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Unsupervised clustering of autonomic temporal networks in clinically distressed and psychologically healthy individuals

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A B S T R A C T

The present study recruited psychologically healthy individuals and individuals with clinically-severe Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnoses, including generalized anxiety disorder, major depressive disorder, social anxiety disorder, posttraumatic stress disorder, panic disorder, persistent depressive disorder, and specific phobia. During the course of a structured clinical interview, 200 individuals provided continuous electrocardiogram and impedance cardiography data. Of these N = 150 were used for exploratory analyses and N = 50 for confirmatory analyses. From these time series, we modeled heart period (i.e. interbeat interval), pre-ejection period, respiratory sinus arrhythmia, and respiration rate. The group iterative multiple model estimation (GIMME) model was used to generate group and individual-level network models which, in turn, were used to conduct unsupervised classification of individual-level models into subgroups. Four subgroups were identified, comprising N = 22, N = 25, N = 26, and N = 61 individuals, with an additional 16 individuals left unclassified. The subgroup models were then used to estimate directed network models, from which out-degree and in-degree centrality were estimated for each group. Two groups, Group 2 and Group 4 exhibited elevated symptoms of depression and anxiety relative to the remaining sample. However, only one of these, Group 2, exhibited additional physiological risk features, including a significantly elevated average heart rate, and significantly reduced parasympathetic regulation (measured via respiratory sinus arrhythmia). We discuss the implications for utilizing network models for conducting systems-level analyses of physiological systems in clinically-distressed and psychologically healthy individuals.

The autonomic nervous system (ANS) has long been a target of interest for researchers in psychology and psychiatry, with particular attention paid to the relationship between the ANS and the heart. The heart plays an integral role in the maintenance of bodily homeostasis, adjusting the speed and strength of its contractions to meet shifting environmental demands. Because the relative rate and contractive strength of the heart—known as chronotropy and inotropy, respectively—are modulated on a moment-to-moment basis by autonomic influences, understanding momentary chronotropic and inotropic shifts in the heart can inform our understanding of the ANS and vice versa. To this end, psychophysiological methods have been employed to understand a host of psychological constructs such as self-regulation (Thayer, Hansen, & Johnsen, 2010), habituation (Garrido et al., 2020), and emotional reactivity (Aleknaviciute et al., 2016). Beyond these broader dimensional constructs, the relationship between psychopathology and cardiac morbidity has also been an area of great interest. Heart disease is the leading cause of death in industrialized nations (World Health Organization, 2014) and psychiatric disorders such as depression, posttraumatic stress disorder (PTSD), and panic disorder have been linked to increased incidence of coronary heart disease (Carney, Freedland, & Veith, 2005; O'Neil et al., 2016; Seldenrijk et al., 2015). The ANS is thought to be a principal mediating factor between the presentation of psychological distress and the development of heart disease, with causal theories of cardiopathogenesis often focusing on impaired parasympathetic inhibitory control (Thayer & Lane, 2007) and endothelial dysfunction resulting from adrenergic stress reactivity (Curtis & O'Keefe, 2002).[1]

Nevertheless, research into autonomic functioning in psychiatric and psychologically distressed populations has too often utilized single measures of the ANS, and has almost exclusively employed cross-sectional, between-subject designs for the analysis of autonomic functioning. Composed of the parasympathetic, sympathetic, and enteric nervous systems, the ANS is a complex regulatory system, itself embedded within a larger network of endocrine (Sapolsky, Romero, & Munck, 2000) and immunologic (Alen, Deer, & Hostinar, 2020) processes. Moreover, although the idea has remained persistent among laypersons and researchers alike, the doctrine of reciprocal antagonism—the notion that the sympathetic and parasympathetic nervous

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[1] Cardiopathogenesis is the initiation (genesis) of cardiovascular (cardio) illness (patho). The endothelium is a thin lining on the inside of blood vessels that allows them to expand and contract. The release of adrenaline in response to sympathetic stimulation (e.g. fear or stress) causes the endothelium to contract and it is hypothesized that over extended periods of time, this contraction can lead to tearing and reduced responsiveness.

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system (PNS) are in direct and balanced opposition to each other—has been soundly rejected (Berntson, Cacioppo, & Quigley, 1991), and multiple calls have been made for concurrent measurement and modeling of sympathetic and parasympathetic inputs (c.f. Fisher & Newman, 2013).

Consistent with this perspective, our group has recently called for an integrated, systems-based approach that contextualizes autonomic functioning within a network of time-varying regulatory processes (Fisher, Song, & Soyster, 2021). Moreover, we argue that electrophysiological time series constitute an ideal source of data for conducting dynamic, intraindividual analyses of autonomic variables and target organs such as the heart. Electrophysiological measures such as respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) provide information about parasympathetic and sympathetic influences on cardiac chronotropy and inotropy, respectively. Although a complete description of these measures is outside of the scope of the present study, readers should be advised that RSA reflects parasympathetic influences on beat-to-beat variation in heart rate (i.e. heart rate variability) and PEP reflects sympathetic influences on how hard the heart is beating (i.e. inotropy; see Cacioppo, Tassinary, & Berntson, 2007 for greater detail). Because reliable RSA measurements in adults can be derived from bins as short as 30-s (Fisher & Woodward, 2014), an hour of data collection can yield a multivariate time series of up to 120 observations. Paradigms that continuously measure participants for an hour or more are ideal for concurrent modeling of variables like RSA, PEP, and heart rate, yielding a relatively complete picture of autonomic cardiac control and its target organ, the heart. In the present paper, we employ a multivariate time series of cardiorespiratory variables to model autonomic cardiac regulation as a dynamic system of interrelated components influencing each other over time. We believe this approach is vital to overcoming the limitations of existing psychophysiological paradigms, specifically, the reliance on cross-sectional estimates of mean levels as comparators for inferences about autonomic functioning and cardiovascular health.

Our group has argued extensively in recent years that between-subject means levels represent a limited and potentially problematic source of information for generating inferences about individual functioning (Fisher, Medaglia, & Jeronimus, 2018). However, the problem may be especially glaring for the ANS and autonomic cardiac control. To wit, the ANS is a regulatory system, dynamically and reflexively responding to shifting environmental and bodily demands moment to moment. Changes in individual system components are both transient and interdependent—unlikely to be reflected in tonic levels captured at a single moment of time. Changing our perspective from stable differences in mean levels between individuals to the dynamic organization of system components within individuals may advance our understanding of pathogenic processes. For instance, depression has been consistently shown to relate to and prospectively predict the onset of coronary heart disease (Carney & Freedland, 2017; O'Neil et al., 2016), leading researchers to propose mechanisms such as sympathetically-mediated endothelial dysfunction as a likely source of cardiopathogenesis. However, evidence for SNS dysfunction in depression has been equivocal (Carney et al., 2005; Udupa et al., 2007), and some evidence has even pointed to diminished SNS reactivity in depressed individuals under laboratory stress conditions (Fisher, Granger, & Newman, 2010). Yet, a systems perspective has been entirely absent from the literature to date. We hypothesize that an intraindividual network perspective could shed light on the regulatory dynamics of autonomic cardiac control and point to individuals for whom sympathetic predominance is reflected in differences in system-wide calibration, rather than single-variable levels from person to person.

It follows that such analyses should be carried out at a person-by-person level. The dynamic, time-varying processes in question unfold within the nervous systems and chest cavities of individual human beings, making them naturally idiographic. Yet, it should be acknowledged that the systems in question are inherently delimited in their structure and function. For instance, the heart has four chambers and two major coronary arteries. It is innervated at the sinoatrial node by vagal and sympathetic fibers. These features are, in the absence of congenital heart disease, consistent across individuals. It is reasonable to assume that there are some set of organizational features that create commonalities across groups of individuals. That is, while everyone is different to some degree, these differences likely converge into appreciably homogenous clusters of individuals. In the case of the heart, individual differences in resting heart rate can be effectively clustered based on variables such as body mass, age, and exercise capacity (Antelmi et al., 2004; Ehrenwald et al., 2019). The question for researchers in clinical psychology and psychiatry is whether the categories of the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5; American Psychiatric Association, 2013) represent the best organizing principles for such clusters.

In the following, we endeavored to move beyond a fully idiographic perspective in hopes of clustering individuals into groups of meaningfully differentiable autonomic-cardiac dynamics. Thus, we adopted an agnostic perspective on the behavioral and symptomological content of such person-clusters. Although we recruited participants based on DSM-5 diagnoses, we utilized an unsupervised approach for recovering model clusters. Specifically, the present study employed the S-GIMME algorithm (Gates, Lane, Varangis, Giovanello, & Guiskewicz, 2017), a method for identifying subgroups of vector-autoregressive structural equation models (SEMs) in multivariate time series data. The present study recruited individuals with and without clinically-severe DSM-5 disorders. The mixed sample was employed to evaluate the potential goodness-of-fit of data-driven clusters of psychophysiological dynamics to the putative taxonomic structure of the DSM-5—both in terms of the ability to differentiate clinical from non-clinical participants, as well as potentially more granular delineations between specific disorder categories. Participant diagnoses included generalized anxiety disorder (GAD), major depressive disorder (MDD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), panic disorder, persistent depressive disorder, and specific phobia.

During the course of a structured clinical interview for DSM-5 disorders, 200 individuals provided continuous ECG and impedance cardiography data. Of these, the data for 150 participants were used as an exploratory sample and the data for 50 additional participants were used as an external validation sample. In the exploratory stage of the current research, we used the group iterative multiple model estimation procedure (GIMME; Gates & Molenaar, 2012) to estimate individual psychophysiological network models for the 150 individuals in the exploratory sample. Network models included: the interbeat intervals of the ECG signal (IBI; a measure of heart period), the pre-ejection period (PEP), respiratory sinus arrhythmia (RSA), and respiration rate (see Method for more detail). The Walktrap algorithm (Pons & Latapy, 2006) was employed within the GIMME procedure to search for clusters of similar network connectivity in the N = 150 person-level network models. Finally, two validation approaches were applied, one to the original N = 150 sample and one to the N = 50 validation sample. The first validation analysis assessed the validity and reproducibility of the clustering outcomes, and the second assessed the reproducibility of within-cluster clinical features in an external validation sample.

1. Method

1.1. Participants

Participants in the current study were drawn from two recruiting initiatives, one for individuals with generalized anxiety disorder (GAD) and/or major depressive disorder (MDD) and another for individuals with posttraumatic stress disorder (PTSD). The GAD and MDD recruitment also targeted individuals without DSM-5 diagnoses or subclinical psychological distress for statistical control and comparison. In the current study, the sample recruited for GAD, MDD, and non-clinical controls was employed as an exploratory analysis sample and the

sample recruited for PTSD was employed as validation sample. In both samples, diagnoses other than the targeted diagnoses have been included and described below.

1.1.1. General

English-literate adults (18-65 years-old) were recruited via flyers, referrals, and online advertisements. Postings for clinical participants requested individuals experiencing symptoms congruent with GAD and/or MDD (exploratory sample) and PTSD (validation sample), and postings for control participants requested individuals experiencing little-to-no such symptoms (exploratory sample). Potential participants who passed a brief phone screening were invited to an in-person structured clinical interview for diagnostic assessment and concurrent physiological monitoring at the first author's laboratory at the University of California, Berkeley. Inclusion criteria for clinical participants in the present study were a current diagnosis of a DSM-5 depressive disorder, anxiety disorder, or PTSD. Exclusion criteria included any history of mania or psychosis, and a primary substance use disorder. Inclusion criteria for control participants was the absence of any DSM-5 diagnosis within the past year. Potential control participants were also excluded for any history of mania or psychosis.

1.1.2. GAD and MDD sample

A total of 241 individuals presented to the laboratory: 173 potential clinical participants, and 73 potential control participants. Inclusion criteria were met by 146 of the clinical and 68 of the control participants. At the point of data cleaning and analysis, participants were excluded if true physiological signal was undetectable due to noise (i.e. data collection interrupted by participant movement and/or faulty electrode placement; clinical = 5, control = 1), if physiology data were uninterpretable (i.e. cases in which, although uniform, participant data did not conform to known wave patterns; clinical = 2, control = 5), or if physiology datasets were an insufficient length for the present analyses (fewer than 40 30-s segments; clinical = 23, control = 28). The present analyses included the remaining eligible 150 participants: 116 clinical and 34 control participants.

Clinical participants met criteria for one to five diagnoses each, including generalized anxiety disorder (GAD; N = 66), social anxiety disorder (SAD; N = 61), major depressive disorder (MDD; N = 46), persistent depressive disorder (PDD; N = 16), post-traumatic stress disorder (PTSD; N = 12), panic disorder (N = 16), and specific phobia (N = 19). Table 1 presents the diagnostic data for the overall sample and specific GIMME subgroups. The mean clinician ratings for the clinical participants on the Hamilton Rating Scale for Depression (HRSD) and the Hamilton Anxiety Rating Scale (HARS) were 13.49 (SD 4.83) and 15.73 (SD 6.18), respectively. For this group, mean self-reported ratings of depression and anxiety symptoms via the Depression, Anxiety, and Stress Scale (DASS) were 21.76 (SD 11.03) and 13 (SD 8.09) respectively. The mean overall clinician ratings for the control group on the HRSD and the HARS were 1.31 (SD 2.80) and 1.61 (SD 2.23), respectively. For this group, mean ratings of DASS-D and DASS-A were 3.11 (SD 5.42) and 2 (SD 3.47) respectively. Table 2 presents the means and standard deviations for physiological and psychological variables by group.

1.1.3. PTSD sample

A total of 73 individuals presented to the laboratory. Inclusion criteria were met by 64 participants. Nine participants were excluded due to psychosis (N = 2), bipolar disorder (N = 6), and primary substance use disorder (N = 1). Consistent with the exploratory sample, participants were excluded at the data cleaning and analysis stage if true physiological signal was undetectable due to noise, if physiology data were uninterpretable, or if physiology datasets were an insufficient length for the present analyses. Insufficient data led to the exclusion of an additional 14 participants. The present analyses included the remaining eligible 50 participants. Although recruitment for the PTSD sample did not explicitly target non-clinical participants, 10 participants failed to meet criteria for any DSM-5 diagnoses. These individuals were retained in the present analyses.

Clinical participants met criteria for one to five diagnoses each, including PTSD (N = 31), GAD (N = 10), SAD (N = 13), MDD (N = 5), PDD (N = 9), panic disorder (N = 16), and specific phobia (N = 13). The mean clinician ratings for the clinical participants on the HRSD and the HARS were 16.30 (SD = 5.57) and 19.48 (SD = 7.55), respectively. The mean overall clinician ratings for the non-clinical participants on the HRSD and the HARS were 7.50 (SD = 5.72) and 8.40 (SD = 9.77), respectively.

1.2. Measures

1.2.1. Anxiety and related disorders interview schedule for DSM–5 (ADIS-5; Brown & Barlow, 2014)

The ADIS-5 is a semi-structured clinical interview for diagnosing current anxiety, mood, and related disorders under DSM-5 criteria.

Table 1
Sample characteristics by group.

	Total N = 150	Group 1 N = 22	Group 2 N = 25	Group 3 N = 26	Group 4 N = 61	Unclassified N = 16
Diagnostic Status						
Clinical	116 (77.3%)	13 (59.0%)	25 (100%)	20 (76.9%)	54 (88.5%)	4 (25.0%)
Control	34 (22.7%)	9 (40.9%)	0 (0.0%)	6 (23.1%)	7 (11.5%)	12 (75.0%)
GAD	66 (44.0%)	5 (22.7%)	16 (64.0%)	11 (42.3%)	32 (52.5%)	2 (12.5%)
SAD	61 (40.7%)	5 (22.7%)	15 (60.0%)	10 (38.5%)	30 (49.2%)	1 (6.3%)
MDD	46 (30.7%)	3 (13.6%)	12 (48.0%)	7 (29.9%)	22 (36.0%)	2 (12.5%)
Phobia	19 (12.7%)	0 (0.0%)	2 (8.0%)	6 (23.0%)	11 (18.0%)	0 (0.0%)
Panic	16 (10.7%)	1 (4.5%)	6 (24.0%)	1 (3.8%)	7 (11.5%)	1 (6.3%)
PDD	16 (10.7%)	3 (13.6%)	5 (20.0%)	0 (0.0%)	8 (13.1%)	0 (0.0%)
PTSD	12 (8.0%)	1 (4.5%)	5 (20.0%)	0 (0.0%)	6 (9.8%)	0 (0.0%)
Demographics						
White	62 (41.3%)	13 (59.0%)	8 (32.0%)	11 (42.3%)	25 (42.0%)	5 (31.3%)
Latino	19 (12.7%)	2 (9.0%)	4 (16.0%)	4 (15.4%)	7 (11.5%)	2 (12.5%)
Asian/AA	34 (22.7%)	5 (22.7%)	4 (16.0%)	5 (19.2%)	14 (23.0%)	6 (37.5%)
Black	8 (5.3%)	1 (4.5%)	1 (4.0%)	2 (7.7%)	3 (4.9%)	1 (6.3%)
Multiple	22 (14.7%)	1 (4.5%)	6 (24.0%)	3 (11.5%)	10 (16.4%)	2 (12.5%)
Other	5 (3.3%)	0 (0.0%)	2 (8.0%)	1 (3.8%)	2 (3.3%)	0 (0.0%)

Note: Percentages indicate percent per GIMME subgroup. GAD = generalized anxiety disorder; SAD = social anxiety disorder; MDD = major depressive disorder; PDD = persistent depressive disorder; PTSD = posttraumatic stress disorder.

Table 2
Mean (standard deviation) for physiological and psychological variables by group.

	Total N = 150	Group 1 N = 22	Group 2 N = 25	Group 3 N = 26	Group 4 N = 61	Unclassified N = 16
Physiological Variables						
Heart Rate	73.61 (11.58)	67.02* (7.61)	83.77 (12.88)	74.32* (10.07)	71.36* (10.81)	74.24* (9.54)
IBI	836.91 (130.63)	908.51* (105.29)	734.01 (99.41)	824.63 (120.78)	861.83* (132.80)	824.23 (123.16)
RSA	6.13 (1.10)	6.68$^{\#}$ (0.93)	6.22 (1.18)	5.61 (1.28)	6.01 (1.00)	6.54$^{\#}$ (0.81)
PEP	101.31 (10.66)	102.84 (9.85)	96.29 (13.13)	99.20 (8.90)	103.11 (10.53)	103.60 (8.31)
Respiration	16.10 (0.94)	16.22 (0.63)	15.97° (1.09)	16.03° (0.88)	15.93° (0.82)	16.93 (1.20)
IBI AR(1)	0.45 (0.22)	0.20 (0.12)	0.60^{+o} (0.21)	0.55^{+o} (.19)	0.50^{+o} (0.14)	0.17 (0.16)
RSA AR(1)	0.03 (0.13)	−0.01 (0.16)	−0.03 (0.06)	−0.02 (0.13)	0.06$^{\#}$ (0.13)	0.03 (0.11)
PEP AR(1)	0.39 (0.22)	0.50$^{\#o}$ (0.16)	0.46$^{\#o}$ (0.18)	0.14 (0.14)	0.48$^{\#o}$ (0.17)	0.15 (0.20)
Psychological Variables						
HRSD	10.71 (7.68)	7.82^{*x} (7.03)	14.95 (4.41)	8.86* (6.70)	12.96 (7.73)	3.36^{*x} (6.49)
DASS-D	17.29 (12.77)	11.45 (10.46)	24.12^{+o} (10.81)	17.38° (13.90)	19.69^{+o} (11.95)	5.31 (9.08)
DASS-A	10.36 (8.64)	6.86* (7.50)	15.08 (9.20)	9.31 (8.35)	11.84 (7.77)	3.88^{*x} (7.68)
NEO-N	41.32 (11.77)	36.45^{*x} (13.12)	49.64 (5.65)	38.32* (11.99)	44.54 (8.29)	27.44^{*xo} (12.56)

Note: $^{+}$ = different than Group 1, * = different than Group 2, $^{\#}$ = different than Group 3, ^{x} = different than Group 4, ^{o} = different than Unclassified (based on Tukey's multiple comparisons of means). All differences were significant at $p < 0.05$ or lower. IBI = interbeat interval; RSA = respiratory sinus arrhythmia; PEP = pre-ejection period; Respiration = respiration rate; HRSD = Hamilton rating scale for depression; DASS-D = depression, anxiety, stress scales, depression subscale; DASS-A = depression, anxiety, stress scales, anxiety subscale; NEO-N = NEO PI-R neuroticism subscale.

1.2.2. Clinician administered PTSD scale for DSM-5 (CAPS-5; Blake et al., 2000)

The CAPS-5 is a structured clinical interview used to diagnose and assess severity of DSM-5 PTSD. It has strong interrater reliability (κ ranging from 0.78 to 1.00), test-retest reliability (κ = 0.93), and correspondence with a diagnosis based on the DSM-IV CAPS (CAPS-IV; Weathers et al., 2018).

1.2.3. Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960)

The HRSD is a 17-item clinician-administered scale developed to assess the severity of depressive symptomatology. The scale provides a rating of severity for each overarching symptom cluster on a scale from 0 (not present) to 4 (very severe/incapacitating), with internal consistency ranging from adequate to good (0.73–0.81; Moras, Di Nardo, & Barlow, 1992; Steer, Beck, Riskind, & Brown, 1987). Self-report measures of depression in clinical samples correlate significantly with HRSD scores, and interrater reliabilities of the HRSD total score range from 0.78 to 0.82 (Moras et al., 1992; Steer et al., 1987).

1.2.4. Depression, anxiety and stress scale (DASS; Lovibond & Lovibond, 1995)

The DASS is 42-item self-report scale that assesses three factors of negative emotionality: depression (DASS-D), anxiety (DASS-A), and stress (DASS-S). Individuals rate the severity of each item on a scale from 0 (did not apply to me at all/never) to 4 (applied to me very much, or most of the time/almost always). The DASS has excellent internal consistency: 0.97 for DASS-D, 0.92 for DASS-A, and 0.95 for DASS-S (Antony, Bieling, Cox, Enns, & Swinson, 1998).

1.3. Procedures

1.3.1. Clinical assessment

During the assessment, clinical psychology graduate students administered the ADIS-5 and obtained clinician ratings of symptom severity via the HRSD under the supervision of a doctoral level clinical psychologist. Participants also completed a battery of self-report symptom measures including the DASS.

1.3.2. Physiological measurement

For the duration of the clinical interview, continuous electrocardiogram (ECG) and impedance cardiography data were collected at 500 Hz (Hz) using MindWare Mobile Hardware. Prior to the structured clinical interview, a research assistant prepared participants for physiological data collection, affixing electrodes on the front and back of participants' torsos. Electrodes were placed (1) on the midpoint of the right clavicle, (2) on the bottom left rib, (3) on the bottom right rib to ground, (4) left of the jugular notch, (5) at the xiphoid process below sternum, (6) on the spine (1.5 inches higher than 4), and (7) on the spine (1.5 inches lower than 5). Electrodes (1) and (2) collected ECG data, electrode (3) was the ground, and electrodes (4) thru (7) collected impedance cardiography data. Participants were instructed to minimize movement throughout the clinical interview and the research assistant monitored data collection throughout the interview, making note of significant participant movements.

Data were cleaned in 30-s bins, following recommended procedures of MindWare (MindWare Technologies Ltd.; https://mindwaretech.com/), using the MindWare HRV Analysis Application 3.1.7 for the ECG data and the MindWare Impedance Cardiography Analysis Application 3.1.7 for the impedance cardiography data. Once cleaned, these data were used to calculate four statistics for the present analyses: Mean inter-beat interval (IBI), respiratory sinus arrythmia (RSA), pre-ejection period (PEP), and respiration rate (RR). IBI refers to the time between heartbeats. Changes in mean IBI across the sampling period may indicate influences of the parasympathetic and/or sympathetic nervous systems on the heart. RSA reflects variations in heart period associated with respiratory oscillations and is a widely used non-invasive indicator of parasympathetic tone. PEP refers to the timing between the initial electrical stimulation of the heart and mechanical opening of the aortic valve, and is used as an indicator of sympathetic nervous system activity. RR is included as a necessary control variable when analyzing RSA. For each 30-s segment of data, all four statistics were calculated automatically by the same software used to clean the data: MindWare HRV Analysis Application 3.1.7 calculated mean IBI, RSA, and RR, and MindWare Impedance Cardiography Analysis Application 3.1.7 calculated PEP.

1.4. Approach to data analysis: Exploratory stage

1.4.1. GIMME

The GIMME algorithm has been shown to reliably recover group- and individual-level networks from time series data for fMRI (Gates & Molenaar, 2012) and behavioral data (Lane, Gates, Pike, Beltz, & Wright, 2019). The current study represents the first use of GIMME for autonomic network data. Patterns of temporal effects are estimated from idiographic time series data, with unique models generated for each individual. The GIMME model is situated within a unified SEM (Gates, Molenaar, Hillary, Ram, & Rovine, 2010) framework. The uSEM model itself is part of the larger family of vector-autoregressive time series

models and can be seen as a special case of the dynamic factor model (Molenaar, 1985). Whereas in the dynamic factor model, contemporaneous effects in the time-forward portion of the model (i.e. t+1) are undirected, the uSEM model estimates directional effects among time-forward contemporaneous relationships after controlling for the time-lagged autoregressions and cross-predictions in the model. The advantage of this approach—in addition to estimating directed effects in contemporaneous data—is that the inclusion of directed contemporaneous effects precludes the potential inflation of lagged statistical estimates (Gates et al., 2017).

The uSEM is especially useful in circumstance where the sampling rate for the data collection or binning results in undersampled data. Under such circumstances, the causal (time-lagged, directional) information is likely contained within the contemporaneous observations (Granger, 1969). In the present case, data have been captured at 500 Hz, but binned in 30-s epochs. Given that ANS signals and cardiac dynamics often operate on a millisecond to second time scale, the contemporaneous information in the present study likely contains important, temporally sequential predictive information.

1.4.2. GIMME estimation

Complete details for GIMME estimation can be found in Gates and Molenaar (2012) and Lane et al. (2019). Here, we briefly describe the methods employed to arrive at individual models. All individual models began by freely estimating the diagonal of the lagged regression matrix (often referred to as β in SEM models, φ in uSEM notation). This represents the AR (1) for each construct. Modification indices (i.e. Lagrange Multiplier tests) were then examined in a hierarchical, stepwise fashion to assess fixed paths that should be freed. These paths represent relationships in the model which, if included, would significantly improve model fit (i.e. significantly reduce model chi-square values). For each potential path, GIMME counts the number of individuals in the sample for whom the given path would be statistically significant and adds the path with the highest proportion in the sample. During GIMME estimation, this step is repeated iteratively until a prespecified cutoff is reached. The current study used a cutoff of 75%, as recommended by Gates and Molenaar (2012). Once the group-level search was completed, a pruning procedure was applied in which paths that were no longer significant for 75% of the sample were removed sequentially.

1.4.3. S-GIMME

Once the group-level model was identified, the S-GIMME procedure was applied to identify clusters of individuals in the sample. Specifically, S-GIMME uses a community detection procedure known as the Walktrap algorithm (Pons & Latapy, 2006) to identify subgroups of temporal dynamics. First, model comparisons are made between each possible dyad in the data, in order to count the number of similar effects. Similarity is based on the presence and direction of effects in the individual models. An adjacency matrix is created that counts the number of similar effects. The Walktrap algorithm is then applied to the adjacency matrix in order to merge individual models in subgroups in a bottom-up fashion. For complete details, see Gates et al. (2017) and Lane et al. (2019).

All GIMME analyses were run in the R package GIMME (Lane, Gates, Molenaar, Hallquist, & Pike, 2014).

1.5. Between-group analyses

Once the GIMME and S-GIMME procedures had been completed, participants were dummy-coded based on subgroup membership. All unclassified cases were coded together as a single subgroup, however, an aggregate network model was not conducted for this group, given that the estimation of a subgroup network was dependent on an assumption of structural homogeneity among constituent time series. Unclassified individuals were included in between-subject estimates of averages and standard deviations for study variables.

1.5.1. Network models

For each identified subgroup, the constituent individual-level models were aggregated to arrive at an average network structure for each group. These networks were visualized via qgraph in R (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012) and centrality estimates were extracted for each group.

1.5.2. Regression models

Regression models were used to examine subgroup differences in physiological and psychological variables. In each model, biological sex assigned at birth and age were included as control variables.

1.6. Approach to data analysis: Validation stage

Having completed the exploratory analyses detailed above, we were interested in evaluating the generalizability and reproducibility of the findings. We were concerned *a priori* with the potential generalizability of two aspects of the analysis: the clustering outcomes within the exploratory sample and the participant features defined by each cluster—that is, whether the relative physiological and psychological features of the clusters generalized to an external sample. We planned two validation approaches, one to evaluate the reproducibility of the clustering under an alternative algorithm and the second to evaluate the reproducibility of potentially clinically meaningful cluster features (i.e. mean levels). The first validation procedure was carried out on the original, exploratory sample, to directly cross-reference the potential agreement in clustering. The second validation procedure was carried out on the external validation sample to evaluate the degree to which potentially defining features of the cluster generalized outside of the original sample. Both validation procedures were *post-hoc* and dependent on the results of the exploratory stage of analysis, thus greater detail is provided in the Results, below. That is, given the exploratory nature of the current research, we held no *a priori* assumptions about whether or to what degree the network models would produce differentiable clusters, what kinds of network dynamics would inform potential clustering, nor what the clinical features of the clusters would be. However, once identified, we were interested in evaluating whether (a) an additional clustering algorithm—specifically, a Gaussian finite mixture model—could successfully locate one or more similar clusters and (b) the clinical features of the identified clusters could be recovered in an external sample.

2. Results

Input time series for GIMME and S-GIMME procedures, complete R code for setup, analyses, and results, as well as complete sets of idiographic model results are available on the Open Science Framework at https://osf.io/h6zu8/.

2.1. GIMME

The S-GIMME procedure returned four groups with N = 22, N = 25, N = 26, and N = 61 group members, respectively. In addition, 16 individuals were unclassified. Thus, the dynamics of these 16 individual models were effectively idiosyncratic. No aggregate network was conducted for these individuals. For each of the four GIMME subgroups, the individual network matrices were aggregated in order to estimate an average network model. The centrality estimates reported below (out-degree and in-degree) were estimated from these average models.

2.1.1. Network dynamics

Fig. 1 presents the out-degree (top panel) and in-degree (bottom panel) for each network node, for each group and the overall average. The most consistent patterns of results relate to Groups 1 and 2. The pattern of results for Group 1 reflect a structural organization consistent with adaptive autonomic regulation of the heart. The nodes for

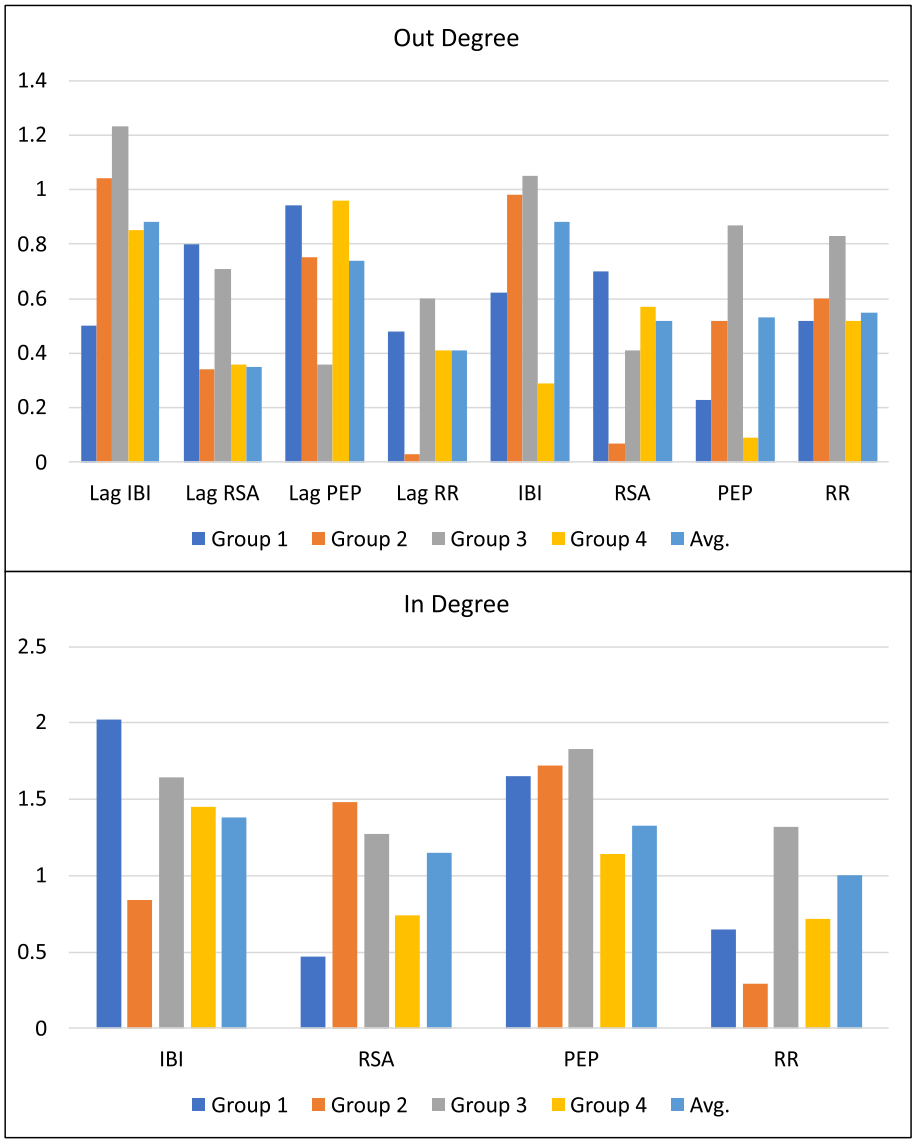

Fig. 1. Out degree and in degree centrality.
IBI = interbeat interval; RSA = respiratory sinus arrhythmia; PEP = pre-ejection period; Respiration = respiration rate; Lag = lag-1 (t-1) variables.

contemporaneous and lagged IBI exhibit relatively lower out-degree and relatively higher in-degree. Conversely, lagged and contemporaneous RSA, and lagged PEP exhibit relatively higher out-degree. Taken together, these results reflect heart rate variability that is being regulated moment-to-moment by autonomic influences, rather than vice versa. However, Group 2 exhibited relatively high out-degree from both lagged and contemporaneous IBI nodes, demonstrating that moment-to-moment variation in heart period had outsize influence on the overall network. Moreover, Group 2 exhibited the lowest levels of out-degree from lagged and contemporaneous RSA, compared to the other three groups, reflecting very little parasympathetic regulatory influence. Both lagged and contemporaneous PEP nodes exhibited relatively high out-degree, indicating a high degree of sympathetic influence. Taken together, the low parasympathetic influence, high sympathetic influence, and predominance of heart period all point to a poorly regulated and sympathetically predominant autonomic-cardiac network.

2.1.2. Group 1

Clinical participants comprised 59% (N = 13) of group 1, with healthy controls comprising 40.9% (N = 9). Tukey's multiple comparisons of means revealed that this group exhibited levels of psychological distress that were significantly below Groups 2 and 4, including the HRSD (p's = 0.008 and 0.03), DASS-D (p's = 0.003 and 0.04), and DASS-A (Group 2 only; $p = 0.006$). Additionally, this group exhibited levels of neuroticism that were significantly below Groups 2 and 4 ($p < 0.001$ and $p = 0.01$). Group 1 exhibited lower average heart rate than Group 2 ($p < 0.001$), and higher average RSA than Group 3 ($p = 0.005$). Regarding network dynamics, Group 1 exhibited the lowest IBI autoregression of the four subgroups (all p's < 0.001). Conversely, Group 1 exhibited a higher degree of autoregression in PEP than Group 3 ($p < 0.001$).

Finally, Group 1 was the only group (including unclassified cases) that was majority White (59%, N = 13), although this proportion did not significantly differ from the overall proportion of White participants in the total sample (41.3%; $z = 1.37$, $p = 0.17$).

2.1.3. Group 2

Clinical participants comprised 100% of Group 2 (N = 25). Consistent with this composition, Group 2 exhibited elevated levels of psychological distress, including higher average HRSD than Group 1 ($p = 0.008$) and Group 3 ($p = 0.04$); and higher average DASS-D and DASS-A than Group 1 (p's = 0.003 and 0.006). In addition, Group 2 exhibited higher average levels of neuroticism than Groups 1 and 3 ($p < 0.001$ and

$p = 0.001$). Group 2 also exhibited a higher average heart rate than all other groups (Group 1, $p < 0.001$; Group 3, $p = 0.01$; Group 4, $p < 0.001$).

2.1.4. Group 3

Clinical participants comprised 76.9% (N = 20) of Group 3, with healthy controls comprising 23.1% (N = 6). Regarding inter-group differences, Group 3 exhibited lower HRSD and neuroticism compared to Group 2 (*p's* = 0.04 and 0.001).

2.1.5. Group 4

Group 4 was the largest of the four GIMME subgroups, with 61 total participants. Clinical participants comprised 88.5% (N = 54) of Group 4, with healthy controls comprising only 11.5% (N = 7). Group 4 exhibited higher HRSD ($p = 0.03$), DASS-D ($p = 0.04$), and neuroticism ($p = 0.01$) compared to Group 1.

2.1.6. Unclassified cases

The unclassified cases were predominantly healthy control participants (75%, N = 12), with 25% clinical participants (N = 4). Although not a formal GIMME subgroup, we nevertheless combined these individuals to derive average levels of psychological and physiological variables for comparison with the four subgroups. Unsurprisingly, given the composition of the group, the unclassified cases exhibited the lowest levels of all distress variables, with significantly lower levels than Groups 2 and 4 on the HRSD (*p's* < 0.001), the DASS-D (*p's* < 0.001), and the DASS-A ($p < 0.001$ and $p = 0.005$). Additionally, these individuals exhibited the lowest degree of neuroticism compared to Group 1 ($p = 0.05$), Group 2 ($p < 0.001$), Group 3 ($p = 0.007$), and Group 4 ($p < 0.001$). Unclassified individuals likewise exhibited the lowest degree of IBI autoregression compared to Group 2 ($p < 0.001$), Group 3 ($p < 0.001$), and Group 4 ($p < 0.001$).

Means and standard deviations for psychological and physiological variables are provided in Table 2.

2.2. Regression models for study variables

Finally, we examined the degree to which GIMME subgroups explained the variance in psychological distress, neuroticism, and mean levels of physiological variables. Table 3 presents the results of the multiple regression models for study variables on dummy-coded group membership. All analyses controlled for biological sex and age in years. Group 4 was the reference group. Regression models explained 17%–48% of the variance in physiological variables and 16%–30% of the variance in psychological variables. Age was a significant predictor of RSA, RSA autoregression, and respiration rate, with older participants exhibiting lower RSA, higher RSA autoregression, and fewer breaths per minute. Biological sex significantly predicted PEP, with female participants exhibiting longer pre-ejection period intervals and, thus, lower average sympathetic activity, compared to male participants.

2.3. Sensitivity analysis: Isolating clinical participants

Although we made no *a priori* assumptions that the taxonomic organization of the DSM-5 would have any bearing on the clustering of autonomic dynamics in the present study, it may still be reasonable to suspect that the organizing principles of the DSM exerted some influence over the cluster solutions reported above. Thus, we reran the S-GIMME procedure for the N = 116 clinical participants (excluding control participants), in order to examine the consistency of the cluster solution and composition. Group 1 was not recovered. Group 2, Group 3, and Group 4 were recovered and found to be highly consistent with the original analysis. Group 2 added two participants, one previously allocated to Group 1 and one previously unclassified. Group 3 was unchanged, outside of the loss of six control participants. Group 4 added 12 participants previously allocated to Group 1. Complete results—including tables comparable to Table 1 and Table 2—can be found in Supplemental Materials.

2.4. Cluster validation

The Walktrap algorithm is an explicitly graph-theoretical approach that assesses the structure of the constituent networks for similarities in node connectivity. However, one might be left to question whether these clusters reflect gestalt features of the overall network dynamics or if they are instead a better representation of nodewise structures. Having utilized the Walktrap algorithm for clustering the N = 150 exploratory networks, we were interested in assessing the degree to which an expectation-maximization algorithm—the Gaussian finite mixture model—could recover clusters related to salient features of the Walktrap classifications.

As noted above, the most salient feature of the original clustering was the atypical regulatory organization of cardiac dynamics in Group 2. This group exhibited an absence of inflowing regulation (i.e. low IBI in-degree), an almost total absence of parasympathetic regulation (RSA out-degree), and a high degree of outflowing information from the heart (lagged and contemporaneous IBI out-degree). Of note, Group 3 shared this final feature, exhibiting the highest levels of contemporaneous and lagged IBI out-degree. Thus, we chose IBI outflow as the network feature to target in our attempt to validate the Walktrap clustering.

We used the Mclust Package in R (Scrucca, Fop, Murphy, & Raftery, 2016) to conduct mixture models, relying on the package's automated

Table 3
Unstandardized betas (SE) for multiple regression models for study variables on Group, biological sex (female = 1), and age in years.

	Group 1	Group 2	Group 3	Unclassified	Sex	Age	R^2
Physiological Variables							
Heart Rate	−4.33 (2.66)	11.40*** (2.59)	3.39 (2.50)	2.19 (3.02)	1.52 (1.90)	−0.09 (0.07)	0.20
IBI	46.23 (30.61)	−118.13*** (29.85)	−42.34 (28.82)	−30.51 (34.76)	16.11 (21.95)	1.00 (0.78)	0.17
RSA	0.47* (0.23)	−0.09 (0.23)	−0.26 (0.22)	0.19 (0.27)	0.17 (0.17)	−0.04*** (0.01)	0.32
PEP	−0.12 (2.55)	−5.18* (2.49)	−3.48 (2.40)	2.03 (2.90)	5.01** (1.83)	0.08 (0.07)	0.12
Respiration	0.22 (0.22)	−0.05 (0.21)	0.16 (0.21)	0.83** (0.25)	−0.13 (0.16)	−0.02*** (0.01)	0.18
IBI AR(1)	−0.29*** (0.04)	0.10* (0.04)	0.04 (0.04)	−0.32*** (0.05)	−0.02 (0.05)	0.001 (0.001)	0.48
RSA AR(1)	−0.07* (0.03)	−0.03 (0.03)	−0.03** (0.03)	−0.02 (0.03)	0.01 (0.02)	0.022** (0.0008)	0.12
PEP AR(1)	0.02 (0.04)	−0.03 (0.04)	−0.33*** (0.04)	−0.34*** (0.05)	−0.03 (0.03)	−0.002 (0.001)	0.46
Psychological Variables							
HRSD	−5.06** (1.76)	1.95 (1.82)	−4.89** (1.76)	−9.01*** (1.99)	−0.53 (1.29)	0.08 (0.05)	0.24
DASS-D	−9.13** (2.94)	3.69 (2.87)	−3.12 (2.77)	−14.84*** (3.34)	1.54 (2.11)	0.03 (0.08)	0.20
DASS-A	−5.70** (2.03)	2.03 (1.98)	−2.23 (1.91)	−8.81*** (2.30)	1.46 (1.45)	−0.10 (0.05)	0.17
NEO-N	−8.48** (2.55)	4.48 (2.49)	−6.14 (2.44)	−17.79*** (2.90)	−0.05 (1.85)	−0.07 (0.07)	0.31

Note: Reference group = Group 3. *, **, *** = significant differences with overall average at p < 0.05, 0.01, 0.001, respectively. IBI = interbeat interval; RSA = respiratory sinus arrhythmia; PEP = pre-ejection period; Respiration = respiration rate; HRSD = Hamilton rating scale for depression; DASS-D = depression, anxiety, stress scales, depression subscale; DASS-A = depression, anxiety, stress scales, anxiety subscale; NEO-N = NEO PI-R neuroticism subscale.

features to select a best-fit model. The mclust function in the Mclust package iterates models from two to nine classes and uses the Bayesian Information Criterion (BIC; Schwarz, 1978) to select the best model from a set of possible parameterizations. Of these, six parameterizations were included that allowed variation in the volume and shape of potential clusters (EII, VII, EEI, VEI, EVI, and VVI; see Scrucca et al., 2016 for more detail). We used the mclust BoostrapLRT function to assess whether solutions with fewer classes would be a better fit. Lastly, we used the estimated posterior probabilities for the likelihood that each row belonged in each class to generate forced-choice class assignments for each participant. Four variables were extracted from person-level network models and entered into the mixture model for analysis: the autoregression for IBI, the effect of IBI on RSA, the effect of IBI on PEP, and the effect of IBI on respiration rate.

The mclust procedure returned a seven-class solution and the bootstrap likelihood ratio test confirmed that a seven-class solution was a better fit to the data than a solution of six or fewer classes. Fig. 2 provides a visualization of the mean level profiles for the seven-class solution. We then assessed the correlations between each mixture model class and the Walktrap-identified subgroups. The best confirmatory match was found for Group 2, which exhibited a strong positive correlation with Class 3 ($r = 0.81$). Seventy-six percent (19/25) of the participants previously allocated to Group 2 were classified into Class 3, and 95% (19/20) of the participants classified into Class 3 were previously allocated to Group 2. Group 2 also exhibited a moderate negative correlation with Class 2 ($r = -0.41$). Conversely, Group 4 exhibited a moderate positive correlation with Class 2 ($r = 0.43$). Finally, Group 1 and Group 3 exhibited modest positive correlations with Class 4 ($r = 0.30$) and Class 7 ($r = 0.25$), respectively. Taken together, the mixture modeling provided strong validation for Group 2 and only modest validation of the remaining three groups.

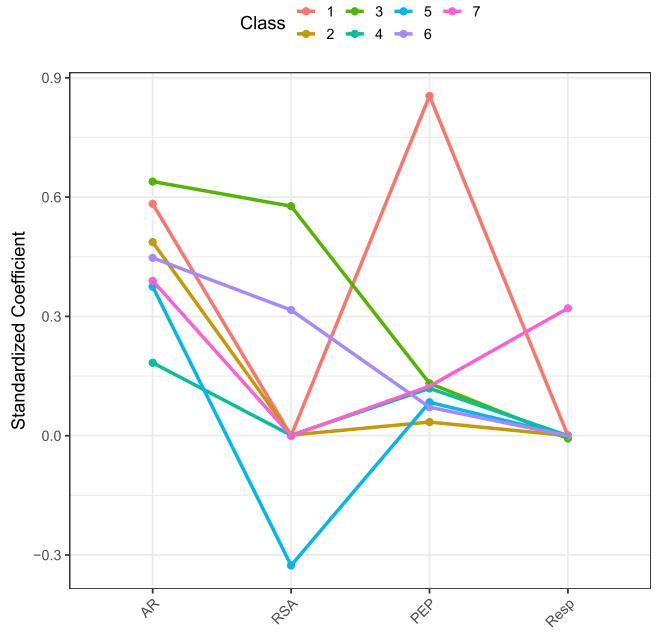

Fig. 2. Results of finite mixture model derived from aggregated person-level cardiac predictive dynamics (i.e. directional network paths from the interbeat interval node to remaining time-forward nodes).
Note: AR = autoregression (influence of interbeat interval on successive interbeat interval); RSA = influence of interbeat interval on respiratory sinus arrhythmia; PEP = influence of interbeat interval on pre-ejection period; Resp = influence of interbeat interval on respiration rate. All coefficients are on a standardized (i.e. −1 to 1) scale.

2.5. Group characteristic validation

Finally, we were interested in the generalizability of the Walktrap cluster characteristics in an external sample. Perhaps most pressing was that, whereas Group 2 and Group 4 both exhibited elevated psychological symptoms relative to the remaining sample, only Group 2 exhibited corresponding elevations in heart rate. Moreover, Group 2 exhibited significantly lower PEP, compared to Group 4. Thus, distinguishing between these two relatively highly distressed groups may provide clinical utility if proven to be reliable and generalizable out-of-sample. To this end, we trained two logistic regression models to predict the presence of Group 2 and Group 4, respectively. In both training models, four independent variables were included in the logistic regression: HRSD, neuroticism, heart rate, and PEP. The N = 150 exploratory sample was used to train the models, and the N = 50 validation sample was used to generate predicted values from the training model. Finally, in order to assess the degree to which these predictions explained the validation data, we correlated the predicted values with the four input variables from the validation sample. That is, the predicted probabilities for Group 2 and Group 4 were entered as predictors in a linear regression predicting each of the study variables listed in Table 2. Results supported the out-of-sample generalizability of the group characteristics. The relative proportion of variance accounted for in the validation sample by the predicted Group 2 probabilities were: HRSD ($R^2 = 0.20$), DASS-D ($R^2 = 0.07$), DASS-A ($R^2 = 0.18$), neuroticism ($R^2 = 0.34$), PEP ($R^2 = 0.07$), and IBI ($R^2 = 0.52$). The relative proportion of variance accounted for in the validation sample by the predicted Group 4 probabilities were: HRSD ($R^2 = 0.26$), DASS-D ($R^2 = 0.20$), DASS-A ($R^2 = 0.12$), neuroticism ($R^2 = 0.44$), PEP ($R^2 = 0.33$), and IBI ($R^2 = 0.27$). Thus, the relative likelihood of being assigned to a classification equivalent to Group 2 or Group 4 accounted for an appreciable degree of variance in both psychological and physiological variables in an external sample. Moreover, this finding extended to two variables (the depression and anxiety scales of the DASS) that were not included in the training models.

3. Discussion

The present study was interested in using an unsupervised algorithm to identify potential subgroups of autonomic cardiac control networks in a group of 150 individuals. Although we recruited a mixture of healthy controls and individuals with clinically-severe DSM-5 disorders (e.g. GAD, MDD, SAD, and PTSD), we were agnostic to the utility of these classifications for organizing and clustering the underlying cardioregulatory dynamics of the constituent individuals. We employed the S-GIMME function, utilizing the Walktrap algorithm to estimate individual, group, and subgroup unified SEM (uSEM) models. Four subgroups were identified, comprising 22, 25, 26, and 61 individuals. An additional 16 individuals were left unclassified by the S-GIMME algorithm. The individual uSEM models were then aggregated by subgroup into four temporal network models, from which average out-degree and in-degree centrality were estimated for each group. After we examined differences between GIMME subgroups in network dynamics and psychological and physiological variables, we carried out two validation procedures, one to examine the reproducibility of the cluster classifications within the N = 150 sample and one to examine the out-of-sample generalizability of the cluster characteristics (i.e. mean levels of psychological and physiological variables) in an external sample of N = 50.

The Walktrap algorithm returned clusters with relatively stratified levels of psychological distress. Nearly 62% of the nonclinical participants were found among the unclassified individuals or Group 1, with nonclinical participants making up 75% and 41% of those groups, respectively. Unsurprisingly, these groups exhibited the lowest levels of psychological distress and neuroticism. Conversely, Groups 2 and 4 largely comprised clinical participants (100% and 89%, respectively). These groups likewise exhibited the highest levels of psychological

distress and neuroticism. Although this result may seem unremarkable, it should be underscored that the Walktrap clustering was based on the dynamic organization of physiological networks. There was no reason to assume *a priori* that clustering would preserve clinical differences, whether between specific disorder categories or between clinical and nonclinical populations.

Additionally, the Walktrap algorithm appears to have successfully differentiated between two physiologically distinct high-symptom groups. That is, whereas both Group 2 and Group 4 exhibited elevated psychological distress, only Group 2 exhibited concurrent elevations in cardiac risk factors such as elevated heart rate and reduced autonomic regulation. Compared to the rest of the sample, Group 2 exhibited reduced autonomic regulatory in-degree, including an almost complete absence of contemporaneous parasympathetic regulation. The heart is known to be tonically inhibited by parasympathetic influences and modulated under stress by parasympathetic withdrawal and sympathetic stimulation (Berntson et al., 1997). This set of relations should give rise to a dynamical structure in which moment-to-moment variation in heart period (IBI) is influenced by RSA and PEP, and although some feedback from the heart should be present, directional influences from the heart to the ANS should not predominate. Group 2 exhibited a clear divergence from this putative structure. That this group was differentiated by mean levels in psychological and physiological variables, as well as by structural dynamics in autonomic regulatory networks, indicates that the present analyses may have identified a particular psychopathological group with elevated cardiac risk. Clearly, more research is needed to further substantiate this assertion.

The RSA out-degree measured in the current study is a statistical proxy for efferent vagal signals to the sinoatrial node. This tonic parasympathetic inhibition provides anti-arrhythmic and anti-inflammatory effects that are thought to be crucial for maintaining cardiovascular health (Friedman, 2007; Rosas-Ballina & Tracey, 2009; Thayer & Lane, 2007). Dysregulation of these effects has been found to limit adaptive cardiac responsiveness (Levy, 1990; Verrier, 1987), and has been shown to be a significant risk factor for all-cause mortality (Tsuji et al., 1994). Conversely, greater parasympathetic tone has been found to predict survival after myocardial infarction (i.e. heart attack; Stein, Bosner, Kleiger, & Conger, 1994).

Sympathetic predominance in autonomic cardiac control can reflect increased sensitivity to perceived stress and activation of adaptive stress response systems (Fisher et al., 2021; Sapolsky et al., 2000). The stress response serves to mobilize energy to meet shifting environmental demands, stimulating proinflammatory cytokines (Irwin & Cole, 2011; Nance & Sanders, 2007), and increasing cardiovascular tone through vasoconstriction and increases in heart rate and contractility (Berntson, Quigley, Norman, & Lozano, 2017). These increases in cardiovascular tone can result in shear stress and injury to the endothelium (the inner layer of the vasculature)—hypothesized to be a primary causal factor in the development of coronary artery disease (Chatzizisis et al., 2007). Moreover, concurrent increases in inflammation from cytokine stimulation and immune responses to vascular injury can serve to exacerbate cardiopathogenic effects (Ross, 1999). Although these mechanisms have been understood for decades, evidence connecting sympathetic predominance to group differences in psychologically distressed individuals has proved elusive or equivocal (Carney et al., 2005; Fisher et al., 2021). Yet, there has been a pressing motivation to identify these connections, given the consistent evidence linking coronary disease to DSM diagnoses such as MDD (O'Neil et al., 2016; Seldenrijk et al., 2015), PTSD (Sumner et al., 2015), and panic disorder (Seldenrijk et al., 2015).

Importantly, our group has recently argued for a dynamic, systems-based perspective of autonomic regulation in DSM-defined distress disorders (Fisher et al., 2021). Given equivocal and null findings in the literature related to the measurement of tonic levels of autonomic variables, we argue that examining time-dependent regulatory dynamics from a systems perspective is likely to yield more consistent and valid information. Moreover, because the autonomic nervous system is a regulatory system that is itself embedded within a larger regulatory network of immunologic and endocrine systems, there is likely sufficient complexity to lead to multifinality in autonomic and cardiac profiles. Quite simply, the same symptom topographies and taxonomic classifications are likely to belie heterogeneous subpopulations. Thus, the identification of subgroups—and reliable subgroup identifiers—may be paramount to mapping the role of psychological distress in the development of coronary heart disease and other physiologic disease processes. The identification of Group 2 in the present study speaks to the potential impact of such an approach. Group 2 comprised only 22% of the clinical participants in the present sample, with no clear pattern of DSM-5 diagnoses. The utilization of a bottom-up classification approach with systems-level data was necessary to delineate this high-risk subpopulation.

Given the potential importance of these findings, we were interested in evaluating the generalizability and replicability of both the cluster classifications and the intra- and intergroup characteristics—that is, the relative mean levels of psychological and physiological variables in each group. To assess the validity of the clustering, we chose a deliberately *post hoc* approach in which we first estimated subgroups via the Walktrap algorithm in order to evaluate the defining characteristics of the subgroups. Because the Walktrap algorithm clustered participants based on uSEM network dynamics, this evaluative step focused on the patterns of in-degree and out-degree among the four groups. Next, we conducted a second clustering analysis in the N = 150 sample using a Gaussian finite mixture model. The four outgoing paths for IBI (IBI on IBI, RSA, PEP, and respiration rate), were entered into the model as class indicators. A seven-class solution was found to best-fit the data and the agreement between Walktrap clusters and mixture model classes was assessed via Pearson's correlations. These analyses returned strong validation evidence for Group 2, which exhibited 86% overlap with Class 3. The remaining Walktrap clusters exhibited more modest validation results, though all three correlated significantly with at least one mixture model class.

Finally, we trained two logistic regression models—one for Group 2 and one for Group 4—to individual levels of depression, neuroticism, heart rate, and PEP in the N = 150 sample. Data from the N = 50 external sample were then used to generate predicted values for the probability of Group 2 membership and Group 4 membership, respectively. These predicted values were then correlated with the study variables reported in Tables 2 and 3, to assess the degree to which predicted class membership predicted relative levels of psychological and physiological variables. Results demonstrated comparable performance—in R^2—to the model results reported in Table 3, indicating that the variable profiles associated with the Walktrap clusters generalized to a comparable external sample.

3.1. Limitations

Two potential limitations are worth outlining. First, the physiological data analyzed in the present study can be effectively considered convenience data insofar as they were collected during the course of structured clinical interviews for a larger study. Although the conditions for collection—e.g. the training of research assistants, the measurement and placement of electrodes, the monitoring of the data capture in real time—were all done with high degrees of professionalism and care, no specific paradigm for physiological measurement was employed and physiology was simply measured for as long as the interview took to complete. This resulted in time series lengths with a relatively normal distribution (skewness = 0.25, kurtosis = −0.67), and an average number of epochs of 166.44 (SD = 78.06) and range from 41 to 377. Unsurprisingly, healthy control participants comprised the majority of the shorter time series, due to the correspondingly short durations of their structured clinical interviews. For instruments such as the ADIS, consistently answering in the negative—which healthy control participants are inherently likely to do—will dramatically shorten the length of

the interview. This may explain why healthy control participants constituted 75% of the unclassified cases. It is possible that these models were deemed to be distinct due to insufficient statistical power. Future work should endeavor to standardize the measurement period to obviate this potential confound.

Second, the context in which the data were captured should be taken into consideration. Although prior work from our lab examining these data determined that the interview was not significantly stressful for participants (Diamond & Fisher, 2017), it remains entirely possible that it was, in fact, stressful for some subset of the participants. Given that the present study used an unsupervised algorithm to recover subsets, it is plausible that individual differences in threat appraisals—e.g. cognitive schemas that shaped the interpretation of and reactions to the clinical interview (Disner, Beevers, Haigh, & Beck, 2011)—could have generated differential levels of threat perception and corresponding activation of physiologic stress responses. Thus, one may consider whether the cardioregulatory dynamics for Group 2 were a function of an active, adrenergic stress response. At minimum, future research should measure subjective reports of perceived stress.

3.2. Conclusion

Despite these limitations, the present study provides a promising new paradigm in the measurement and modeling of cardioregulatory variables in psychologically distressed participants. In a sample of healthy controls and clinical participants with multiple DSM-5 disorders, we recovered four distinct subpopulations of cardioregulatory network dynamics. These subgroups correlated strongly with both psychological and physiological variables. Thus, there is reason to have some degree of confidence in the validity of these groups. Future work should look to replicate these findings and further interrogate the roles the identified dynamics play in cardiopathogenesis.

CRediT authorship contribution statement

Aaron J. Fisher: Conceptualization, Methodology, Formal analysis, Writing. **Esther Howe:** Data curation, Writing, generation of tables and figures, contribution to article revision. **Zoe Y. Zong:** Led primary, Data curation, training of research team for physiological, and cleaning. Contributed to coding and proofreading.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2022.104105.

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