**	0.339	0.027*	0.032*
DS	1.2374	0.09398							
T5									
Normal	1.1876	0.04379	7.313	0.010*	0.001**	0.026*	0.553	0.014*	0.037*
DS	1.2441	0.09375							
P3									
Normal	1.1978	0.04351	6.680	0.013*	0.000***	0.049*	0.381	0.015*	0.019*
DS	1.2722	0.13825							
Pz									
Normal	1.1776	0.02863	9.380	0.004**	0.000***	0.003**	0.826	0.009**	0.012*
DS	1.2541	0.12336							

Table 2 continued

	KFD of EEG				Delta	Theta	Alpha	Beta	Gamma
	Mean	SD	<i>F</i>	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value	<i>p</i> value
P4									
Normal	1.1791	0.02924	10.585	0.002**	0.000***	0.001**	0.700	0.005**	0.014*
DS	1.2485	0.10359							
T6									
Normal	1.1884	0.03408	6.910	0.012*	0.000***	0.019*	0.630	0.012*	0.024*
DS	1.2426	0.09767							
O1									
Normal	1.2414	0.07809	1.529	0.223	0.001**	0.149	0.072	0.283	0.117
DS	1.2790	0.12585							
O2									
Normal	1.2692	0.09938	0.164	0.687	0.001**	0.398	0.052	0.574	0.259
DS	1.2827	0.12427							

It presents the associated *p* values in each frequency subband as well

SD standard deviation

*** Correlation is significant at the 0.001 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed)

channels and theta subband in almost all frontal and right and midline posterior channels and the beta and gamma subbands majorly in frontal regions, while the alpha subband does not show any significant difference (*p* value more than the Bonferonni corrected threshold of 0.0027).

Discussion and conclusion

As life expectancy is increasing in the population with DS (Danés 2012), learning more about the neuroanatomy and neuropathophysiology of their brains seems to become increasingly important for providing better care during their lifetime. Many studies based on neuro-imaging techniques have been carried out for this purpose. Severely

reduced number of dendritic spines in the hippocampus is one of the major neuroanatomic effects of DS (Ferrer and Gullotta 1990; Kaufmann and Moser 2000). There are two major findings obtained through MRI-based volumetric studies and EEG-based studies on DS patients: reduced total brain volume as well as gray and white matter volumes (Pinter et al. 2001) and a slow wave brain (Babiloni et al. 2009). The high temporal resolution of EEG provides the possibility for studying the nonlinear dynamics of the brain which is not possible by imaging tools such as MRI (Ahmadlou et al. 2012a). However so far, to the best knowledge of the authors, all EEG-based findings about the DS brain have been based only on the spectrum analysis and coherence which are forms of linear analyses. Hence in this study the authors attempted to determine differences in

Fig. 3 Mean values of KFD in each channel for the DS group (depicted by circles) and the normal group (depicted by squares)

Fig. 4 Mean values of KFD in each channel in the intervals 1 (triangle) and 2 (inverted triangle) in the DS and normal groups (int: interval)

Fig. 5 Mean values of KFD in each channel for the DS group (depicted by circles) and the normal group (depicted by squares) at EEG subbands **a** delta, **b** theta, **c** alpha, **d** theta, and **e** delta

the nonlinear dynamics and complexity of the DS brain. For this purpose FD of EEG, as a key characteristic of brain dynamics, measured by the KFD algorithm, was chosen. The results showed higher fractality of the DS brain in almost all regions compared to the normal brain, which indicates less centrality and higher irregular or random functioning of the DS brain regions. The results showed that the higher EEG fractality in the DS is associated with the higher fractality in the low frequencies (delta and theta), in broad regions of the brain, and the high frequencies (beta and gamma), majorly in the frontal regions. Also, laterality analysis of the frontal lobe showed that the normal brain had a right frontal laterality of complexity whereas the DS brain had an inverse pattern (left frontal laterality). Furthermore, the high accuracy of 95.8 % obtained by the EPNN classifier, in discrimination of the normal and DS children, shows the potential of nonlinear dynamic analysis of the brain (e.g. complexity) for revealing the underlying neuropathophysiology of the DS brain, which in turn can serve as a diagnostic method as

well as a candidate for monitoring cognitive and language rehabilitation outcomes of DS patients.

However, the relation between the obtained abnormal brain dynamics (the higher complexity overall brain and the left frontal laterality of complexity) and the deficient language, low intelligence and logics (Nadel 2003), the memory deficits and other cognitive dysfunctions in DS patients remains unclear. The lack of behavioral/cognitive scores of the DS and normal subjects is of limitations of the current study which could reveal these relationships.

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