Functional clustering of continuous cardiovascular and brain oxygenation signals during an active stand test in The Irish Longitudinal Study on Ageing (TILDA)

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In this study, we performed K-shape functional clustering of two non-invasive continuous cardiovascular (systolic Blood Pressure: sBP) and brain oxygenation (left frontal lobe Tissue Saturation Index: TSI) times series signals, simultaneously collected 20 seconds before to 40 seconds after an active stand (AS) test in 2158 participants of The Irish Longitudinal Study on Ageing. Both signals were normalised and adjoined prior to clustering, and the gap statistic method was used to determine the optimum number of clusters. Eight clusters were obtained and characterised. Cluster 5 (n=287) and Cluster 1 (n=173) were independently predictive of not reporting dizziness post-AS or falls after 8 years, and were characterised by complete (Cluster 5) or near-complete (Cluster 1) sBP recovery and a moderate/transient (Cluster 5) or large/sustained (Cluster 1) TSI overshoot. Cluster 3 (n=304) and Cluster 6 (n=326) were independently predictive of post-AS dizziness and had large sBP recovery deficit/lack of TSI overshoot (Cluster 3) or moderate sBP recovery deficit/TSI overshoot (Cluster 6). Cluster 8 (n=289) was the most multimorbid and showed both sBP and TSI recovery deficits. This data-driven approach produced clinically meaningful results and may help clinicians recognise combined neurovascular signatures of orthostatic regulation in older people, both in health and disease.

Keywords—functional clustering, K-shape, active stand, cardiovascular, brain oxygenation, signal coupling.

I. INTRODUCTION

In older adults, standing up from lying down causes a gravity-induced drop in blood pressure (BP) within the first 10 seconds that normally is counteracted during the following 20-40 seconds by both peripheral mechanisms to recover BP (e.g. increasing heart rate and constriction of small arteries), and cerebral autoregulatory mechanisms to avoid a reduction in brain oxygenation [1]. However, in pathological states these compensatory mechanisms may fail [2] increasing the risk of adverse outcomes such as dizziness on standing (orthostatic intolerance: OI) or future falls [3].

The active stand test is a procedure for assessing the spectrum of hemodynamic responses to standing in adults [4]. During an active stand, an individual's BP is continuously monitored using digital artery photoplethysmography. More recently, continuous near-infrared spectroscopy (NIRS) monitoring of the left frontal region (as a surrogate measure of brain oxygenation) has been added to the active stand test [5]. However, the combined understanding of these signals remains obscure, including the extent to which the cerebral autoregulation may be able to potentiate the peripheral post-stand BP-rising mechanisms, or even replace them when they are diseased; or the extent to which the peripheral BP-rising mechanisms may be sufficient when the cerebral autoregulation is diseased. In practice, this is likely to translate into different types of responses, but these combined signatures remain unknown.

As a branch of unsupervised machine learning, functional clustering is used to group functional data (such as time-series) into clusters based on their similarity in the functional space [6]. Functional clustering is a powerful tool that has been applied to a variety of fields, but not to data from the active stand experiment. In this study, we performed K-shape functional clustering of two non-invasive continuous cardiovascular (systolic Blood Pressure: sBP) and brain oxygenation (left frontal lobe Tissue Saturation Index: TSI) signals, simultaneously collected during an active stand test in 2158 participants of The Irish Longitudinal Study on Ageing (TILDA).

II. METHODS

A. Study population

Active stand and cross-sectional characterisation data was from wave 3 of TILDA (2014-2015). Details of the cohort have been described elsewhere [7]. Longitudinal outcomes were collected from waves 4 (2016), 5 (2018), and 6 (2022). Ethical approval for each wave was granted from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, Ireland. All participants provided written informed consent. All research was performed in accordance with the Declaration of Helsinki.

B. Active stand instumentation

Prior to standing, participants were asked to lay supine for 5 minutes, after which they stood up as quickly as possible (with assistance if required) and remained standing for 3 minutes. BP waveforms were measured continuously at 200 Hz using a non-invasive digital photoplethysmography-based Finapres® Finometer MIDI device (Finapres Medical Systems, Amsterdam, The Netherlands) and recorded via a 12-bit resolution analogue-to-digital converter, from which beat-to-beat systolic blood pressure (sBP), diastolic blood

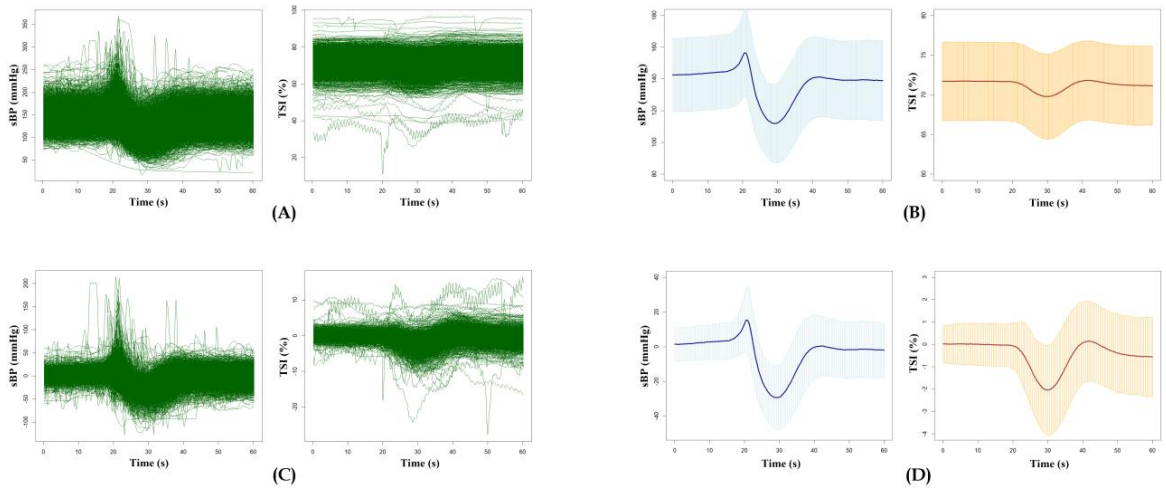

Fig. 1. (A) Plots of unprocessed time-series data of sBP (left) and TSI (right); (C) Plots of the changes in sBP and TSI over the baseline values of each participant; (B) and (D) are the plots of the mean with standard deviation of (A) and (C), respectively.

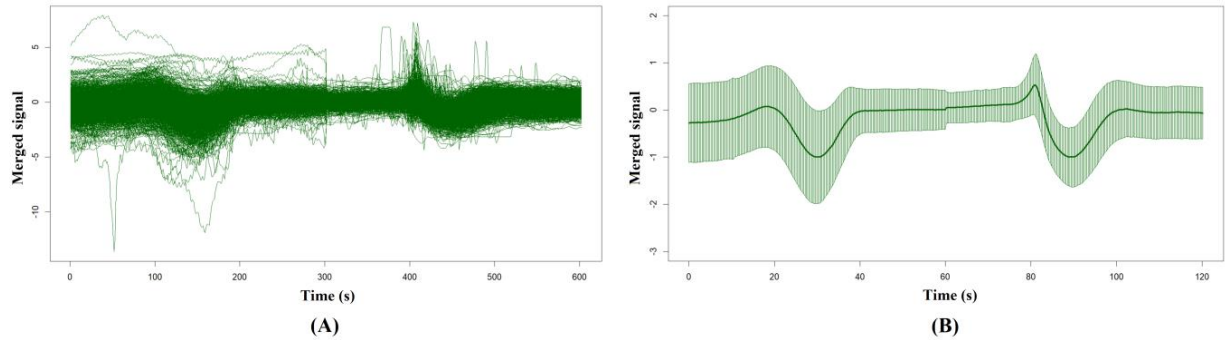

Fig. 2. Normalised reversed TSI and sBP signals were joined together as shown in (A). The mean with standard deviation plot in (B) shows a smooth connection between the two signals.

pressure (dBP) and heart rate (HR) were extracted. NIRS signals, namely oxygenated haemoglobin concentration (Oxy), deoxygenated haemoglobin concentration (Deoxy), and tissue saturation index (TSI), were recorded at 50 Hz with the PortaLite® device (Artinis Medical Systems, The Netherlands), affixed approximately 2 cm above the left eye. All measurements were carried out at an ambient temperature of 21 to 23 ˚C in a comfortably lit room.

C. Signal acquisition and pre-processing

A one-minute section of active stand data, from 20 seconds before to 40 seconds after standing, was used in this study. The beat-to-beat Finapres® NOVA signals were interpolated at 5 Hz and merged with the NIRS signals, which were down-sampled to the same frequency from 50 Hz. Plots of unprocessed and normalised time-series data, separately for sBP and TSI, are shown in Figure 1. To prepare them for K-shape clustering analysis, normalised TSI and sBP (time-series) signals were adjoined. As shown in Figure 2, the normalised TSI time series was reversed before the merge, to ensure a smooth connection between the two signals. This greatly reduced the difference in magnitude at the junction between the two signals.

D. Functional clustering

We implemented the K-shape functional clustering algorithm, developed by Paparrizos and Gravano in 2015 [8]. Like K-means, K-shape starts by initialising a predefined number of clusters and assigns each time-series to the corresponding cluster based on the distances to the updated centroid locations in an iterative fashion. However, unlike K-means (which groups data points based on positional information in the Euclidean space), K-shape uses shape-based distance (SBD) defined in (1) below:

$$SBD(\vec{x}, \vec{c_k}) = 1 - \max_{\omega}\left(\frac{CC_{\omega}(\vec{x},\ \vec{c_k})}{\sqrt{R_0(\vec{x},\ \vec{x}) \cdot R_0(\vec{c_k},\ \vec{c_k})}}\right) \quad (1)$$

where ω is the position at which the cross-correlation $CC\omega(\vec{x}, \vec{c_k})$ between each z-normalised sequence $\vec{x}$ and the centroid vector of each cluster $\vec{c_k}$ was maximised; R_0 is the geometric mean of autocorrelation of each individual sequence $\vec{x}$ or $\vec{c_k}$. Cross-correlation measures the degree of similarity between two sequences, in this case two time

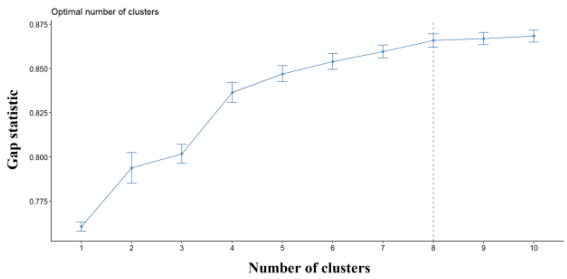

Fig. 3. Gap statistic plot of the merged TSI-sBP signals, which suggests that the optimal number of clusters is 8 (dotted line).

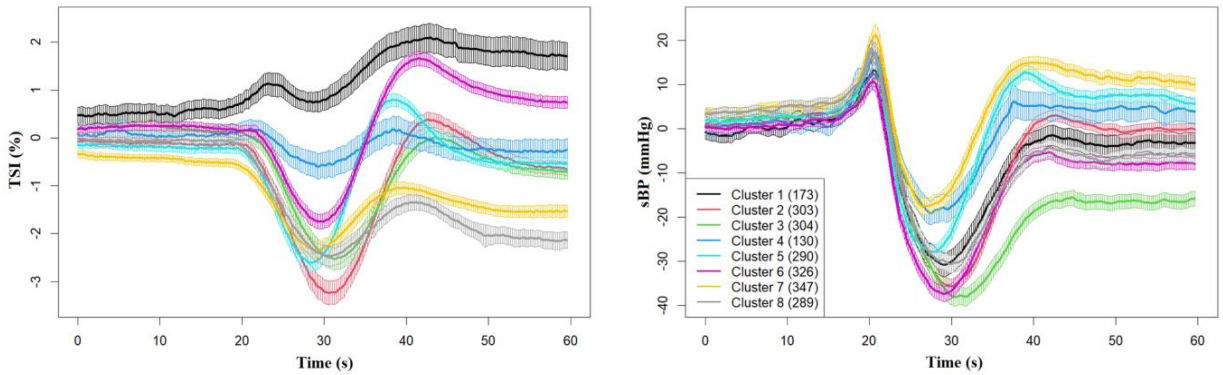

Fig. 4. Visualisation of the 8 clusters, separately for TSI (left) and sBP (right). For each signal, the mean is the solid line and the 95% confidence interval is the surrounding shaded area. Standing took place at 0 second, as shown on the x-axis in each plot.

series, calculated as a function of the displacement of $\vec{x}$ over the centroid of the cluster it belongs to, $\vec{c_k}$.

The K-shape clustering algorithm was implemented in the *dtwclust* package (version 5.5.11) in R version 4.0.5 using RStudio 2022.07.1+554 (Boston, MA, USA). The joined TSI_sBP data were entered into the K-shape algorithm, with type = "partitional", distance = "sbd", centroid = "shape" and the number of clusters set at 8 based on gap statistic measures for the data [9]. The R package *factoextra* (version 1.0.7) was used to compute the gap statistic. With the maximum number of clusters set to 10 and a bootstrap of 100, 8 was indicated as the optimum number of clusters for the data, as shown in Figure 3.

E. Characterisation of clusters

Statistical analyses for the characterisation of the clusters were performed with IBM® SPSS® Statistics Version 27 (IBM Corp., Armonk, NY). For overall comparisons across the eight clusters, one-way ANOVA was used for normally distributed continuous variables, the independent-samples Kruskal-Wallis test for non-normal continuous variables, and the Chi-square test for categorical variables. For further characterisation, binary logistic regression models were computed to see how each cluster independently predicted post-AS OI and future falls (i.e. any falls reported by wave 6, approximately 8 years later), whilst controlling for the following covariates: age, sex (1: male; 2: female), and self-reported history of hypertension (0: no; 1: yes), diabetes (0: no; 1: yes), heart disease (angina, heart attack or heart failure: 0: no; 1: yes), and cerebrovascular disease (stroke or TIA/mini-stroke: 0: no; 1: yes). Further logistic regression models were computed to see how each cluster was predicted by each of the above covariates. The significance level was set at $p<0.05$.

III. Results

2158 wave 3 participants were included (mean age 64.3 years, 54.5% women). The graphical overview of the 8 clusters (TSI and sBP separately) is shown in Figure 4. In Figure 5, additional NIRS (Oxy, Deoxy) and cardiovascular parameters (dBP and HR) are visualised for each cluster. Table 1 summarises the characterisation of the 8 clusters.

TABLE I. Cluster Characteristics

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 8	p
Cross-sectional characteristics (wave 3)									
Mean age (years)	64.2	65.1	66.1	64	62.4	64.1	63.4	64.8	<0.001*
Male sex (%)	51.4	58.1	45.4	44.6	47.4	52.8	32.1	35.3	<0.001#
Hypertension (%)	28.3	31.4	37.8	30.8	27.5	22.4	32.9	38.1	<0.001#
Diabetes (%)	5.8	7.9	8.2	6.2	2.4	6.4	5.8	7.3	0.130#
Heart disease (%)	2.3	7.3	1.6	6.9	2.1	3.1	2.6	6.6	<0.001#
Cerebrovascular disease (%)	4	3.3	2.6	3.8	3.5	1.8	4.3	6.6	0.120#
On antihypertensive medication (%)	36.4	39.6	44.7	35.4	28.9	28.5	37	43.9	<0.001#
Mean baseline sBP (mmHg)	143.2	139.1	143.3	140.7	141.3	141.9	137.8	142	0.028*
Mean baseline TSI	71.3	72	71.4	70.9	71.8	70.8	72.7	72.2	<0.001*
OI post-AS	23.1	28.7	37.2	27.7	21.6	35	30.6	30.8	<0.001#
Longitudinal outcome									
Any fall by wave 6 (%)	19.7	28.5	30.3	26.2	20.3	30.7	29.5	29.9	0.051#

[a.] * Independent-Samples Kruskal-Wallis Test; # Chi-square test; OI: orthostatic intolerance (self-reported dizziness); AS: active stand; sBP: systolic blood pressure; TSI: tissue saturation index.

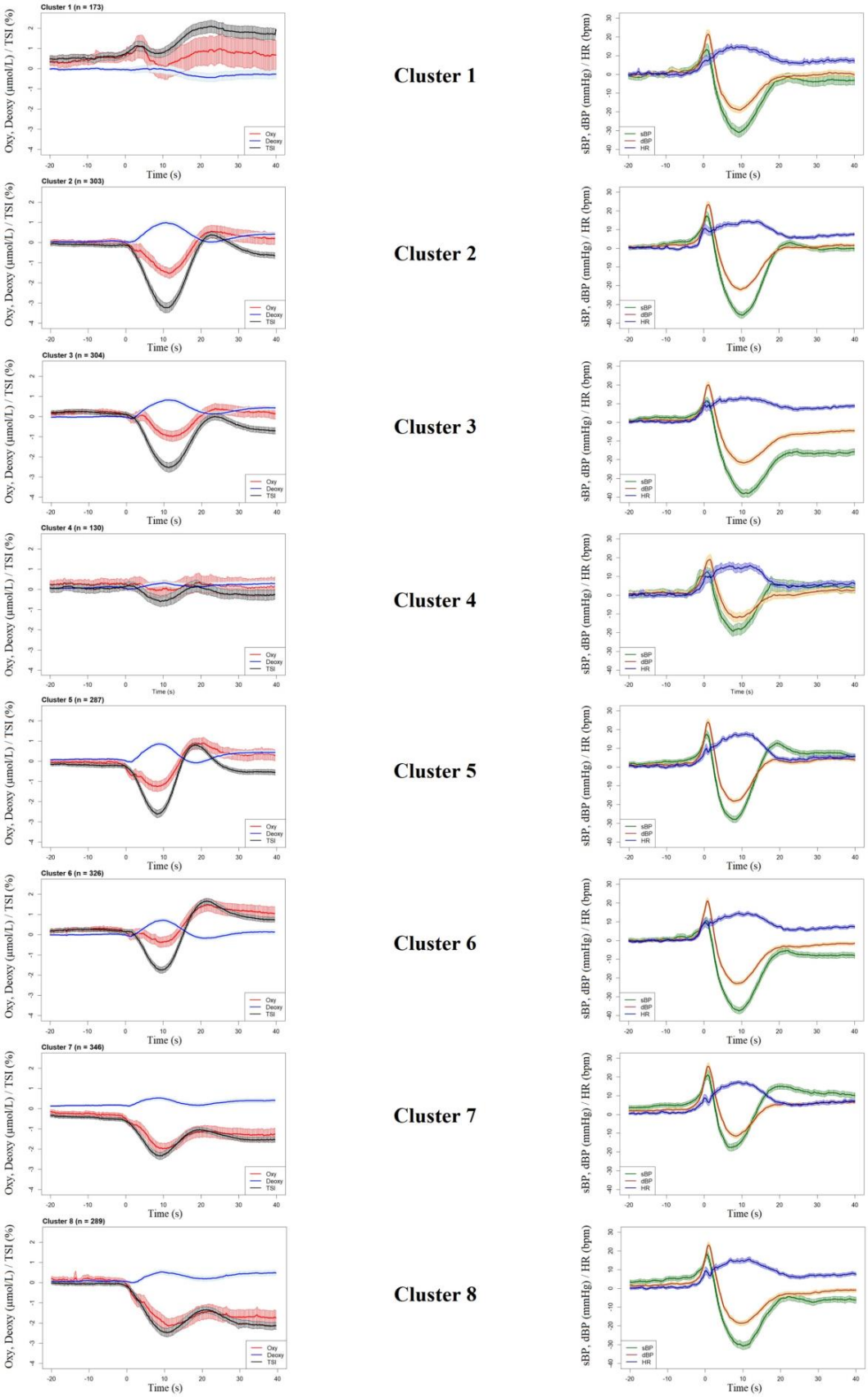

Fig. 5. Visualisation of the 8 clusters with additional parameters, including cerebrovascular signals: oxygenated haemoglobin concentration (Oxy), deoxygenated haemoglobin concentration (Deoxy); and cardiovascular signals: diastolic blood pressure (dBP) and heart rate (HR). For each signal, the mean is the solid line and the 95% confidence interval is the surrounding shaded area. Standing took place at 0 seconds in each plot.

In the logistic regression analyses, clusters independently predictive of not having OI or future falls were Cluster 5 ($p<0.001$ and $p=0.027$, respectively), and Cluster 1 ($p=0.037$ and $p=0.042$). Cluster 5 was independently predicted by younger age ($p<0.001$), and not having diabetes ($p=0.014$); and Cluster 1 was not predicted by any of the variables entered.

Clusters independently predictive of having OI were Cluster 3 ($p=0.002$) and Cluster 6 ($p=0.046$). Cluster 3 was predicted by older age ($p<0.001$), hypertension ($p=0.037$), and not having heart disease ($p=0.012$); whilst Cluster 6 was predicted by male sex ($p=0.002$) and not having hypertension ($p<0.001$).

Cluster 8 was the most multimorbid and was predicted by female sex ($p<0.001$), hypertension ($p=0.029$), heart disease ($p=0.043$), and cerebrovascular disease ($p=0.019$). Cluster 2 was predicted by male sex ($p<0.001$), and heart disease ($p=0.005$). Cluster 7 was predicted by female sex ($p<0.001$). For Cluster 4, there were no significant predictors.

No clusters were independently predictive of future falls.

IV. Discussion

In this study, we performed K-shape functional clustering of two non-invasive continuous cardiovascular and brain oxygenation signals in a large population-based sample. We aimed to gain new insights into their combined shape signatures, both in health and disease. Eight clusters were automatically obtained and characterised.

The "healthiest" cluster, 5, was characterised by complete sBP recovery and a transient TSI overshoot. In Cluster 1 (mildly incomplete sBP recovery and large sustained TSI overshoot), it is suggested that a healthy, vigorous cerebrovascular compensation was sufficient to avoid OI. In Cluster 4, a smaller, fully-recovered BP drop seemed to be easily compensated centrally. Perhaps Cluster 2 had larger BP and TSI drops due to its male predominance (faster standing), and the very mildly incomplete sBP recovery may have been due to higher prevalence of heart disease, but this seemed well compensated with a small TSI overshoot. In Cluster 6 (moderately incomplete sBP recovery with TSI overshoot), a healthy-looking TSI response may not have been sufficient to avoid OI given the larger sBP recovery deficit. In Cluster 3 (most predictive of OI), the very large sBP recovery deficit was insufficiently compensated by a TSI that recovered but did not overshoot, suggesting peripheral and possibly central regulation deficits. Cluster 7 (second highest proportion of cerebrovascular disease) could illustrate a more selective failure of the cerebral autoregulation. Clearly, Cluster 8 was the "unhealthiest" (most multimorbid) and showed both sBP and TSI recovery deficits, suggestive of combined failure of peripheral and central regulatory mechanisms.

A limitation is that causal relationships cannot be assumed given the observational design. Although none of the clusters was independently predictive of future falls, the two healthiest clusters (5 and 1) were predictive of not having future falls, reinforcing their healthiness.

In conclusion, this data-driven clustering approach produced clinically meaningful results and offers new insights into combined neurovascular signatures of orthostatic regulation in older people, both in health and disease.

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