Towards making Ireland the best place in the world to grow old

Associations between entropy in cardiovascular/neurovascular measures and frailty

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Data from:

- Nationally representative sample
- Over 8,500 participants
  - Running for 10+ years (est. 2009)

The most comprehensive study of ageing ever conducted in Ireland
Data collection every 2 years for interview, every 4 - 6 years for health assessment

SCQ: self-completion questionnaire
CAPI: computer-assisted personal interview
Health: TILDA health assessment

Wave 1: 2009-2011
Wave 2: 2012
Wave 4: 2016
Wave 5: 2018
Wave 6: 2020-2021

Refresh sample

Resting-state Cardiovascular / Neurovascular measures
Frailty is a biologically driven decrease in reserve and resistance to stressors.

It results from **collective declines across multiple physiological systems**.
**Frailty** causes increased vulnerability to adverse outcomes such as mortality, institutionalisation, falls, and hospitalisation\(^{[1-4]}\)

It is important to detect frailty early - *before* it manifests as a visible disability

Research has shown that interventions can delay and even reverse frailty, especially when it presents in the early stages\(^{[4,5]}\)

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\(^{[2]}\) Rockwood, K. et al. *Lancet* 1999  
\(^{[5]}\) Dent, E. et al. *Lancet* 2019  
\(^{[6]}\) Travers, J. et al. *Br J Gen Pract* 2019,
Entropy is a measure of the amount of ‘disorder’ in a closed system.

Higher Entropy indicates Greater Disorder.
Entropy can be used to quantify disorder in physiological signals.

In this study we used two methods: Approximate Entropy (ApEn) and Sample Entropy (SampEn).
Can we detect subtle signs of frailty in the neurocardiovascular system using signal entropy?..
Research Question:
Is cardiovascular and neurovascular signal entropy associated with pre-disability frailty status?
Fried’s Frailty Phenotype used: 5 Components

- Unintentional Weight Loss
- Low Physical Activity
- Slow Walking Speed
- Weakness (Grip Strength)
- Self-reported Exhaustion

Non-frail: 0
Pre-frail: 1-2
Frail: 3+
Active Stand Protocol

‘Rest’ - Participants laid supine for ~10 minutes
Active Stand Protocol

‘Rest’ - Participants laid supine for ~10 minutes

‘Challenge’ - Participants asked to stand (unassisted) as fast as possible
Active Stand Protocol

‘Rest’ - Participants laid supine for ~10 minutes

‘Challenge’ - Participants asked to stand (unassisted) as fast as possible

‘Recovery’ - Participants remained standing for 3 minutes
Continuously Monitored:

Near Infrared Spectroscopy (NIRS)
- Oxygenated and deoxygenated haemoglobin concentrations (O2Hb, HHb)
- Tissue Saturation Index (%TSI) (Frontal lobe, ~2cm below the scalp)

Finometer
- Beat-to-beat blood pressure (sBP, dBP, MAP)
- Heart rate (HR)
Approximate Entropy (ApEn)\textsuperscript{[1]} and Sample Entropy (SampEn)\textsuperscript{[2]} Analysis

- MATLAB (R2019a; The MathWorks Inc., Massachusetts, USA)
- Data down-sampled to 5Hz (1 minute windows)
- $m = 2$, $\tau = 1$ (@ 5Hz), and optimal $r$ derived via multiple iterations (ApEn)\textsuperscript{[3]} / $r = 0.15$ (SampEn)

\begin{align*}
\text{ApEn}(m, r, N) &:= \frac{1}{(N - m + 1)} \sum_{i=1}^{N-m+1} \log \frac{C_i^m(r)}{C_i^{m+1}(r)} \\
\text{SampEn}(m, r, N) &:= \log \left( \sum_{i=1}^{N-m} C_i^m(r) \right) - \log \left( \sum_{i=1}^{N-m-1} C_i^{m+1}(r) \right)
\end{align*}

Statistical Analysis

- STATA (v15.1; StataCorp, Texas, USA)

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\textsuperscript{[1]} Pincus et al. J Clin Monit 1991 \hspace{1em} \textsuperscript{[2]} Richman & Moorman Am J Physiol Heart Circ Physiol 2000 \hspace{1em} \textsuperscript{[3]} Chon et al. IEEE Eng Med Biol 2009
Demographics

Finometer: sBP, dBP, MAP, HR

\[ N = 2,645 \]
Age = 64.3 ± 7.7 years
53% Female

NIRS: TSI, O2Hb, HHb

\[ N = 2,225 \]
Age = 64.3 ± 7.7 years
52% Female
Entropy values were calculated for 1 minute sections of data from 'Rest', 'Challenge', and 'Recovery'. Shown here are example data from 3 participants with 'low', 'medium', and 'high' entropy in resting state systolic BP signals.
Main Findings

Significantly higher entropy in BP and HR signals for both Pre-frail and Frail individuals (vs. Non-frail)

- Higher entropy for Frail vs. Pre-frail

- Higher HR entropy results for ‘Challenge’ and ‘Recovery’ vs. ‘Rest’ data

- Higher entropy in TSI for Frail individuals during ‘Recovery’

* vs. non frail; ‘Fully Controlled’ - controlling for age, sex, education, antihypertensive medication, diabetes, cardiovascular conditions, smoking, alcohol, and depression
Discussion

Strengths

• Largest study to date (N = 2,225/2,645)
• First study to examine frontal lobe oxygenation entropy (as measured using NIRS) with the physical frailty phenotype
• Rich data available as part of TILDA meant that models could be comprehensively controlled
• Rich, continuously and simultaneously measured neurovascular and cardiovascular data allowed for the assessment of several physiological measurements, recorded within the same experimental paradigm.
Clinical Advantages of NCV Entropy Measure

The methodologies presented herein were specifically designed to be highly transferable for use in a clinical setting:

- 60s of data sufficient
- Resting-state - relatively quick and easy to measure
- Computationally fast – could provide an ‘at-the-bedside’ measure
- Easy to interrupt and track over time (single value measure)
- Quantitative and objective

Study Limitations and Future Direction

- Small N for Frail group
- Single signal scale investigated, multiscale?
- Cross-sectional design - Longitudinal tracking of entropy would be of interest to determine the clinical significance of these findings as well as causal direction of the relationship
Entropy in short length neurocardiovascular signals could provide a clinically useful marker of the multiple physiological dysregulations that underlie physical frailty.
Knight, SP, Newman, L, O’Connor, JD, Davis, J, Kenny, RA, Romero-Ortuno, R. *Associations between neurocardiovascular signal entropy and physical frailty* doi: 10.3390/e23010004 Entropy 2021; 23(1),4
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