Higuchi fractal dimension applied to RR intervals in children with Attention Deficit Hyperactivity Disorder

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Resumo

Introdução: O transtorno de deficit de atenção e hiperatividade (TDAH) é caracterizado por um período reduzido de atenção, impulsividade e hiperatividade. O desequilíbrio na função do sistema nervoso autônomo (SNA) tem sido previamente estudado utilizando-se técnicas globais da teoria do caos.

Objetivo: comparar a função autonômica de crianças com TDAH e controles por meio da análise da variabilidade da frequência cardíaca (VFC).

Método: 28 crianças com TDAH (22 meninos, com média de idade de 10,0 anos ± 1,9 anos) e 28 controles (15 meninos, com média de idade de 9,9 anos ± 1,8 anos) permaneceram em decúbito dorsal, com respiração espontânea por 20 minutos. A frequência cardíaca foi registrada batimento a batimento e a análise da VFC foi realizada pela técnica de Dimensão Fractal Higuchi.

Resultados: TDAH promoveu um aumento na Dimensão Fractal Higuchi. O valor ideal de Kmax foi 10.

Conclusão: O TDAH alterou significativamente a modulação autonômica cardíaca, como demonstrado pela Dimensão Fractal Higuchi da VFC. Assim, pode-se afirmar que crianças com TDAH apresentaram aumento das respostas caóticas neste tipo de análise da modulação autonômica cardíaca.

Palavras-chave: transtorno de déficit de atenção e hiperatividade, criança, fisiologia fractal, variabilidade da frequência cardíaca, dimensão fractal Higuchi.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a well-known mental condition in children[1]. It is typified by lowered levels of cognitive ability, impulsiveness, and hyperactivity[2, 3]. The exact pathological mechanisms of these psychiatric indications is unclear[4]. Nevertheless, ADHD has proven more prevalent and associated with cardiac abnormalities. Pharmacological treatment of these symptoms in children can affect their heart rate and blood pressure[3,5]. Considering that cardiac function is synchronized by the autonomic nervous system (ANS); mediated through the sinus (SA) node[6], heart rate variability (HRV) can be used to assess variation in autonomic modulation. It is an easy, non-invasive and low-cost method of monitoring the ANS and is used extensively in the research laboratory and clinically.

The apparent benefit for testing the correlation with HRV in subjects with ADHD is that it can offer a benchmark to the risk of the so called "dynamical diseases"[7]. We are assuming that the ADHD subjects RR-intervals behave in a non-linear way akin to other medical conditions such as asthma[8], cardiac failure[9,10] and epilepsy[11-14]. In addition, fractal indices are also able to detect slight changes in the dynamics of RR intervals better than conventional spectral analyses[15]. Further information on such "complex" conditions can be found in the article by Seely and Macklem[16].

In this study the cardiac autonomic modulation was examined by the Higuchi Fractal Dimension al-

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gorithm[11-19]. In previous studies, a similar computation, correlation dimension (D_2)[20-23] had been applied. These proved significant in mainly neurological assessments in Schizophrenia[24], Parkinson's disease[25], and Creutzfeldt-Jakob disease[26].

■ METHODS

Population

Twenty-eight children with ADHD (22 boys, mean age 10.0 ± 1.9 years) and 28 controls (15 boys, mean age 9.9 ± 1.8 years) were recruited from the Núcleo Especializado em Aprendizagem da Faculdade de Medicina do ABC (Learning Disabilities Center of Medicine ABC University), Santo André, Brazil, where they are treated by a multidisciplinary team. All volunteers in this study had the medical diagnosis of ADHD, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, published by the American Psychological Association[27,28], and the following inclusion criteria were satisfied by all subjects: i) absence of congenital anomalies such as congenital heart disease, pulmonary malformations, diaphragmatic hernia, and defects of abdominal wall closure; ii) absence of central nervous system malformations and/or neurological syndromes; iii) absence of metabolic disorders; iv) absence of medication such as methylphenedite that influences cardiac autonomic modulation since that drug treatment has effects on cardiovascular parameters such as heart rate and blood pressure. The control group consisted of healthy children without a diagnosis of ADHD. Parents of the children were asked for consent. The study received approval from the Ethics Committee of Faculdade de Medicina do ABC (protocol number 312/11) and was in compliance with Resolution 196/96 of the Conselho Nacional de Saúde.

Procedure

Datasets were collected under controlled temperature (21°C – 23°C) and humidity (40%–60%). Participants attended the laboratory each time between 8:00 and 11:00 to avoid circadian influences. They were instructed to avoid consuming ANS stimulants for 24 hours before evaluation. Parents and guardians of the children stayed in the room during the entire protocol. Demographics and anthropometric measurements were obtained following the standard recommendations proposed by Lohman et al[29]. A heart monitor strap was placed on the chest, over the distal third of the sternum, and the heart rate receiver (Polar RS800 CX monitor; Polar, Kempele, Finland) was placed on the wrist. This type of equipment has been previously validated for beat-by-beat measurements and for HRV analysis[30-32]. Children rested in supine position with spontaneous breathing for 20 minutes and were instructed to avoid talking during data collection.

For HRV analysis, the heart rate was recorded beat-by-beat with a sampling frequency of 1000 Hz. The data series was first digitally filtered using Polar Precision

Performance SW software (version 4.01.029; Polar), in which only series with more than 95% sinus rhythm beats were included[33]. It was then manually complemented, and the visual inspection of the time series on the computer showed absence of artifacts. 1000 RR intervals were selected for data analysis.

Higuchi's Fractal Dimension

Previously, Higuchi developed a new algorithm for measuring the fractal dimension of discrete time sequences[19]. It is applied directly to the time-series; rather than power spectra. It can quantify self-similarity and complexity of the signal and has been applied to brain[33-35] and other biological signals[36,37]. Higuchi's algorithm is described by Khoa et al[17] below. It is based on a measure of length, L(k), of the curve that represents the considered time series while using a segment of k samples as a unit, if L(k) scales like:

$$L(k) \sim k^{-Df}$$

The curve is said to show fractal dimension D_f. A simple curve has dimension equal to 1. Nevertheless, a plane has a dimension equal 2. This, the value of D_f is always between 1 and 2. D_f measures complexity of the curve and so of the time series this curve represents on a graph.

From a given time series, X(1), X(2), ... , X(N), the algorithm constructs k new time series:

$$X_{km} : X(m), x(m+k), X(m+2k),..........,$$
$$X\left(m + int\left(\frac{(N-m)}{k}\right) \cdot k\right) \quad for\ m = 1, 2, ...k,$$

where m is initial time, k is interval time, int(r) is integer part of a real number r.

For example, for k = 4 and N = 1000, the algorithm produces 4 time series:

$$X_{41} : X(1), X(5), X(9),.......X(997),$$
$$X_{42} : X(2), X(6), X(10),.......X(998),$$
$$X_{43} : X(3), X(7), X(11),.......X(999),$$
$$X_{44} : X(4), X(8), X(12),.......X(1000),$$

The "length" $L_m(k)$ of each curve Xkm is then calculated as:

$$L_m = \frac{1}{k}\left[\left(\sum_{i=1}^{int((N-m)/k)} |X(m+i\cdot k) - X(m+(i-1)\cdot k|\right)\right]$$
$$\times \frac{N-1}{int\left(\frac{(N-m)}{L}\right)\cdot k}$$

Where, N is total number of samples.

$L_m(k)$ is not "length" in Euclidean sense, it represents the normalized sum of absolute values of difference coefficient in ordinates of pair of points distant k (with initial point m). The "length" of curve for the time interval k, $L(k)$, is calculated as the mean of the k values $L_m(k)$ for m = 1, 2, ... , k:

$$L(k) = \frac{1}{k} \sum_{m=1}^{k} L_m(k)$$

The value of fractal dimension, D_f, is calculated by a least-squares linear best-fitting procedure as the angular difference coefficient of the linear regression of the log-log graph.

So, when $L(k)$ is plotted against $1/k$ on a double logarithmic scale, with $k = 1,2,...,k_{max}$, the data should fall on a straight line, with a slope equal to the Fractal Dimension of X. Thus, Higuchi fractal dimension is defined as the slope of the line that fits the pairs $\left\{ \ln\left[L(k)\right], \ln(1/k) \right\}$

in a least-squares sense. In order to choose an appropriate value for the parameter k_{max}, Higuchi fractal dimension values were plotted against a range of k_{max}. The point at which the Fractal Dimension plateaus is considered a saturation point and that k_{max} value should be selected.

With a = D_f, according to the following formulae:

$$y = ax + b$$

$$D_f = \frac{n \sum (x_k . y_k) - \sum x_k \sum y_k}{n \sum x_k^2 - \left(\sum x_k \right)^2}$$

where $y_k = \ln L(k)$, $x(k) = \ln(1/k)$.

$k = k_1, ... , k_{max}$, and n denotes the number of k values for which the linear regression is calculated ($2 \leq n \leq k_{max}$).

Table 1: The descriptive statistics of the Higuchi Fractal Dimension from the control subjects (N = 28) 1000 RR-intervals. The parameter was calculated repeatedly for values of Kmax between 10 and 150 at intervals of 10

| Property	Higuchi Fractal Dimension Statistics (Control)							
K_{max}	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Max
10	1.7278	0.01460	0.0771	1.5338	1.6869	1.7211	1.7587	1.9055
20	1.8051	0.01070	0.0567	1.6397	1.7683	1.8101	1.8451	1.9120
30	1.8373	0.00998	0.0528	1.7013	1.7992	1.8430	1.8759	1.9326
40	1.8569	0.00922	0.0488	1.7734	1.8132	1.8603	1.8973	1.9402
50	1.8702	0.00863	0.0457	1.7878	1.8276	1.8769	1.9072	1.9472
60	1.8808	0.00826	0.0437	1.8034	1.8402	1.8858	1.9150	1.9531
70	1.8892	0.00799	0.0423	1.8154	1.8463	1.8985	1.9209	1.9580
80	1.8962	0.00779	0.0412	1.8246	1.8558	1.9069	1.9280	1.9650
90	1.9020	0.00765	0.0405	1.8314	1.8630	1.9080	1.9325	1.9695
100	1.9065	0.00725	0.0384	1.8395	1.8735	1.9078	1.9364	1.9726
110	1.9117	0.00685	0.0362	1.8480	1.8820	1.9125	1.9400	1.9768
120	1.9164	0.00649	0.0344	1.8534	1.8904	1.9201	1.9436	1.9800
130	1.9203	0.00631	0.0334	1.8566	1.8992	1.9216	1.9471	1.9825
140	1.9226	0.00622	0.0329	1.8572	1.9012	1.9212	1.9494	1.9825
150	1.9250	0.00619	0.0327	1.8593	1.9006	1.9235	1.9541	1.9827
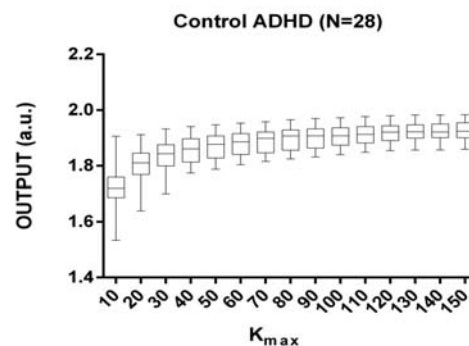
Figure 1: The box-and-whiskers plot for Higuchi fractal dimension of RR–intervals illustrates the median values. Where the line in the middle of the box is the median, the whiskers of the outer points are the maximum and minimum, with the outer edge of the boxes representing the 25th and 75th percentiles. The difference between the outer box edges is the inter-quartile range. For the Higuchi fractal dimension of the RR-intervals the control subjects calculated multiple times between 10 and 150; equidistantly for different levels of Kmax.. The number of RR-intervals is 1000 and number of subjects is 28.

Table 2: The descriptive statistics of the Higuchi Fractal Dimension from the subjects exhibiting ADHD (N = 28) 1000 RR-intervals. The parameter was calculated repeatedly for values of Kmax between 10 and 150 at intervals of 10

Property			Higuchi Fractal Dimension Statistics (ADHD)					
K_{max}	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Max
10	1.8050	0.02150	0.1139	1.5135	1.7132	1.8325	1.8807	1.9800
20	1.8596	0.01610	0.0852	1.6734	1.7867	1.8868	1.9241	1.9725
30	1.8816	0.01330	0.0702	1.7304	1.8446	1.8971	1.9427	1.9750
40	1.8953	0.01160	0.0613	1.7730	1.8554	1.9120	1.9547	1.9745
50	1.9044	0.01090	0.0574	1.7845	1.8657	1.9232	1.9575	1.9754
60	1.9094	0.01040	0.0552	1.7871	1.8706	1.9257	1.9555	1.9764
70	1.9150	0.00984	0.0521	1.7941	1.8797	1.9304	1.9578	1.9792
80	1.9210	0.00911	0.0482	1.8042	1.8880	1.9364	1.9606	1.9825
90	1.9257	0.00860	0.0455	1.8158	1.8943	1.9407	1.9621	1.9843
100	1.9297	0.00824	0.0436	1.8275	1.8990	1.9433	1.9670	1.9884
110	1.9331	0.00788	0.0417	1.8393	1.9043	1.9441	1.9702	1.9889
120	1.9366	0.00742	0.0393	1.8489	1.9102	1.9466	1.9716	1.9885
130	1.9395	0.00706	0.0374	1.8580	1.9167	1.9478	1.9727	1.9883
140	1.9422	0.00688	0.0364	1.8641	1.9219	1.9500	1.9747	1.9886
150	1.9444	0.00662	0.0350	1.8692	1.9243	1.9539	1.9755	1.9876

ADHD (N=28)
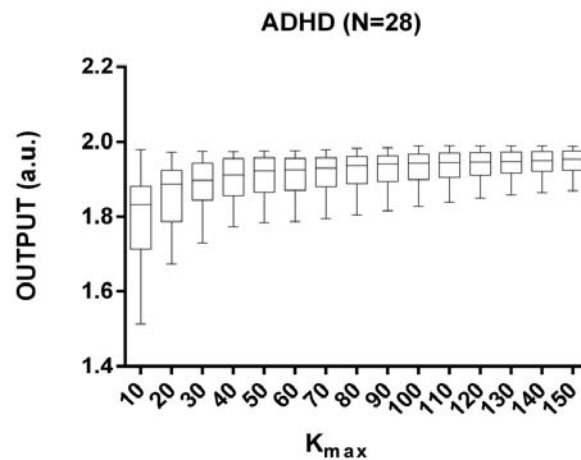
Figure 2: The box-and-whiskers plot for Higuchi fractal dimension of RR–intervals illustrates the median values. The line in the middle of the box is the median, the whiskers of the outer points are the maximum and minimum, with the outer edge of the boxes representing the 25th and 75th percentiles, the difference between the outer box edges is the inter-quartile range. For the Higuchi fractal dimension of the RR-intervals the ADHD subjects calculated multiple times from 10 to 150 in equidistant units for different levels of Kmax. The number of RR-intervals is 1000 and number of subjects is 28.

Table 3: The levels of significance parametric (ANOVA1) and non-parametric (Kruskal-Wallis) for values of the Higuchi Fractal Dimension at varying levels of K_{max} between 10 and 150 at equidistant intervals of 10

Property	Higuchi Fractal Dimension Statistics (Control v ADHD)	
K_{max}	ANOVA1 (p-value)	Kruskal-Wallis (p-Value)
10	0.0044	0.0035
20	0.0067	0.0059
30	0.0100	0.0053
40	0.0122	0.0087
50	0.0170	0.0111
60	0.0360	0.0183
70	0.0470	0.0248
80	0.0436	0.0281
90	0.0436	0.0281
100	0.0398	0.0293
110	0.0446	0.0318
120	0.0459	0.0270
130	0.0471	0.0345
140	0.0392	0.0258
150	0.0369	0.0270

RESULTS

Normalization of the data is important so we know which statistical test of significance to apply. So, we applied the Anderson-Darling[38], and Lilliefors tests[39]. The Anderson–Darling test for normality applies an empirical cumulative distribution function. The Lilliefors test is suitable when the number of subjects is short. In this study there are 28 subjects per category. The results from both tests are inconclusive. Consequently, we must apply both the parametric one-way analysis of variance; ANOVA1 and the non-parametirc Kruskal-Wallis[40] test of significance. Differences were considered significant when the probability of a type I error was less than 1% ($p < 0.01$). Here, for Higuchi fractal dimension we found significant reduced values in subjects with ADHD ($p \approx 0.004$). The Kruskal-Wallis test of significance provided a p-value of 0.0035 and ANOVA1 provided a p-value of 0.0044. Both optimum values were obtained at a value of K_{max} of 10.

DISCUSSION

The ANS plays an important role in regulation of physiological mechanisms, such as cardiac and metabolic systems; and alterations in autonomic activity in children with ADHD have been investigated in several studies[1,3]. HRV analysis using nonlinear methods is useful because mechanisms involved in cardiovascular regulation likely interact between each other in a nonlinear way[9,11]. To the best of our knowledge, this is the first study to examine the effect of ADHD on cardiac autonomic modulation using Higuchi Fractal Dimension analysis of HRV.

A literature search revealed three studies that addressed the effect of ADHD on cardiac autonomic modulation using a nonlinear analysis of HRV. In the first investigation[41], according to the frequency and time domains and the Poincaré plot, the indexes that indicate parasympathetic component were higher in children with ADHD than in children without the disorder. The second study investigated the effect of ADHD[42] on the RR-intervals using the chaotic global techniques[43]; and thus cardiac autonomic modulation therein.

In another study[5] that evaluated ANS functioning and the effects of methylphenidate in stimulant-free children with ADHD and controls, the authors also found that stimulant-free children with ADHD have a parasympathetic dominance of the autonomic balance relative to control subjects. We could suggest that increased parasympathetic is related to increased chaosity found in this work.

A recent investigation[44] analyzed heart rate asymmetry as a qualitative profile of heart rate complex dynamics in ADHD untreated children at rest and in response to postural change manoeuvre (orthostatic stimulation). Opposite to our results, the authors reported atypical complex autonomic cardiac regulatory system. In this sense, there are important issues to be raised. Tonhajzerová et al[44] studied only severe ADHD, while we did not divide the ADHD group based on disorder degree.

There are other techniques which could be applied such as approximate entropy[45-47] and sample entropy[48-50]. However considerable skill and expertise is required with these techniques to set the appropriate parameters for run length m and, tolerance window r.

Studies on changes in fractal properties dynamics of HRV help clinical professionals to manage disease development, since some of them indicate that the loss of fractal dynamics represents autonomic dysfunction[51]. This study is the first to apply Higuchi fractal dimension analysis of HRV in ADHD patients. In this context, this information is useful to further investigations to raise innovations into and to the advance of therapies for this disorder.

In conclusion, the chaotic response measured by Higuchi Fractal Dimension of HRV in child subjects with ADHD increases. This is useful in the risk assessment as a benchmark of dynamical diseases associated with ADHD.

COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this article.

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is categorized by a lowered attention span, recklessness, and hyperactivity. Autonomic nervous system inequality has previously been studied using the same data by chaotic global techniques. We aim to compare the autonomic function of children with ADHD and controls by analyzing heart rate variability (HRV).

Methods: 28 children with ADHD (22 boys, mean age 10.0 years ± 1.9 years) and 28 controls (15 boys, mean age 9.9 years ± 1.8 years) rested in supine position with spontaneous breathing for 20 minutes. Heart rate was recorded beat by beat. HRV analysis was performed by Higuchi Fractal Dimension technique.

Results: ADHD promoted an increase in the Higuchi Fractal Dimension. The optimum value of K_{max} was 10.

Conclusion: ADHD significantly altered cardiac autonomic modulation as measured by the Higuchi fractal dimension of HRV. It can therefore be stated that ADHD has increased the complexity of the HRV signal through cardiac autonomic modulation.

Key words: attention deficit hyperactivity disorder, children, fractal physiology, heart rate variability, higuchi fractal dimension.