# Unveiling the Structure of Heart Rate Variability (HRV) Indices: A Data-drive Meta-clustering Approach

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Heart Rate Variability (HRV) can be estimated using a myriad of mathematical indices, but the lack of systematic comparison between these indices renders the interpretation and evaluation of results tedious. In this study, we assessed the relationship between 57 HRV metrics collected from 302 human recordings using a variety of structure-analysis algorithms. We then applied a meta-clustering approach that combines their results to obtain a robust and reliable view of the observed relationships. We found that HRV metrics can be clustered into 3 groups, representing the core variability features, extreme variability features and frequency/complexity features. From there, we described and discussed their associations, and derived recommendations on which indices to prioritize for parsimonious, yet comprehensive HRV-related data analysis and reporting.

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Heart Rate Variability (HRV), reflecting the heart's ability to 23 effectively regulate and adapt to internal and external envi-24 ronmental changes, has been linked to many physical and 25 mental health outcomes Forte et al. (2019). Convention-26 ally, the various indices used in the assessment of HRV 27 are broadly categorized based on their mathematical under-28 pinnings, with categories traditionally including the *time*-29 domain, frequency-domain, and nonlinear dynamics.

Time-domain indices are overall the simplest and most <sup>32</sup> straightforward method of quantifying the variability of nor-<sup>33</sup> mal (i.e., excluding abnormal beats such as ectopic beats) <sup>34</sup> heartbeat intervals (NN intervals - NNIs). Some com-<sup>35</sup> monly derived indices include *SDNN*, the standard devi-<sup>36</sup> ation of all NN intervals, *RMSSD*, the root mean square <sup>37</sup> of the sum of successive differences of NN intervals, and <sup>38</sup> *pNN50*, the percentage of adjacent NN intervals separated <sup>39</sup> by more than 50ms. While time-domain methods offer computational ease, they are less sensitive to distinguish be-<sup>41</sup> tween the contributions of sympathetic and parasympathetic <sup>42</sup> branches (Acharya et al., 2006). Frequency-domain indices, <sup>43</sup> on the other hand, target the assessment of these different regulatory mechanisms by investigating how the HRV <sup>45</sup>

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power spectrum distributes across different frequency bands (e.g., low frequency, LF or high frequency, HF). Other indices that fall under the frequency domain include derivatives of the aforementioned components, such as the ratio of LF to HF (LF/HF) power and their normalized (e.g., LFn, HFn) and natural logarithmic variants (e.g., LnHF). Finally, drawn from concepts of non-linear dynamics and chaos theory (Golberger, 1996; Lau et al., 2021), non-linear indices were introduced to better characterize the complex physiological mechanisms underlying HRV. Prominent indices include measures obtained from a Poincaré plot where an ellipse is fitted to a scatterplot of each NN interval against its preceding one (e.g., the standard deviation of the short-term, SD1 and long-term, SD2 NN interval variability, as well as its corresponding ratio, SD1/SD2, Brennan et al., 2001). Other non-linear indices that fall under this category, such as Detrended Fluctuation Analysis (DFA), multi-fractal DFA (MF-DFA) and correlation dimension (CD), account for the fractal properties of HRV, while entropy measures like approximate entropy (ApEn), sample entropy (SampEn), and multiscale entropy (MSE) quantify the amount of regularity in the heart rate (HR) time series (Voss et al., 2009). However, new methods are continually being developed, including timefrequency domain analysis (Faust et al., 2004) and HR fragmentation (Costa et al., 2017). For a more comprehensive description of all HRV indices, see Pham et al. (2021).

In light of the popularity of HRV analysis for investigating health and disease, the multitude of existing metrics warrants some concerns. Firstly, the functional association of

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these indices with physiological mechanisms is poorly un-105 derstood (Fatisson et al., 2016; Hayano & Yuda, 2019), with 106 the indices often used interchangeably to describe HRV as<sub>107</sub> a general concept. This not only makes it difficult to in-108 terpret and report the complex patterns of (sometimes in-109 consistent) results but can also aggravate replicability issues,110 as different studies, when examining the same phenomenon111 (e.g., cognitive flexibility, ageing), might rely on different<sub>112</sub> indices to describe the relationships with HRV. Apart from 113 this conceptual hurdle pertaining to the unclear relationship<sub>114</sub> between the mathematical indices and their physiological<sub>115</sub> meaning, another pragmatic issue lies in the shared similar-116 ities and overlaps between many of these metrics. For instance, early studies have investigated the relationships between time-domain and frequency-domain indices, showing that not only were RMSSD and pNN50 strongly correlated with each other (above 0.9, Bigger Jr et al., 1989), they were 118 also highly associated with HF power (Bigger Jr et al., 1989;<sup>119</sup> Kleiger et al., 2005; Otzenberger et al., 1998), suggesting 120 that these measures could be treated as surrogates for each 121 other in assessing the parasympathetic modulation of HRV. 122 This observation is warranted given that the former is com-123 puted from the differences across consecutive NN intervals, 124 and hence, they reflect mainly high-frequency oscillatory 125 patterns in HR and are independent of long-term changes. 126 On the other hand, SDNN, which has been thought to reflect both sympathetic and parasympathetic activity, is correlated<sub>127</sub> to total power in the HRV power spectrum (Bigger Jr et al., 1989). Recent years also witnessed the emergence of de-128 bates regarding the traditional conceptualization of SD1 and  $_{129}$ SD2 as non-linear indices, particularly when Ciccone et al., 130 (2017) pointed out that RMSSD and SD1 are actually mathe-131 matically equivalent. Consequently, studies that report both,32 of these short-term HRV indices often independently arrive,133 at identical statistical results without addressing this equivalence Leite et al. (2015). Additionally, other studies have 134 also drawn similarities between SD1/SD2 and LF/HF in their 135 indexing of the balance between short- and long-term HRV136 (Brennan et al., 2002; Guzik et al., 2007). These overlaps, 137 if not taken into account in analyses, can lead to statistical 138 issues, such as inflated confidence in the results (shown by 139 an artificially high number of indices seemingly agreeing, 40 with a given trend), collinearity issues (if multiple indices,141 are jointly used as predictors), potential over-correction (e.g., for Bonferroni-type p-value adjustment methods), and need-143 lessly complex and cluttered patterns of results (Dormann et,144 al., 2013; Mela & Kopalle, 2002; Næs & Mevik, 2001).

The aim of this study is thus to increase the understanding <sup>146</sup> of the relationships between HRV indices using a data-driven<sub>147</sub> approach. Beyond simply computing and reporting the corre-<sub>148</sub> lations between the indices, the goal is to assess the presence<sub>149</sub> of groups (i.e., clusters) of metrics, subsequently describe<sub>150</sub> them, and discuss hypotheses as to their existence. While<sub>151</sub>

there exist different approaches to assign data to different groups based on their level of associations (see Nguyen Phuc Thu et al., 2019), there is no gold standard or clear guidelines to determine the most appropriate method for grouping these physiological indices. As such, choosing one method and presenting its solution as a definitive one can be misleading. Thus, we will explore the structure of HRV indices using a consensus-based methodology (Bhattacharjee et al., 2001; Kuncheva, 2014; Monti et al., 2003), henceforth referred to as *meta-clustering*, where the results of multiple structure analysis approaches are systematically combined to highlight the most robust associations between HRV indices.

## Methods

The electrocardiogram (ECG) data of 302 participants were extracted from 6 open-access databases described below. The script to download and format the databases are available at https://github.com/neuropsychology/NeuroKit/data/The processed data, as well as the full reproducible analysis script, including additional descriptions of each approach and the solutions of each individual clustering method, are available at this GitHub repository (https://github.com/Tam-Pham/HRVStructure).

# **Databases**

The Glasgow University Database (GUDB) database (Howell & Porr, 2018) contains ECG recordings from 25 healthy participants (> 18 years old) performing five different two-minute tasks (sitting, doing a maths test on a tablet, walking on a treadmill, running on a treadmill, using a handbike). All recordings were sampled at 250 Hz.

The MIT-BIH Arrhythmia Database (MIT-Arrhythmia and MIT-Arrhythmia-x) database (Moody & Mark, 2001) contains 48 ECG recordings (25 men, 32-89 years old; 22 women, 23-89 years old) from a mixed population of patients. All recordings were sampled at 360 Hz and lasted for 30 minutes.

The Fantasia database (Iyengar et al., 1996) contains ECG recordings from 20 young (21-34 years old) and 20 elderly (68-85 years old) healthy participants. All participants remained in a resting state in sinus rhythm while watching the movie Fantasia (Disney, 1940) that helped to maintain wakefulness. All recordings were sampled at 250 Hz and lasted for 120 minutes.

The MIT-BIH Normal Sinus Rhythm Database (MIT-Normal) database (Goldberger et al., 2000) contains long-term ( $\approx$ . 24h) ECG recordings from 18 participants (5 men, 26-45 years old; 13 women, 20-50 years old). All recordings were sampled at 128 Hz and due to memory limits, we kept

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only the second and third hours of each recording (with the<sub>201</sub> loose assumption that the first hour might be less representa-<sub>202</sub> tive of the rest of the recording and a duration of 120 minutes<sub>203</sub> to match those from Fantasia database).

The MIT-BIH Long-term ECG Database (MIT-Long-term) database (Goldberger et al., 2000) contains long-term (14 to 22 hours each) ECG recordings from 7 participants (6 men, 46-88 years old; 1 woman, 71 years old). All recordings were sampled at 128 Hz and due to memory limits, we kept only the second and third hours of each recording.

The last dataset came from resting-state https://github.com/ neuropsychology/RestingState recordings of authors' other<sup>211</sup> empirical studies. This dataset contains ECG recordings sampled at 4000 Hz from 43 healthy participants (> 18 years<sup>212</sup> old) that underwent 8 minutes of eyes-closed, seated posi-<sup>213</sup> tion, resting state.

## Data Analysis

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The NeuroKit2 software (Makowski et al., 2021) was used to preprocess the raw ECG signals (when available), locate R-peaks and subsequently compute all the HRV in-220 dices (see **Table 1** for the abbreviations and description of 221 all HRV indices). The rest of the data analysis was carried 222 out with R (R Core Team, 2019) and the *easystats* ecosystem 223 (Ludecke et al., 2019; Lüdecke, Patil, et al., 2021; Makowski 224 et al., 2019, 2020). Reproducible scripts are available at 225 https://github.com/Tam-Pham/HRVStructure.

We started by identifying indices that were near-perfect duplicates (|r| > 0.999) and removed them (to prevent further228 statistical issues such as positive definite correlation matri-229 ces). For each index, we then removed extreme observations230 (> .9999 percentile of the median absolute deviation from<sup>231</sup> the median) -  $\approx 4\%$  of data - using the check outliers<sup>232</sup> function in the performance R package (Lüdecke, Ben-233 Shachar, et al., 2021). On average, 5.61% of data was de-234 tected as outliers and removed. Multiple structural meth-235 ods were then applied to analyze the associations between236 the HRV indices, such as dimensionality analyses (includ-237 ing Principal Component Analysis - PCA, and Exploratory238 Factor Analysis - EFA), clustering (including k-means, k-239 medoids, hierarchical clustering, DBSCAN, HBSCAN, mix-240 ture model algorithms), as well as network-based approaches<sup>241</sup> (exploratory graph analysis; EGA). While the individual so-242 lutions are described in the Supplementary Materials, the243 study aimed to aggregate them to identify the robust groups identified across these methods.

The *meta-clustering* approach (Lüdecke et al., 2020; which<sub>246</sub> finds echoes in *consensus clustering*; see Monti et al., 2003)<sub>247</sub> treats the unique clustering solutions as an ensemble, from<sub>248</sub> which a probability matrix is derived (see **Figure 1**). This<sub>249</sub>

matrix contains, for each pair of HRV indices, the probability of being grouped together. For instance, if two indices have been assigned to a similar cluster by 5 out of 10 clustering methods, then the probability associated with this pair is 0.5. This probability matrix is then treated as a distance matrix and submitted to hierarchical clustering. Essentially, this approach is based on the notion that, as each clustering algorithm embodies a different angle by which it sees the data, cross-validating the phenomenon of interest using different angles leads to more accurate results.

## Results

Indices that were appeared as redundant in the correlation analysis, and subsequently removed, included 1) *SDSD*, *SD1*, *SD1a* and *SD1d* (duplicates of RMSSD); 2) *SDNNa* and *SDNNd* (duplicates of *SDNN*); 3) *SD2a* and *SD2d* (duplicates of *SD2*); 4) *Cd* (duplicate of *Ca*); 5) *C1d* (duplicate of *C1a*); and 6) *C2d* (duplicate of *C2a*). The indices that were kept were selected based on their higher popularity (e.g., *RMSSD*) or functional meaning (e.g., acceleration for *Ca*).

PCA solutions with 9 and 12 components were deemed suitable (see the n\_components function in the *parameters* package, Lüdecke et al., 2020) and extracted, and each component was treated as a cluster containing indices with the highest loadings. Following a similar optimizing procedure, two solutions of 9 factors and 12 factors were extracted using EFA. See **Tables 1-4** in *Supplementary Material* for the item loadings of dimension solutions.

Three optimal structure solutions of 2-cluster, 7-cluster, and 10-cluster were identified for k-means clustering (see the n\_clusters function in the parameters package) and a 3-cluster solution was extracted for k-medoids clustering (see pamk function, Hennig & Imports, 2015). Two hierarchical clustering models were also constructed using Euclidean distance method and average linkage method. These bootstrapping-based solutions to cluster selection with a confidence level of 90% and 95% identified 13 and 11 significant clusters respectively (see Suzuki & Shimodaira, 2006). Other unsupervised clustering approaches, DBSCAN and HDBSCAN, suggested two additional structure solutions of respectively 6 and 15 clusters, and the mixture model yielded a solution of 6 clusters. See **Figure 1-9** in *Supplementary* Material for the clustergrams/ deprograms results of clustering solutions.

Finally, two solutions were extracted from the network-based EGA approach using two network estimation algorithms, *GLASSO* and *TMFG*, in combination with the *louvian* network community detection algorithm (H. Golino et al., 2020; Hudson Golino et al., 2020). The two networks were associated with structures of 7 and 6 clusters respectively. See

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**Figure 10-11** in *Supplementary Material* for the results of<sub>274</sub> network solutions.

Using the fifteen structure solutions from the aforementioned<sup>276</sup> methods, we computed the probability matrix representing<sup>277</sup> each pair of HRV indices being assigned to the same cluster<sup>278</sup> (see Figure 1). The matrix was inverted to form a distance<sup>279</sup> matrix and submitted to hierarchical cluster analysis with av-280 erage linkage method. The results of the meta-clustering ap-281 proach are presented in Figure 2. The most closely related<sup>282</sup> clusters of indices include the cluster of time-domain indices<sup>283</sup> (e.g., RMSSD, pNN50, SDNN, MadNN), the cluster of heart<sup>284</sup> rate asymmetry indices (HRA; e.g., PAS, PSS, PIP), the cluster of heart rate fragmentation indices (HRF; e.g., PI, GI, AI), and the cluster of DFA indices with the low-frequency indices (e.g., LFHF, LFn). The remaining indices, which include the high-frequency indices (e.g., HF, HFn) and the different non-linear indices (e.g., CD, LZC, SampEn, FuzzyEn) were relatively closely related to each other in the final structure. The cluster memberships (Level 2 in **Table 1**) were determined by a vertical height cut at 0.8 and within each cluster, the center was identified as the average value of all members. The relative distances from the center, representing the members' centrality values or degree of cluster representativeness, were calculated and summarized in Table 1.



Figure 1. Probability Matrix that represents the probability each pair of HRV indices being assigned to the same cluster. The prob- 291 ability can take any value from 0, which indicates that no solution 292 assigned the two indices to the same cluster, to 1, which indicates that all solutions suggested the two indices belong to the same group. The absolute proximity of every variable with itself is rep-295 resented by the main diagonal in red (probability = 1). From the 296 heatmap, we can see a clear structure of 6 clusters, corresponding 297 to the Level 2 groupings in Table 1, emerged. As compared to the 298 other clusters, the two big clusters in the centre of the heatmap, 'Absolute' and Relative', are less clear. 299

#### Discussion

In this study, we applied various structure analysis techniques to explore the relationships between HRV indices. By combining the domain knowledge from a multitude of statistical methods, the meta-clustering approach maximizes the stability of the final HRV structure and circumvents the lack of objective criteria for the selection of techniques. The meta-clustering solution presented in **Figure 2** yielded an intriguing and complex pattern of associations and groupings, with three overarching clusters observed at the top level (Level 1 in **Table 1**) that we will now describe and discuss.

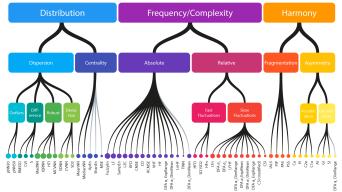


Figure 2. Meta-Clustering Hierarchical Structure. The Level 1 clusters, determined at a vertical height cut of 0.9, include Distribution, Frequency/Complexity and Harmony. The Level 2 clusters, determined at a vertical height cut of 0.8, include Dispersion, Centrality, Absolute, Relative, Fragmentation and Asymmetry. The Level 3 clusters were only determined for groups where literature corrborates the associations between the indices. The hierarchical links are grey for associations that are less clear. The colors and the sizes of the nodes are according to their Level 2 groupings and their centrality values respectively; the bigger the nodes, the closer the indices to the cluster centres and the more representative they are of the indices's shared characteristics.

The first main group, henceforth labelled as "distribution," comprises predominantly time-domain indices. The groupings within this cluster suggest that it includes indices particularly sensitive to two fundamental statistical features of a variable distribution (Cardinal, 2015), namely central tendency and dispersion. One can observe the presence of a distinct sub-cluster made of MeanNN and MedianNN, which describes the centre of the distribution of HR. The second sub-cluster includes different mathematical descriptions of dispersion (e.g., the SD, the IQR or the MAD of NN intervals). These dispersion indices are further grouped in accordance with their statistical properties and formulations. For instance, pNN20 and pNN50, which share the same statistical origin of threshold-based variability (Kim et al., 2009), are the closest to each other. MCVNN or MadNN are dispersion indices that are more robust against extreme values (Pham et al., 2021), are closer to the geometrical-based in-353 dex HTI, while CVNN, SDNN and SD2, which are more sen-354 sitive to outliers (Leys et al., 2013), are in close proximity355 to each other. Indices that focus on the difference between356 successive NN intervals, such as RMSSD, CVI and S, are 357 clustered together. These groupings are consistent with the358 existing literature (Antink et al., 2021; Guzik et al., 2007;359 Malik, 1996; Pham et al., 2021; Shaffer et al., 2014). Re-360 garding their relative importance, measured by their central-361 ity values, MadNN, IQRNN, HTI, pNN20, and SDNN appear362 to be the most representative dispersion indices. However, 363 the difference between their centrality level is marginal (as<sub>364</sub> illustrated by the size of the nodes in Figure 2 and their cen-365 trality values in Table 1). Consequently, choosing to pri-366 oritize the most commonly used dispersion indices, such as<sub>367</sub> SDNN and RMSSD (Billman, 2011) can be seen as appro-368 priate. An alternative option would be to focus on MadNN,369 pNN20, and RMSSD, which together offer better coverage of<sub>370</sub> the fine-grained sub-groupings.

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The second main group, henceforth labelled as "harmony," comprises indices that are formulated to capture the abnor-375 mal properties of sinus rhythm and are sensitive to the stabil-976 ity of HRV. One of the two sub-clusters in this group includes<sub>977</sub> only HRA indices which measure the asymmetric contribu-378 tion of HR acceleration and deceleration to HRV (Guzik et 379 al., 2006; Piskorski & Guzik, 2011; Yan et al., 2017). At the  $_{\mbox{\tiny 380}}$ lower level in the hierarchical structure, depending on the 381 asymmetric focus of the indices, the HRA sub-cluster is fur-382 ther divided into two groups, namely acceleration (e.g., PI,383 Ca) or deceleration (e.g., AI, GI, SI). At the higher level, this<sub>384</sub> sub-cluster is joined with a distinct group of HRF indices, which measure the "erratic" behaviours in heart rhythm,385 manifesting as abrupt and high frequency switching between386 the increases and decreases of HR (Costa et al., 2017, 2018).387 This study is the first that examined the relationships between 388 HRA and HRF indices and therefore, the specific physiolog-389 ical mechanisms underlying their close proximity should be390 further investigated. Nevertheless, as existing literature has391 highlighted the diagnostic values of both indices, especially392 for cardiac disorders (Bergfeldt & Haga, 2003; Costa et al., 393 2017, 2018; Costa & Goldberger, 2019; Guzik et al., 2013;394 Karmakar et al., 2012; Rohila & Sharma, 2020b), possi-395 ble explanations for their close associations could stem from 396 their ability to capture specific shared cardiac abnormalities.397 The centrality values of the indices in this group suggest that 398 PI and AI are the most representative indices of HRA. While399 there exists only a minute difference between the centrality<sub>400</sub> values of HRF indices, given that PAS quantifying a sub-type<sub>401</sub> of fragmentation that is not always accordant with the other 402 values (Costa et al., 2017), we recommend reporting PAS403 with at least another HRF indices to more comprehensively<sub>404</sub> capture the nature of fragmentation.

The third high-level cluster comprises mainly frequencydomain and complexity-based HRV indices, and is henceforth descriptively labelled as "frequency/complexity." The high level of similarity between DFA and frequencyweighted spectral indices align with previous literature that has theoretically demonstrated and empirically verified their proximity (Captur et al., 2017; Francis et al., 2002; Lensen et al., 2020; Young & Benton, 2015). Specifically, al component has been shown to be particularly sensitive to the proportion of low-frequency fluctuations (e.g., LFn, LFHF) in the signal and α2 component to that of very-low-frequency variabilities (Captur et al., 2017; Francis et al., 2002). Nevertheless, due to the constraint of recording lengths, VLF indices could not be properly examined in this study to verify their relationship with  $\alpha 2$ . The sub-cluster of *DFA* and lowfrequency components also includes some MDFA indices such as multi-fractal dimensional ranges and dimensional means. These indices are relatively new quantifications of HRV, and thus future studies should attempt to explore them in tandem with more traditional HRV indices to better understand the underlying reason for these observed relationships. Except for three entropy-based measures - ApEn, ShanEn and MSE - which seem to be more related to the centralitybased indices in the core variability features, all complexitybased indices appear to fall within this frequency-complexity cluster. To our knowledge, given the novelty of complexitybased indices in the study of HRV, only one study has examined their relationships with other HRV indices. In line with our results, Rohila and Sharma (2020a) similarly observed a strong association between frequency-based and complexitybased measures. Further investigation is thus needed to understand the origins underlying their stable associations.

A few limitations have to be underlined. Firstly, the lack of data with very long recordings limited the exploration of indices sensitive to very slow rhythms. Additionally, there were substantial discrepancies in the recording lengths of the different databases used. Although recording length can affect the quality and accuracy of several HRV indices (Chou et al., 2021), our data analysis assumed - by design - that the relationship between indices is invariant across time (i.e., that the proximity of two indices does not change for short and long recordings). Although this assumption seems mathematically justified, the alternative hypothesis remains an avenue opened for exploration. Secondly, the databases involved participants with different characteristics (in terms of health or demographic variables). Similarly, this is not an issue in and of itself, as our study was focused on the relationship between indices, rather than between (groups of) individuals. It is, however, also not impossible that the relationship between indices (and thus, the cluster structure) might marginally change in specific populations (e.g., severe heart diseases), and such speculations could be investigated in further studies. Finally, we treated each clustering approach and

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solution equally and assigned equal weights to the different<sub>447</sub> methods in our final meta-clustering model. Future studies providing evidence that some approaches are inherently bet-<sub>448</sub> ter or worse for the analysis of these physiological indices<sub>449</sub> could be integrated within a meta-clustering approach by as-<sub>450</sub> signing different weights to different methods, based on prior<sub>451</sub> knowledge, that was unfortunately not available for the current study.

In conclusion, this study aimed at describing the structure<sub>454</sub> and relationships between the multitude of existing HRV in-455 dices, to provide users and readers with empirical evidence as<sub>456</sub> to the latent dimensions that these indices capture, and guidelines as to which to prioritize. Indeed, given that resource-457 intensive efforts are needed to compute and discuss results<sup>458</sup> related to every single HRV measure, most studies opt to<sup>459</sup> report a few of them, often without a clear justification for<sup>460</sup> their choice of indices. Such a conundrum can benefit from a<sub>461</sub> greater in-depth understanding of the relationships between 462 the HRV indices, that could in turn allow more informed<sub>463</sub> selections of HRV index specific to research- or clinical-464 oriented purposes. By recognizing the similarities and differences across these indices, groups of measures could be465 identified based on their ability to provide distinct informa-466 tion about the underlying HRV characteristics. Our work<sup>467</sup> here establishes a framework that could guide the develop-468 ment of a more parsimonious categorization of HRV indices<sup>469</sup> based on their actual level of similarity or shared physiologi-470 cal origins, above and beyond their mathematical origins and 471 associations. 472

## **Author Contributions**

DM conceived and TP coordinated the study. TP and ZL par-<sup>476</sup> ticipated in the manuscript drafting. DM and AC performed<sup>477</sup> a critical review of the manuscript. All authors read and ap-<sup>478</sup> proved the final manuscript.

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# **Conflict of Interest Statement**

The 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.

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**Table 1**A summary of HRV indices according to their respective cluster memberships in the final meta-clustering solution, together with their centrality values which were quantified as their relative distances from the respective cluster centres.

Level 1	Level 2	HRV Indices	Description	Centrality
- Distribution		ApEn	The Approximate Entropy	20.3
	Centrality	ShanEn	The Shannon Entropy	16.9
		MeanNN	The mean of the NN intervals.	16.9
		MedianNN	The median of the NN intervals.	16.7
		MSE	The Multiscale Entropy	11.5
	Dispersion	MadNN	The median absolute deviation of the NN intervals	22.5
		IQRNN	The interquartile range (IQR) of the NN intervals	22.2
		HTI	Integral of the density of the NN interval histogram divided by its height	21.1
		SDNN	The standard deviation of the RR intervals	20.8
		pNN20	Proportion of successive NN interval differences larger than 20ms	20.6
		pNN50	Proportion of successive NN interval differences larger than 50ms	20.2
		RMSSD	Root mean square of successive NN interval differences	18.6
		MCVNN	MadNN divided by MedianNN	18.3
		CVNN	SDNN divided by MeanNN	17.0
		CVI	Cardiac Vagal Index	16.8
		SD2	The spread of NN intervals on the Poincaré plot along the line of identity.	15.7
		S	Area of ellipse in Poincaré plot	15.6
Frequency/Complexity	Absolute Frequency/Complexity	FuzzyEn	The Fuzzy Entropy	22.1
		LF	Power spectrum in the frequency range of 0.04-0.15 Hz	20.4
		SampEn	The Sample Entropy	19.0
		LZC	The Lempel-Ziv complexity	18.9
		KFD	Katz Fractal Dimension	18.6
		CMSE	The Composite Multiscale Entropy	17.9
		CD	Correlation Dimension	17.6
		DFA a1 ExpMean	The MDFA corresponding to short-term correlation. ExpMean is the mean of singularity exponents	17.4
		RCMSE	The Refined Composite Multiscale Entropy	16.6
		VHF	Power spectrum in the frequency range of 0.4-0.5 Hz	16.6
		HF	Power spectrum in the frequency range of 0.15-0.4 Hz	15.9
		DFA a1 ExpRange	The MDFA corresponding to short-term correlation. ExpRange is the range of singularity exponents	15.9
		DFA a2 DimMean	The MDFA corresponding to long-term correlations. Dimmean is the mean of singularity dimensions	15.8
		LnHF	The natural logarithm of HF	12.3
		TINN	The baseline width of the NN interval histogram	8.6
		LFn	The normalized LF	18.6
	Relative Frequency/Complexity	DFA a1	The DFA corresponding to short-term corrleation	16.4
		DFA a2	The DFA corresponding to long-term correlation	16.3
		LFHF	The ratio between LF and HF	16.3
		DFA a2 DimRange	The MDFA corresponding to long-term correlation. DimRange is the range of singularity dimensions	15.9
		HFD	Higuchi Fractal Dimension	15.9
		SD1SD2	The ratio between short and long term fluctuations of the NN intervals	15.9
		DFA a2 ExpMean	The MDFA corresponding to long-term correlation. ExpMean is the mean of singularity exponents	15.6
		DFA a1 DimMean	The MDFA corresponding to short-term correlation. DimMean is the mean of singularity dimensions	15.5
		DFA a2 ExpRange	The MDFA corresponding to long-term correlation. ExpRange is the range of singularity exponents	15.4
		CSI (modified)	The Cardiac Symapathetic Index (modified)	13.5
		HFn	The normalized HF	13.2
		CSI	The Cardiac Sympathetic Index	11.1
		AI	The Area Index	16.5
		GI	The Guzik's Index	15.6