Comparison of autonomic signals between healthy subjects and chronic low back pain patients at rest and during noxious stimulation

S. Moscato[1,2], W. Zhu[1], Y. Guo[1], S. Kamarthi[1], C. A. Colebaugh[3], K. L. Schreiber[3], R. R. Edwards[3], R. D. Urman[4], Y. Xiao[5], L. Chiari[2,6], and Y. Lin[1*]

[1]*Intelligent Human Machine Systems Lab, Mechanical and Industrial Engineering Department, Northeastern University, Boston, MA, USA*
[2]*Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi" (DEI) University of Bologna, Italy*
[3]*Department of Anaesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard University, Boston, MA, USA*
[4]*Department of Anaesthesiology, College of Medicine, The Ohio State University, OH, US*
[5]*College of Nursing and Health Innovation University of Texas at Arlington TX, Arlington, TX, US*
[6]*Health Sciences and Technologies - Interdepartmental Center for Industrial Research (CIRI-SDV), University of Bologna, Italy*
[*]*The Corresponding Author: yi.lin@northeastern.edu*

***Abstract*—Chronic pain is a major cause of disability worldwide. While acute pain may serve as a protective function, chronic pain and the associated changes in neural processing negatively impact function and quality of life. This neural plasticity may include changes to the autonomic nervous system (ANS) potentially detectable as changes in various physiological signals. Our aim is to evaluate differences in the physiological signals reflecting ANS changes, by comparing healthy subjects and patients with chronic low back pain during standardized pain stimuli. We extracted several features from photoplethysmography (PPG), electrodermal activity (EDA), and respiration, both at rest and during a repeated pinprick test. We found significant group differences in some PPG parameters at rest and in response to the repeated pinprick test. Chronic pain patients had consistently higher basal sympathetic activity, as well as a blunted autonomic response when subjected to nociceptive stimuli.**

***Keywords*—Pain assessment, physiological signals, autonomic nervous system.**

I. Introduction

Pain is an "unpleasant sensory and emotional experience associated with, or resembling that is associated with, actual or potential tissue damage" [1]. Different types of pain can be experienced. One of the main distinctions is between acute and chronic pain.

Acute pain is the pain arising from the activation of nociceptors when a thermal, mechanical, or chemical nociceptive stimulus affects the body. Noxious stimuli activate neural transduction at the peripheral, spinal, and brain level, collectively falling under the concept of "pain neuromatrix". Acute pain has a protective function to the body, acting as an alarm bell for a potential threat [2].

On the other hand, chronic pain is defined as persistent or recurrent pain that lasts for more than three months [3]. It is now well known that chronic pain leads to a significant neural plasticity [4], with substantial functional and anatomical changes to reach a new equilibrium different from that of healthy subjects [5]. Chronic pain does not serve a protective function, being maintained despite the absence of the inciting stimulus, and is associated with physiologic and psychosocial changes [6].

Manifestations of physiologic change may include activity of the Autonomic Nervous System (ANS). Pain and ANS are anatomically and functional linked, as pain influences the activity of ANS and vice versa [7]. In the case of chronic pain, previous studies have observed decreased ANS reactivity, potentially leading to a reduced ability of the body to promptly respond to internal and external stimuli [8].

ANS activity can be evaluated by monitoring some physiological signals, commonly called "autonomic" signals precisely because of the ANS' regulation of them. Examples of these signals are Photoplethysmography (PPG), representing the blood volume changes occurring at each heartbeat, Electrodermal Activity (EDA), referring to variations of the electrical properties of the skin due to sweat secretion, and Respiration (Resp).

Autonomic signals have been extensively used in "emotion recognition" studies so far, representing a new way to analyse emotions, and increasingly bridging the gap in human-computer interaction [9]. Gaining greater facility with measurement of fluctuations and variability of autonomic signals under the condition of pain transduction is twofold: from a clinical point of view, this may allow insight into the impact of nociceptive activation on physiology, both in the acute and chronic phase ; from a more technical point of view, it would allow to better tailor algorithms to more sensitively detect a wide variety of painful stimuli in different individuals, and to distinguish the extent of neural remodeling inherent in an individual with chronic disease.

The aim of this study is to explore differences in autonomic signals by comparing healthy control (HC) subjects and chronic Low Back Pain (cLBP) patients i) under rest conditions and ii) when stimulated with a noxious stimulus. This is a further work based on the Intelligent Human Machine System (IHMS) laboratory's exploration work in the past [10], [11].

II. Materials and Methods

A. Protocol

The study involves enrolment of both HC subjects and cLBP patients. The inclusion criteria in common for the two samples are the following:

- 18 years or older
- No evidence of neurological and/or cognitive impairment
- No history of myocardial infarction or other serious cardiovascular condition in the prior 12 months
- Ability to speak sufficient English to complete questionnaire measures.

In addition, HC subjects had to be free of any history or diagnosis of chronic pain. cLBP patients were required to have a history of cLBP for at least 3 months, with an average pain intensity higher than 3/10.

The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, MA, USA, (protocol code2019P002781, 18/11/2019). The protocol included Quantitative Sensory Testing, where defined nociceptive stimuli are applied in a clinical lab setting to assess pain transduction across a variety of modalities.

For the purpose of this study, two experimental conditions have been evaluated:

- Rest: as a baseline, the participant is asked to remain quiet for 1 minute while the signals are recorded
- Repeated, mildly to moderately painful, punctate mechanical stimuli: the participant is non-invasively stimulated with a weighted, fine metal probe on the right hand, 10 times in a row at 1 Hz frequency. The stimulus intensity is tailored to an individual's pain sensitivity, choosing a probe weight that induces mild pain upon single stimulation.

B. Autonomic signals

In the following, the recorded autonomic signals are presented, together with the pre-processing applied to each of them.

All signals used in this study have been recorded with the Flexcomp system, with a sampling frequency of 256 Hz.

PPG sensor is placed on the left hand's middle finger. The recorded signal has been subjected to a 5th order Butterworth band-pass filter, with [0.5 12] Hz as cut-off frequencies. The filtered PPG signal has been then segmented into PPG pulses by detecting systolic feet [12]. Each pulse was then normalized with a z-score procedure.

EDA has been recorded through electrodes placed on the left hand's ring and index finger. EDA signal has been subjected to a 5th order low-pass Butterworth filter, with 1 Hz as cut-off frequency. We applied a z-score normalization procedure on a subject basis and then we extracted the tonic and phasic component by using the *cvxEDA* algorithm [13].

Respiratory signal was recorded using a band placed around the low chest. The signal has been subjected to a 4th order Butterworth low-pass filter, with 0.1 Hz as cut-off frequency. We implemented the Advanced Counting Method to detect the respiration cycle [14].

C. Autonomic parameters extraction

For the baseline recording, features have been extracted by the whole recording (i.e., 1 minute).

For the repeated pinpricks test, the recording has been segmented into four phases:

- Pre-test: 5 seconds before the beginning of the test
- Between 1st and 5th repetition (5 seconds)
- Between 5th and 10th repetition (5 seconds)
- Post-test: 5 seconds after the end of the test

Twelve parameters have been extracted from the analysis of PPG pulses:

- Heart Rate Variability (HRV) analysis - we estimated the Interbeat Intervals (IBIs) as time differences between two consecutive systolic feet (i.e., the minimum point of a PPG pulse). The obtained IBIs time series has been then filtered by using the approach described in [15]. Extracted HRV parameters are mean value of IBIs (meanIBI), standard deviation of normal heartbeats (SDNN), root mean squared of successive differences (RMSSD), Poincaré plot standard deviation perpendicular (SD1) and along (SD2) the line of identity.
- Morphological analysis: by analysing the morphology of each PPG pulse, we estimated PPG pulse amplitude (PulseAmpl), area under the curve between systolic foot and successive systolic peak (A1), area under the curve between the systolic peak and the successive systolic foot (A2), area under the PPG pulse (A), time between systolic foot and the successive systolic peak (T1), time between systolic peak and the successive systolic foot (T2) [16].

For the EDA, we estimated a total of 8 parameters:

- Whole EDA signal: mean (meanEDA) and standard deviation (stdEDA), and the symbolic information entropy (SIE) [17]
- Tonic component: mean (meantonic) and standard deviation (stdtonic)
- Phasic component: relevant peaks have been retrieved as those peaks with a slope (by analysing the first derivative) higher than 0.01. From the relevant peaks, the mean (meanampEDR) and standard deviation (stdampEDR), together with the frequency (freqEDR) expressed as number of peaks per minute have been retrieved.

For the Resp signal, we retrieved the mean respiration rate (meanRR). Since we used the Advanced Counting Method as an automatic algorithm to detect the respiration cycle, we discarded those estimates exceeding 30 breaths/min.

D. Statistical analysis

To compare the parameters during the rest condition between HC subjects and cLBP patients, we used a Mann-Whitney U test. To assess any statistical differences in different phases during repeated pinprick test, we used a Wilcoxon signed-rank test for paired data by comparing rest and pain phases. We applied a Bonferroni correction for the multiple comparison for the repeated pinprick test, resulting in a corrected significance level of 0.05/6 = 0.008.

III. RESULTS

A. Dataset

Twenty-three subjects were enrolled in this study, 15 HC subjects (age 27.20 ± 11.58, 4 M, 11 F) and 9 cLBP patients (age 43.67 ± 14.97, 4 M, 5 F). Recordings failed for one cLBP patient, who therefore was not included in the analysis.

B. Baseline recording

Results about the comparison between HC subjects and cLBP patients are presented in Table 1.

By analysing the baseline recordings, mean IBI, A2, A, and T2 were significantly different between HC subjects and cLBP patients, such that all these parameters are significantly lower for cLBP patients than for HC subjects.

C. Repeated pinpricks test

We compared the four different phases of the repeated pinpricks test separately for HC subjects and cLBP patients. Below, and in Figure 1, are the significant changes in

autonomic variables:

- Mean IBI for HC subjects: significantly higher values were detected during the 5th-10th rep phase, compared to pre- and post-test, and a significant decrease from 1st-5th rep to post-test.
- SDNN, RMSSD, and SD1 for cLBP patients: significant lower value from the pre-test to post-test.
- A for cLBP patients: significant decrease from the pre-test to 1st-5th rep and 5th-10th rep.
- T2 for HC subjects: significant increase by comparing 1st-5th rep with 5th-10th rep and post-test.
- meanEDA and meantonic for HC subjects: significant lower values in pre-test compared to all the other phases.
- stdEDA and stdtonic for HC subjects: significant decrease from 1st-5th rep to post-test.
- SIE for cLBP patients: significant decrease from 1st-5th rep to post-test.
- stdampEDR for HC subjects: significant decrease from 5th-10th rep to post-test.
- freqEDR for cLBP patients: significant decrease from pre-test to 1st-5th rep and 5th-10th rep, and a significant increase by comparing 1st-5th rep and 5th-10th rep with post-test.
- meanRR for HC subjects: significant decrease by comparing pre-test with post-test. For cLBP patients: significant increase from 1st-5th rep to the post-test phase.

Numerical values are reported in the Appendix.

Table 1 – Baseline recordings' results. HC = Healthy controls, cLBP = chronic low back pain patients

	HC *mean (std)*	*cLBP* *mean (std)*	*p-value*
meanIBI [ms]	865.51 (93.80)	720.20 (133.36)	**0.048**
SDNN [ms]	58.68 (12.99)	26.14 (27.99)	0.067
RMSSD [ms]	66.76 (29.69)	38.16 (34.16)	0.057
SD1 [ms]	47.19 (21.00)	26.96 (24.13)	0.057
SD2 [ms]	65.30 (12.20)	41.55 (31.94)	0.078
PulseAmpl [a.u.]	3.27 (0.15)	3.28 (0.26)	0.944
*A1 [a.u.*sample]*	69.01 (20.25)	61.93 (20.25)	0.159
*A2 [a.u.*sample]*	269.55 (42.91)	211.62 (62.26)	**0.014**
*A [a.u.*sample]*	338.56 (53.13	2743.55 (64.91)	**0.034**
T1 [ms]	156.78 (30.17)	146.72 (44.24)	0.290
T2 [ms]	710.48 (104.42)	575.70 (110.74)	**0.024**
meanEDA [n.u.]	-1.32 (0.55)	-0.91 (0.97)	0.438
stdEDA [n.u.]	0.11 (0.11)	0.16 (0.25)	0.944
SIE [ ]	0.78 (0.29)	0.74 (0.25)	0.833
meantonic [n.u.]	-1.33 (0.55)	-0.91 (0.97)	0.438
stdtonic [n.u.]	0.10 (0.10)	0.16 (0.25)	0.888
meanampEDR [n.u.]	0.04 (0.06)	0.01 (0.02)	0.488
stdampEDR [n.u.]	0.04 (0.08)	0.01 (0.02)	0.384
freqEDR [peaks/min]	3.14 (3.04)	1.80 (1.42)	0.438
meanRR [breaths/min]	16.17 (2.58)	17.40 (5.03)	0.672

IV. Discussion

We carried out a study to assess the different autonomic activity by comparing healthy control subjects and chronic low back patients both in a rest condition and when subjected to an acute noxious mechanical stimulus.

In the rest condition, only certain parameters extracted from the PPG were statistically different between HC subjects and cLBP patients. In particular, mean IBI was significantly lower in cLBP patients. This is in line with previous study findings on chronic pain patients [18]. Greater basal sympathetic nervous system outflow could potential lead to a higher basal heart rate (corresponding to a lower meanIBI) [19].

Some PPG morphological parameters, namely A2, A, and T2, were also found to be significantly lower in cLBP patients compared to HC subjects. Both A2 and A are related to T2, that is the time difference between the systolic peak and the successive systolic foot. This can be also the basis for the lowering of the meanIBI: chronic pain induces a change in the second part of the cardiac cycle, during the diastolic phase. Morphological parameters have been studied in relation to stress, finding similar results as the ones reported in this study [20].

Regarding the analysis of physiologic parameters during the repeated pinpricks test, HC subjects and cLBP patients showed a different autonomic reaction. Overall, cLBP patients appeared to exhibit a blunted degree of change, in agreement with some previous studies [21].

With regards to EDA, while HC subjects showed a dynamic change in several parameters, cLBP patients only demonstrated change in the SIE parameter, related to the complexity of the signal, and the frequency of EDA peaks (freqEDR). Specifically for freqEDR, since EDA is influenced only by the sympathetic branch of the ANS, it is supposed that a noxious stimulus should increase the number of EDA peaks [22]. Conversely, for cLBP patients the frequency of EDA peaks diminished during a noxious stimulus. This also suggests the possibility that a maladaptive functional neural rearrangement may have taken place over time in cLBP patients.

The study presents some limitations that can hamper the generalizability of the results. Firstly, our dataset consisted in an unbalanced number of subjects for the two populations (15 HC vs 8 cLBP). Some changes may have not been detected because of the small number of patients with cLBP. More subjects for both populations, with also more similar age distributions, should be involved in this study. Another limitation is given by the short phases related to noxious stimuli test. A strategy to gain more robust results could be to repeat the same nociceptive stimulus or to making last longer. Another important limitation is given by the different age for the two groups, which can be a confounding factor for our analysis.

As future studies, we are planning to compare reactions in the two populations to different noxious stimuli and to develop automatic methods to assess pain.

V. Conclusion

We carried out a study to explore differences in the autonomic activity, as measured by a set of physiologic measures, between HC subjects and cLBP patients both at rest and during a noxious stimulation. Our findings suggest a higher basal sympathetic activation at rest for cLBP patients,

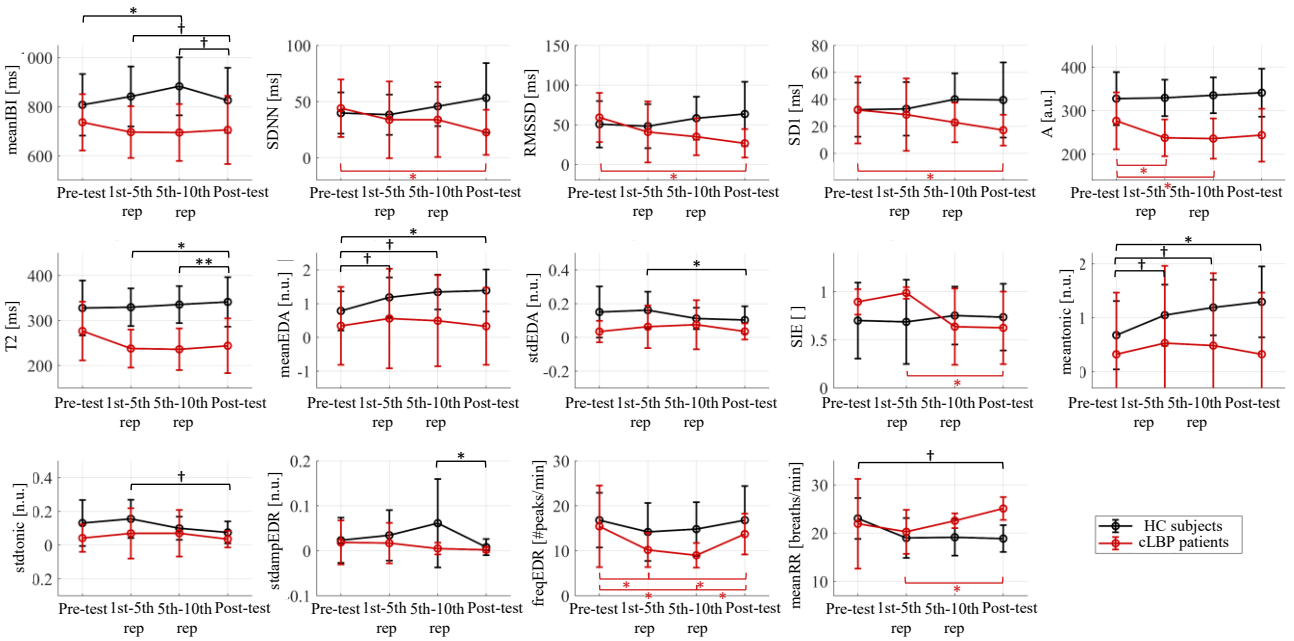

Figure 1 - Statistically significant changes during repeated pinpricks test in healthy controls and cLBP patients.
*** p-value < 0.05, **p-value < 0.01. †Bonferroni correction : p-value (=0.05/6) < 0.008**

but a less dynamic response when subjected to a noxious stimulus.

APPENDIX

Tables related to the results of the repeated pinprick tests are reported as Appendix.

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Table A1 Results from Repeated pinpricks test - Healthy control subjects

	Pre	1st-5th rep	5th-10th rep	Post	p-value					
	mean (std)	mean (std)	mean (std)	mean (std)	Pre – 1st-5th rep	Pre - 5th-10th rep	Pre - Post	1st-5th rep - 5th-10th rep	1st-5th rep - Post	5th-10th rep - Post
meanIBI [ms]	807.89 (125.40)	841.93 (122.36)	883.35 (117.97)	826.21 (132.24)	0.208	0.018*	0.934	0.303	0.008†	0.001†
SDNN [ms]	39.85 (18.27)	38.40 (17.89)	45.83 (17.53)	53.34 (30.96)	0.890	0.599	0.135	0.151	0.135	0.639
RMSSD [ms]	50.68 (29.20)	48.30 (27.68)	58.30 (26.97)	63.61 (40.55)	0.934	0.277	0.389	0.169	0.083	0.720
SD1 [ms]	32.41 (20.05)	33.01 (19.82)	40.07 (19.19)	39.56 (27.85)	0.639	0.229	0.524	0.169	0.303	0.934
SD2 [ms]	30.39 (16.00)	33.88 (18.40)	40.09 (18.40)	40.61 (26.79)	0.720	0.135	0.151	0.252	0.489	0.847
PulseAmpl [a.u.]	3.10 (0.30)	3.12 (0.35)	3.21 (0.32)	3.20 (0.38)	0.762	0.489	0.208	0.524	0.252	0.847
A1 [a.u.*s]	71.75 (30.40)	67.70 (23.72)	64.56 (17.49)	81.98 (68.27)	0.229	0.679	1.000	0.978	0.720	0.720
A2 [a.u.*s]	256.08 (39.74)	261.83 (39.21)	270.90 (37.33)	259.31 (55.60)	0.421	0.252	0.303	0.121	0.599	0.389
A [a.u.*s]	327.82 (60.93)	329.52 (41.91)	225.45 (41.20)	341.29 (55.08)	0.561	0.489	0.489	0.639	0.599	0.599
T1 [ms]	158.31 (46.45)	151.87 (48.27)	145.04 (27.80)	168.57 (95.40)	0.498	0.296	0.715	0.498	1.000	0.679
T2 [ms]	667.04 (104.71)	686.57 (106.65)	706.39 (101.79)	646.90 (146.47)	0.720	0.135	0.815	0.421	0.035*	0.003
meanEDA [n.u.]	0.79 (0.58)	1.19 (0.59)	1.34 (0.52)	1.39 (0.62)	0.001†	0.008†	0.010*	0.303	0.489	0.599
stdEDA [n.u.]	0.15 (0.15)	0.16 (0.11)	0.11 (0.06)	0.10 (0.08)	0.762	0.679	0.277	0.135	0.015*	0.389
SIE [ ]	0.70 (0.39)	0.69 (0.44)	0.75 (0.30)	0.74 (0.35)	0.804	0.934	0.847	0.761	0.847	0.978
meantonic [n.u.]	0.68 (0.63)	1.05 (0.57)	1.19 (0.52)	1.30 (0.66)	0.002†	0.005†	0.010*	0.421	0.303	0.252
stdtonic [n.u.]	0.13 (0.14)	0.16 (0.11)	0.10 (0.07)	0.08 (0.07)	0.489	0.804	0.454	0.095	0.003†	0.073
meanampEDR [n.u.]	0.12 (0.25)	0.18 (0.23)	0.17 (0.29)	0.08 (0.14)	0.080	0.330	0.735	1.000	0.110	0.268
stdampEDR [n.u.]	0.02 (0.05)	0.03 (0.06)	0.06 (0.10)	0.01 (0.02)	0.492	0.123	0.461	0.232	0.160	0.014*
freqEDR [#peaks/min]	16.80 (6.09)	14.18 (6.45)	14.81 (5.98)	16.80 (7.59)	0.352	0.421	1.000	0.761	0.454	0.551
meanRR [breaths/min]	23.04 (4.25)	18.98 (4.13)	19.14 (3.80)	18.86 (2.77)	0.054	0.193	0.008†	0.787	1.000	1.000

* p-value < 0.05, **p-value < 0.01. †Bonferroni correction: p-value (=0.05/6) < 0.008

Table A2 Results from Repeated pinpricks test – Chronic low back pain patients

	Pre	1st-5th rep	5th-10th rep	Post	p-value					
	mean (std)	mean (std)	mean (std)	mean (std)	Pre – 1st-5th rep	Pre - 5th-10th rep	Pre - Post	1st-5th rep - 5th-10th rep	1st-5th rep - Post	5th-10th rep - Post
meanIBI [ms]	736.68 (114.50)	696.85 (105.38)	695.07 (116.07)	705.71 (139.08)	0.469	0.297	0.688	0.578	0.688	0.813
SDNN [ms]	44.14 (25.50)	33.84 (34.19)	33.94 (33.18)	22.70 (20.03)	0.375	0.375	0.031*	0.578	0.375	0.375
RMSSD [ms]	59.21 (31.07)	41.00 (38.36)	35.06 (23.40)	26.69 (18.04)	0.375	0.109	0.031*	0.688	0.219	0.297
SD1 [ms]	32.18 (24.82)	28.69 (26.85)	22.91 (14.67)	17.22 (11.41)	1.000	0.219	0.047*	0.688	0.219	0.297
SD2 [ms]	29.52 (27.68)	33.89 (38.79)	35.02 (40.05)	18.05 (22.20)	0.938	0.813	0.156	0.578	0.219	0.219
PulseAmpl [a.u.]	3.32 (0.20)	3.21 (0.33)	3.24 (0.29)	3.25 (0.26)	0.297	0.297	0.375	1.000	0.578	0.469
A1 [a.u.*s]	70.63 (25.96)	55.90 (9.53)	55.85 (5.61)	67.06 (23.94)	0.109	0.469	0.688	0.938	0.297	0.578
A2 [a.u.*s]	206.00 (63.57)	181.81 (41.17)	180.24 (43.95)	176.80 (61.10)	0.109	0.078	0.219	1.000	0.375	0.297
A [a.u.*s]	276.64 (65.19)	237.71 (42.30)	236.09 (46.28)	243.86 (60.79)	0.047*	0.031	0.219	1.000	0.813	0.813
T1 [ms]	180.40 (73.95)	137.99 (20.50)	149.14 (28.34)	171.05 (61.56)	0.109	0.688	0.813	0.156	0.297	0.813
T2 [ms]	567.84 (122.49)	560.06 (99.24)	545.67 (98.77)	548.06 (106.24)	0.938	0.219	0.469	0.219	0.219	0.813
meanEDA [n.u.]	0.34 (1.16)	0.56 (1.48)	0.49 (1.35)	0.33 (1.14)	1.000	1.000	0.688	0.688	0.375	0.219
stdEDA [n.u.]	0.03 (0.06)	0.06 (0.13)	0.08 (0.15)	0.04 (0.05)	0.297	0.156	0.688	0.375	0.578	0.469
SIE [ ]	0.89 (0.13)	0.99 (0.06)	0.64 (0.40)	0.62 (0.38)	0.156	0.219	0.297	0.078	0.016*	0.813
meantonic [n.u.]	0.32 (1.14)	0.53 (1.43)	0.49 (1.34)	0.33 (1.14)	1.000	0.938	0.813	0.688	0.375	0.219
stdtonic [n.u.]	0.04 (0.08)	0.07 (0.15)	0.07 (0.14)	0.04 (0.05)	0.578	0.156	0.688	0.938	0.688	0.469
meanampEDR [n.u.]	0.02 (0.06)	0.04 (0.08)	0.003 (0.01)	0.003 (0.0.01)	0.250	1.000	1.000	0.250	0.375	1.000
stdampEDR [n.u.]	0.02 (0.05)	0.02 (0.05)	0.001 (0.004)	0.005 (0.008)	1.000	1.000	1.000	1.000	1.000	1.000
freqEDR [#peaks/min]	15.43 (9.07)	10.20 (3.81)	8.99 (2.73)	13.71 (4.54)	0.016*	0.031*	1.000	0.203	0.016*	0.031
meanRR [breaths/min]	21.94 (9.32)	20.27 (4.56)	22.56 (1.53)	25.11 (2.37)	1.000	1.000	1.000	0.625	0.031	0.187

* p-value < 0.05, **p-value < 0.01. †Bonferroni correction: p-value (=0.05/6) < 0.008