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Innovative approaches in investigating inter-beat intervals: Graph theoretical method suggests altered autonomic functioning in adolescents with ADHD

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Abstract
Cardiac inter-beat intervals (IBIs) are considered to reflect autonomic functioning and self-regulatory abilities and are often investigated by traditional time- and frequency domain analyses. These analyses investigate IBI fluctuations across relatively long time series. The similarity graph algorithm is a nonlinear method that analyzes segments of IBI time series (i.e., time windows)—possibly being more sensitive to transient and spontaneous IBI fluctuations. We hypothesized that the similarity graph algorithm would detect differences between Attention-Deficit/Hyperactivity Disorder (ADHD) and control groups. Resting electrocardiogram (ECG) recordings were collected in 10–18-year-olds with ADHD ($n = 37$) and controls ($n = 36$). IBIs were converted to graphs that were subsequently investigated for similarity. We varied the criterion for defining IBIs as similar, assessing which setting best distinguished ADHD and control groups. Using this setting, we applied the similarity graph algorithm to time windows of 2–5, 6–13 and 12–25 s, respectively. We also performed traditional IBI analyses. Independent samples t tests assessed group differences. Results showed that a 1.5% criterion of similarity and a time window of 2–5 s best distinguished

adolescents with ADHD and controls. The similarity graph algorithm showed a higher number of edges, maximum edges and cliques, and lower edges10+10/edges2+2 in the ADHD group compared to controls. The results suggested more similar IBIs in the ADHD group compared to the controls, possibly due to altered vagal activity and less effective regulation of heart rate. Traditional analyses did not detect any group differences. Consequently, the similarity graph algorithm might complement traditional IBI analyses as a marker of psychopathology.

KEYWORDS

ADHD, autonomic nervous system, graph theory, heart rate variability, interbeat interval, nonlinear

1 | INTRODUCTION

Heart rate variability (HRV) indexes autonomic activity by assessing differences in consecutive inter-beat intervals (IBIs; Camm et al., 1996) of an electrocardiogram (ECG) recording. HRV is often analyzed by time- and frequency domain methods (Thayer et al., 2010) based on linear models, although the adaptive mechanisms that regulate heart rate (HR) are considered to be nonlinear (see Huikuri et al., 2003; Rajendra Acharya et al., 2006). Further, HRV indices typically depend on calculations from one to five minutes of an IBI series (Camm et al., 1996). As the indices are expressed as mean values or summary statistics from relatively long recordings (Camm et al., 1996; Shaffer & Ginsberg, 2017), they can be similar despite being from recordings with distinctly differently organized IBIs. Hence, valuable information about IBI organization might go undetected by use of linear methods.

IBIs are influenced by complex regulatory systems causing frequent spontaneous fluctuations in HR, leading to nonlinearity of IBI organization (see Huikuri et al., 2003; Rajendra Acharya et al., 2006). Nonlinear methods based on concepts such as chaos, fractality, and complexity have as such led to important insights into IBIs dynamics (de Godoy, 2016; Henriques et al., 2020; Voss et al., 2009), although not without limitations (see Henriques et al., 2020). These methods might be hard to compute or interpret, or vulnerable to erroneousness if parameter choices are non-optimal (Henriques et al., 2020). Others are highly sensitive to ECG length or artifacts, or do not utilize all data (Henriques et al., 2020). Some methods might also reflect autonomic activity inaccurately (Cepeda et al., 2018). On account of such limitations, the development of nonlinear methods is still warranted.

Graph theory is a promising mathematical field for application to nonlinear methods, which has provided new insights into various brain disorders in neuroimaging studies (e.g., Ahmadlou et al., 2012; Bullmore & Sporns, 2009; Stam & Reijneveld, 2007). As opposed to assessing values across an entire IBI series, graph theory allows for the investigation of smaller segments of the time series. These *time windows* provide information about moment-to-moment IBI fluctuations, as represented in a *graph*. The term "*graph*" refers to the visualization of a set of *nodes* and *edges* (Kleinberg & Tardos, 2006). Each IBI is visualized as a point—a node. Similar IBIs are connected by a line—an edge. Thus, a graph highlights similarities in IBIs (Figure 1). Different *criteria of similarity*—thresholds for defining IBIs as similar—provide different graphs. There are numerous indices that can be deducted from such graphs. Yet, previous graph theory-based studies of IBIs appear to have performed analyses of only one specific variable (Choudhary et al., 2019, 2020). This might be insufficient for characterizing complex physiological systems such as IBI organization (see Voss et al., 2009).

In the current study we applied a graph theory-based, nonlinear method that might complement other IBI analyses*:* the *similarity graph algorithm*. It has previously been applied in studies of motor activity (Fasmer et al., 2018, 2020). The algorithm assesses several indices familiar from graph theory in relatively short time windows, providing information about moment-to-moment IBI similarity - termed *inter-relatedness*. As further detailed in the method section, the indices represent different perspectives on inter-relatedness and lack of inter-relatedness. A ratio of inter-relatedness across a longer compared to a shorter time window is also calculated: edges10+10/edges2+2. This might be compared to the inverse of the previously criticized (Billman, 2013) low frequency/high frequency (LF/HF) ratio from HRV analysis (Camm et al., 1996), although our use of time windows might provide a more refined index.

We suggest that a higher inter-relatedness reflects altered ANS activity, similar to a lower HRV. Supporting this, graph theory-based methods have found lower IBI complexity (i.e., more similarity) in individuals with heart disease and the elderly (Choudhary et al., 2020, 2019), which are populations that often have a lower

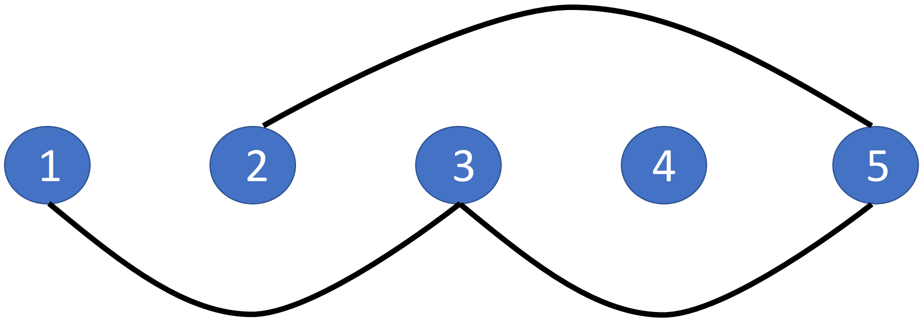


FIGURE 1 Illustration of nodes and edges in a graph. We introduce an *edge* (black line in the figure) between two *nodes* (blue dots 1–5 in the figure) if they are similar to each other and within the same time window. Each node corresponds to an IBI in the time series. The time window in the figure consists of five nodes. Node nr. 1, 3, and 5, as well as node 2 and 5, are connected by edges

HRV (Camm et al., 1996; Thayer & Lane, 2007; Voss et al., 2012). Of the ANS components, the vagus nerve is crucial for adaptive changes in HR and variability in IBIs (Berntson et al., 1997). The vagus nerve has a rapid course of action, compared to sympathetic activity that has a peak effect after about five seconds (Nunan et al., 2010). As such, higher inter-relatedness in shorter time windows (i.e., less than five seconds) might reflect vagal alterations most accurately, whereas longer time windows might also represent other ANS functions. Vagal alterations indexed by lower vagally mediated HRV have been associated with less effective self-regulatory abilities and general psychopathology (Beauchaine, 2015; Beauchaine & Thayer, 2015; Holzman & Bridgett, 2017). This is likely because activity in brain areas important for adaptability, such as the prefrontal cortical areas and amygdala, is connected to ANS centers in the brainstem and reflected in vagal modulation on the heart (Thayer & Lane, 2000). Possibly, such self-regulatory abilities and vulnerability to psychopathology might also be reflected in inter-relatedness indexes of vagal modulation.

As traditional IBI indices have been associated with self-regulatory abilities and general psychopathology (Beauchaine, 2015; Beauchaine & Thayer, 2015; Holzman & Bridgett, 2017), we investigated as a proof of concept if the similarity graph algorithm could detect IBIs differences between adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) and controls. A meta-analysis concluded with no differences in vagally mediated HRV in individuals with ADHD compared to controls (Koenig et al., 2016). Still, lower vagal activity has been associated with ADHD symptoms such as inattention, impulsivity, behavioral disinhibition, and difficulties with goal-directed behavior (see Rash & Aguirre-Camacho, 2012), giving reason to suspect vagal alterations in this group. Further, ADHD is likely characterized by altered noradrenaline and dopamine functioning (Sharma & Couture, 2014; Tripp & Wickens, 2009), which affects the ANS (LeBouef et al., 2020; Thorner, 1975). Importantly, dopamine is discharged in bursts (Tripp & Wickens, 2009), which might manifest as transient and spontaneous IBI alterations that could be detected in analyses of shorter time windows.

In the current study, we first investigated which criterion of similarity best illustrated differences between the ADHD and control group with the similarity graph algorithm. In line with previous work with the sample entropy (SampEn) method (Hauge et al., 2011; Richman & Moorman, 2000), we expected group differences to be most prominent for a criterion of similarity corresponding to 20% of the standard deviation (*SD*) of the IBIs. Second, we ran the algorithm for three different time windows in the ADHD and control group, investigating inter-relatedness. Our hypothesis was that the ADHD group would display higher inter-relatedness, and that this would be most prominent in shorter time windows (i.e., less than five seconds), which might provide the most refined indices of vagal alterations. We expected indices of higher inter-relatedness to be more sensitive to such vagal alterations than indices of lacking inter-relatedness, as it is generally easier to distinguish groups on a present rather than absent occurrence. Further, we expected to find lower edges10+10/edges2+2 in the ADHD group compared to controls, as LF/HF ratios tend to be higher in ADHD samples (Griffiths et al., 2017; Tonhajzerova et al., 2009). Third, HRV differences between the ADHD and control groups were investigated. Our expectation was that indices of vagal activity (i.e., RMSSD, HF-HRV) would not show group differences, in line with meta-analytical evidence (see Koenig et al., 2016). Still, we expected other indices to reflect ANS alterations in ADHD (i.e., lower SDNN, higher LF-HRV and LF/HF ratio). Fourth, we investigated if significantly different IBI indices were confounded by comorbidities or anxiety symptoms. We hypothesized that these variables would affect the HRV indices, which are associated with emotion dysregulation and general psychopathology (Beauchaine, 2015; Beauchaine & Thayer, 2015; Holzman & Bridgett, 2017), but not the graph theory-based indices. The latter indices might be more sensitive to subtle alterations and capture the complexity of IBI organization more accurately, and thus the detected alterations might be more ADHD-specific.

2 | METHOD

2.1 | Design and procedure

The current study is cross-sectional in design, investigating data from the second wave of a follow-up project on ADHD (See Supporting Information for details). The study protocol was approved by the Regional committee for medical research ethics of western Norway (Study number: 2014/1304). Participants received a reimbursement of £80 ($115).

Test administrators were blinded to group status throughout the two-day assessments. On the first day, adolescents and their parents received extensive information about the project and procedures. ECG recordings were conducted between 9 a.m. and 1 p.m. to control for effects of circadian variation on IBIs (Malpas & Purdie, 1990). On the second day, adolescents and their parents were separately interviewed with a semi-structured diagnostic interview (K-SADS; *outlined below*). This interview reviewed the diagnostic group statuses (ADHD/control) that had been assigned during similar interviews in the first wave of the project and assessed current comorbid diagnoses. Parents also completed the DSM-IV ADHD-rating scale (ADHD-RS; *outlined below*) for assessment of dimensional ADHD symptoms. Further, factors that have been associated with HRV (Gutin et al., 2005; Koenig et al., 2014; Tsang et al., 2015) and often differ in ADHD and control groups (Cook et al., 2015; Cortese et al., 2008; Fliers et al., 2013; Sharma et al., 2011) were examined: Physical activity levels as assessed during the diagnostic interview; body mass index (BMI) computed from height and weight measurements; and anxiety symptoms assessed by adolescent reports on the State-Trait Anxiety Inventory (STAI; *outlined below*).

2.2 | Participants

2.2.1 | Recruitment

In the first wave of the project, children with suspected ADHD were referred from child and adolescent psychiatry units in the Bergen municipality, Norway. Controls were recruited from schools in the same geographical area. An equal age and sex distribution in the ADHD and control groups was strived for. Participants in the first wave were asked by mail to take part in the second wave, and signed written informed consent in accordance with the Helsinki declaration. Exclusion criteria were a full-scale IQ score of <75, suspected autism spectrum disorder, former head trauma with loss of consciousness, or birth before gestation week 36.

2.2.2 | Diagnostic assessments

Subjects were assigned to an ADHD or control group by use of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS; Kaufman et al., 1997). The Norwegian translation was used (Sund & Aalberg, 2009), which has shown adequate convergent and divergent validity for ADHD diagnostics (Villabø et al., 2016). Diagnostic and Statistical Manual of Mental Disorders – Fourth edition (DSM-IV) criteria were applied (American Psychiatric Association, 2000). Interviews were performed by one of two experienced psychologists. The non-interviewing psychologist provided a second opinion on the participants' diagnoses.

2.3 | Sample properties

The sample comprised $n = 37$ adolescents with ADHD and $n = 36$ controls between 10 and 18 years of age (mean age 14.38; *SD* 1.51; Table 1). The majority of the participants were male ($n = 48$, 65.75%). All adolescents in the ADHD group met the criteria for the diagnosis, except for one who had ADHD in remission. Participants with ADHD were diagnosed as primarily inattentive, hyperactive-impulsive or combined subtypes, and were frequently diagnosed with comorbid disorders (See Table 2 for comorbidities and ADHD subtypes in the sample). Twenty two (59.46%) of the adolescents with ADHD used ADHD medication. Except for one who used atomoxetine hydrochloride, all were on central stimulants (nine used fast-acting formulas, nine used extended-release formulas and four a combination or alternation between the two). Further, two participants with ADHD used lamotrigine, and one used sertraline. One control participant used risperidone and melatonin.

2.4 | Measures

2.4.1 | Inter-beat intervals

To rule out short-term effects on IBIs (Buchhorn et al., 2012), participants were asked to conduct a washout period of medication 48 h prior to participation. 90.91% of the adolescents on ADHD medication ($n = 20$, of 22)

TABLE 1 Descriptive statistics for ADHD and control groups

Variable	ADHD (n = 37)	Controls (n = 36)	t	χ^2	df
Sex (n, %)				.68	1
Male	26 (70.27)	22 (61.11)			
Female	11 (29.73)	14 (38.88)			
Age	14.19 (1.74)	14.58 (1.21)	−1.11		71
BMI	22.37 (5.59)	21.01 (2.91)	1.30		54.52
Physical activity levels	1.73 (.77)	2.62 (1.20)		16.56**	5
ADHD-RS	26.33 (10.83)	5.91 (7.32)	8.96**		53.76
STAI-T	31.11 (7.08)	27.77 (4.79)	2.36*		71
Comorbidities	1.16 (1.12)	.33 (.63)		13.63**	4
HF peak	.25 (.063)	.26 (.051)	-1.05		69.00

Note: Comorbidities: The number of comorbidities each participant had. HF peak: Peak frequency of the high frequency band, as a proxy for respiration. Physical activity levels were scored on a Likert-type scale from 1 (lowest) to 5 (highest). Data are given as (mean, *SD*).

Abbreviations: BMI, Body Mass Index; ADHD-RS, ADHD Rating Scale; STAI-T, State-Trait Anxiety Inventory, trait anxiety subscale.

*$p \leq .050$;; **$p \leq .010$.

TABLE 2 Comorbid diagnoses and ADHD subtypes

	ADHD (n = 37)	Controls (n = 36)
ADHD subtype		
IA	11 (29.73)	–
HI	1 (2.70)	–
C	25 (67.57)	–
TS	13 (35.14)	7 (19.44)
Anxiety disorders	10 (27.03)	3 (8.33)
ODD	10 (27.03)	–
CD	1 (2.70)	–
OCD	2 (5.41)	2 (5.56)
MDD	2 (5.41)	–
Eneuresis	2 (5.41)	–
Epilepsy	1 (2.70)	–
Chronic motor tics	1 (2.70)	–
Transient motor tics	1 (2.70)	–
Anorexia nervosa	–	1 (2.78)

Note. Table displays number of participants (% of diagnostic group).

Abbreviations: C, combined subtype; CD, conduct disorder; HI, hyperactive-impulsive subtype; IA, inattentive subtype; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; TS, tourette syndrome.

conducted a washout period of minimum 24 h. Two participants on methylphenidate had washout periods of 18 and >12 h, respectively. Although shorter than requested, these timeframes were acceptable as methylphenidate has a half-life of two to three hours (i.e., the active ingredient is eliminated after 10–15 h; Ito, 2011; Kimko et al., 1999). Both participants on lamotrigine conducted a (48-h) washout period, while the participant on risperidone and melatonin did not.

Resting ECG recordings were assessed. As resting IBI indices have shown excellent test-retest reliability (Bertsch et al., 2012; Li et al., 2009), they might reflect "trait" neurophysiological tendencies of self-regulation (Beauchaine & Thayer, 2015; Porges, 2007; Thayer & Lane, 2000). Therefore, they could generalize to situations in everyday life to a larger degree than "state" IBI responses during experimental protocols (i.e., vagal reactivity; Balzarotti et al., 2017). Further, comparing our results to previous studies was more convenient with the use of resting ECGs, as they are often based on standardized protocols (Berntson et al., 1997; Camm et al., 1996).

Before initiation of the ECG recording, adolescents were instructed to lie down and relax while trying not to move or fall asleep. The ECG was recorded for six minutes as participants were breathing spontaneously. A simple lead II setup at a sampling rate of 1000 Hz was used. An A/D converter (Biopac, MP36, Biopac System Inc., Santa Barbara, CA) obtained the signal, which was conducted through three adhesive Ag/AgCl electrodes (T815 Dia. 55) and recorded with Biopac 4.0 BSL (Biopac Systems Inc. Santa Barbara, CA). The IBIs were manually inspected in Kubios HRV version 2.2 (Tarvainen et al., 2014), where 11 IBI corrections were made (.4%–1.5% of IBIs in the corrected recordings) in six recordings (ADHD, n = 3; controls, n = 3). One extra systole was removed. Then, the number of IBIs in the first five minutes of every series was calculated (See Supporting Information Figure S1 for flow chart of IBI analysis). The lowest IBI number in any of the series—237—was analyzed. This was due to the need to investigate the same number of time windows with the similarity graph algorithm in every IBI series, to compare their relative inter-relatedness. Although five-minute ECG recordings is the standard in HRV analyses (Camm et al., 1996), we used the first 237 IBIs of the recordings also in these analyses, in order to compare all IBI indices on equal premises.

The similarity graph algorithm (*outlined below*) was applied to the IBI series. We also performed time domain analyses of the *SD* of normal IBIs (SDNN) and the root mean square of successive RR interval differences (RMSSD). SDNN indexes total variability in HR, and RMSSD reflects vagal modulation (Camm et al., 1996). Further, a frequency analysis with the Fast Fourier Transformation yielded a power spectrum of activity in the LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) bands (Camm et al., 1996), expressed in non-normalized units. Activity in the LF band is frequently interpreted as sympatho/vagal activity, and the HF band indexes vagal activity (Camm et al., 1996). We also calculated the LF/HF ratio, which is—although debated (Billman, 2013)—often considered to index sympatho/vagal balance, in that a low LF/HF ratio reflects vagal dominance of the ANS (Camm et al., 1996). Further, respiration rates were estimated by the ECG-derived respiration, based on changes in R-wave amplitude (Moody et al., 1985). We assessed whether respiration rates were within the normal range for adults (.20–.33 Hz; McCance & Huether, 2018), supporting our use of adult frequency bands (see Shader et al., 2018). Lastly, we assessed peak frequencies of the HF band, HF peak, reflecting respiratory effects on IBIs (Grossman et al., 1991; Thayer et al., 2002).

2.4.2 | Physical activity levels

Engagement in sports and exercise was reported by the adolescents in the K-SADS interview, and physical activity levels were thereafter scored on a five-point scale from 1 ("zero times a week") to 5 ("seven times or more a week"). The scoring norm was adapted from the Physical Activity Questionnaire for Adolescents (PAQ-A; Kowalski et al., 2004) due to its convergent validity (Kowalski et al., 1997). Data reported between two categories were lowered to the nearest category (see Sallis et al., 1996). One participant in the current study did not provide information on physical activity.

2.4.3 | Body mass index

The participants' BMI was calculated by dividing weight in kg by height in meters squared. In the current study, it was impossible to calculate BMI for four participants (ADHD, $n = 2$; Controls, $n = 2$) as they declined to be weighed or due to a technical error with the scale.

2.4.4 | ADHD symptoms

ADHD symptoms were indexed by total scores on the Norwegian translation (Kvilhaug et al., 1998) of the parent-reported ADHD-RS (DuPaul et al., 1998). Eighteen items about symptom levels of inattention (e.g., "Is forgetful in daily activities") and hyperactivity-impulsivity (e.g., "Talks excessively") were rated on a four-point Likert-type scale from 0 ("Never") through 3 ("Very Often"). The ADHD-RS has shown high internal consistency (Cronbach's α in the current sample: .96) and adequate validity (DuPaul et al., 1998). ADHD-RS data were missing for one participant (with ADHD) in the current study.

2.4.5 | Anxiety symptoms

The Norwegian translation (Haseth et al., 1990) of the STAI (Spielberger et al., 1983) assessed self-reported symptoms of trait anxiety (STAI-T). The inventory has shown adequate internal consistency (Cronbach's α in the current sample: .87), test-retest reliability (Spielberger et al., 1983), and construct- and concurrent validity (Spielberger, 1989). The STAI-T score is based on 20 items (e.g., "I feel nervous and restless") rated on a four-point Likert-type scale from 1 ("Almost never") to 4 ("Almost always"). In the current study, STAI-T scores were missing for three participants with ADHD and two controls.

2.5 | Measures

2.5.1 | Graph theory

The overview of graph theory principles and description of the similarity graph algorithm are based on the original publication of this method (Fasmer et al., 2018). There are some additional features and adaptations to the analysis of IBI data, as outlined below.

Graphs are mathematical structures that model relations between objects. *A* graph $G = (V, E)$ consists of a collection V of nodes (vertices) and a collection E of edges (if any) (Bondy & Murty, 2008). An edge $e \in E$ is a two-element subset of V that associates two nodes: $e = \{u, v\}$, for some u, $v \in V$ (Lian, 2000). A *subgraph* is a graph formed from a subset of the nodes and edges (if any) of G.

2.5.2 | The similarity graph algorithm

We apply a heuristic algorithm that is nonlinear and not chaos-based that transforms a time series into a *similarity graph* $G = (V, E)$ (see Fasmer et al., 2018. Program code can be accessed at https://github.com/erlfas/SimilarityGraph). In the current study every IBI in a time series is represented by a node in the graph. Thus, in a time series S each node u_i in V, $1 \leq I \leq n$, corresponds to the element $x_i \in S$, and the node u_i is assigned a weight equal to x_i. An edge between two nodes signifies that the nodes fulfill the *criterion of similarity*: that the difference in IBIs is below a predefined threshold. This similarity is calculated as $\max(x_i, x_j)/\min(x_i, x_j)$ or $\max(x_i, x_j) - \min(x_i, x_j)$.

In the current study, every node in the graph will be the *index node* considered by the algorithm (Figure 2). Thus, every IBI will be analyzed in relation to a given section of other IBIs in the time series: a *time window* (Figure 2). To describe the size of a time window, we use the term *neighbors*: the number (k) of preceding or subsequent nodes around the index node. Thus, every node has a total number of 2k neighbors, denoted as $k+k$. When analyzing the IBI series, the applied time window "slides" and centers around every index node, except for the first k and last k IBIs of the time series. Different time windows create different *subgraphs* (Figure 2), which may reveal different properties of the underlying time series.

In sum, we introduce an edge between two nodes if and only if they fulfill the criterion of similarity and are within the same time window. The number of edges in a given time window reveal how similar the index nodes are to the other nodes. Minimum similarity is revealed when the index node has no edges. Conversely, maximum similarity is revealed when the index node has an edge to every other node in the time window. In the current study, graphs with a higher number of similar IBIs are described as having higher *inter-relatedness*.

The described methods create a graph that can be studied by well-known algorithms from graph theory (See Figure 3 for the transformation of an IBI series to graphs and subsequent indices). The indices investigated in the current study and their possible interpretation in terms of inter-relatedness and vagal activity are described in Table 3. The index of bridges is more complex to interpret (e, an edge of G, is a bridge if G–e has more components than G; see Fasmer et al., 2020), and was thus included in supplemental analyses.

2.5.3 | Additional nonlinear analyses

To compare the similarity graph algorithm to other nonlinear methods, we performed recurrence quantification analyses (RQA) and analyses of SampEn. Both methods assess complexity and have frequently been applied to IBI data (Henriques et al., 2020).

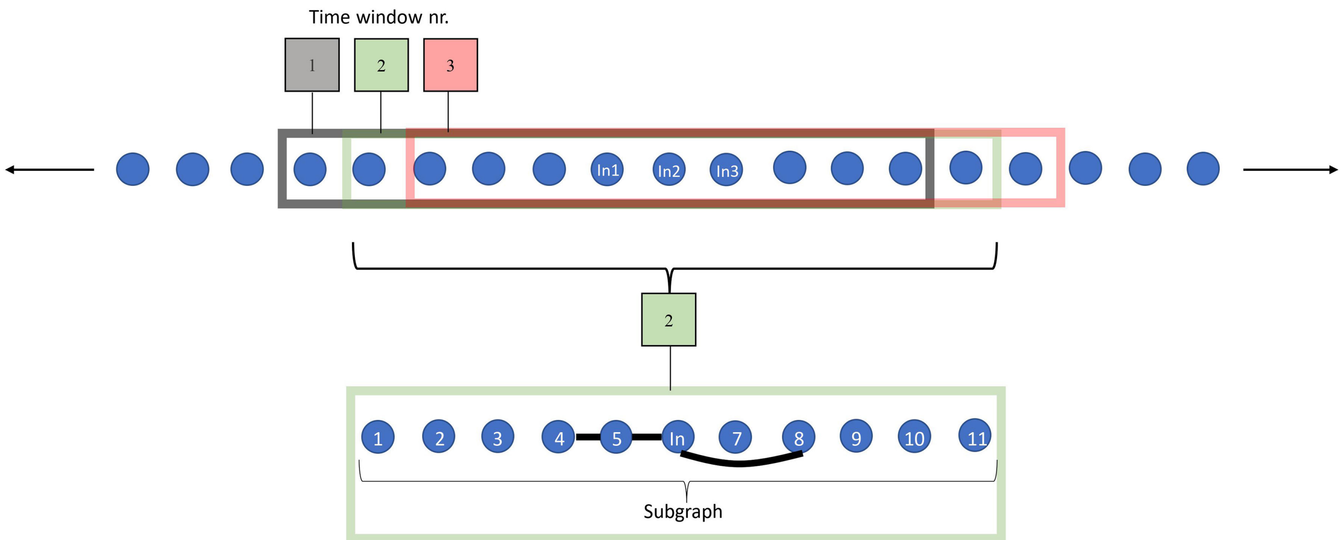
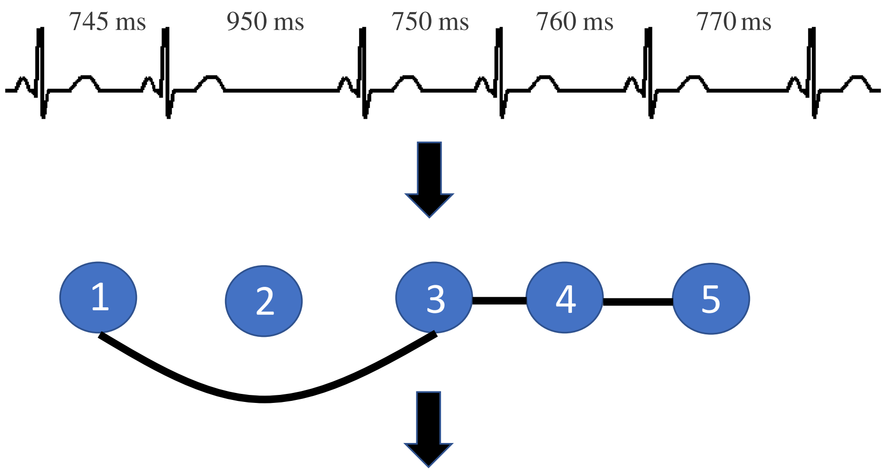


FIGURE 2 Illustration of the concept of index nodes, time windows and subgraphs. The figure illustrates three time windows of 5+5 neighbors. Each node in the time series is used as an index node (In1–3) considered by the similarity graph algorithm. Five nodes (i.e., neighbors) on the left and right side of the index node, respectively, make up a time window of 5+5 neighbors. Within the time window, nodes are connected by edges based on the similarity of the nodes. This collection of nodes and edges within a time window makes up a subgraph



Index	Value
Edges	3
Components	2
Missing edges	2
Max edges	3
Zero edges	0
Cliques	1

FIGURE 3 Illustration of the procedure for deriving graph theoretical indices from inter-beat intervals (IBIs). First, IBIs are collected. Then, the IBIs are converted to a graph, where nodes that fulfill the criterion of similarity (in the current figure: 1.5%) and are within the same time window are connected by edges. Lastly, the values of the graph theory-based indices are derived from the properties of the graph

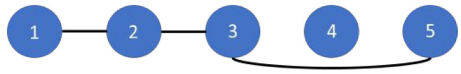
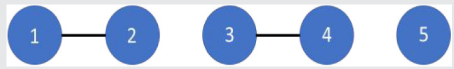
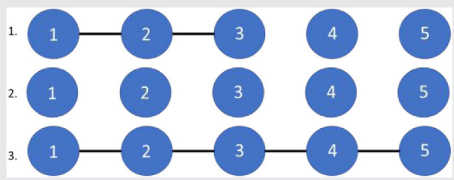
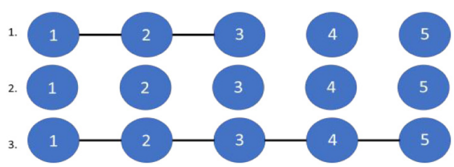
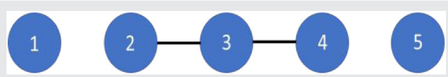
2.6 | Statistical analyses

Statistical analyses were performed in the Statistical Package for the Social Sciences version 24.0 (SPSS; IBM Corp., Armonk, NY, 2016). HRV frequency bands were transformed with their natural logarithm to approximate a normal distribution (Ellis et al., 2008). We examined potential outliers, i.e., values > ±3 *SD* from the mean, in variables used as covariates (i.e., age, sex, BMI, physical activity levels, HF peak, number of comorbidities and STAI-T scores). Outliers were imputed with the value of the sample mean ±3 *SD*. Missing data were imputed with the sample mean, or the mean of the ADHD group (for the missing ADHD-RS score). Differences between the ADHD and control groups in age, sex, BMI, physical activity levels, ADHD-RS and STAI-T scores, number of comorbidities, and HF peak were investigated with the independent samples *t* test or chi-square tests. Unless otherwise noted, differences between the ADHD and control group in the remaining analyses were investigated with independent samples *t* tests, with Cohen's *d* as an effect size measure.

First, to investigate which setting of the similarity graph algorithm best accentuated IBI differences between the ADHD and control groups, we ranged criteria of similarity from 1% to 5% (i.e., 95%–99% similarity) and 5 to 50 ms. Differences in edges between the ADHD and control groups were assessed. We used a time window of 2+2 neighbors, hypothesized to provide the most refined index of vagal activity. The settings that yielded the largest effect size of a significant difference from the percentage-based and msec-based approaches were then compared. Here, we investigated differences in edges between the ADHD and control groups for time windows of 2+2 and 10+10 neighbors, and edges10+10/edges2+2. The criterion yielding the largest significant effect size in any index was applied in the remaining analyses.

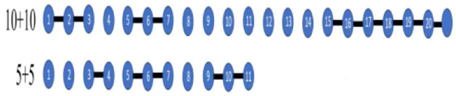
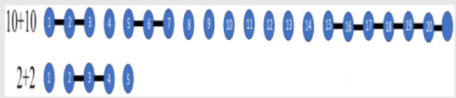
Second, we ran the similarity graph algorithm with three different time windows to test the hypothesis that we would find higher inter-relatedness in the ADHD group compared to the control group. Based on our hypothesis that vagal activity might be captured best in a time window of 2–5 s, which we aimed to compare to two longer time windows, we applied values of $k = 2$, $k = 5$ and $k = 10$. This corresponded to approximately 2–5, 6–13, and 12–25 s, respectively (mean IBI: 900.61 ms; range: 606–1261 ms). In these time windows, we investigated differences between the ADHD and control groups in the average number of edges, components, missing edges, maximum edges, zero edges, and cliques. We also calculated edges10+10/edges5+5 and edges10+10/2+2. Group differences in cliques were investigated with the Mann-Whitney *U* test. As post-hoc analyses, we investigated differences in edges and ratios derived from the number of edges in two different time

TABLE 3 Overview of graph theory-based indices calculated in the current study, and their suggested physiological interpretation in terms of inter-relatedness

Index	Definition	Illustration	Interpretation of high value
Edges	A two-element subset that associates two nodes that a) fulfill the criterion of similarity, and b) are located within the same subgraph (i.e., time window). The index refers to the mean of the number of edges in all subgraphs	 *The subgraph has three edges: Those connecting nodes nr. 1, 2 and 3, and nr. 3 and 5*	↑ Inter-relatedness ↓ Vagal activity
Components	A graph can be divided into separate *components*. The nodes in each component are connected by edges and the different components are not interconnected by edges. A node with no edges is itself a component. We are for each subgraph interested in the total count of these components	 *The subgraph consists of three components: Those including node nr. 1 and 2, nr. 3 and 4, and nr. 5, respectively*	↓ Inter-relatedness ↑ Vagal activity
Missing edges	The total count of the number of nodes that are nearest neighbors in a subgraph and do not have an edge connecting them	 *The subgraph has two missing edges: There are no edges between node nr. 2 and 3, or nr. 3 and 4*	↓ Inter-relatedness ↑ Vagal activity Comparable to RMSSD (see Fasmer et al., 2020)
Maximum edges	The highest number of edges found in any subgraph of the time series	 *The number of maximum edges is four. Subgraph 1 has two edges, subgraph 2 has zero edges, and subgraph 3 has four edges*	↑ Inter-relatedness ↓ Vagal activity
Zero edges	The number of subgraphs with zero edges	 *The number of subgraphs with zero edges is one: Subgraph 1 has two edges, subgraph 2 has zero edges, and subgraph 3 has four edges*	↓ Inter-relatedness ↑ Vagal activity
(3-) Cliques	The total count of subsets of three nodes in which every pair of distinct nodes are connected by an edge (i.e., a sequence of three nodes with similar values)	 *The subgraph has one clique: The one consisting of nodes nr. 2, 3, and 4*	↑ Inter-relatedness ↓ Vagal activity

(Continues)

TABLE 3 (Continued)

Index	Definition	Illustration	Interpretation of high value
Edges10+10/ edges 5+5	The ratio between the number of edges detected when analyzing 10+10 neighbors (i.e., the longest time window applied in the current study) and 5+5 neighbors (i.e., the intermediate-length time window applied in the current study)	 *Edges10+10/edges5+5 is 2. The time window of 10+10 neighbors has ten edges, and the time window with 5+5 neighbors has five edges (i.e., 10/5)*	Relatively ↑ vagal activity of total ANS activity Inverse of LF/HF ratio Less refined than edges10+10/ edges2+2
Edges10+10/ edges2+2	The ratio between the number of edges detected when analyzing 10+10 neighbors (i.e., the longest time window applied in the current study) and 2+2 neighbors (i.e., the shortest time window applied in the current study)	 *Edges10+10/edges2+2 is 5. The time window of 10+10 neighbors has ten edges, and the time window with 2+2 neighbors has two edges (i.e., 10/2)*	Relatively ↑ vagal activity of total ANS activity Inverse of LF/HF ratio More refined than edges10+10/ edges5+5

windows, between the ADHD and control group in time windows close to the k value ($k \pm 1$) that had best distinguished the groups, to investigate if this yielded even larger effect sizes.

Third, we performed time- and frequency domain analyses to investigate HRV differences between the ADHD and control groups. This tested the hypothesis that we would find a lower SDNN, and a higher LF-HRV and LF/HF ratio in the ADHD group compared to controls, but no significant differences in RMSSD or HF-HRV.

Fourth, we performed follow-up ANCOVAs on significantly different IBI indices in the ADHD and control groups from the graph theory-based and HRV analyses, investigating potential confounding effects. The IBI indices, respectively, were used as the dependent variable, and diagnostic group status (ADHD/control) as the independent variable. As covariates, we used (A) Age, sex, BMI, physical activity levels, and HF peak. Covariates that significantly predicted any of the indices were included in a final ANCOVA model, (B) The number of comorbid disorders each participant had, and (C) STAI-T scores.

Fifth, supplemental analyses assessed (A) Differences between the ADHD and control groups in RQA and SampEn, to compare results from the similarity graph algorithm to other nonlinear approaches, (B) Bivariate correlations between HRV indices, edges10+10/edges2+2 and edges10+10/edges5+5, aiding in the interpretation of the ratios, (C) The probability of an index node having an edge to a neighbor for time windows of 2+2, 5+5 and 10+10 neighbors, in the ADHD and control groups. The largest group difference in this probability further elucidated which time window best illustrated group differences, (D) Differences in bridges between the ADHD and control groups for time windows of 2+2, 5+5, and 10+10 neighbors, providing additional information about inter-relatedness, (E) Bivariate correlations of ADHD-RS scores and significant IBI indices from the main analyses, investigating if ADHD symptom severity correlated with the indices, and (F) HRV analyses of five-minute IBI series, to see if this yielded comparable results to analysis of the first 237 IBIs of the series.

3 | RESULTS

3.1 | Preliminary analyses

There were no outliers for values obtained by time- and frequency domain analyses or the similarity graph algorithm, or for physical activity levels, HF peak, number of comorbidities, ADHD-RS or STAI-T scores. The exception was one outlier for missing edges (in the ADHD group), and that the cliques displayed a skewed distribution in both groups. There was one outlier in the BMI values (in the ADHD group).

The adolescents with ADHD reported significantly higher STAI-T scores than the control group (for

TABLE 4 IBI analyses based on the similarity graph algorithm. 2+2 neighbors

	ADHD (*n*=37)	Controls (*n* = 36)	*p*	*d*	CI
Edges	.70 ± .38	.54 ± .26	.037*	.50	[.030, .96]
Components	162.43 ± 35.68	177.03 ± 26.54	.052	.46	[.00, .93]
Missing edges	189.14 ± 24.59	198.00 ± 17.81	.083	.41	[-.050, .88]
Max edges	3.24 ± .72	2.69 ± .86	.0040**	.69	[.23, 1.16]
Zero edges	120.14 ± 41.21	137.25 ± 35.26	.061	.45	[-.021, .91]
Cliques	7.78 ± 9.58	3.31 ± 4.07	.0080*	.61	[.14, 1.07]
Edges10+10/edges2+2	4.52 ± .88	5.57 ± 1.20	<.0010**	1.00	[0.54, 1.47]

Note: Data were analyzed by the independent samples *t* tests, except for cliques, where the Mann-Whitney U test was applied. CI: 95% confidence interval of *d*. Data are given as (mean ± *SD*).

*$p \le .050$;; **$p \le .010$.

descriptive statistics for the ADHD and control group, see Table 1). The ADHD group also had higher parent-rated ADHD-RS scores than the controls, and a higher number of comorbidities. Further, controls reported higher levels of physical activity than their ADHD counterparts. There were no significant differences in age, sex, BMI or HF peak between adolescents with ADHD and controls. The mean ECG-derived respiratory frequency in the sample corresponded to .26 Hz (*SD* .050; Supporting Information Table S1).

3.2 | IBI assessment with the similarity graph algorithm

3.2.1 | Systematically varying criteria of similarity

First, we systematically varied the criterion of similarity from 1% to 5% (Supporting Information Figure S2) and 5–50 ms (Supporting Information Figure S3), respectively, to investigate which setting best illustrated differences in IBI organization between the ADHD and control group. The only significant differences in the number of edges between adolescents with ADHD and controls were found applying the 1.5% criterion and the 10 msec criterion. For both these approaches, we found significant group differences in the number of edges in a time window of 2+2 neighbors but not 10+10 neighbors. Further, group differences in edges10+10/edges2+2 were significant for both approaches (Supporting Information Table S2). The largest effect size for both approaches was found for edges10+10/edges2+2. The effect size was larger using the 1.5%-based approach compared to the 10 ms-based approach. Therefore, 1.5% was chosen as the criterion of similarity for the remainder of the analyses.

3.2.2 | IBI assessment in different time windows

Second, in order to investigate differences in interrelatedness between adolescents with ADHD and controls, and which time window best illustrated such differences, we ran the similarity graph algorithm in three different time windows. Applying a time window of 2+2 neighbors, we found a significantly higher number of edges, maximum edges and cliques, and a lower edges10+10/edges2+2 in the ADHD group compared to controls as analyzed by the independent samples *t* test (Table 4). Differences in components, missing edges, and zero edges were non-significant.

Analyzing a time window of 5+5 neighbors, the independent samples *t* test found no significant differences in the number of edges, components, missing edges, maximum edges, zero edges, cliques or edges10+10/edges5+5 between the ADHD and control groups (Table 5).

Analysis of a time window of 10+10 neighbors detected no significant differences between the ADHD and control groups regarding number of edges, components, missing edges, maximum edges, zero edges or cliques (Table 6).

As a time window of 2+2 neighbors best distinguished differences in IBI organization in the ADHD and control group, we performed post-hoc analyses investing group differences in time windows of 1+1 and 3+3 neighbors to see if these yielded even larger effect sizes (Supporting Information Table S3). Independent samples t-tests detected a significantly lower edges10+10/edges1+1 and edges10+10/edges 3+3 in the ADHD group compared to controls. However, effect sizes were smaller compared to what was found for edges10+10/edges2+2. The differences in number of edges were non-significant for both time windows.

3.3 | Time- and frequency domain analyses

Third, applying time- and frequency domain analyses to investigate differences in HRV between the ADHD and control groups, independent samples t-tests showed a significantly higher LF/HF ratio in the ADHD group compared to controls. There were no significant group differences in SDNN, RMSSD, LF-HRV or HF-HRV (Table 7).

3.4 | Follow-up analyses

Fourth, we adjusted for effects of possible confounding factors. We performed ANCOVAs with the significantly different IBI indices, respectively, as dependent variables, and diagnostic group status (ADHD/controls) as the independent variable. As covariates, we included (A) Age, sex, physical activity levels, BMI, and HF peak. HF peak predicted edges10+10/edges2+2 ($R^2 = .29$, $F = 4.43$, $p = .033$). Age ($R^2 = .26$, $F = 8.12$, $p = .0060$) and physical activity levels ($R^2 = .26$, $F = 5.53$, $p = .022$) predicted the LF/HF ratio. Neither sex nor BMI significantly predicted any of the IBI indices. Thus, HF peak, age, and physical activity levels were included as covariates in a follow-up ANCOVA on significant results. In this final model, the effect of diagnostic status was still significant for edges, maximum edges, cliques, and edges10+10/edges2+2, but not for the LF/HF ratio (Table 8, Figure 4). HF peak significantly predicted edges10+10/edges2+2, but no other indices. Age and physical activity levels covaried with the LF/HF ratio, but no other indices.

(B) The number of comorbidities. The effect of diagnostic status on maximum edges and edges10+10/edges2+2 remained significant (Supporting Information Table S4). The effect of diagnostic status on edges, cliques, and the LF/HF ratio was no longer significant. The number of comorbidities covaried significantly with the LF/HF ratio, but not with any of the graph theory-based indices, and (C) STAI-T scores. The effect of diagnostic status on maximum edges, cliques, and edges10+10/edges 2+2 remained significant (Supporting Information Table S5). The effect of diagnostic status on the number of edges and the LF/HF ratio was no longer significant. STAI-T scores covaried significantly with the LF/HF ratio, but not with any of the graph theory-based indices.

3.5 | Supplemental analyses

Fifth, we performed supplemental analyses. These analyses found that (A) Comparing our method to established nonlinear approaches, there were no significant differences between the ADHD and control groups by applying RQA (Supporting Information Table S6) or SampEn, (B) Aiding in the interpretation of the graph theory-based ratios, edges10+10/edges2+2 and edges10+10/edges5+5 correlated positively with each other, RMSSD and HF-HRV, and negatively with the LF/HF ratio. The ratios did not covary with SDNN or LF-HRV (Supporting Information Table S7), (C) Aiding in the question of which time window best illustrated differences in IBI organization between adolescents with ADHD and controls, the largest group difference in the probability of an index node having an edge to one of its neighbors was found for a time window of 2+2 neighbors (Supporting Information Table S8), (D) As an additional index of inter-relatedness, we did not find any significant differences in the number of bridges between the ADHD and control groups (Supporting Information Table S9), (E) Higher ADHD-RS scores correlated significantly with a lower edges10+10/edges2+2 ($\rho = -.37$, $p = .0010$) and a higher number of maximum edges ($\rho = -25$, $p = .030$). The LF/HF ratio, number of edges or cliques did not correlate significantly with the ADHD-RS scores, and (F) In order to compare

TABLE 5 IBI analyses based on the similarity graph algorithm. 5+5 neighbors

	ADHD ($n = 37$)	Controls ($n = 36$)	p	d	CI
Edges	1.64 ± .89	1.50 ± .65	.44	.18	[−.29, .65]
Components	105.24 ± 41.25	106.14 ± 37.83	.92	.023	[−.44, .49]
Missing edges	190.30 ± 24.16	198.83 ± 17.37	.088	.40	[−.062, 0.87]
Max edges	5.62 ± 1.53	5.22 ± 1.27	.23	.28	[−.18, .75]
Zero edges	67.95 ± 30.36	67.19 ± 30.69	.92	.025	[−.44, .49]
Cliques	73.51 ± 85.19	52.19 ± 49.39	.58	.31	[−.16, .77]
Edges 10+10/edges 5+5	1.88 ± .12	1.91 ± .14	.32	.24	[−.23, .70]

Note: Data were analyzed by the independent samples t tests, except for cliques, where the Mann-Whitney U test was applied. CI: 95% confidence interval of d; Data are given as (mean ± SD).

*$p \le .050$;; **$p \le .010$.

TABLE 6 IBI analyses based on the similarity graph algorithm. 10+10 neighbors

	ADHD ($n = 37$)	Controls ($n = 36$)	p	d	CI
Edges	3.06 ± 1.61	2.83 ± 1.18	.50	.16	[−.31, .62]
Components	66.05 ± 29.98	62.44 ± 30.29	.61	.12	[−.35, .59]
Missing edges	192.35 ± 23.16	200.72 ± 16.18	.078	.42	[−.049, .88]
Max edges	8.92 ± 2.95	8.42 ± 2.37	.43	.19	[−.28, .65]
Zero edges	46.78 ± 17.11	44.47 ± 17.37	.57	.13	[−.33, .60]
Cliques	310.30 ± 340.48	231.61 ± 209.91	.81	.28	[−.019, .74]

Note: Data were analyzed by the independent samples t tests, except for cliques, where the Mann-Whitney U test was applied. CI: 95% confidence interval of d. Data are given as (mean ± SD).

*$p \leq .050$;; **$p \leq .010$.

TABLE 7 Time- and frequency domain analyses of HRV

	ADHD ($n = 37$)	Controls ($n = 36$)	p	d	CI
SDNN	69.75 (30.33)	68.34 (27.27)	.84	.049	[−.42, .52]
RMSSD	69.93 (42.74)	75.27 (36.23)	.57	.13	[−.33, .60]
LF (ms^2)	6.67 (1.05)	6.51 (1.05)	.51	.16	[−.31, .62]
HF (ms^2)	7.19 (1.28)	7.46 (1.08)	.33	.23	[−.24, .70]
LF/HF	.94 (.11)	.88 (.11)	.018*	.54	[.079, 1.01]

Note: CI: 95% confidence interval of d. HRV frequency bands were naturally log transformed to approximate a normal distribution. Data are given as (mean, SD).

Abbreviations: HF (ms^2), high frequency-HRV given in ms^2; HRV, heart rate variability; LF (ms^2), low frequency-HRV given in ms^2; LF/HF, low frequency/high frequency ratio; RMSSD, root mean square of successive differences; SDNN, standard deviation of normal IBIs.

*$p \leq .050$;; **$p \leq .010$.

results from analyses of the first 237 of the IBI series to analyses of the conventional recording length, we did not detect any group differences in time- and frequency domain analyses when analyzing five-minute ECG recordings (Supporting Information Table S10).

4 | DISCUSSION

The purpose of the current study was to assess IBI organization with a nonlinear, graph theory-based method not hitherto applied to IBIs: the *similarity graph algorithm*. We investigated whether the algorithm could detect group differences in IBI organization as exemplified in a sample of adolescents with ADHD compared to a control group. As hypothesized, we found higher inter-relatedness (i.e., a higher number of similar IBIs) in a time window of 2–5 s in the ADHD group compared to controls. This might suggest altered vagal activity in the ADHD group. As expected, traditional HRV analyses detected a higher LF/HF ratio in the ADHD group. However, this effect was non-significant after controlling for possible confounding factors. In contrast, the graph theory-based indices were in large part unaffected by such confounding factors. Other nonlinear approaches (RQA and SampEn) did not detect any significant IBI differences between the ADHD and control groups. Altogether, our findings suggest that the similarity graph algorithm might provide additional information to other methods for IBI analysis as a proxy for ANS functioning.

Using the similarity graph algorithm, we detected the largest effect size for differences in IBI organization between the ADHD and control groups when applying a 1.5% criterion for defining IBIs as similar. This was in line with our hypothesis based on previous work with the SampEn method (Hauge et al., 2011; Richman & Moorman, 2000), where it is customary to use a threshold of 20% of the SD for defining two points as similar. The mean SD of the IBI time series in the current study was approximately 70 ms, and the mean IBI approximately 900 ms, giving 1.5% of the mean as a reasonable threshold for similarity (0.20*SD/mean = 14/900 ≈ 1.5%).

Applying the 1.5% criterion of similarity in the similarity graph algorithm, several differences between the adolescents with ADHD and controls were detected in the graph theory-based IBI indices. The ADHD group displayed a higher number of edges, maximum edges, and cliques. These indices reflect higher inter-relatedness, as a result of a higher number of similar IBIs. Contrary to our expectations, the difference in components was

TABLE 8 Prediction of diagnostic status on selected IBI indices, controlling for potential confounders

Predictor	R^2	*df*	*F*	*p*
Edges				
ADHD	.13	4	4.32	.041*
HF peak			3.62	.061
Age			2.51	.12
Physical activity levels			.46	.50
Maximum edges				
ADHD	.14	4	7.46	.0080**
HF peak			.11	.75
Age			2.22	.14
Physical activity levels			.12	.73
Cliques				
ADHD	.11	4	5.32	.024*
HF peak			1.37	.25
Age			.28	.60
Physical activity levels			.24	.63
Edges10+10/edges2+2				
ADHD	.27	4	11.32	<.0010**
HF peak			4.20	.044*
Age			.27	.61
Physical activity levels			.41	.53
LF/HF				
ADHD	.22	4	2.81	.098
HF peak			.53	.47
Age			5.45	.023*
Physical activity levels			4.06	.048*

Note: Time window applied: 2+2 neighbors .

Abbreviations: ADHD, ADHD diagnostic status; LF/HF, Low frequency/high frequency ratio; HF peak, Peak of high frequency heart rate variability.

*$p \le .050$;; **$p \le .010$.

non-significant, although this index also reflects higher inter-relatedness. This non-finding could be due to lack of statistical power in our study. Still, as expected, the indices reflecting inter-relatedness generally appeared to be more sensitive than the indices representing lack of inter-relatedness (i.e., missing edges and zero edges), which were non-significant. The similarity graph algorithm further detected a significantly lower edges10+10/edges2+2 in the ADHD group compared to controls. As expected, this index was inversely related to the LF/HF ratio calculated by HRV analyses. Although the interpretation is debated (Billman, 2013), a higher LF/HF ratio is frequently considered to index sympathetic dominance of the ANS, and a lower edges10+10/edges2+2 might represent a comparable construct. Our results therefore seem to be in line with previous findings of higher LF/HF ratios in ADHD samples (Griffiths et al., 2017; Tonhajzerova et al., 2009).

Differences between the ADHD and control groups in our sample were most prominent in analyses of time windows of 2–5 s. In line with our hypothesis, this suggests that the IBI organization occurring over a few seconds is most affected in ADHD. This could be due to altered functioning of the vagus nerve, which normally has a rapid course of action compared to the sympathetic nervous system (Nunan et al., 2010). As a result of altered vagal functioning, HR changes are not induced as rapidly as with optimal functioning, resulting in more similar IBIs. This could be reflected in higher inter-relatedness and relatively more sympathetic regulation of IBIs—in line with the aforementioned results from analyses of the graph theory-based indices in the ADHD group. As the control group, on the other hand, displayed lower inter-relatedness, our findings are in line with expectations of higher vagally medicated HRV in controls compared to individuals with ADHD (Rash & Aguirre-Camacho, 2012). There were no significant differences between adolescents with ADHD and controls in the time windows of 6–13 or 12–25 s, respectively. In line with our hypothesis, we suggest that these time windows provide less refined indices of vagal activity compared to the time window of 2-5 seconds. As vagally mediated HRV is considered to mark self-regulatory abilities and general psychopathology (Beauchaine, 2015; Beauchaine & Thayer, 2015; Holzman & Bridgett, 2017), we suggest that our indices of inter-relatedness in a time window of 2–5 s, as well as edges10+10/2+2, could represent similar constructs. This is supported by ADHD symptom severity correlating negatively with edges10+10/edges2+2 and positively with maximum edges. Interestingly, maximum edges and edges10+10/edges2+2 appeared to be the most robust of the graph theory-based indices when controlling for comorbidities and trait anxiety symptoms, and therefore seem to be most sensitive to ADHD-specific IBI alterations.

It is crucial to address the question of whether our study is sufficiently powered in terms of the ability to detect group differences in IBI organization, as we have investigated a method not previously applied to IBI analysis. Performing an *a priori* power analysis was challenging due to no previous studies applying a similar method to ours in an ADHD sample. We could therefore not calculate appropriate estimates of expected effect sizes. However, we will suggest that the similarity graph algorithm might provide larger power than traditional methods as the algorithm systematically compares every IBI in a given time window to every other IBI in the time window. This gives a substantially higher number of data points compared to traditional analyses of whole IBI series. It is important to note in this regard that our analyses were performed in

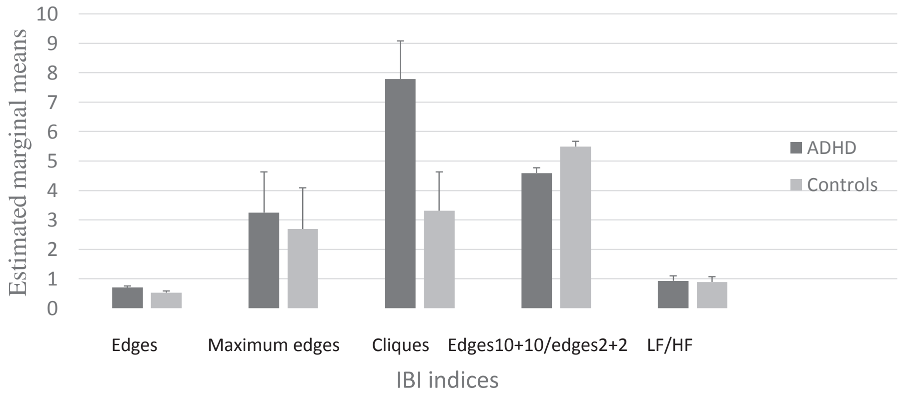


FIGURE 4 Estimated marginal means for inter-beat interval indices that show significant group differences in adolescents in ADHD and controls. The means were adjusted for the effect of HF peak as a proxy of respiration, age, and physical activity levels. Error bars represent standard errors. Abbreviations: LF/HF: low frequency/high frequency ratio.

a relatively small sample, and we therefore cannot rule out that some of the statistically significant graph theory-based differences have occurred due to multiple testing or sampling error. With regard to the traditional HRV analyses, we did not find group differences in SDNN or LF-HRV, contrary to expectations. This could be due to a lack of statistical power in these analyses. Further, also of relevance to the statistical power is the IBI recording length. Often, 30,000 data points are used to validate novel methods that assess indices of complexity (see Costa et al., 2002; Yang et al., 2020). Our investigation of 237 IBIs does not provide as many data points. However, the reason that a longer data series is often required is to gain enough complexity for the method to detect group differences (Costa et al., 2002; Yang et al., 2020). Although we had a shorter data length than often required, the statistically significant group differences detected by the similarity graph algorithm were in line with our *a priori* hypotheses. This supports the notion that our findings did not appear by coincidence, along with the fact that several of the detected group differences appeared to be robust also when controlling for confounding factors.

The current study has several strengths and limitations. Among several strengths, we assessed IBIs approximately at the same time of day for all participants, controlling for circadian influences. In addition, we assessed physical activity levels and BMI, which are not regularly investigated in IBI studies despite influencing IBIs (Gutin et al., 2005; Koenig et al., 2014). Further, the ADHD and control groups were matched on age and sex, and there were no significant group differences in BMI, reducing potential confounding effects of these factors on IBIs. Individuals with ADHD generally have higher BMI than controls (Cortese et al., 2008; Fliers et al., 2013); however, our finding of a non-significant BMI difference could be due to a substantial number of adolescent girls with ADHD in our sample, who seem to be at lower risk of being overweight (Fliers et al., 2013). However, the control group had higher physical activity levels than the ADHD group, and the adolescents with ADHD had higher symptoms of trait anxiety and number of comorbidities, in line with expectations (Cook et al., 2015; Gnanavel et al., 2019; Sharma et al., 2011). Regarding limitations and threats-to-validity, in addition to the already discussed aspects related to the power of the current study, possible effects of medication on IBIs cannot be ruled out. Still, short-term effects were reduced by almost all participants conducting a washout period. Also important to note is that ADHD medication tend to shift IBI indices toward control values (see Buchhorn et al., 2012; Kim et al., 2015; Negrao et al., 2011), and have probably not contributed to any false group differences in the current study. Yet, a participant in the control group used other types of medication that were not subjected to a washout period, which could have influenced their IBIs. The graph theory-based indices have further not been investigated in relation to ANS functioning, and our interpretation of them is of an explorative nature. In addition, IBI organization investigated in short time windows might not be reproducible for a given individual to the same extent as the traditionally used HRV indices. Future studies investigating the reliability of the graph theory-based indices from the similarity graph algorithm, and their sensitivity and specificity as "trait" markers of self-regulatory abilities are called for.

5 | CONCLUSION

Our study suggests that the similarity graph algorithm can provide complementary information to other analyses of IBI organization, which has potentially important theoretical and clinical implications. The indices computed by the algorithm seem to detect complex features of the IBI series that reveal spontaneous or transient ANS alterations and might thus be sensitive markers of psychopathology. As the graph theory-based indices were largely unaffected by comorbidities or trait anxiety symptoms, the indices might represent more disorder-specific patterns of vagal alterations compared to traditional HRV indices – which have been suggested as transdiagnostic markers of psychopathology (Beauchaine & Thayer, 2015). This might have further implications for the etiological understanding and treatment of various disorders. These implications are, however, largely hypothetical as of now, and further research is needed to investigate them.

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CONFLICT OF INTEREST

During the past three years, JH has received lecture honoraria as part of continuing medical education programs sponsored by Shire, Takeda, Medice and Biocodex. Otherwise, all authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Elisabet Kvadsheim: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Ole Bernt Fasmer:** Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; writing – original draft; writing – review and editing. **Erlend Eindride Fasmer:** Conceptualization; data curation; formal analysis; methodology; software; writing – original draft; writing – review and editing. **Erik R. Hauge:** Conceptualization; investigation; methodology; writing – original draft; writing – review and editing. **Julian F. Thayer:** Methodology; writing – review and editing. **Berge Osnes:** Data curation; writing – review and editing. **Jan Haavik:** Supervision; writing – review and editing. **Julian Koenig:** Conceptualization; methodology; supervision; writing – review and editing. **Steinunn Adolfsdottir:** Investigation; writing – review and editing. **Kerstin Jessica Plessen:** Funding acquisition; project administration; writing – review and editing. **Lin Sørensen:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

FIGURE S1 Flow chart of inter-beat interval preparation and analysis. ECG, electrocardiogram; IBI, inter-beat interval; Msec, milliseconds

FIGURE S2 Effect sizes for diagnostic group differences in number of edges detected with a systematically varied percentage-based approach to criterion of similarity. Time window: 2+2 neighbors. $^{*}p \leq .050$; $^{**}p \leq .010$

FIGURE S3 Effect sizes for diagnostic group differences in number of edges detected with a systematically varied msec-based approach to criterion of similarity. Time window: 2+2 neighbors. Msec, milliseconds. $^{*}p \leq .050$; $^{**}p \leq .010$

TABLE S1 EDR values in the total sample and diagnostic groups

TABLE S2 Number of edges detected with a 1.5%- and 10msec-based approach, respectively, to criterion of similarity

TABLE S3 Number of edges as analyzed with time windows of 1+1 and 3+3 neighbors

TABLE S4 Effect of comorbidities on selected IBI indices

TABLE S5 Effect of STAI-T scores on selected IBI indices

TABLE S6 Reccurence quantification analyses

TABLE S7 Bivariate correlations among selected HR organization indices

TABLE S8 Probability of the index node having an edge to one of its neighbors, dependent on size of time window

TABLE S9 Group differences in bridges for varying numbers of neighbors

TABLE S10 Time- and frequency domain analyses of HRV based on 5-min recordings

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