One-dimensional statistical parametric mapping identifies impaired orthostatic cerebrovascular and cardiovascular response in frailty index

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Abstract

Background: Orthostasis is a potent physiological stressor which adapts with age. The age-related accumulation of health deficits in multiple physiological systems may impair the physiological response to orthostasis and lead to negative health outcomes such as falls, depression and cognitive decline. Research to date has focused on changes with orthostasis at prespecified intervals of time, without consideration for whole signal approaches.

Methods: One-dimensional statistical parametric mapping (SPM 1d) identified regions in time of significant association between variables of interest using a general linear model. Frailty index operationalized accumulated health and social deficits using 32-items from an computer-assisted interview. This study examined the association of frailty index on blood pressure, heart rate and cerebral oxygenation during an orthostatic test in a sample of 2,742 adults aged 50 or older from The Irish Longitudinal Study on Ageing.

Results: Frailty index was seen to be negatively associated with cerebral oxygenation changes from baseline over a period of 7 seconds ($p = 0.036$). Heart rate and systolic blood pressure were positively and negatively associated with frailty index over periods of 17 seconds ($p = 0.001$) and 10 seconds ($p = 0.015$) respectively.

Conclusions: SPM demonstrated these significant regions of cerebral oxygenation during orthostasis provide indirect evidence of impaired autoregulation associated with frailty. SPM also replicated prior relationships in heart rate and systolic blood pressure associated with a higher frailty index. These findings highlight the utility of one dimensional statistical parametric modelling in identifying significant regions of interest in physiological recordings.

Keywords:

fNIRS, orthostatic hypotension, heart rate response

Background

Frailty is a state of increased vulnerability to stressors and considered a consequence of multi-system physiological dysregulation over a lifetime. Frailty can be considered as phenotypic (i.e. robust, pre-frail and frail), according to the number of criteria present among slowness, weakness, exhaustion, unintentional weight loss and low physical activity (1). This phenotype is closely related to sarcopenia and impaired physical function (2). Alternatively, the frailty index considers the graded accumulation of health deficits (3) and is calculated as a ratio of deficits present in an individual from a pre-determined list of 30 or more. Deficits encompass a broader range of age-related abnormalities (including symptoms, signs, diseases, disabilities) than those which define the phenotype.

Although dynamic responses underpin the state of increased vulnerability i.e. frailty, the characteristics of dynamic responses to physiological stress have not been widely examined (4). Orthostasis is the act of achieving upright posture and is a physiological stressor repeated many times each day and across the lifespan. It requires an integrated neuro-cardiovascular response to maintain adequate blood pressure and subsequently end-organ (e.g. brain) perfusion (5). Hypotension in response to orthostasis has been considered as a final pathway of disordered physiology (6) and impairs cerebral function which commonly governs organ systems regulated via the autonomic nervous system. Prevalence of orthostatic hypotension increases with advancing age (7) and emerging evidence also suggests that orthostatic hypotension increases in frailty (8).

Impaired cerebral autoregulation is characterized by a mismatch between circulatory requirements of the brain and the ability of the body to generate and maintain brain blood flow requirements via neurocirculatory and humoral systems. Responses to physiological stress such as postural change, are determined by neuronal and hormonal responses to peripheral hemodynamic change (9). Maintenance of consistent cerebral oxygenation is critical for appropriate responses to stressors. The absence of this control highlights the bi-directional interdependence of these systems i.e. cerebral function controls peripheral haemodynamics and peripheral haemodynamic function controls cerebral autoregulation and perfusion (10).

To date, investigation of orthostatic response has been predicated on peripheral physiological measures, without direct evidence of central dysfunction. Frailty is associated with orthostatic hypotension and more impairments in blood pressure and heart rate recovery after standing (8,11,12). Heart rate variability is a marker of autonomic control and is attenuated in frail individuals (13). To our knowledge, continuous measurements of cerebral oxygenation coupled with peripheral hemodynamic changes have not been described before in frail individuals.

Statistical Parametric Mapping (SPM) is a form of vector-field analysis most commonly applied in the study of brain anatomy or functional brain activity (e.g. fMRI) (14). More recently this statistical approach has been validated for use in one-dimensional data (15) and is appropriate for use in temporal conditions (e.g. a measure which changes with time).

SPM 1d permits identification of regions significantly associated with the variable of interest. Traditional 'zero dimensional' statistical tests would be difficult to conduct at multiple time points (e.g. 1 second intervals) given the need to adjust for multiple comparisons. SPM 1d can utilize a general linear model and mitigates against type-1 and type-2 statistical errors (16) to assess this form of correlated data. Similar to fMRI, it is a method well suited to identifying regions in a physiological trace for further investigation and future quantification of effect size.

The aim of this study was to apply one-dimensional SPM in this novel context to examine the association of accumulated health deficits on blood pressure, heart rate and cerebral oxygenation during an orthostatic test in a large population sample of adults aged 50 or more from The Irish Longitudinal Study on Ageing (TILDA).

Methods

Participants

The Irish Longitudinal Study on Ageing (TILDA) is a nationally representative prospective cohort study of community dwelling adults aged 50 years and over residing in Ireland (17). It is designed using the Irish Geodirectory (a listing of all residential addresses in the Republic of Ireland) as a sampling frame. A random, clustered sample of addresses was chosen using the RANSAM system with residents aged ≥50 years and their spouses/partners (of any age) invited to participate in the study (n = 8,175). Ethical approval for TILDA was granted by the Health Sciences Research Ethics Committee at Trinity College Dublin, Ireland. All participants provided written informed consent prior to assessment. Data was collected via Computer

Aided Personal Interviewing (CAPI), self-completed questionnaire and a center- or home-based physical health assessment.

This analysis included participants who had completed the center-based health assessment and CAPI (n = 5,364) at wave 3 (March 2014 – April 2016). Individuals without valid continuous recordings during active stand were then excluded (leaving n = 2,820). Further exclusions were made for those younger than 50 years (n =30); MMSE less than 24, diagnosis of Alzheimer's disease or dementia (n = 38) and those with a diagnosis of Parkinson's disease, as this condition may cause autonomic nervous system impairment (n = 11).

Frailty

Frailty was operationalized as a frailty index (FI) encompassing 32 self-reported deficits which cover multiple dimensions of health in older adults (18,19). Deficits included within the FI calculation are provided in *supplemental table 1*. Dichotomous variables are considered in their original form where 0 = absent and 1 = present. Categorical variables are considered as five fractions of the all possible responses (range: 0, 0.25, 0.5, 0.75, 1; where 0 is no deficits and 1 is all deficits). In practice the calculation is considered valid where up to 20% of the measures are absent. In these instances, the denominator is altered from the total number of measure (i.e. 32) to the number of measures with complete responses. For visualization purposes, participants were classified as robust, pre-frail (cut-off: >0.10) and

frail (cut-off: >0.25) as per previous studies (19). FI was considered as a continuous variable in all statistical analyses.

Active Stand Protocol

In TILDA, the majority of participants attending the health center assessment during the third wave of data collection (2014–2015) completed an orthostatic test. This is an instrumented assessment described as an 'active stand' and has been reported on in this sample extensively elsewhere (20,21). Participants were asked to stand as quickly as possible following a period of supine rest for a duration of ten minutes. Participants with mobility difficulties were assisted by a research nurse if required. Continuous non-invasive beat-to-beat blood pressure was recorded using a Finometer MIDI device (Finapres Medical Systems BV, Amsterdam, The Netherlands) at a sampling rate of 200 Hz. Data recording was initiated during supine resting and extended for 180 seconds after the participant had achieved orthostasis. Baseline values are calculated using data in 60 to 30 second period prior to orthostasis. The beginning of the orthostatic test, estimated using an integrated height sensor, was set to time zero for each participant. Beat-to-beat systolic blood pressure (SBP) and heart rate (HR) were recorded. Nadir is the term employed in describing the initial drop in blood pressure following orthostatic change.

Near Infrared Spectroscopy

Real-time cerebral oxygenation was measured during the active stand using a continuous wave Artinis Portalite near infrared spectroscopy (NIRS) system (Artinis Medical Systems, BV, Zetten, The Netherlands). Implementation of this technique has been described

extensively in other settings (22) and also within TILDA active stand protocol (23). Briefly, an optical sensor on the patient's forehead (over the left frontal lobe) measures changes in concentrations of oxyhemoglobin (O2Hb) and deoxyhemoglobin (HHb) continuously at a rate of 50 Hz. This is possible as a consequence of human tissue demonstrating relative permeability to light in the near-infrared spectrum. Tissue saturation index (TSI) was calculated from values of O2Hb and HHb (Eq. 1) and considered as the primary measure of cerebral oxygenation in this study. TSI is a commonly used value for cerebral oxygenation, representing the ratio of oxygenated hemoglobin to the sum of oxygenated and deoxygenated hemoglobin detected.

Equation 1.

$$TSI = \frac{O2Hb}{O2Hb + HHb} \times 100$$

Statistical Analysis

Descriptive statistics were performed using STATA 15.0 (StataCorp, College Station, TX, USA) to demonstrate demographic and clinical characteristics of the cohort. Temporal analyses of peripheral and central physiological measures were conducted within Python 3.6 (Python Software Foundation, https://www.python.org/) using the bundled Iterated Design Learning Environment. Open-source package SPM1d 0.4 (http://www.spm1d.org/) (24) was used for the analyses and is dependent primarily on SPM8 (https://www.fil.ion.ucl.ac.uk/spm/), originally described by Friston et al. (14).

All data was examined as changes from baseline values established in a supine position prior to standing. Heart rate, systolic blood pressure and cerebral oxygenation data were resampled to 1 Hz, following which moving average and median filters were applied. The initial 30-second window after standing of data collected was analyzed using a 'region-of-interest' (ROI) approach (25). This *a priori* decision was justified given that the majority of participants normalize to their baseline values of cardiovascular function within this time-frame (21). This facilitates a more accurate estimation of the true within-region association. Inclusion of the resting period prior to and long after orthostasis in the SPM analysis would not be informative regarding the outcomes, as the cardiovascular curves of these resting periods are inherently flat in nature. The ROI chosen was justified given the extensive literature to date which examines the orthostatic response (i.e. increase in blood pressure (or heart rate), followed by an initial orthostatic drop and a final recovery to baseline).

The alpha level was set at 0.05 for all analysis and specific p-values are reported for each significant region of the curve analyzed. Univariate regression considered the association of higher frailty index on dependent variables. Multivariate regressions used the same model with the addition of covariates sex, age and an age-squared term (to account for potentially non-linear association with age). Residuals were inspected visually for normality of distribution, which was found to be the case. PP and QQ plots were also produced to confirm this which gave a linear fit of $R^2 = 0.97$. Sex was adjusted for given the well-described differences evident in frailty (26) and age was included to isolate the association attributed to the accumulation of deficits. One-dimensional SPM analysis returns regions of significance in the form of clusters. These are contiguous values over which the curve is

determined to be not consistent with random sampling (i.e. two clusters would indicate that two regions of contiguous values were significantly associated with the independent variable). Temporal range, reported in the results tables, is the period following standing (in seconds) over which significant associations with frailty index were identified. Extent is analogous with duration of this significant region of the curve and reported as seconds in our analysis.

Results

This analysis was conducted with a sample of 45.9% female participants, with a mean age of 64.4 years (± 7.7 years). Calculated values of frailty index for this sample ranged from 0 to 0.51 based on 32-items representing a range of health deficits, with a mean of 0.1 (± 0.08). According to Rockwood classifications based on frailty index (where >0.10 indicates pre-frailty and >0.25 indicates frailty); the majority of this sample were Robust (60.5%) or Pre-Frail (32.6%). Frail participants with the highest accumulation of health deficits represented 6.9% of the sample analyzed. Baseline summary statistics of heart rate, systolic blood pressure and tissue saturation index (measured using functional near-infrared spectroscopy [NIRS]) are provided in table 1. All reported findings are expressed in changes from this calculated baseline.

Using statistical parametric mapping, frailty index was seen to have a significant association with regions of heart rate, systolic blood pressure and cerebral oxygenation recordings when adjusting for demographic confounders (table 2). Using multivariate regression, the association with heart rate was significant ($p = 0.001$) over a period up to 17 seconds after

standing. Participants with higher frailty index demonstrated curves with lower heart rate recovery over this period (figure 1). There was a significant contralateral association with blood pressure for those with a high frailty index ($p = 0.015$). Higher systolic blood pressure values were recorded over the period from 5 to 15 seconds after standing (figure 2). This corresponds to lower magnitude nadir in peripheral pressures after achieving standing position.

In comparison to associations noted with heart rate and peripheral blood pressure, cerebral oxygenation was seen to be associated with frailty index at a later time-point (figure 3). Significant differences were observed between 20 to 26 seconds after standing ($p = 0.036$). Higher frailty index was associated with a reduced cerebral oxygenation ($t = -2.771$). This region is described as following the initial orthostatic nadir, where oxygenation appears to trend towards recovery to baseline. No significant difference in cerebral oxygenation were observed for participants with higher frailty index during the initial nadir, in contrast to blood pressure and heart rate.

Significant associations for covariates (age and sex) within the multivariate regression were noted across heart rate, systolic blood pressure and cerebral oxygenation. The duration and limits of these periods are detailed within the supplemental material. Supplemental figures 1-3 demonstrating statistical parametric maps with contrast vectors for age and sex are also provided for each peripheral and central hemodynamic variable.

Conclusions

For the first time, we demonstrate that frailty is associated with differences in cerebral oxygenation following orthostasis. Uniquely we utilized an application of vector field analysis, statistical parametric mapping, which detailed differences in neuro-cardiovascular responses to orthostasis.

Our group have previously reported an association between frailty phenotype and failure of stabilization of BP after orthostasis using beat to beat BP recordings and a linear spline approach within a mixed-associations model in the TILDA cohort (11). This built upon a prior univariate analysis in a convenience sample of older adults which emphasizes the importance of a beat-to-beat approach to BP measurement (12). The use of novel SPM analysis in this study is a major strength and provides evidence for further utilization of this technique in the field. Notably, the approach utilizes all the temporal data recorded from a recording device such as a Finometer. The significant regions of cerebral perfusion, blood pressure and heart rate change following orthostasis are identified as potentially subtle. With regards cerebral perfusion, a standard analysis utilizing only pre-specified arbitrary time-points (e.g. 5, 10, 20 seconds post orthostasis) would have potentially missed the signal identified using one-dimensional SPM.

In line with previous studies, we also demonstrated differences in peripheral hemodynamic parameters (i.e. blood pressure, heart rate) in the setting of orthostasis and frailty. Frailty index demonstrated an incremental slowing of heart rate in response to orthostasis. This

slowing effect was confined to the initial period following standing. These differences may represent a progressive deconditioning and/or autonomic decoupling of neurocardiovascular integration. In keeping with frailty being a predictor of mortality (27), early impairment in the vector of heart rate changes during orthostasis (within the same temporal window - 10 to 20 seconds) is a risk factor for cardiovascular disease and for all-cause mortality (28,29).

A novel finding is that there was a significant relationship between frailty index and cerebral oxygenation. A greater frailty index significantly decreased the tissue saturation index during the period 20 to 27 seconds following postural change. The timing and duration of this deficit is significant given that there is evidence to suggest that some latency exists in the ability of the cerebral blood flow to respond to peripheral changes (e.g. those brought about by orthostasis) (30). Ní Bhuachalla et al. propose that this neurocardiovascular instability may precipitate oxidative stress and a cascade-like effect, contributing to potential end-organ damage (31). Similarly, Canney et al. reported a relationship between kidney function and impaired orthostatic blood pressure control (32). These pathways may in turn contribute to impaired homeostasis of adequate end-organ oxygenation and predispose to further insult.

There is a growing quantitative data to support impaired physiological response to stressors which define frailty. Publications have focused on demonstrating relationships with biomarkers representing brain, endocrine, inflammatory, immune and metabolic and oxidative stress dysfunction (33). Wang et al. highlight the difficulties in attributing causation in these instances given the cross-sectional nature of the majority of studies.

Associations with frailty have been demonstrated in a variety of intrinsic physiological processes including diurnal cortisol variation (34) and muscle energetics, metabolism and repair (35). Kalyani et al. provide an example of impaired stressor response in frailty by exploring the performance in older women during oral glucose tolerance test (36). Dysregulation in these frail individuals is interpreted as physiological vulnerability and decreased reserve. Specifically related to haemodynamics our group reported impaired peripheral haemodynamic compensation following orthostasis in the TILDA study at baseline (11). The inability of cerebral autoregulation to account for these changes and maintain consistent tissue oxygenation as reported in this current study provides further evidence of decrement in homeostatic response in more frail individuals. This is proposed as a further indicator of health in ageing, adding to the broad collection of such markers already in use (37).

Exploration of cerebral blood flow or oxygenation in frailty has been limited to date. The cardinal study by Lutski et al. identified a differences in cerebral hemodynamics for patients with Fried frailty (38). Using breath holding index and transcranial Doppler to measure resting readings of cerebrovascular reactivity (divided into tertiles), an association was identified with incident frailty phenotype at two-year follow-up. The analysis was confined to individuals with cardiovascular disease. This analysis in TILDA presents results of a cross-sectional nature (frailty index was quantified at the same time-point as the health assessment) and a larger and more generalizable population. While breath-holding index utilized by Lutski may be considered a similar mild stressor (the key component in the definition of frailty), this TILDA analysis uses measurement of organ oxygenation directly as opposed to blood flow through a feeding artery (for which alternative compensatory

mechanisms may play a significant role). There is limited evidence to date comparing the interplay between cerebral oxygenation, frailty and white matter hyperintensity (WMH) burden. Given that frailty index and WMH burden are correlated (39), the results presented here suggest scope for WMH to be an underlying process, or consequence of, impaired cerebral oxygenation.

This study demonstrates the advantage of a one-dimensional approach to analysis of physiological signals over traditional methods, a technique usually applied to biomechanical analysis but of which the pre-requisites are also satisfied by hemodynamic trace measurements. Given the robustness of SPM analysis stemming from MRI research over the past three decades, this group suggests that adoption of one-dimensional statistical parametric mapping may be of benefit to this field of research. One-dimensional SPM facilitates hypothesis driven research using mathematical models which are well developed and extensively validated (40). SPM is reported to mitigate against regional conflation and *a priori* assumption of timepoints of interest (41). In this dataset, previous analysis of continuously measured blood pressure demonstrated moderate associations with frailty. This study has demonstrated that associations are distributed in a temporal manner which would not have been readily identifiable at discrete time-points. Furthermore, these differences are shown to be consistent across a single time period and not isolated at the time-points previously analyzed (i.e. 10, 20, 30 seconds etc.) (11).

Strengths of this analysis include the large population from which the data is collected. The impact of accumulated deficits (frailty index) on cerebral oxygenation has not been examined in such a large cohort to date. This analysis contributes significantly to the body of literature on frailty and neurocardiovascular instability. Similarly, this is the largest study to

date which implements one-dimensional statistical parametric mapping analysis. SPM use to date has been confined to smaller samples with limited ability to adjust for confounding variables. The combination of our large sample and detailed data on comorbidities allows for some generalizability of the results to the population from which they are sampled, namely older community dwelling adults.

This study is limited by measurement of frontal cerebral oxygenation without any objective measure of total brain area perfusion. However, literature on appropriate analysis of NIRS recordings note that there is good correlation between these two functions (42). NIRS is noted to have good correlation with transcranial doppler, a methodology used widely in the measurement of cerebral hypotension (43). The python implementation of the SPM toolbox does not enable survey settings to be applied to regression models. Therefore, we were unable to make use of the health assessment weighting and information on sampling strata within TILDA. Interpretations of the above findings should consider that participants who attended health center assessment were healthier than participants who did not. Effect sizes were not calculated in this analysis. Furthermore, the participants in TILDA present with relatively low accumulated deficits with 92.8% of participants being classified as Robust or Pre-Frail. A broader analysis of hospitalized or patients attending clinic may demonstrate more pronounced changes in peripheral and central cardiovascular function. Not examined in this study, an SPM1d analysis of frailty phenotype response to orthostasis would further elaborate on differences between the two cohorts. Use of three-level variables within the SPM regression toolbox were not validated at the time of analysis and therefore this research question was not explored. While not possible to date, integration of all neurocardiovascular data recorded during an activity such as orthostasis may provide a

comprehensive overview of the systematic response to an external stressor. Future studies should consider this approach and the potential role of one-dimensional SPM to achieve robust results.

In conclusion, this study demonstrates a dose-dependent relationship between the burden of health deficits and cerebral oxygenation in older adults. This finding provides further evidence to support progressive physiological dysregulation with maladaptive ageing, which has previously been shown to be linked with mortality and poor health outcomes (44). Evidence that physiological stressors in more frail individuals brings about relative oxygenation deficits could support a feed-forward process, whereby frailer individuals deteriorate in ageing at a more rapid rate than their healthy peers. We propose that further investigations into the role of white matter hyperintensities in such a process may be insightful. In addition to specific decrements in oxygenation, this analysis also provides support for the definition of frailty, whereby individuals express impaired ability to maintain homeostasis when faced with a mild physiological stressor (3). Results reported above for differences in heart rate, blood pressure and cerebral oxygenation response demonstrate that physiological regulation in these individuals is potentially a global phenomenon. This highlights the importance of assessing dynamic system response in frail individuals (45). Further exploration of deranged physiological systems in frail individuals may highlight further pathways of maladaptive ageing.

Conflicts of Interest

None.

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Table 1. Participant characteristics (n = 2,742)

	Robust (n = 1,659)	**Pre-Frail** (n = 894)	**Frail** (n = 189)
Age (years)	62.6 ± 7.0	66.7 ± 7.9	68.4 ± 8.1
Sex (% female)	48.8 %	42.1 %	38.0 %
Baseline Heart Rate (BPM)	64.9 ± 9.9	65.4 ± 9.8	67.1 ± 10.9
Baseline Systolic Blood Pressure (mmHg)	139.9 ± 20.5	142.5 ± 22.2	144.0 ± 22.7
Baseline Tissue Saturation Index (%)	72.7 ± 4.9	72.4 ± 5.0	72.5 ± 4.7

Table 2. Relationship between frailty index and hemodynamic function within 30 seconds of standing estimated by statistical parametric mapping

		Association of frailty index							
		Univariate Regression				*Multivariate Regression*			
	Clusters	**Temporal Range (s)**	**Duration (s)**	**t-value**	**p-value**	**Temporal Range (s)**	**Duration (s)**	**t-value**	**p-value**
Heart Rate	1	0.9 – 19.3	18.5	-2.56	0.0005	0.8 – 17.5	16.6	-2.56	0.0011
Systolic Blood Pressure	2	4.7 – 13.2	8.5	2.54	0.0218	5.3 – 15.6	10.2	2.54	0.0149
		18.4 – 24.4	6.0	-2.54	0.0328	-	-	-	-
Tissue Saturatio	1	17.7 – 29.0	11.3	-2.48	0.0199	20.1 – 26.9	6.8	-2.47	0.0363

n Index		

The alpha level was set at 0.05 for all analysis and specific p-values are reported for each significant region of the curve analyzed. Univariate regression considered the association of higher frailty index on dependent variables. Multivariate regressions used the same model with the addition of covariates sex, age and an age-squared term (to account for potentially non-linear association with age). Temporal range is consistent with the period following standing (in seconds) over which significant differences between curves were identified. Extent is analogous with duration of the significant region of the curve.

Figure Legends

Figure 1. **A.** Mean ± SD values of change from baseline in heart rate within 30 seconds of orthostasis. Separate traces are provided for frailty phenotypes (derived from values of frailty index). **B.** Statistical parametric map demonstrating the consecutive values (in seconds) of heart rate change from baseline for which frailty index is significantly associated. Notation *spm{t}* refers to the t-statistic and the threshold for significance is provided within the figure.

Figure 2. **A.** Mean ± SD values of change from baseline in systolic blood pressure within 30 seconds of orthostasis. Separate traces are provided for frailty phenotypes (derived from values of frailty index). **B.** Statistical parametric map demonstrating the consecutive values (in seconds) of systolic blood pressure change from baseline for which frailty index is significantly associated. Notation *spm{t}* refers to the t-statistic and the threshold for significance is provided within the figure.

Figure 3. **A.** Mean ± SD values of change from baseline in cerebral oxygenation within 30 seconds of orthostasis. Separate traces are provided for frailty phenotypes (derived from values of frailty index). **B.** Statistical parametric map demonstrating the consecutive values (in seconds) of cerebral oxygenation change from baseline for which frailty index is significantly associated. Notation *spm{t}* refers to the t-statistic and the threshold for significance is provided within the figure.

Figure 1

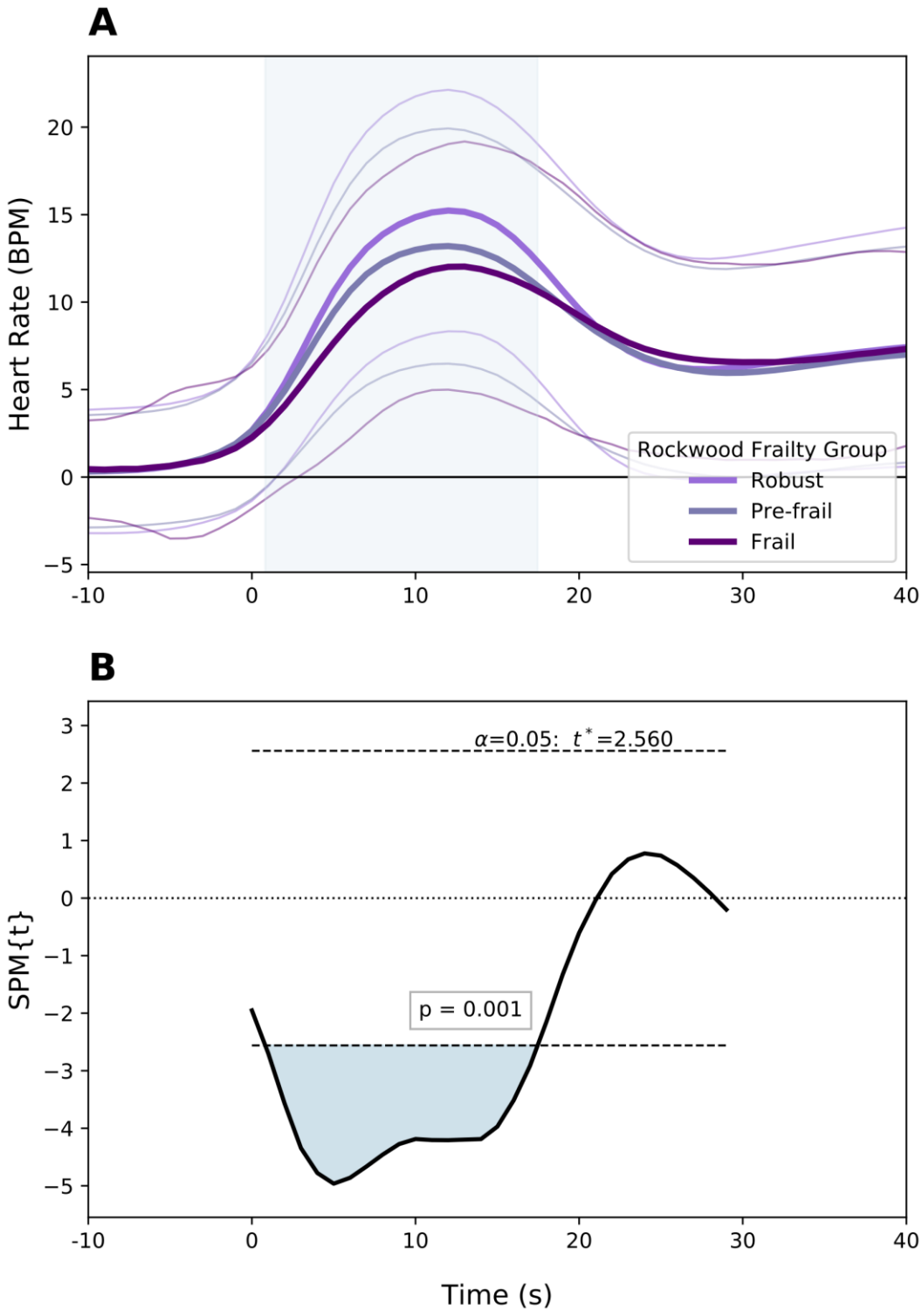


Figure 2

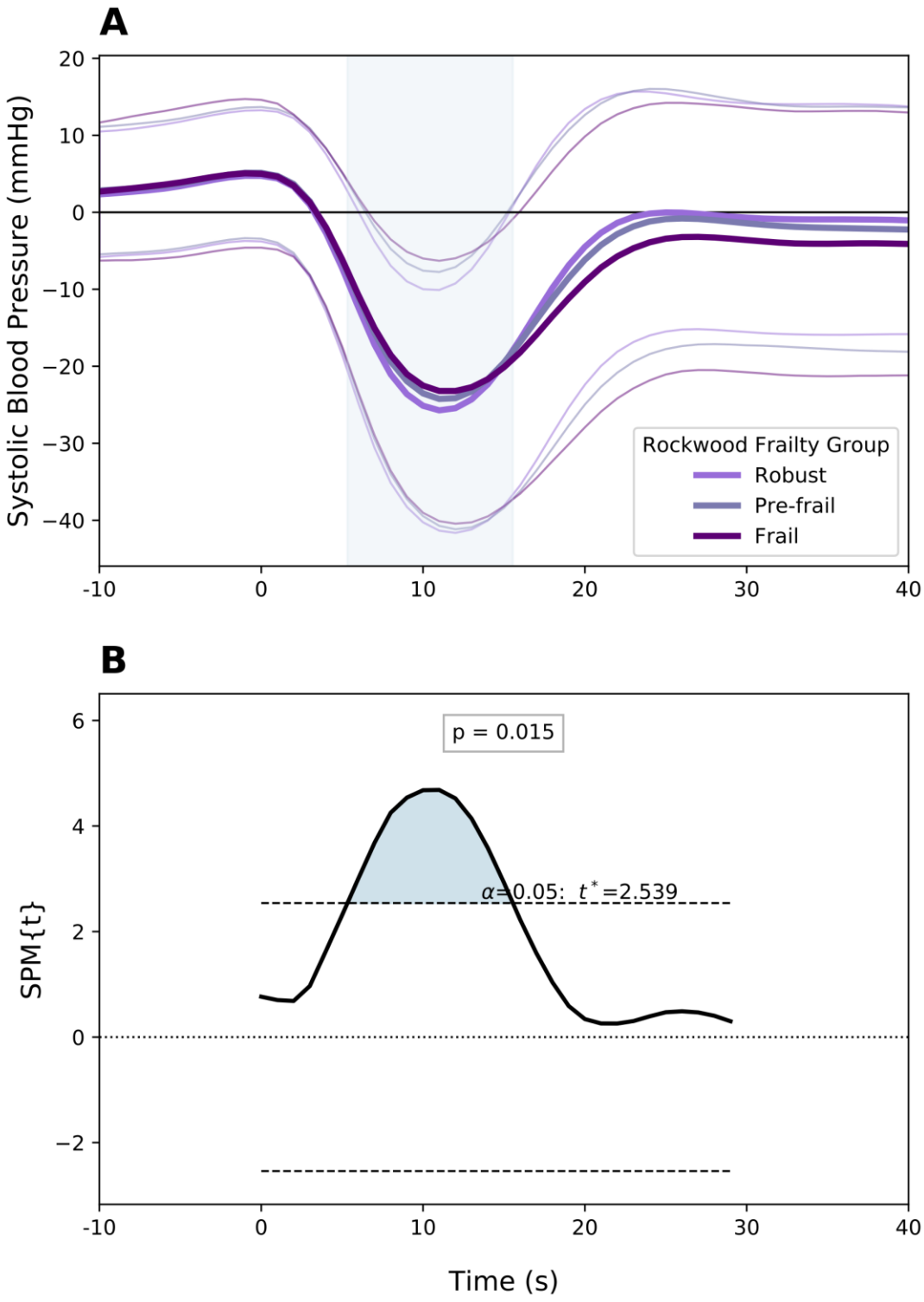
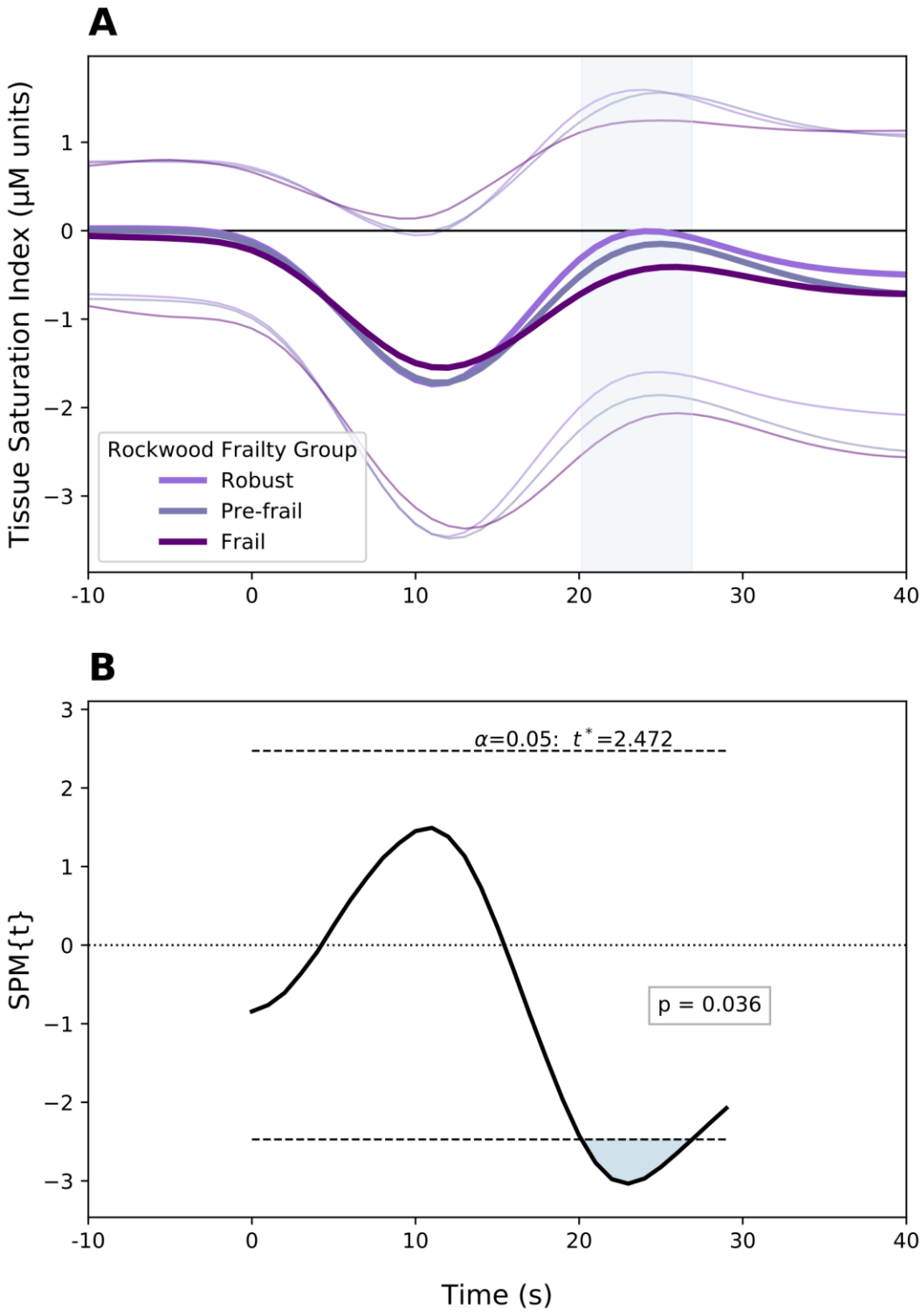
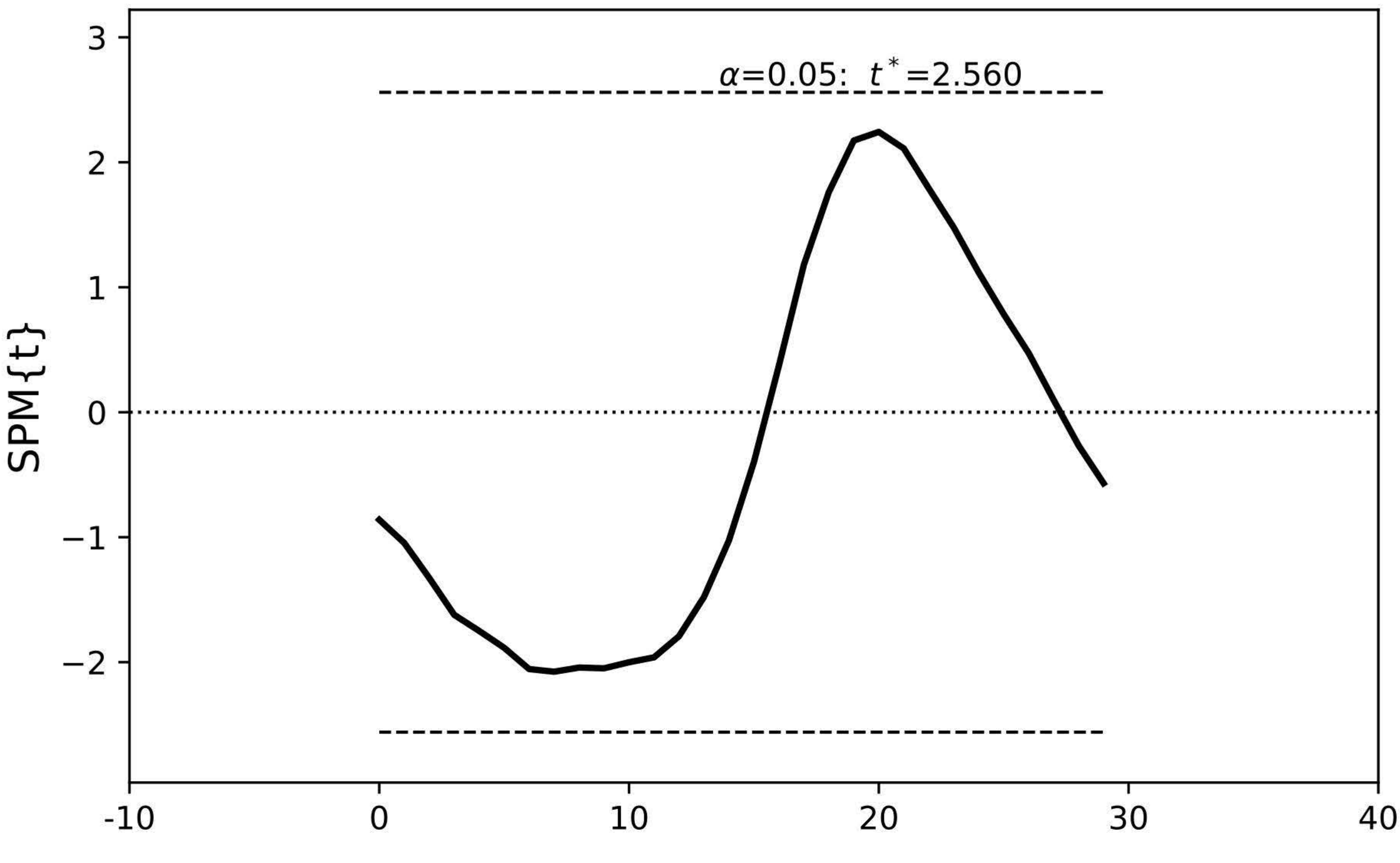


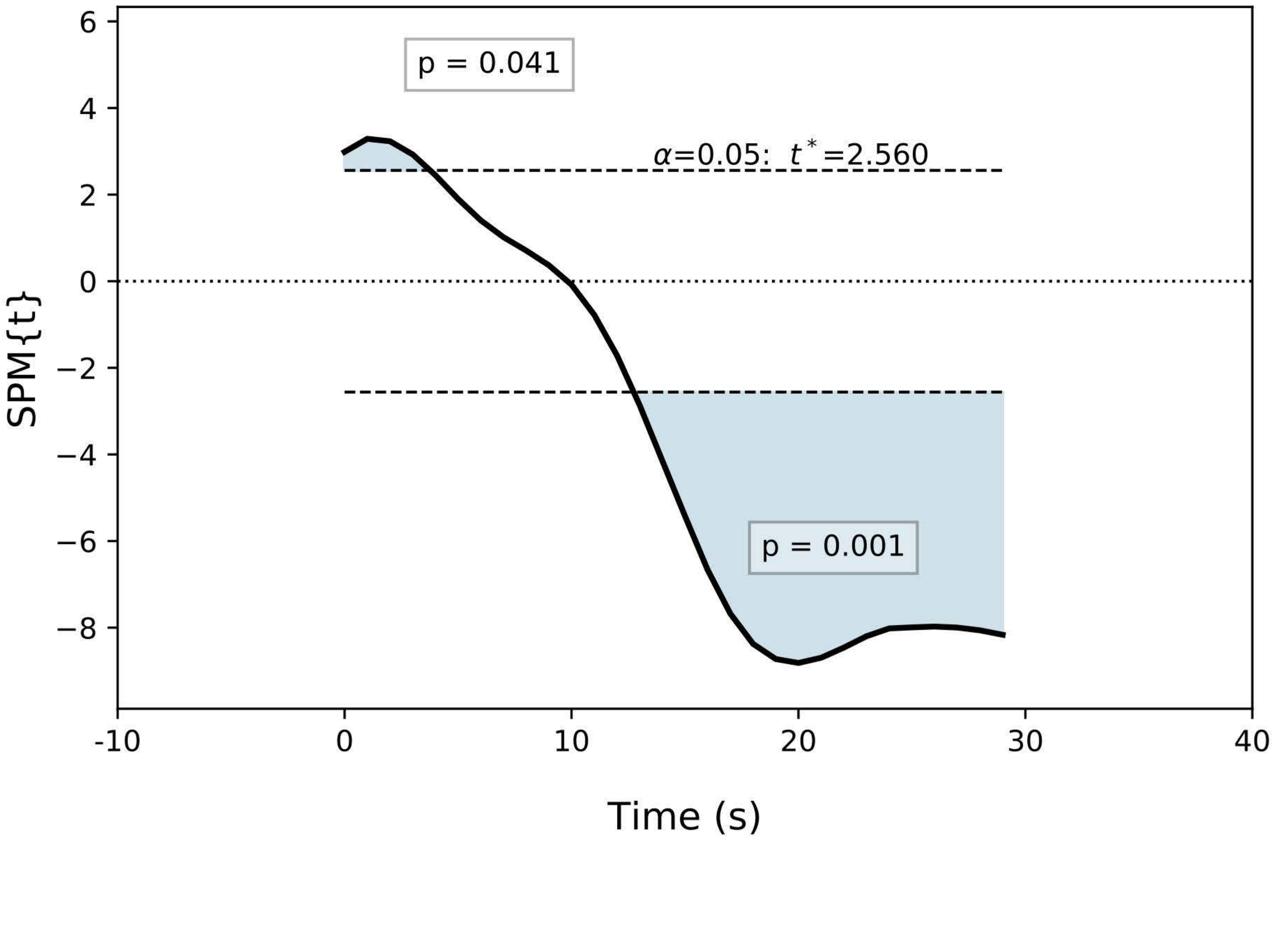
Figure 3



Age

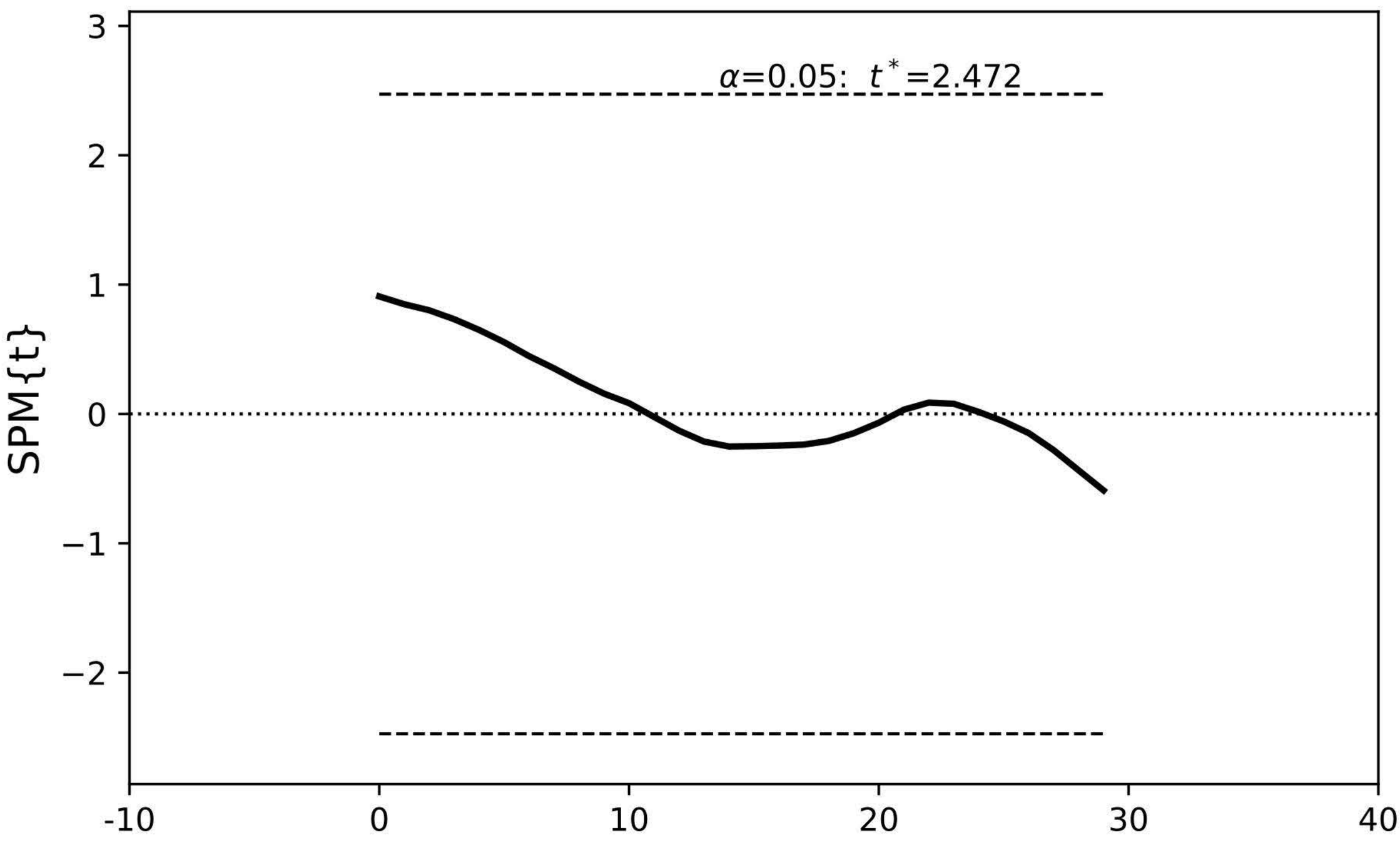

α=0.05: t*=2.560
SPM{t}
3
2
1
0
−1
−2
-10
0
10
20
30
40
Time (s)

Sex

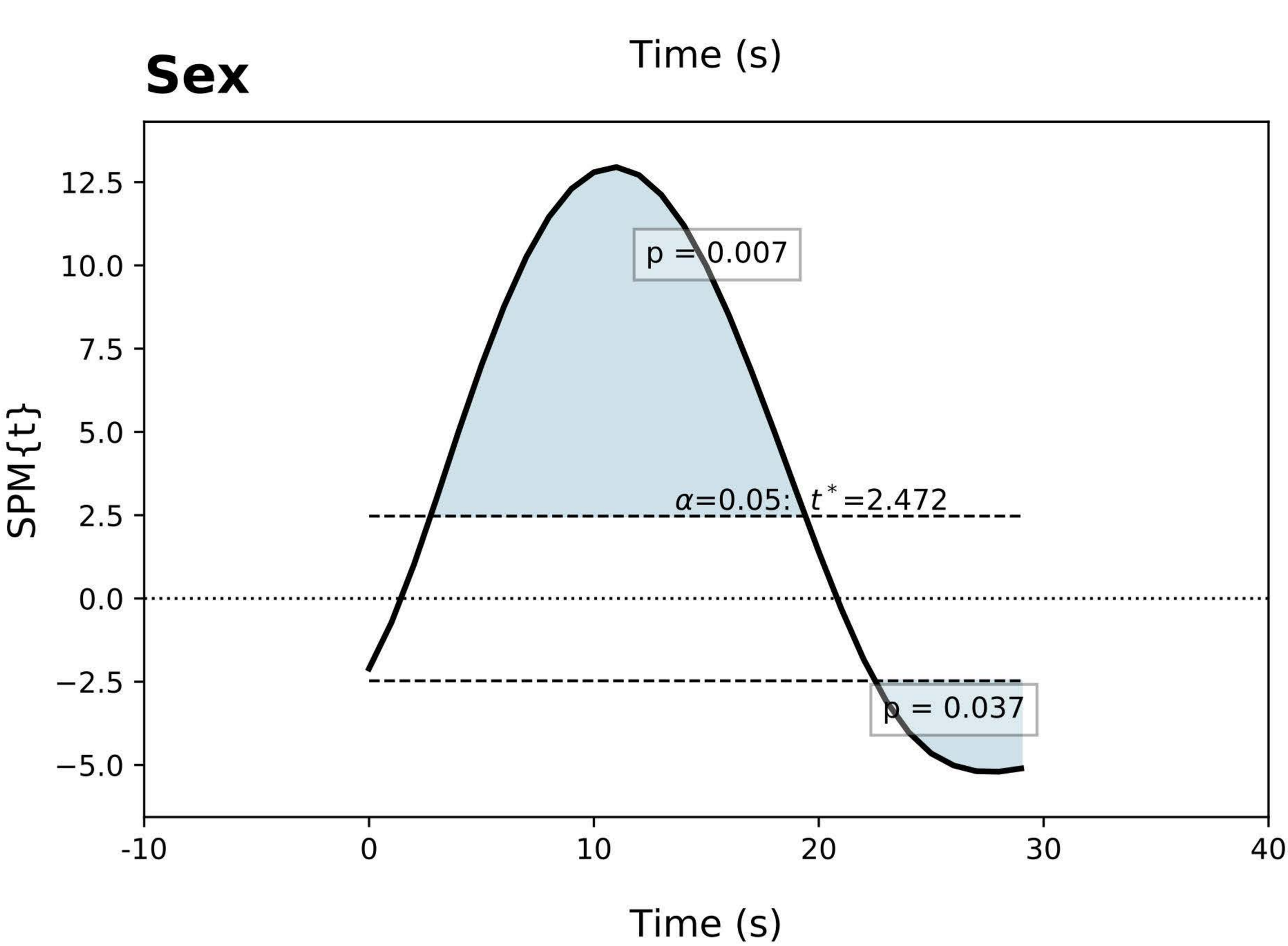

p = 0.041
α=0.05: t*=2.560
p = 0.001
SPM{t}
6
4
2
0
−2
−4
−6
−8
-10
0
10
20
30
40
Time (s)

Age
α=0.05: t^*=2.539
p = 0.004
SPM{t}
Time (s)
Sex
p = 0.046
α=0.05: t^*=2.539
SPM{t}
Time (s)

Age


α=0.05: t*=2.472
SPM{t}
3
2
1
0
−1
−2
-10
0
10
20
30
40
Time (s)

Sex


p = 0.007
α=0.05: t*=2.472
p = 0.037
SPM{t}
12.5
10.0
7.5
5.0
2.5
0.0
−2.5
−5.0
-10
0
10
20
30
40
Time (s)

Supplemental Data

1. Rationale of One-Dimensional Statistical Parametric Mapping

SPM facilitates a hypothesis driven approach to the analysis of experimental phenomena. There is no requirement to specify time-points of interest in one-dimensional SPM, an important advantage over traditional approaches to correlated data. Hemodynamic variables and measured cerebral perfusion as recorded during orthostasis are examples of continuous physiological data suitable for SPM analysis. Because SPM is a whole-signal analytical approach, it obviates the need (and possible subsequent controversies) of finding an 'optimum' cuff-off within an inherently continuous signal. Furthermore, as there is no need to smooth, average or ignore certain sections of data, SPM allows comparison of curves with high fidelity. SPM can be utilized to estimate significant differences between groups and estimate relationships using general linear model regression.

SPM1d does not require any further assumptions than traditional statistical tests. Namely;

1. Random sampling of participants: which is satisfied by the design of the TILDA study in-so-far as is possible;
2. Homologous data: Mean continua of the variables analyzed by SPM are often reported and therefore this criterion is presumed to be satisfied;
3. Normally distributed data: Tested implicitly by comparing statistical outputs from linear and non-linear SPM regression.

The suitability of SPM for analysis of the current data is supported by methodological consideration of covariance amongst vector components in the temporal dimension (i.e. across

the entire window of data analyzed each time point is not independent). One-dimensional residuals are calculated which represent the variance around mean trajectories. Field smoothness and size are examined, allowing computation of a critical threshold (t statistic) applicable to the entire window of data analyzed. Finally, random field theory is applied to compute the probability that this threshold will be crossed (field-wide p-value). According to SPM nomenclature, regions which reach this critical threshold are reported as 'clusters' with an accompanying cluster-specific probability (p-value).

In practice, a statistical parametric map was calculated for each dependent variable (physiological measure). Random Field Theory was then utilized to estimate the critical threshold above which equally smoothed random data would cross in 5% of cases subsequent to the specified alpha level (i.e. 0.05). The field-wide probability (p-value) that smooth random data would reach the calculated threshold is supplied. The extent (i.e. duration in seconds), location (i.e. seconds since orthostasis) and cluster-specific probability (p-value) are then reported for each cluster. Clusters of values reaching the critical threshold within the statistical parametric map have an implicit probability < 0.05. Therefore, only if no significant cluster was identified would reported p-values be in excess of the supplied alpha.

For the purpose of statistical inference general linear models (GLM) were specified within SPM1d. Model 1 was a univariate analysis of the association between frailty index (linear values) and each dependent variable (i.e. systolic blood pressure, heart rate and cerebral perfusion). Model 2 added a further term to adjust for sex differences, age and age squared term (to account for potential non-linear effects of age). The residual was retained in all models. This analysis was limited to applications of general linear models within SPM given that only a single orthostatic test is available per participant. Where multiple recordings of orthostatic test

were recorded per participant, the use of Hotellings T2 within SPM may have provided increasingly robust and generally applicable results. This is due to the one-sample per participant which was acquired during TILDA health assessment. Repeated testing of orthostatic response in individuals would facilitate more complex methods of statistical analysis. The python toolbox of SPM1d provides an output of the statistical parametric map for one variable of interest. The physiological measure in each model was determined as the variable of interest. In addition to the tables created from the statistical outputs, the accompanying graphics are provided in the main document.

2. Components included for calculation of frailty index

Supplemental Table 1. Frailty index components (32 items)

Difficulty walking 100 meters	Intrusive pain
Difficulty running or jogging 1.5 km	Knee pain
Difficulty rising from a chair	Urinary incontinence
Difficulty climbing several flights of stairs	Hypertension
Difficulty climbing one flight of stairs	Angina
Difficulty stooping, kneeling or crouching	Heart attack
Difficulty reaching above shoulder height	Diabetes
Difficulty pushing/pulling large objects	Stroke
Difficulty lifting/carrying weights (> 10 lbs.)	Transient Ischemic Attack (TIA)
Difficulty picking up a coin from a table	Irregular heart rhythm
Difficulty preparing a hot meal	Hypercholesterolemia
Difficulty with household chores	Other cardiovascular disease
Difficulty shopping for groceries	Cataracts

Feeling lonely	Age-related macular degeneration
Poor self-rated physical health	Lung disease
Poor self-rated vision	Arthritis
Poor self-rated hearing	Osteoporosis
Difficulty following a conversation with one person	Cancer
Daytime sleepiness	Varicose ulceration
Polypharmacy	

3. Statistical parametric maps for covariates within the multivariate regression for cerebral oxygenation, heart rate and systolic blood pressure

One-dimensional SPM are provided for each variable of interest. Contrast vectors were amended to demonstrate the association of each covariate with the variables of interest. Note that the associations reported here are from the same multivariate regression including frailty index, sex, age and age-squared terms.

With respect to **heart rate**, female sex showed an association during the period from 0 to 4 seconds ($p = 0.04$) and 12 to 29 seconds ($p = 0.001$) following orthostasis (supplemental figure 1). These participants were noted to have a lower heart rate during the 17 seconds within the recovery period following nadir. The initial 4 second period extended from the beginning of the region for analysis and indicates a higher heart rate during the initial drop associated with orthostasis. No association was identified for age.

Systolic blood pressure and age demonstrated a significant association over a singular region extending 15 seconds ($p = 0.004$). Female sex was also associated with high blood pressure over a 3 second period ($p = 0.04$) consistent with initial period following orthostasis.

Tissue saturation index was seen to show associations with sex over two distinct periods; 3 to 19 seconds ($p = 0.007$) and 22 to 30 seconds ($p = 0.037$). Age was not seen to be associated with cerebral oxygenation in this model.

Figure Legends

Supplemental Figure 1. Statistical parametric map demonstrating the consecutive values (in seconds) of heart rate change from baseline for which age (above) and sex (below) are significantly associated. Notation *spm{t}* refers to the t-statistic and the threshold for significance is provided within the figure.

Supplemental Figure 2. Statistical parametric map demonstrating the consecutive values (in seconds) of systolic blood pressure change from baseline for which age (above) and sex (below) are significantly associated. Notation *spm{t}* refers to the t-statistic and the threshold for significance is provided within the figure.

Supplemental Figure 3. Statistical parametric map demonstrating the consecutive values (in seconds) of tissue saturation index change from baseline for which age (above) and sex (below) are significantly associated. Notation *spm{t}* refers to the t-statistic and the threshold for significance is provided within the figure.