The test-retest reliability of the respiratory-related evoked potential

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Abstract

The respiratory-related evoked potential (RREP) is an established technique to study the neural processing of respiratory sensations. We examined the test-retest reliability of the RREP during an unloaded baseline condition (no dyspnea) and an inspiratory resistive loaded breathing condition (dyspnea) over a one-week period. RREPs were evoked by short inspiratory occlusions (150 ms) while EEG was continuously measured. The mean amplitudes of the RREP components Nf, P1, N1, P2, and P3 were studied. For the no dyspnea condition, moderate test-retest reliability for Nf (intraclass correlation coefficient ICC: 0.73) and P1 (ICC: 0.74), good test-retest reliability for N1 (ICC: 0.89) and P3 (ICC: 0.76), and excellent test-retest reliability for P2 (ICC: 0.92) was demonstrated. For the dyspnea condition, moderate test-retest reliability was found for Nf (ICC: 0.69) and P1 (ICC: 0.57) and good test-retest reliability for N1 (ICC: 0.77), P2 (ICC: 0.84), and P3 (ICC: 0.77). This indicates that the RREP components Nf, P1, N1, P2, and P3, elicited by inspiratory occlusions, show adequate reliability in a test-retest study design with or without parallel sustained resistive load-induced dyspnea.

Keywords: Test-retest reliability; Respiratory-related evoked potentials; Dyspnea; EEG; Breathlessness

Introduction

The respiratory-related evoked potential (RREP) is an established non-invasive technique used to study the neural processing of respiratory sensations in the EEG (Chan & Davenport, 2010; Chou & Davenport, 2007; Hammond, Gaeta, Sapienza, & Davenport, 1999; Redolfi et al., 2005; Strobel & Daubenspeck, 1993; Webster & Colrain, 2000a). It has been successfully used in studying pediatric and adult healthy individuals (Davenport, Colrain, & Hill, 1996; Harver, Squires, Bloch-Salisbury, & Katkin, 1995) as well as in patient groups including those with asthma (Davenport, Cruz, Stecenko, & Kifle, 2000; Webster & Colrain, 2002), COPD (Reijnders et al., 2020), obstructive sleep apnea (Eckert et al., 2011; Ruehland et al., 2017), cystic fibrosis, and neuromuscular disease (Fauroux et al., 2007). Commonly, the RREP is evoked by applying occlusions to the inspiration (Afifi, Guilleminault, & Colrain, 2003; Chan & Davenport, 2010; Davenport, Friedman, Thompson, & Franzen, 1986; Donzel-Raynaud et al., 2004; Redolfi et al., 2005; Webster & Colrain, 2000b). Expiratory occlusions (Hammond et al., 1999), resistive loads (Knafelc & Davenport, 1999), and negative airway pressure (Akay & Daubenspeck, 2000) have also been used to elicit an RREP. The RREP quantifies the initial arrival and further processing of afferent respiratory sensory information in the cortex (Chan & Davenport, 2010). This temporal sequence in neural processing of respiratory information is mirrored by the different RREP components including the Nf, P1, and partly N1 which are considered early components (< 130 ms) and to represent mostly sensory first-order processing. The subsequent components P2 and P3 are considered later components (> 150 ms) representing second-order cognitive processing (Chan & Davenport, 2010).

An increasing number of studies has used the RREP to examine interactions between psychological factors (i.e., emotion, attention) and the neural processing of respiratory sensations (Chan et al., 2015; Chan, Cheng, Jhu, Chen, & von Leupoldt, 2016; Chan, von Leupoldt, Bradley, Lang, & Davenport, 2012; Chenivesse et al., 2014; Harver et al., 1995; von Leupoldt, Chan, Bradley, Lang, & Davenport, 2011a; von Leupoldt, Chan, Esser, & Davenport, 2013; Webster & Colrain, 2000b). Some of these studies also combined inspiratory occlusions that evoke the RREP with the parallel induction of dyspnea by resistive loaded breathing (Chou & Davenport, 2007; Herzog, Sucec, Van Diest, Van den Bergh, Chan, et al., 2018a; Herzog, Sucec, Van Diest, Van den Bergh, & von Leupoldt, 2019a; Herzog, Sucec, Vucovic, Van Diest, Van den Bergh, et al., 2019b). Breathing through externally applied resistive loads alters breathing parameters by increasing the resistance to airflow and leads to an increase in work

and effort of breathing, which mimics airflow limitations and dyspnea of patients with obstructive lung disease (Ritz et al., 2002). Despite the wide application of the RREP in respiratory research, nothing is known about the reliability of the RREP, which holds for conditions with and without parallel induction of dyspnea. Confirming the reliability of RREP measurements could support its intensified future use in experimental and/or clinical contexts, for example in longitudinal studies, for individual difference assessments, or even as potential diagnostic tool in clinical settings.

Therefore, the present study investigated the test-retest reliability of the RREP components Nf, P1, N1, P2, and P3, elicited by inspiratory occlusions, over a one-week period in healthy participants during conditions with and without parallel sustained inspiratory resistive load-induced dyspnea. Additionally, in an exploratory analysis the test-rest reliability of the respiratory variables was investigated.

Methods

Participants

Twenty healthy participants (16 females) took part in this study after providing written informed consent, which is in accordance with common sample sizes of previous RREP studies (e.g., Chan et al., 2014; Chou & Davenport, 2007; Eckert et al., 2011; Reijnders et al., 2020; Ruehland et al., 2017; von Leupoldt et al., 2011b; Webster & Colrain, 2000b). Participants reported being non-smokers with no acute or chronic respiratory, cardiovascular, neurological, or psychiatric disorder. Additionally, participants were excluded if medication usage, pregnancy, or alcohol consumption in the preceding 24 hours was reported. Furthermore, pulmonary function within normal values was confirmed prior to testing by spirometry performed in accordance with international guidelines (Miller et al., 2005). The study was approved by the ethics committee of the University of Leuven (S58400). Participants received course credits for their participation.

Breathing circuit

Participants wore a nose clip while breathing through a mouthpiece that was connected to a breathing circuit (Figure 1). The breathing circuit contained a two-way non-rebreathing valve (Series 2700, Hans Rudolph Inc., Shawnee, USA). At the center of this non-rebreathing valve,

mouth pressure was recorded continuously (Flow-Pressure-Amplifier Series 1110B, Hans Rudolph Inc., Shawnee, USA). The expiratory port of the non-rebreathing valve was left open while the inspiratory port was connected via tubing (274 cm length, 3.5 cm inner diameter) to a pneumotachograph sampling airflow (Series 4830A, Flow-Pressure-Amplifier Series 1110B, Hans Rudolph Inc., Shawnee, USA), a loading manifold to administer inspiratory resistive loads (Series 7100, Hans Rudolph Inc., Shawnee, USA), and an occlusion valve that was connected to an occlusion controller device (Aspire Products, Gainesville, USA). The background resistance of the breathing circuit was approximately 1.6 $cmH_2O/L/s$. The occlusion controller device was used to apply the short occlusions for eliciting the RREP after the onset of inspirations (i.e., early inspiration) as indicated by the monitored mouth pressure signal. Occlusions were manually triggered with a joystick which activated a solenoid that closed the occlusion valve with pressurized room air resulting in a transient occlusion of the inspiration. Comparable set-ups have been used in previous studies (Herzog et al., 2019a, 2019b; von Leupoldt et al., 2010). During each condition, airflow and mouth pressure were measured continuously. Afterwards, AcqKnowledge 4.2 (Biopac, Goleta, USA) was used to calculate the respiratory variables including breathing frequency (f), inspiratory time (T_I), tidal volume (V_T), mean airflow (V') and peak inspiratory mouth pressure (P_{Imax}). Occluded breaths were excluded from the calculation of T_I, V_T, V' and P_{Imax} during tidal breathing. In addition, P_{Imax}, elicited by the inspiratory occlusions (i.e., occlusion peak inspiratory mouth pressure), was calculated for both unloaded and loaded conditions to examine the reliability of the stimulus characteristics.

###Figure 1###

Dyspnea calibration phase

In the dyspnea calibration phase, an individual level of 'strong' dyspnea intensity corresponding to a rating of '5' on a modified Borg Scale (Borg, 1982) was determined. This was achieved by presenting stepwise increasing magnitudes of inspiratory resistive loads for twenty seconds each while participants were respiring through the breathing circuit. For each inspiratory resistive load, participants indicated their experienced level of dyspnea intensity on the Borg Scale ranging from 0 ('not noticeable') to 10 ('maximum that can be tolerated'). Inspiratory resistive loads rated around '5' on the Borg Scale were again presented twice in a random order and rated by the participants. Finally, the lowest inspiratory resistive load corresponding to a 'strong' dyspnea intensity rating during the dyspnea calibration phase of the first testing session was selected to induce dyspnea during the experimental phase in both testing sessions (*M* =

24.4 $cmH_2O/L/s$, *SD* = 15.2). To keep the respiratory strain for both testing sessions identical, the same dyspnea calibration phase was performed during the second testing session. An identical dyspnea calibration procedure was used in previous studies (Herzog et al., 2019a; Sucec, Herzog, Van Diest, Van den Bergh, & von Leupoldt, 2018a, 2018b; Sucec, Herzog, Van den Bergh, Van Diest, & von Leupoldt, 2019).

Experimental phase

While respiring through the breathing circuit, participants underwent an experimental phase consisting of an unloaded baseline condition (no dyspnea) and a sustained resistive loaded breathing condition (dyspnea). During the dyspnea condition, the predetermined inspiratory resistive load from the first testing session was applied to the breathing circuit while in the no dyspnea condition no inspiratory resistive load was applied. Each condition contained two blocks which lasted four minutes each resulting in a total recording time of eight minutes per condition. To reduce strain on participants, dyspnea and no dyspnea blocks were alternated with the order being counterbalanced across participants. The block order for each participant was identical for both testing sessions. During each block, a fixation cross was presented on a monitor in front of the participants while EEG was continuously recorded. RREPs were evoked by short, transient inspiratory occlusion (150 ms) applied randomly to every second to fifth inspiration. After each block participants gave ratings on their perceived dyspnea and affective state during the preceding block and underwent a rest period.

Ratings of dyspnea and affective state

Dyspnea was explained to participants as 'difficult and uncomfortable breathing'. After each block, ratings of dyspnea intensity and dyspnea unpleasantness during the preceding block were obtained using a visual analog scale ranging from 0 (= 'not noticeable/not unpleasant') to 100 (= 'maximally imaginable intensity/unpleasantness') (Aitken, 1969; Wilson & Jones, 1989). Furthermore, after each block, participants indicated their affective state during the preceding block on a valence (1 = 'unpleasant' to 9 = 'pleasantness') and arousal dimension (1 = 'calm' to 9 = 'aroused') using the 9-point Self-Assessment Manikin (Bradley & Lang, 1994).

EEG data recording and reduction

RREPs were recorded continuously in both conditions using a 129-channel EEG system (Philips EGI, Eugene, USA) with a sampling rate of 250 Hz and the vertex electrode (Cz) as the reference electrode (for electrode location see Figure 1). Electrode impedance was kept

below 50 kΩ. Data analyses were performed offline using BESA Research 6.0 (BESA GmbH, Gräfelfing, Germany). After visual inspection of the mouth pressure signal, occlusions outside of the inspiratory cycle were excluded from analysis. This resulted in an average of 28.8 occlusions (*SD* = 7.0, minimum number of occlusions= 17, maximum number of occlusions = 48) for the no dyspnea and 28.8 occlusions (*SD* = 7.2, minimum number of occlusions= 20, maximum number of occlusions = 47) for the dyspnea condition for the further analyses. This resembles occlusion numbers which are commonly used in RREP studies using high-density EEG (e.g., Herzog et al., 2019a, 2019b; 2018b; Reijnders et al., 2020; von Leupoldt, Bradley, Lang, & Davenport, 2010) and which also converges with minimum signal-to-noise criteria for obtaining acceptable RREPs using high-density EEG (von Leupoldt, Keil, & Davenport, 2011b). Data were filtered by applying a high-pass filter of 0.1 Hz (forward-phase Butterworth filter, 6-dB/octave roll-off) and a low-pass filter of 30 Hz (zero-phase Butterworth filter, 24-dB/octave roll-off) with an additional notch filter of 50 Hz (2 Hz width). This was followed by an adaptive artifact correction (i.e., eye blinks) (Ille, Berg, & Scherg, 2002). Then, the signal was re-referenced to the average reference (i.e., calculated across all electrodes) (Dien, 1998; Luck, 2014) and epochs of 200 ms pre- and 1000 ms post-occlusion onset were extracted and averaged with a maximal cut-off amplitude of 200 µV. The 100 ms prior to occlusion onset served as a baseline.

###Figure 2###

Consistent with previous literature (Chan & Davenport, 2010; von Leupoldt et al., 2010; von Leupoldt, Keil, & Davenport, 2011b; Webster & Colrain, 2000b), the RREP components were identified as follows: Nf in the frontal region (latency: 20-45 ms, electrodes: 20, 24, 28, 117, 118, 124); P1 in the centro-parietal region (latency: 30-60 ms, electrodes: 61, 62, 78); N1 in the centro-lateral region (latency: 75-120 ms, electrodes: 6, 7, 13, 106, 112, Cz); P2 in the central region (latency: 160-230 ms, electrodes: 6, 7, 106, Cz); P3 in the centro-parietal region (latency: 240-310 ms, electrodes: 54, 55, 61, 62, 78, 79) (Figure 2). Mean, baseline-corrected amplitudes were calculated for each RREP component by averaging activity over the respective latency window and electrode cluster. Electrode selection and latency windows were identical for all participants, conditions, and testing sessions.

Procedure

After arriving in the laboratory, participants signed an informed consent form, filled out the

exclusion criteria form and performed a spirometric lung function test. Next, participants received standardized instructions regarding the experimental procedure and underwent the dyspnea calibration phase. Then, the EEG net was applied, and participants were seated in a comfortable armchair with their upper body and feet supported. This was followed by a practice phase where participants were familiarized with the inspiratory occlusions. Next, the experimental phase consisting of the four blocks followed. After each block, ratings for perceived dyspnea and affective state were obtained. Finally, participants were debriefed and thanked. The procedure for both testing sessions was identical. All participants took part in two testing sessions separated by seven days. Both testing sessions took place at the same time of the day (time between testing sessions: mean = 6 days 23.34 hours, *SD* = 1.32 hours).

Statistical analysis

Due to excessive (muscle) artifacts in the EEG recording, four participants of the no dyspnea condition and eight participants of the dyspnea condition had to be excluded from the analysis. Therefore, the final sample for the no dyspnea condition consisted of 16 participants and 12 participants for the dyspnea condition (Table 1). Statistical analyses were performed using SPSS 24 (IBM Corp., Armonk, USA). Ratings, respiratory variables, and RREP mean amplitudes of the two blocks per condition were averaged for each testing session separately. To examine whether ratings and respiratory variables were comparable between testing sessions, dependent t-tests were calculated. If the assumptions of the dependent t-tests were violated, Wilcoxon signed-rank tests were performed. As an effect size, *r* was used (Field, 2009; Rosenthal, 1994). The test-retest reliability of the mean amplitude of the RREP components and the exploratory analysis of the respiratory variables was investigated using two different and independent measures of the relationship between two measurements, namely Pearson's r and intraclass correlation coefficients (ICC) (Liu et al., 2016). Pearson's *r* was used to examine the intersubject stability of the mean amplitudes, whereas the ICC was used to investigate the score agreement between measurements (i.e., reproducibility) calculated by the ratio of true variance over true variance plus error variance (Shrout & Fleiss, 1979). The ICC was based on a two-way mixed-effects model, a mean rating ($k = 2$), and an absolute agreement (Koo & Li, 2016). It should be noted that findings with this specific ICC cannot be generalized to other "raters". ICC values < .50, between .50-.75, between .75-.90, and > .90 indicate poor, moderate, good, and excellent reliability, respectively (Koo & Li, 2016). The level of significance was $p < .05$.

Results

###Table 1###

Ratings of dyspnea and affective state

The ratings of dyspnea intensity and unpleasantness for the no dyspnea (intensity: $t(15) = 1.67$, $p = .116$, $r = .40$; unpleasantness: $z = -1.20$, $p = .230$, $r = -.21$) and dyspnea condition (intensity: $t(11) = 0.79$, $p = .448$, $r = .05$, unpleasantness: $t(11) = 0.38$, $p = .711$, $r = .01$) did not differ between testing sessions. Furthermore, the ratings of affective valence and arousal for the no dyspnea (valence: $z = -0.06$, $p = .952$, $r = -.01$; arousal: $t(15) = 1.23$, $p = .240$, $r = .30$) and dyspnea condition (valence: $t(11) = -0.43$, $p = .674$, $r = .02$, arousal: $t(11) = 2.11$, $p = .059$, $r = .29$) did not differ between testing sessions (Figure 3).

###Figure 3###

Respiratory variables

The respiratory variables for the no dyspnea (f: $t(15) = -0.54$, $p = .599$, $r = .02$; T_I: $t(15) = 2.03$, $p = .061$, $r = .22$; P_{Imax}: $z = -0.71$, $p = .478$, $r = -.13$; V_T: $t(15) = -0.21$, $p = .838$, $r = .002$; occlusion P_{Imax}: $t(15) = 1.85$, $p = .084$, $r = .17$) and dyspnea condition (f: $z = -1.49$, $p = .136$, $r = -.30$; T_I: $t(11) = -0.96$, $p = .360$, $r = .08$; P_{Imax}: $t(11) = 0.42$, $p = .686$, $r = .02$; V_T: $t(11) = -2.16$, $p = .054$, $r = .30$; V': $t(11) = -0.50$, $p = .624$, $r = .02$; occlusion P_{Imax}: $t(11) = 0.36$, $p = .725$, $r = .04$) did not differ between testing sessions except for V' in the no dyspnea condition ($t(15) = -2.38$, $p = .031$, $r = .27$) (Table 2).

###Table 2###

Test-retest reliability of RREPs

Group means of the RREP, and the corresponding scalp topographies for the no dyspnea and dyspnea condition are presented in Figure 4, 5 and 6, respectively. For the no dyspnea condition, the intersubject stability and score agreement demonstrated moderate test-retest reliability for the RREP components Nf and P1. Good test-retest reliability was shown for the RREP components N1 and P3 and excellent test-retest reliability for the component P2 (Table 3).

For the dyspnea condition the intersubject stability and score agreement demonstrated moderate

test-retest reliability for the RREP components Nf and P1, with the ICC of Nf being statistically significant. Furthermore, for the dyspnea condition, good test-retest reliability was found for the components N1, P2, and P3 (Table 3).

###Figure 4, 5 and 6###

###Table 3###

Test-retest reliability of respiratory variables

For the no dyspnea condition, the intersubject stability and score agreement demonstrated poor test-retest reliability for P_{Imax} and moderate test-retest reliability for V'. Good test-retest reliability was shown for f, V_T, and occlusion P_{Imax}, and excellent test-retest reliability was found for T_I (Table 2).

For the dyspnea condition, the intersubject stability and score agreement demonstrated good test-retest reliability for P_{Imax} and occlusion P_{Imax}, while excellent test-retest reliability was found for f, T_I, V_T, and V' (Table 2).

Discussion

This study investigated the one-week test-retest reliability of the RREP components Nf, P1, N1, P2, and P3, elicited by inspiratory occlusions, with and without parallel experience of dyspnea induced by sustained inspiratory resistive loaded breathing. The results showed that ratings of perceived dyspnea and affective state, respiratory variables, as well as occlusion stimulus characteristics were comparable between testing sessions. Most importantly, for the no dyspnea condition moderate to excellent test-retest reliability was demonstrated for all RREP components. Furthermore, for the dyspnea condition moderate to good test-retest reliability for all RREP components was observed. Notably, these test-retest reliability results for the RREP components could be demonstrated using two different and independent measures for the strength of relationships between two measurements, namely Pearson's r (= intersubject stability) and intraclass correlation coefficients (= reproducibility) (Liu et al., 2016). Taken together, the present findings suggest that the RREP as elicited by inspiratory occlusions shows adequate reliability in a test-retest study design with or without parallel sustained resistive load-induced dyspnea.

The present results on the test-retest reliability of the RREP components converge with previous findings regarding the reliability of other event-related potentials. These include event-related potentials such as the error-related negativity and error-related positivity used to investigate error processing, the P3a or P3b evoked in Oddball paradigms, or the P400 during the Sternberg working memory task (Cassidy, Robertson, & O'Connell, 2012; Olvet & Hajcak, 2009). For example, for the mean amplitudes of the error-related negativity and the error-related positivity, an ICC of .70 - .74 and .62 - .75, respectively, was reported for test-retest periods of 4 weeks (Cassidy et al., 2012) and 2 weeks (Olvet & Hajcak, 2009). Furthermore, the ICCs for the P3a and P3b mean amplitudes during an Oddball paradigm, tested twice 4 weeks apart, ranged from .78-.80 (Cassidy et al., 2012). Similarly, for the mean amplitude of the P400 during the Sternberg working memory task an ICC of .85 was found for a test-retest period of 4 weeks (Cassidy et al., 2012). These findings are highly comparable to the current findings of the test-retest reliability of the RREP with ICCs ranging from .57 - .92.

In the present study, we observed slightly better test-retest reliability for the N1 and the later RREP components P2 and P3 compared to the earlier RREP components Nf and P1, especially during dyspnea conditions. This might be related to the circumstance that more occlusions could be necessary to obtain a reliable signal-to-noise ratio for the earlier and typically smaller components Nf and P1 compared to the subsequent and typically larger components N1, P2, and P3, as suggested by von Leupoldt and colleagues (2011b). This might pose a potential limitation of the present study and calls for more systematic exploration in future studies using a higher number of occlusion stimuli.

Moreover, the present study observed that the test-retest reliability was somewhat lower during the dyspnea condition compared to the no dyspnea condition. This observation is in line with previous findings demonstrating potentially reduced signal-to-noise ratio under increased background resistive loaded breathing (Chou & Davenport, 2007; Herzog et al., 2019a). This potentially reduced signal-to-noise ratio might contribute to a slightly lower test-retest reliability under sustained background loaded breathing. Together, these observations suggest that slightly more occlusion presentations might be needed during conditions of increased and sustained background resistive loaded breathing in order to achieve comparable signal-to-noise-ratios and subsequently comparable test-retest reliability as during unloaded breathing.

In an additional exploratory analysis, the test-retest reliability of the respiratory variables was investigated. For the no dyspnea condition, poor test-retest reliability was found for P_{Imax}, moderate test-retest reliability for V', good test-retest reliability for f and V_T as well as excellent test-retest reliability for T_I. Overall, for the dyspnea condition the test-retest reliability was higher with good test-retest reliability for P_{Imax} and excellent test-retest reliability for f, T_I, V_T, and V'. These results show that all respiratory variables except P_{Imax} during the unloaded no dyspnea condition demonstrate acceptable test-retest reliability. These findings are in line with earlier studies showing good test-retest reliability of laboratory and ambulatory measurements of several respiratory variables including f, T_I, V_T, and V' (Benchetrit 2000; Benchetrit et al., 1989; Grossman, Spoerle, & Wilhelm, 2006; Tobin et al., 1988). Notably, the values for P_{Imax} evoked by the inspiratory occlusions (i.e., not P_{Imax} during tidal breathing) were comparable between both test sessions and showed good test-retest reliability for the no dyspnea (ICC: .82) and dyspnea condition (ICC: .83). This demonstrates that the characteristics of the occlusion stimuli used to elicit the RREP were comparable between both measurements with adequate test-retest reliability. Moreover, this converges with previous findings demonstrating good test-retest reliability of other inspiratory pressure measurements including maximum inspiratory pressure and airway occlusion pressure $P_{0.1}$ (Dimitriadis, Kapreli, Konstantinidou, Oldham, & Strimpakos, 2011; Kera, Aihara, & Inomata, 2013).

When interpreting the present results, certain limitations should be noted. Sustained inspiratory resistive loaded breathing increases the mechanical strain on participants' respiratory system. This resulted in excessive artifacts in the EEG in some participants and increased loss of participants for analyses. This should be considered when calculating the sample size for future studies using similar methodologies, which might profit from including larger participant numbers. In addition, it will be important to investigate the use of different background dyspnea induction techniques such as CO_2 inhalation, hyperinflation, or vicarious dyspnea (Herzog, Sucec, Van Diest, Van den Bergh, Chenivesse, et al., 2018a) to assess the RREP. Moreover, our sample consisted of healthy and predominantly female students which limits the generalizability of the present results to other populations. Therefore, the RREP test-retest reliability should further be investigated in other populations including different age groups and clinical populations, e.g., patients with asthma, chronic obstructive pulmonary disease, or anxiety disorders who suffer from frequent episodes of dyspnea. Finally, future studies need to investigate the test-retest reliability of the RREP over longer time periods. These would benefit from including further measures of airway pressure (e.g., epiglottic pressure) in order to control

for potential contributions of changes in airway resistance and/or compliance, which may impact stimulus transmission as well as stimulus and RREP variability.

In summary, the present results indicate that the RREP components Nf, P1, N1, P2, and P3, elicited by inspiratory occlusions, show adequate reliability over a one-week period with or without parallel sustained resistive load-induced dyspnea.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest related to the present manuscript.

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Table 1

Mean (*SD*) characteristics of participants for the no dyspnea and dyspnea condition.

Characteristics	No dyspnea (n = 16)*	Dyspnea (n = 12)
Gender (female/male, No.)	(12/4)	(9/3)
Age (years)	20.88 (2.60)	20.33 (2.06)
Height (cm)	170.88 (7.63)	169.00 (7.95)
Weight (kg)	66.13 (17.52)	65.67 (19.92)
FEV_1 (L)	3.71 (0.68)	3.71 (0.78)
FEV_1 (% predicted)	101.19 (6.64)	100.83 (7.15)
FVC (L)	4.39 (0.87)	4.40 (0.98)
FVC (% predicted)	103.50 (8.48)	105.58 (8.66)

Note: FEV_1 = forced expiratory volume in 1s; FEV_1 (% predicted) = forced expiratory volume in 1s in % predicted; FVC = forced vital capacity; FVC (% predicted) = forced vital capacity in % predicted. * All participants (n=12) of the dyspnea condition were included in the no dyspnea condition.

Table 2

Mean (*SD*), Pearson's correlation coefficient, and intraclass correlation coefficients of the respiratory variables for the no dyspnea and dyspnea conditions for both testing sessions.

Condition	Respiratory variable	T1	T2	*r*	ICC (95% CI)
No dyspnea	Breathing frequency (breaths/min)	13.63 (4.28)	13.98 (3.87)	.80***	.89*** (0.69 – 0.96)
	Inspiratory time (s)	2.06 (0.72)	1.88 (0.59)	.88**	.91*** (0.72 – 0.97)
	Tidal volume (L)	0.73 (0.22)	0.74 (0.20)	.77***	.87*** (0.63 – 0.96)
	Mean airflow (L/s)	0.37 (0.06)	0.40 (0.09)	.69**	.72** (0.21 – 0.90)
	Peak inspiratory mouth pressure (cmH_2O)	-1.17 (0.33)	-1.30 (0.29)	.07	.13 (-1.38 – 0.69)
	Occlusion Peak inspiratory mouth pressure (cmH_2O)	-4.13 (1.10)	-4.60 (1.48)	.73**	.82*** (.49 - .94)
Dyspnea	Breathing frequency (breaths/min)	12.95 (4.03)	12.35 (4.01)	.85***	.92*** (0.73 – 0.98)
	Inspiratory time (s)	2.88 (1.46)	3.00 (1.39)	.96***	.98*** (0.92 – 0.99)
	Tidal volume (L)	0.76 (0.26)	0.81 (0.30)	.97***	.97*** (0.88 – 0.99)
	Mean airflow (L/s)	0.29 (0.09)	0.30 (0.11)	.90***	.94*** (0.78 – 0.98)
	Peak inspiratory mouth pressure (cmH_2O)	-8.89 (3.27)	-9.17 (3.05)	.72**	.84** (0.44 – 0.96)
	Occlusion Peak inspiratory mouth pressure (cmH_2O)	-9.88 (3.76)	-10.19 (3.90)	.70*	.83** (.40 - .95)

Note: T1 = first testing session; T2 = second testing session; *r* = Pearson's correlation coefficient; ICC = intraclass correlation coefficient; CI = confidence interval; * $p < .05$; ** $p < .01$; *** $p < .001$, No significant differences between both testing sessions were found for respiratory variables with the exception of mean airflow in the no dyspnea condition, which was higher at T2 compared to T1 ($p < 0.05$).

Table 3

Mean amplitudes (*SD*) in microvolt (µV), Pearson's correlation coefficient, and intraclass correlation coefficients for the RREP components for the no dyspnea and dyspnea condition for both testing sessions.

Condition	Component	Amplitude T1	Amplitude T2	*r*	ICC (95% CI)
No dyspnea	Nf	-2.03 (1.03)	-1.70 (1.18)	.59*	.73 (0.26 – 0.90)**
	P1	1.00 (1.50)	1.10 (0.89)	.65**	.74 (0.24 – 0.91)**
	N1	-3.49 (1.83)	-3.66 (2.35)	.81***	.89 (0.68 – 0.96)***
	P2	5.09 (3.73)	5.14 (3.52)	.85***	.92 (0.77 – 0.97)***
	P3	3.08 (2.06)	2.25 (1.87)	.65**	.76 (0.32 – 0.91)**
Dyspnea	Nf	-1.68 (1.20)	-1.18 (1.00)	.57#	.69 (0.03 – 0.91)*
	P1	1.15 (1.46)	1.24 (1.28)	.39	.57 (-0.63 – 0.88)
	N1	-1.17 (1.39)	-0.58 (1.78)	.67*	.77 (0.26 – 0.93)**
	P2	2.22 (2.45)	2.74 (3.22)	.74**	.84 (0.45 – 0.95)**
	P3	3.27 (2.07)	2.79 (3.48)	.70*	.77 (0.20 – 0.93)*

Note: T1 = first testing session; T2 = second testing session; *r* = Pearson's correlation coefficient; ICC = intraclass correlation coefficient; CI = confidence interval; # $p < .06$; * $p < .05$; ** $p < .01$; *** $p < .001$.

Figure legends

Figure 1. Schematic illustration of the experimental set-up.

Figure 2. Illustration of the 129-channel HydroCel Geodesic Sensor Net used with permission from Electrical Geodesics, Inc.

Figure 3. Mean of ratings for dyspnea intensity and unpleasantness on a visual analog scale (0-100) as well as affective valence and arousal on a Self-Assessment Manikin scale (1-9) for the no dyspnea (upper panel) and dyspnea condition (lower panel) for both testing sessions. Error bars represent *SD*.

Figure 4. Grand averages for the respiratory-related evoked potential in microvolt (μV) for the no dyspnea (A-C) and dyspnea condition (D-F) for both testing sessions over the frontal (A = No dyspnea condition with used electrodes for illustration: 20, 24, 28, 117, 118, 124; D = Dyspnea condition with used electrodes for illustration: 20, 24, 28, 117, 118, 124), central (B = No dyspnea condition with used electrodes for illustration: 6, 7, 106, Cz; E = Dyspnea condtion with used electrodes for illustration: 106, 112), and parietal region (C = No dyspnea condition with used electrodes for illustration: 54, 61, 62; F = Dyspnea conditon with used electrodes for illustration: 54, 61, 62).

Figure 5. Grand averages for the scalp topographies for the respiratory-related evoked potential in microvolts (μV) for the no dyspnea (A) and dyspnea condition (B) for both testing sessions.

Figure 6. Scatter plots for the respiratory-related evoked potential components during the no dyspnea (A) and dyspnea condition (B) for both testing sessions.

Figure 1

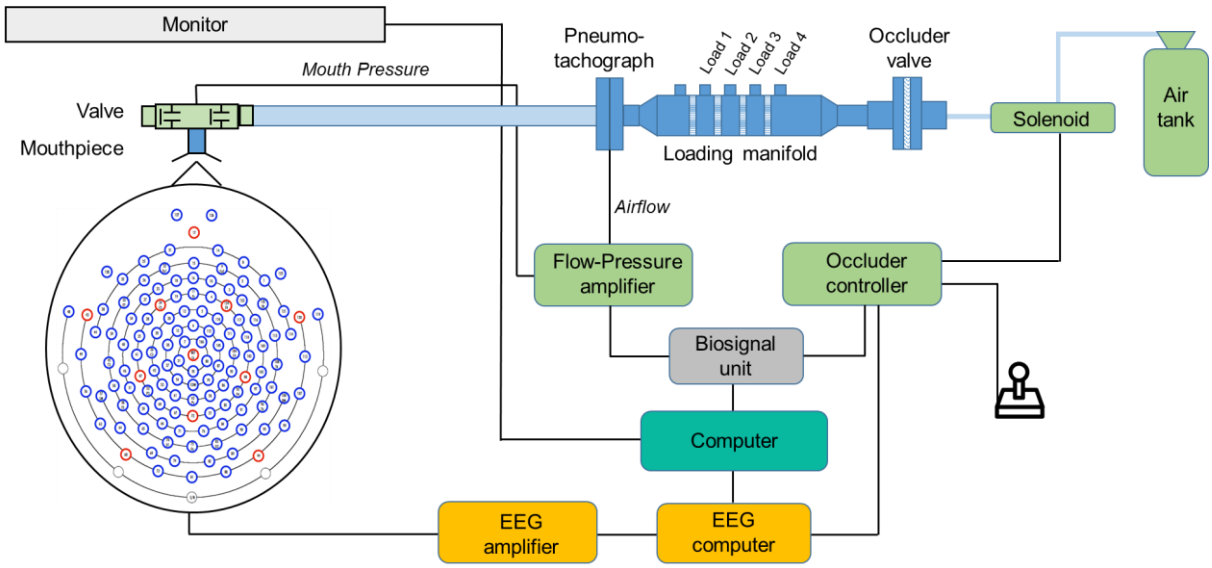
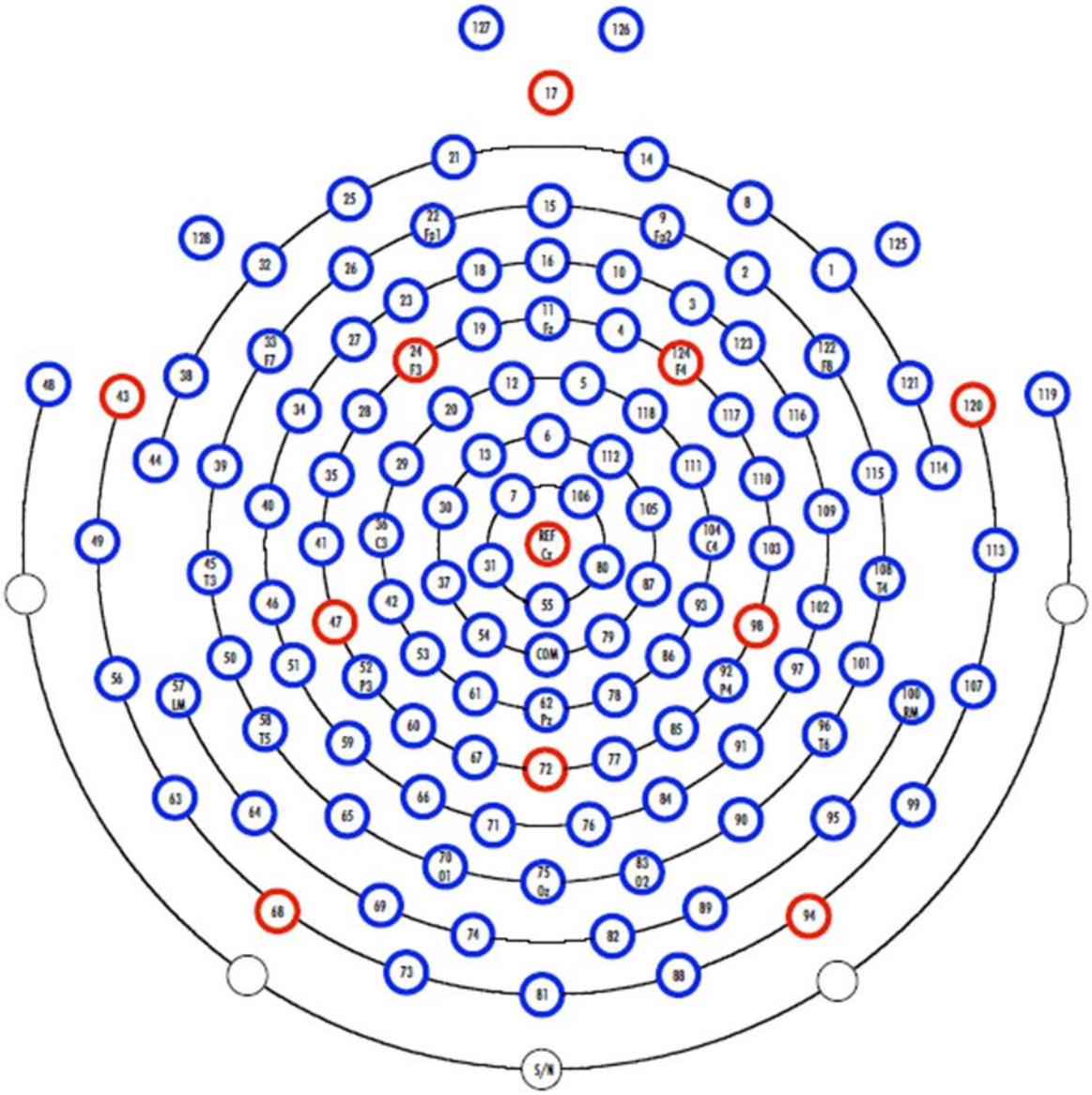

Monitor
Mouth Pressure
Valve
Mouthpiece
Pneumo-
tachograph
Load 1
Load 2
Load 3
Load 4
Occluder
valve
Solenoid
Air
tank
Loading manifold
Airflow
Flow-Pressure
amplifier
Occluder
controller
Biosignal
unit
Computer
EEG
amplifier
EEG
computer

Figure 2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Fp1
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Fp2
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Fz
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F7
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19
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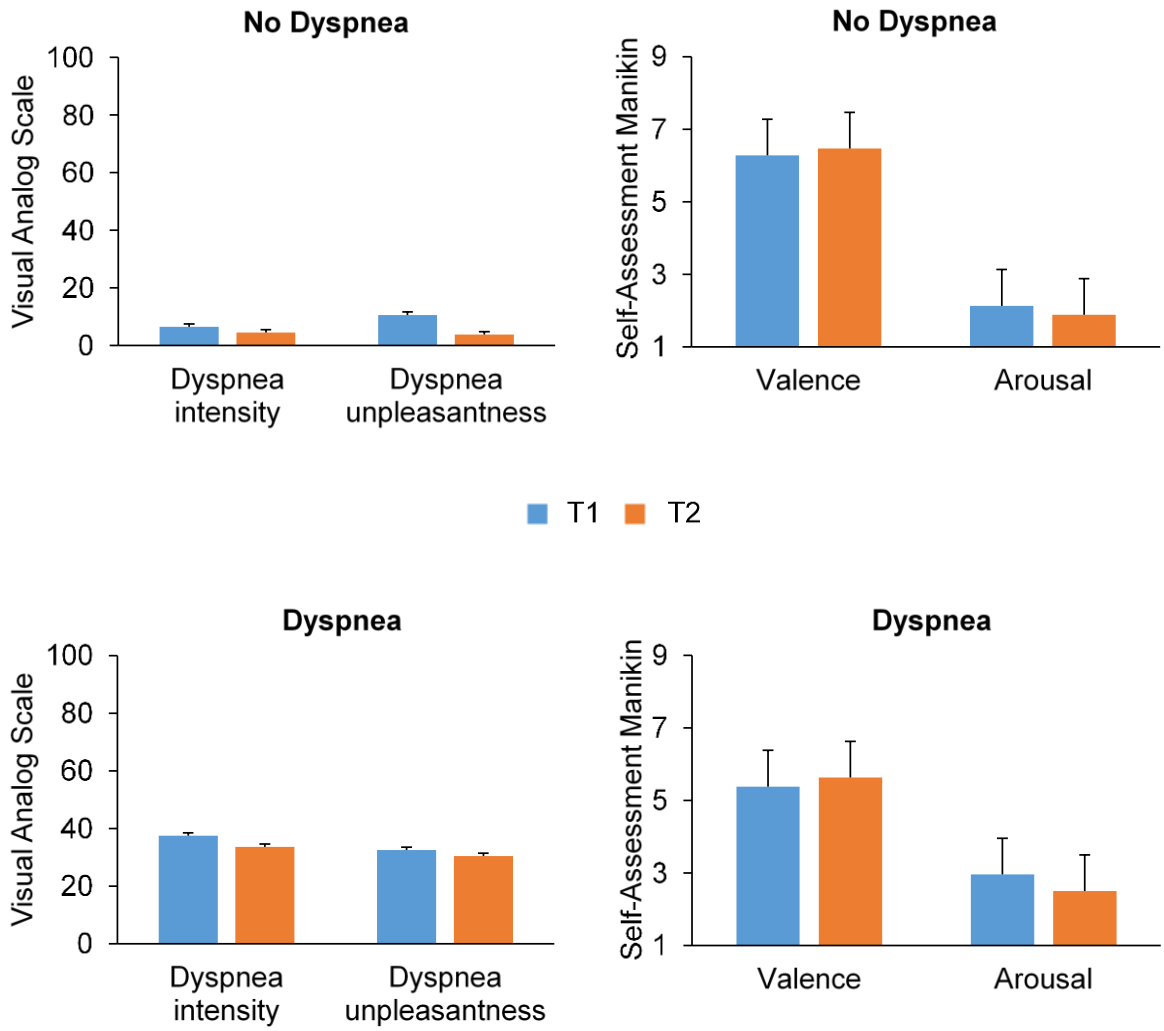
S/N

Figure 3


No Dyspnea
Visual Analog Scale
100
80
60
40
20
0
Dyspnea intensity
Dyspnea unpleasantness
No Dyspnea
Self-Assessment Manikin
9
7
5
3
1
Valence
Arousal
T1
T2
Dyspnea
Visual Analog Scale
100
80
60
40
20
0
Dyspnea intensity
Dyspnea unpleasantness
Dyspnea
Self-Assessment Manikin
9
7
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1
Valence
Arousal

Figure 4

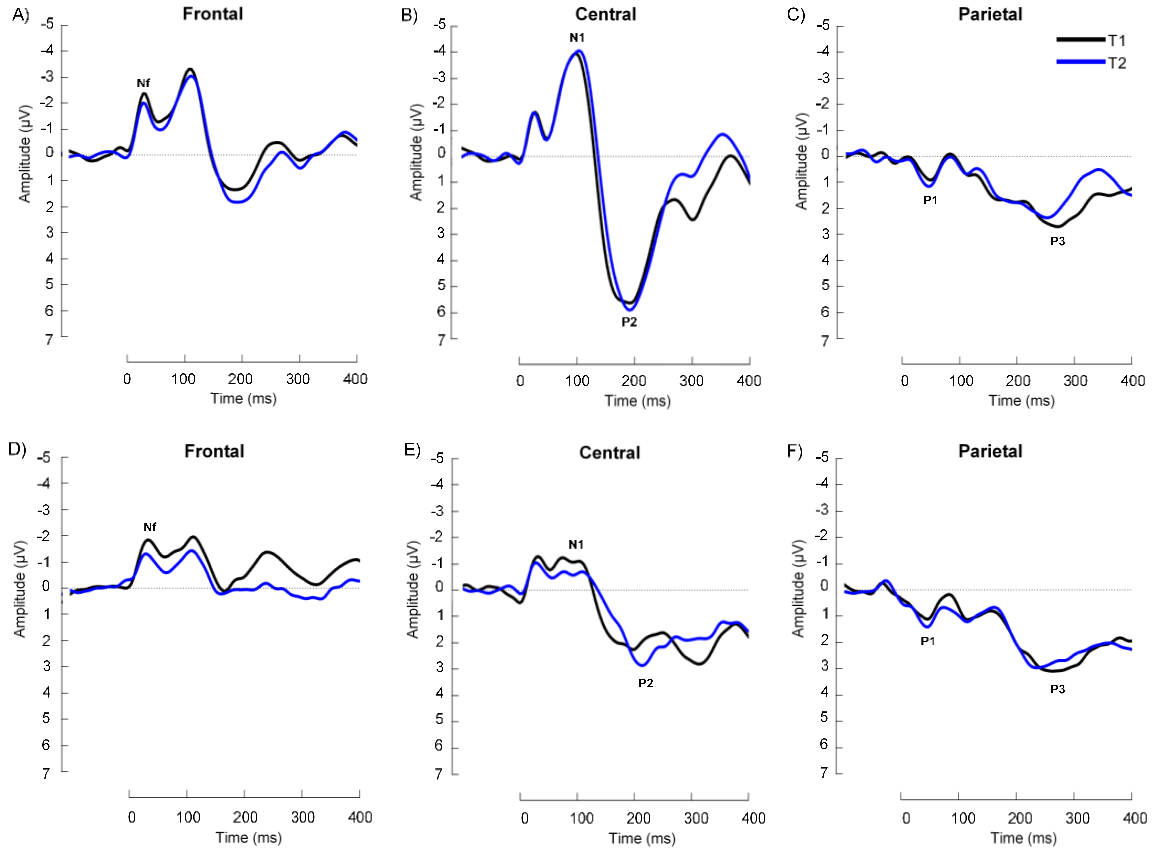
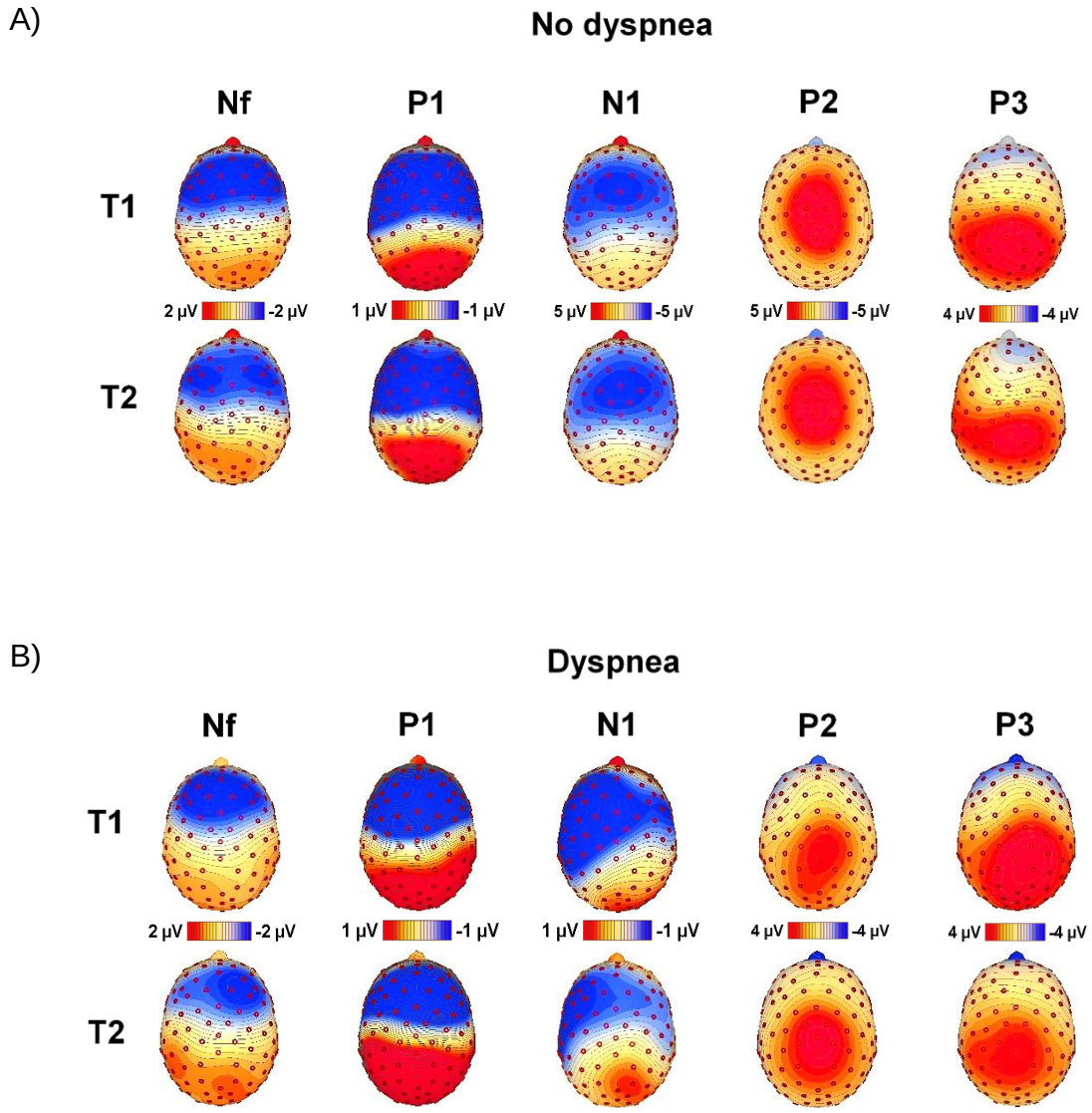

A)
Frontal
Nf
B)
Central
N1
P2
C)
Parietal
T1
T2
P1
P3
D)
Frontal
Nf
E)
Central
N1
P2
F)
Parietal
P1
P3
Amplitude (μV)
Time (ms)

Figure 5


A)
No dyspnea
Nf
P1
N1
P2
P3
T1
T2
2 µV
-2 µV
1 µV
-1 µV
5 µV
-5 µV
5 µV
-5 µV
4 µV
-4 µV
B)
Dyspnea
Nf
P1
N1
P2
P3
T1
T2
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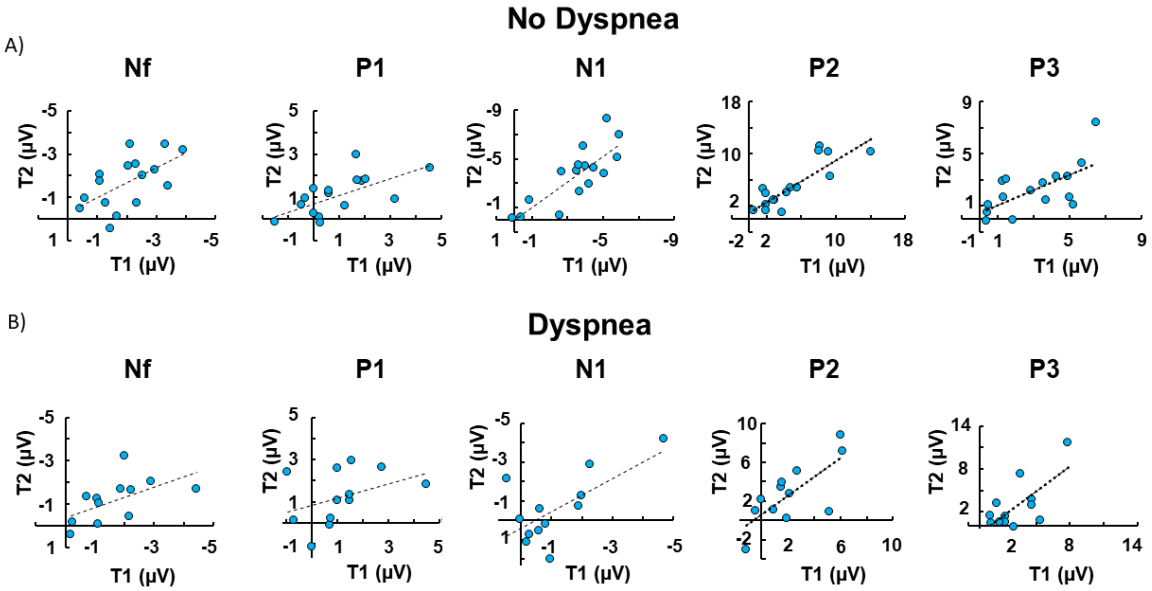
1 µV
-1 µV
1 µV
-1 µV
4 µV
-4 µV
4 µV
-4 µV

Figure 6


No Dyspnea
A)
Nf
P1
N1
P2
P3
T2 (μV)
T1 (μV)
B)
Dyspnea
Nf
P1
N1
P2
P3
T2 (μV)
T1 (μV)