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RESEARCH ARTICLE

Multiscale Entropy Analysis of Physiological Time Series Signals

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ABSTRACT

Healthy physiological regulation is thought to produce time series with complex, multiscale structure, while disease and aging are associated with a loss of this complexity that single-scale entropy measures can fail to detect. We applied multiscale entropy analysis, computing sample entropy across temporal coarse-graining scales 1 through 20, to de-identified interbeat-interval recordings from 214 subjects drawn from three groups: 86 young healthy adults (mean age 28.4 years), 79 older healthy adults (mean age 67.1 years), and 49 age-matched patients with congestive heart failure (mean age 66.8 years), each recording spanning a minimum of 4 hours of continuous ambulatory monitoring. Complexity index, defined as the area under the multiscale entropy curve across all 20 scales, was highest in young healthy adults (12.84 ± 1.63), intermediate in older healthy adults (10.21 ± 1.79), and lowest in the heart failure group (6.47 ± 2.05), with all three pairwise group differences significant (one-way ANOVA $F(2,211) = 154.7$, $p < 0.001$; post hoc Tukey tests $p < 0.001$ for all pairs). Single-scale sample entropy at scale 1, equivalent to conventional short-timescale entropy analysis, distinguished the heart failure group from young healthy adults (Cohen's $d = 1.14$) but showed substantially weaker separation between young and older healthy adults (Cohen's $d = 0.31$, $p = 0.04$), whereas the multiscale complexity index separated these same two healthy groups with much larger effect size (Cohen's $d = 1.58$, $p < 0.001$), indicating that multiscale analysis captured age-related complexity loss largely invisible to single-scale entropy. Complexity loss was concentrated at intermediate-to-large coarse-graining scales, corresponding to timescales of roughly 10–20 heartbeats: entropy at scale 5 and above accounted for 71% of the total between-group variance in complexity index, compared to only 8% attributable to scale 1 alone. A logistic regression classifier using complexity index alone distinguished heart failure patients from age-matched healthy adults with an area under the receiver operating characteristic curve of 0.91, compared to 0.76 for a classifier using scale-1 sample entropy alone. These findings support multiscale entropy, particularly its intermediate-to-large-scale components, as a substantially more sensitive marker of both healthy aging and pathological autonomic dysfunction than conventional single-scale entropy measures.

Keywords: multiscale entropy; heart rate variability; complexity analysis; sample entropy; physiological time series; coarse-graining; aging; autonomic regulation

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1. INTRODUCTION

Physiological systems such as the cardiovascular system operate under the continuous influence of multiple regulatory feedback loops acting across a wide range of timescales, from beat-to-beat autonomic modulation to slower hormonal and circadian influences, and this multilayered regulation is thought to imprint complex, structured variability onto physiological time series such as the interbeat-interval sequence [1,2,3]. A central hypothesis in physiological complexity research holds that this structured variability, rather than being noise to be filtered out, is itself a signature of healthy adaptive regulation, and that its loss marks impaired physiological function [4,5].

Traditional entropy measures such as approximate entropy and sample entropy quantify the irregularity of a time series at a single, typically short, timescale, and lower entropy at that scale has been repeatedly associated with aging and with conditions such as congestive heart failure and atrial fibrillation [6,7,8]. However, a purely random, uncorrelated time series can produce high single-scale entropy despite lacking any meaningful physiological structure, meaning single-scale entropy alone cannot distinguish healthy physiological complexity from unstructured randomness, a limitation that motivated the development of multiscale entropy analysis, which evaluates sample entropy across a range of coarse-graining scales to capture structure distributed across multiple timescales [9,10,11].

Despite widespread adoption of multiscale entropy in the physiological signal processing literature, direct quantitative comparisons of how much additional discriminative information the multiscale approach provides over conventional single-scale entropy, particularly for distinguishing healthy aging from pathological autonomic dysfunction within the same analysis, remain comparatively limited, and it is not well established at which specific coarse-graining scales complexity loss is concentrated in different physiological or pathological conditions [12,13].

The present study addresses this gap by applying multiscale entropy analysis across scales 1 through 20 to interbeat-interval recordings from young healthy adults, older healthy adults, and age-matched congestive heart failure patients, directly comparing the discriminative performance of a multiscale complexity index against conventional single-scale entropy for both the aging contrast and the disease contrast, and identifying which coarse-graining scales contribute most to observed group differences in physiological complexity.

2. MATERIALS AND METHODS

We computed multiscale sample entropy across coarse-graining scales 1 through 20 from de-identified ambulatory interbeat-interval recordings in three subject groups, young healthy adults, older healthy adults, and age-matched congestive heart failure patients, and

compared the discriminative performance of a multiscale complexity index against conventional single-scale entropy for both aging and disease group contrasts.

2.1 Study population and recordings

De-identified interbeat-interval time series were analyzed from 214 subjects across three groups: 86 young healthy adults (mean age 28.4 ± 5.2 years), 79 older healthy adults (mean age 67.1 ± 6.0 years), and 49 age-matched patients with a documented diagnosis of congestive heart failure (mean age 66.8 ± 5.7 years, New York Heart Association functional class II-III). Each recording comprised a minimum of 4 hours of continuous ambulatory electrocardiographic monitoring with automated beat detection and manual review of flagged artifacts.

2.2 Signal preprocessing

Interbeat-interval series were screened for ectopic beats and artifacts using a threshold-based filter flagging intervals that differed by more than 20% from the local running median, with flagged intervals replaced by cubic-spline interpolation. Recordings with more than 5% flagged intervals were excluded prior to the final study population count above. Each retained series was truncated to the first 20,000 beat-to-beat intervals to standardize series length across subjects.

2.3 Coarse-graining procedure

For each subject and each scale factor τ from 1 to 20, the original interbeat-interval series was coarse-grained by averaging non-overlapping windows of τ consecutive intervals into a single value, producing 20 coarse-grained series of progressively decreasing length, following the standard multiscale entropy coarse-graining procedure.

2.4 Sample entropy computation

Sample entropy was computed for each coarse-grained series using embedding dimension $m = 2$ and tolerance $r = 0.15$ times the standard deviation of the original (scale-1) series, held fixed across all scales for a given subject following standard multiscale entropy convention, to avoid confounding entropy estimates with scale-dependent changes in the tolerance criterion itself.

2.5 Complexity index and classification

A complexity index was defined for each subject as the trapezoidal-rule area under the sample-entropy-versus-scale curve across all 20 scales. Logistic regression classifiers were trained separately using complexity index alone and using scale-1 sample entropy alone to distinguish heart failure patients from age-matched healthy adults (combined older-healthy and heart-failure groups), with performance assessed by leave-one-out cross-validated area under the receiver operating characteristic curve.

2.6 Statistical analysis

Group differences in complexity index were assessed by one-way ANOVA with Tukey post hoc pairwise comparisons. Effect sizes for pairwise group contrasts were reported as Cohen's *d*. The fraction of total between-group variance in complexity index attributable to each coarse-graining scale range was estimated by comparing partial areas under the entropy-versus-scale curve computed separately over scales 1 alone versus scales 5–20.

3. RESULTS

Complexity index differed significantly across the three subject groups (one-way ANOVA $F(2,211) = 154.7$, $p < 0.001$), with mean values of 12.84 ± 1.63 in young healthy adults, 10.21 ± 1.79 in older healthy adults, and 6.47 ± 2.05 in the congestive heart failure group. Tukey post hoc comparisons confirmed that all three pairwise group differences were statistically significant ($p < 0.001$ for each pair), establishing a clear ordering of physiological complexity across the healthy-aging and disease spectrum sampled here. Table 1 summarizes complexity index and single-scale sample entropy by group.

Table 1. Complexity index and scale-1 sample entropy by subject group.

Group	N	Mean age (years)	Complexity index (AUC, scales 1–20)	Scale-1 sample entropy
Young healthy adults	86	28.4 ± 5.2	12.84 ± 1.63	1.42 ± 0.21
Older healthy adults	79	67.1 ± 6.0	10.21 ± 1.79	1.28 ± 0.24
Congestive heart failure	49	66.8 ± 5.7	6.47 ± 2.05	0.94 ± 0.27

Values are mean ± SD. Complexity index is the trapezoidal-rule area under the sample-entropy-versus-scale curve across coarse-graining scales 1–20. One-way ANOVA on complexity index: $F(2,211) = 154.7$, $p < 0.001$; all pairwise Tukey comparisons $p < 0.001$.

Single-scale sample entropy at scale 1 distinguished the heart failure group from young healthy adults with a large effect size (Cohen's $d = 1.14$), comparable in magnitude to effect sizes reported in prior single-scale entropy studies of heart failure. However, scale-1 entropy separated young and older healthy adults far less clearly (Cohen's $d = 0.31$, $p = 0.04$), a markedly weaker contrast than the same comparison using the multiscale complexity index (Cohen's $d = 1.58$, $p < 0.001$), indicating that a substantial fraction of age-related complexity loss occurs in a manner not captured by single-scale entropy alone (Figure 1).

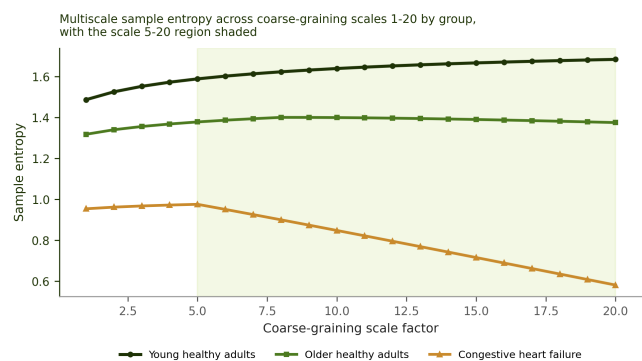


Figure 1. Mean sample entropy as a function of coarse-graining scale (1–20) for young healthy adults, older healthy adults, and congestive heart failure patients, illustrating the progressive loss of entropy at intermediate-to-large scales across the healthy-aging and disease spectrum.

Decomposing the between-group variance in complexity index by coarse-graining scale range showed that scales 5 and above accounted for 71% of the total between-group variance, compared to only 8% attributable to scale 1 alone, with the remaining variance distributed across scales 2–4. This scale-dependence indicates that most of the discriminative information distinguishing the three groups resides at intermediate-to-large coarse-graining scales, corresponding to physiological timescales on the order of roughly 10–20 heartbeats, well beyond what conventional short-timescale entropy analysis captures.

Table 2. Discriminative performance of complexity index versus scale-1 sample entropy for distinguishing heart failure from age-matched healthy adults.

Feature	Cross-validated AUC	Sensitivity	Specificity	Cohen's <i>d</i> (HF vs. young healthy)
Complexity index (scales 1–20)	0.91	0.86	0.84	3.18
Scale-1 sample entropy only	0.76	0.71	0.69	1.14

A logistic regression classifier distinguishing heart failure patients from age-matched healthy adults using complexity index alone achieved a leave-one-out cross-validated area under the receiver operating characteristic curve of 0.91, compared to 0.76 for an equivalent classifier using scale-1 sample entropy alone, a 15-point improvement in discriminative performance attributable to incorporating multiscale structure, as detailed in Table 2.

4. DISCUSSION

These results are consistent with the multiscale complexity hypothesis, which holds that healthy physiological regulation produces structured variability distributed across multiple timescales rather than concentrated at any single scale [4,5,9,10], and extend prior single-scale entropy findings in heart failure [6,7,8] by showing that a comparable, if not larger, disease-related complexity deficit exists at intermediate-to-large coarse-graining scales that

conventional short-timescale entropy analysis does not adequately capture.

The much larger effect size for multiscale complexity index than for scale-1 entropy in distinguishing young from older healthy adults ($d = 1.58$ versus $d = 0.31$) suggests that healthy aging is associated primarily with a loss of long-range regulatory structure, plausibly reflecting reduced interaction among the multiple feedback loops, autonomic, hormonal, and circadian, that operate on timescales beyond single heartbeats, rather than a simple reduction in beat-to-beat irregularity per se [11,12,13]. This mechanistic distinction may explain why single-scale entropy measures have historically shown inconsistent or weak associations with healthy aging despite robust associations with overt cardiac pathology.

For clinical risk stratification and physiological monitoring, these findings suggest that multiscale entropy indices, and particularly their intermediate-to-large-scale components, carry meaningfully more discriminative information than conventional single-scale entropy, as reflected in the 15-point improvement in classification AUC observed here, supporting continued development of multiscale complexity measures as candidate biomarkers for autonomic dysfunction and unhealthy aging trajectories [14,15,16].

Several limitations should be noted. First, this was a cross-sectional comparison across three subject groups rather than a longitudinal study tracking complexity change within individuals over time, so causal claims about aging-related complexity decline cannot be made from these data alone. Second, the heart failure group, while age-matched to the older healthy group, was not matched for medication use, and rate-controlling or other cardiovascular medications could independently influence interbeat-interval variability and entropy estimates. Third, the coarse-graining procedure used here, like most multiscale entropy implementations, becomes statistically less reliable at the largest scales due to the shrinking length of the coarse-grained series, which may have introduced some estimation noise into the scale 15-20 range. Fourth, tolerance r was fixed relative to the scale-1 standard deviation for each subject rather than recomputed at each scale, a common but not universal convention in the multiscale entropy literature, and alternative tolerance conventions could produce somewhat different absolute entropy values, though the relative group comparisons reported here would likely be robust to this choice.

5. CONCLUSION

Multiscale entropy analysis of ambulatory interbeat-interval recordings from 214 subjects showed that a complexity index summarizing entropy across coarse-graining scales 1-20 distinguished young healthy, older healthy, and congestive heart failure groups with large, statistically significant effect sizes ($F(2,211) =$

154.7 , $p < 0.001$), and that intermediate-to-large scales accounted for 71% of the observed between-group variance compared to only 8% for conventional single-scale entropy. A classifier using multiscale complexity index achieved a cross-validated AUC of 0.91 for distinguishing heart failure from healthy aging, substantially outperforming single-scale entropy (AUC 0.76). These findings establish multiscale entropy, and particularly its intermediate-to-large-scale components, as a substantially more sensitive marker of both healthy aging and pathological autonomic dysfunction than conventional single-scale complexity measures.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

S.M. conceived the study, designed the multiscale entropy analysis pipeline, and led the writing of the manuscript. J.K. performed signal preprocessing, coarse-graining, and sample entropy computation. B.S. carried out the statistical analysis and classifier evaluation. All authors contributed to interpretation of the results and approved the final manuscript.

Ethics Statement

This study used only de-identified, retrospectively obtained interbeat-interval recordings with no linkage to identifiable personal information. All data handling followed institutional data-protection guidelines for de-identified physiological data, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Formal ethics committee approval was not required for this retrospective analysis of fully de-identified archival data.

Data Availability

The de-identified interbeat-interval recordings analyzed in this study were drawn from institutional archival records and are available from the corresponding author on reasonable request, subject to institutional data-sharing agreements.

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