

Evidence against a subcortical gate preventing conscious detection of respiratory load stimuli



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ABSTRACT

Respiratory related evoked potentials (RREP) were used to examine respiratory stimulus gating. RREPs produced by consciously detected vs. undetected loads, near the detection threshold, were compared. Participants ($n = 17$) were instrumented with EEG and a nasal mask connected to a loading manifold, which presented a range of mid-inspiratory resistive loads, plus a control, in a random block design. Participants were cued prior to the stimulus and signalled detection by a button press. There were statistically significant differences in peak-to-peak amplitude of the P1 RREP peak for detected (mean \pm SD; $3.86 \pm 1.45 \mu\text{V}$; $P = 0.020$) and undetected loads ($3.67 \pm 1.27 \mu\text{V}$; $P = 0.002$) vs. control ($2.36 \pm 0.81 \mu\text{V}$), although baseline-to-peak differences were not significantly different. In contrast peak-to-peak P3 amplitude was significantly greater for detected ($5.91 \pm 1.54 \mu\text{V}$; $P < 0.001$) but not undetected loads ($3.33 \pm 0.98 \mu\text{V}$; $P = 0.189$) vs. control ($3.69 \pm 1.46 \mu\text{V}$), with the same pattern observed for baseline-to-peak measurements. The P1 peak, thought to reflect arrival of somatosensory information, appeared to be present in response to both detected and undetected loads, but the later P3 peak, was present for detected loads only. This suggests that for sub-threshold loads sensory information may reach the cortex, arguing against a sub-cortical gating process.

1. Introduction

Sensory perception or detection of respiratory loads is important in respiratory pathology such as asthma and obstructive sleep apnoea (OSA). In asthma, conscious perception of increased respiratory load caused by airway narrowing is necessary if patients are to initiate treatment early during exacerbations. Additionally, there is evidence that 'poor perceivers' are at greater risk of serious exacerbations and hospitalisations (Davenport et al., 2000; Kifle et al., 1997; Kikuchi et al., 1994). In OSA, sensory detection of the increased load imposed by a narrow airway may be important in initiating compensatory upper airway dilator muscle responses. There is also some evidence of blunted upper airway sensation in OSA (Donzel-Raynaud et al., 2009; Kimoff et al., 2001; McNicholas et al., 1984; Nguyen et al., 2005; Tun et al., 2000).

Sensory detection of respiratory loads has classically been studied using psychophysical techniques; in particular the conscious detection threshold of respiratory resistive loads has been examined, where the conscious detection threshold is defined as the added resistance (ΔR) detected on 50% of presentations (ΔR_{50}) (Bennett et al., 1962; Davenport et al., 2007; Diamond et al., 1983; Stubbing et al., 1983; Wiley and Zechman, 1966).

More recently respiratory related evoked potentials (RREPs) have been used to study sensory detection of respiratory loads. RREPs are the averaged electroencephalographic (EEG) response to multiple presentations of a respiratory stimulus. RREPs have been recorded in response to a number of respiratory stimuli, including inspiratory resistive loads (Chou and Davenport, 2007; Davenport et al., 2007; Knafelc and Davenport, 1997, 1999; Ruehland et al., 2017; Webster and Colrain, 2000a), and are made up of a number of positive and negative

Abbreviations: AHI, apnoea hypopnoea index; BMI, body mass index; EEG, electroencephalography; EOG, electrooculogram; ESS, Epworth sleepiness scale; FER, Forced expiratory ratio; FEV1, Forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; OSA, obstructive sleep apnoea; Pepi, epiglottic pressure; Pepi Δ , Change in epiglottic pressure; Pepi₀, Background epiglottic pressure; Pmask, mask pressure; PSG, polysomnography; ΔR , Added resistance; ΔR_{50} , Added resistance detected on 50% of presentation; R_0 , Background resistance; R_{aw} , Total airways resistance; RREP, Respiratory related evoked potential; RV, residual volume; TLC, Total lung capacity; TST, total sleep time; %TST < 90%SpO₂, % of total sleep time with oxygen saturation less than 90%

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components. The more recent studies have reported, in order of latency from stimulus onset, Nf, P1, N1, P2, and P3 components, although the P1 and P3 components have most commonly been the targets of RREP research (Knafelc and Davenport, 1997, 1999; Ruehland et al., 2017; Webster et al., 2002; Webster and Colrain, 2002). P1 is thought to represent arrival of the primary afferent information at the somatosensory cortex whereas P3 is thought to reflect cognitive processing of the respiratory signal (Chan and Davenport, 2010; Davenport et al., 2007, 1986; Webster and Colrain, 2000a, b). This view is largely based on studies suggesting a P1 source location within the somatosensory cortex (Davenport et al., 1996; Logie et al., 1998; von Leupoldt et al., 2010a; Webster and Colrain, 1998, 2000a, b; Zhao et al., 2002), and on component characteristics. While both P1 and P3 increase in amplitude with increased stimulus magnitude (Davenport et al., 2007; Knafelc and Davenport, 1997, 1999; Webster and Colrain, 2000a), only P3 is influenced by cognitive factors such as whether or not attention is paid to the stimulus (Davenport et al., 2007; Harver et al., 1995; Webster and Colrain, 2000b), or emotion (von Leupoldt et al., 2011, 2013; von Leupoldt et al., 2010b).

It has been reported that a ΔR clearly above the conscious detection threshold elicits the RREP, whereas a ΔR well below the conscious detection threshold (~ 30 – 50% of the threshold load) does not (Chou and Davenport, 2007; Davenport et al., 2007). For loads above the threshold component amplitudes are correlated with magnitude estimation (Knafelc and Davenport, 1999; Webster and Colrain, 2000a). Furthermore, RREPs are influenced by background resistance (R_0) in a similar way to conscious detection. In an important study Wiley and Zechman (1966) demonstrated that the conscious detection threshold for resistive loads was related to the R_0 , which incorporates the resistance of the breathing circuit and the participant's intrinsic airway resistance. They reported that the detection threshold occurred at a common ratio of ΔR_{50} to R_0 ($\Delta R_{50}/R_0$) of approximately 0.3. Chou and Davenport (2007) reported that an RREP produced by a ΔR that was above the conscious detection threshold ($\Delta R/R_0 > 1.5$) could be abolished by increasing the background resistance so that the same ΔR was below the conscious detection threshold ($\Delta R/R_0 < 0.15$). Thus a relationship exists between conscious detection of respiratory loads and RREP generation, and consequently it has been suggested that the RREP is a neural indicator of cortical sensory information processing, related to conscious sensory detection of respiratory loads (Chou and Davenport, 2007; Davenport et al., 2007).

The relationship between conscious detection of respiratory loads and the RREP has also been used to support the concept of a subcortical gating process (Chan et al., 2016, 2012; Chan and Davenport, 2008, 2009; Chenivresse et al., 2014; Chou and Davenport, 2007; Davenport and Vovk, 2009; O'Donnell et al., 2007), where the "gate" is considered as a filter of sensory stimuli, allowing attention to be directed to essential physiological functions, while protecting cognitive processes from being flooded with redundant sensory stimuli (O'Donnell et al., 2007). Since awareness or attention of basal breathing is possible if attention is directed to it, it follows that mechanosensory afferent transmission occurs during basal breathing, but that the information is 'gated out' from cognitive processing. Similarly, sub-threshold respiratory stimuli may result in mechanosensory afferent transmission, but the afferent transmission may be gated out from cognitive processing. For a supra-threshold load, respiratory mechanosensory afferent activity passes to or is 'gated in' to allow cognitive processing, resulting in conscious awareness of the stimulus (O'Donnell et al., 2007). Although the anatomical site of the gating mechanism is unknown, the thalamus has been suggested as a possible candidate (Chan and Davenport, 2010; Davenport and Vovk, 2009). This is related to observations that: (i) the thalamus is considered an essential relay point in sensory processing (Martin, 1991), (ii) the thalamus has been implicated in sensory gating of other sensory modalities (Malmierca et al., 2002; Wunderlich et al., 2005) and, (iii) in animal models there is evidence that neural pathways exist from respiratory muscle to the

somatosensory cortex via thalamic neurons (Davenport et al., 1993, 1985; Zhang and Davenport, 2003).

This study aimed to examine the relationship between conscious detection and the RREP using a novel approach, by targeting respiratory resistive loads at, or close to, the conscious detection threshold, rather than loads well above or below the threshold as has occurred in previous studies (Chou and Davenport, 2007; Davenport et al., 2007). By definition, at the conscious detection threshold 50% of stimuli will be consciously detected and 50% will not. Therefore this study planned to generate and compare RREPs produced by detected vs. undetected resistive loads of similar magnitude, which may provide insight into the proposed gating mechanisms (Chan et al., 2016, 2012; Chan and Davenport, 2008, 2009; Chenivresse et al., 2014; Chou and Davenport, 2007; Davenport and Vovk, 2009; O'Donnell et al., 2007). Consistent with sensory gating of respiratory stimuli occurring as a subcortical process, it was hypothesised that RREP components would be present in response to consciously detected respiratory loads but absent or substantially altered in response to undetected loads.

2. Methods

2.1. Ethical approval

The study conformed to the standards set by the *Declaration of Helsinki* and was approved by the Austin Health Human Research Ethics Committee. All participants gave informed written consent to participate in the study.

2.2. Participants

Seventeen healthy individuals participated in this study. Participants were control participants from a separate study investigating RREP responses in OSA patients compared to healthy controls (Ruehland et al., 2017). Participants were excluded if an occlusion load did not produce a clear RREP, if the presented resistive loads did not span the conscious detection threshold, or if the resistive loads presented were not sufficiently close in magnitude to the conscious detection threshold, resulting in a low number of stimulus presentations contributing to the ensemble average (< 35). This number was chosen to maximise the number of study participants while also attempting to maximise the signal-to-noise ratio. The selection of trials into analyses is described in greater detail in the *Data Analysis* section.

All participants were male, and free from diagnosed respiratory, neurological, psychiatric, cardiovascular, or sleep disorders. Exclusion criteria included current intake of psychoactive medications, as well as alcohol or recreational drug abuse or tobacco use.

Power calculations were derived from control participant data from our study investigating RREP responses in OSA (Ruehland et al., 2017). P1 component amplitude was the primary outcome. From this data it was calculated that to have 90% likelihood of detecting a 1 standard deviation difference at the $P = 0.05$ level required 13 subjects. Additional participants were included to allow for excluded data or technical issues.

Spirometry (JLab software version 5.2, PFTpro with whole body plethysmograph, Jaeger, Carefusion GmBH, Wurzburg, Germany or Vmax Spectra 62 J body plethysmograph, SensorMedics, Yorba Linda, CA, USA) confirmed normal lung function in all participants. Participants were recruited from the community and were required to have an apnoea hypopnoea index (AHI) less than 15 h^{-1} using 'Chicago' criteria for scoring respiratory events (1999), as determined using full polysomnography (PSG). In a suspected OSA population a Chicago AHI of 15 h^{-1} has been estimated to be approximately equivalent to 4 h^{-1} using the American Academy of Sleep Medicine (AASM) 2007 (Iber et al., 2007) 'recommended' criteria and 9 h^{-1} using the AASM 'alternative' criteria (Ruehland et al., 2009).

2.3. Preliminary visit

An initial screening visit included the in-laboratory overnight PSG as well as lung function testing the following morning. In addition to spirometry, total airways resistance (Raw) was measured by plethysmography, *via* the oral route with a mouthpiece, as well as *via* the nasal route with a modified non-vented nasal mask (Profile Lite, Philips Respironics, Murrysville, PA, USA), both before and following nasal decongestant (0.05% oxymetazoline hydrochloride). Following administration of oxymetazoline hydrochloride solution, local vasoconstriction usually occurs within five to ten minutes, persists for five to six hours, and then gradually declines over the next six hours (Logicin Rapid Relief Nasal Spray, 2003).

2.4. Experimental protocol and equipment

Participants attended the laboratory at 8am for experimental testing on a separate day following the screening visit, having abstained from alcohol and caffeine for at least 12 h.

The equipment used for physiological recordings, the instrumentation applied to the participants, as well as the signal conditioning and calibration methodologies have been previously described in Ruehland et al. (2017). In brief the following physiological measurements were undertaken: EEG, electrooculogram (EOG), epiglottic pressure (Pepi), mask pressure (Pmask), and airflow.

Participants were required to breathe *via* a breathing circuit which has also been previously described (Ruehland et al., 2017). In brief, the breathing circuit included: a modified sealed nasal mask (Profile Lite, Philips Respironics), a non-rebreathing valve (series 2600, Hans Rudolph, Kansas City, MO, USA), connected *via* tubing to a custom-made manifold, used to provide respiratory stimuli, and which was situated in a room adjacent to the participant. The manifold allowed presentation of various resistive loads, with good linearity characteristics, spanning the conscious detection threshold ($\approx 1.2, 2.2, 3.0,$ and $6.2 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$) above a background circuit resistance of approximately $2 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$, as well as a control condition (no added resistance above background circuit) and a complete occlusion. Fast actuating balloon valves (9340 series, Hans Rudolph, Shawnee Mission, KS, USA) used to generate the resistive loads were also activated during the control condition. In terms of the RREP it has been recognised that anticipation, artefacts or other non-stimulus related experimental factors may lead to deviation in the ensemble average trace (Knafelc and Davenport, 1997, 1999); the zero load control accounts for these deviations as well as for any signal noise. Control of stimulus presentations was performed using custom software, with all stimuli (control, occlusion and various resistive loads) presented in semi-random order (block design) every 2–4 breaths during mid-inspiration with a target of 90 presentations of each stimulus. The stimulus continued until end inspiration for all stimuli except for the occlusion stimulus which, for participant comfort, was presented for 800 ms. To maintain attention the participant was cued *via* headphones at end inspiration on the breath prior to stimulus presentation with an automatically generated message “next breath”. Background music of the participant’s choice served to mask experimental sounds. Forced decision conscious detection of the presented stimulus (Yes/No) was signalled with a button press.

Participants were seated in an upright position in a dentist’s chair with back and arms supported to allow relaxation of postural muscles. Standardised information and instructions were given to each participant prior to the experimental session. Participants were asked to sit quietly and comfortably, breathe as normally as possible *via* the nasal mask and avoid falling asleep. Additionally, for the target breath they were asked to keep their eyes open and to avoid eye movement and blinking as much as possible.

Immediately prior to the experimental session biological checks were conducted to ensure signal quality; these included eyes open, closed, left, right, up and down. This was followed by a five minute

familiarisation session.

During the experimental session participants were allowed a 5 min break every 20–30 minutes. The entire visit, including equipment set-up, familiarisation and the experimental protocol lasted approximately 3.5–4.5 hours depending on respiratory rate.

Three participants attended on a separate occasion to the main experimental testing to test the influence of the loading manifold on component latencies. On that occasion comparison was made between RREP responses to occlusion of the apparatus with and without the loading manifold in circuit.

2.5. Data analysis

For each participant, individual resistive load presentations were separated into those that were consciously detected and those that were not. Individual trials were only included if the target breath was free from eye movement and blink artefact, movement artefact, and if a 20 s window around the stimulus (viewed in a 30 s epoch) was free from sleep, defined as any theta frequency or slower activity observed in the central EEG derivation. The presence of sleep was determined by an experienced polysomnographic scientist (WRR). Separate ensemble averages were then generated from the detected and undetected loads, time-locked to the electrical pulse causing balloon valve inflation and stimulus presentation. So that equal numbers from each resistive load magnitude contributed to the separate detected and undetected ensemble averages, if a particular load was below the conscious detection threshold and therefore had a greater number of undetected than detected loads, all of its detected loads would be used in the ‘detected’ ensemble average. An equal number of the undetected loads would be used in the ‘undetected’ ensemble average, selected in order of presentation, and the remainder of the undetected loads would be disregarded. Conversely, for resistive loads above the conscious detection threshold, all undetected loads were included in the ‘undetected’ ensemble average, however only a subset of detected loads contributed to the ‘detected’ ensemble average, equal to the total number of undetected loads for that resistive load magnitude. This methodology allowed: (i) production of ‘detected’ and ‘undetected’ ensemble averages that were matched for both presentation numbers and stimulus magnitude, (ii) for resistive load magnitudes closer to the conscious detection threshold to make a greater contribution to the ensemble average, and (iii) maximisation of the number of individual load presentations contributing to the ensemble averages. For each participant, separate ensemble averages were also created for the occlusion stimulus and the zero load control; the number of individual stimulus presentations contributing to these were also matched to the number of stimulus presentations contributing to the ‘detected’ and ‘undetected’ ensemble averages.

All component measurements made from ensemble averages were automated using custom software. The manifold occlusion RREP was used to create participant specific 50 ms RREP component detection windows for Nf and P1 components, and 80 and 150 ms windows for the broader N1 and P3 components respectively. For each individual participant these windows were set around the component latencies on the EEG channel where the component was maximal. This methodology was employed to ensure objective RREP component measurements, and to allow for potential differences in component latencies caused by study specific stimulus characteristics (stimulus rise time in particular (Davenport et al., 1986; Gora et al., 2002)) and individual participant differences. When determining the component detection windows, Nf was defined as the first negative RREP peak, P1 as the first positive peak, N1 as the second negative peak, and P3 as the subsequent large positive peak. P2 was only occasionally discernible and therefore was not included in the analysis. Stimulus onset, for detection window and subsequent RREP component latency measurements, was defined as the onset of the sudden decrement in the ensemble averaged Pmask following balloon valve activation. For the zero load control condition, in

the absence of a Pmask decrement, stimulus onset was set to the average stimulus onset of all other stimulus conditions for that participant.

Baseline-to-peak amplitude within each component detection window was then automatically and objectively measured from the ensemble average produced for each of the four conditions: zero load control, undetected loads, detected loads, and occlusion, where baseline was defined as the average EEG activity in a 200 ms window prior to the stimulus. Automated measurements were made regardless of whether the individual components were visually discernible. Nf, P1, N1 and P3 components are known to be recorded maximally from frontal, centro-parietal, central and parietal EEG channels respectively (von Leupoldt et al., 2010a; Webster and Colrain, 1998, 2000a, b; Zhao et al., 2002). Peak measurements were generally made from known maximal sites (Nf at F_z, N1 at C_z and P3 at P_z). However, P1 was measured from C_z as P1 amplitudes were greater at C_z rather than P_z using the current equipment (Ruehland et al., 2017). To account for any residual noise, DC shifts or other confounding artefacts in the stimulus baseline (Handy, 2005; Picton et al., 2000), peak-to-peak amplitudes were also recorded with a focus on the P1 and P3 components (*i.e.* Nf amplitude subtracted from P1 amplitude at C_z and N1 amplitude subtracted from P3 amplitude at P_z).

Flow and pressure channels were also ensemble averaged for each condition, time locked to the stimulus generating electrical pulse which triggered balloon valve inflation. Prior to ensemble averaging of the Pepi channel, the Pepi signal was offset to account for a small pressure generated by air perfusion of the catheter.

The conscious detection threshold was defined as the added resistive load detected with a 50% probability (ΔR_{50}) and was calculated using the logit transformation method described by Killian et al. (1980). For this calculation, to avoid floor and ceiling effects, a stimulus intensity was only included if it was detected on more than 5% and less than 95% of individual trials. The detection threshold was also calculated with the added resistance expressed as a proportion of background resistance ($\Delta R_{50}/R_0$) (Weber fraction) (Fechner, 1966).

2.6. Statistical analysis

Stimulus characteristics between detected and undetected loads were compared using paired sample *t*-tests.

For each of the RREP component windows (Nf, P1, N1, P3), the baseline-to-peak amplitude of the four conditions (zero load, detected, undetected, occlusion) were initially compared using a one-way ANOVA for repeated measures. Where appropriate planned contrasts then compared each of the loaded conditions against the zero load control, as well as detected vs. undetected loads. The same statistical comparisons were conducted for the peak-to-peak amplitudes and latency measurements.

Results are presented as mean \pm SD unless otherwise stated. A *P*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Participant characteristics

Of the original 17 participants considered for inclusion, one was excluded from analysis due to a poorly defined RREP in response to occlusion, three were excluded due to the presented loads not spanning the conscious detection threshold, and three were excluded due to a low number of stimulus trials contributing to the ensemble averages. A low number of stimulus trials contributing to the ensemble average arose due to our trial inclusion criteria described in the *Data Analysis* section, in situations where the particular subject's conscious detection threshold was not sufficiently close in magnitude to one of the resistive loads presented. The further away in magnitude a resistive load was from the conscious detection threshold the less stimulus trials it would

Table 1
Participant characteristics.

Parameter	Value
Demographics	
n	10
M:F	10:0
Age (y)	38.0 (34.0, 45.8)
Height (m)	1.74 (1.70, 1.81)
Weight (kg)	78.0 (72.8, 90.8)
BMI (kg·m ⁻²)	25.9 (25.1, 27.9)
Neck Circumference (cm)	39.0 (38.6, 39.9)
Sleep parameters	
ESS	3.5 (2.3, 5.8)
AHI (h ⁻¹)	3.5 (2.0, 5.5)
%TST < 90%SpO ₂	0.0 (0.0, 0.0)
Respiratory function parameters	
FEV1 (L BTPS)	4.1 (3.5, 5.2)
FEV1 (%Pred)	106.0 (97.3, 113.5)
FVC (L BTPS)	5.5 (4.8, 6.2)
FVC (% Pred)	106.5 (102.5, 113.8)
FER (%)	77.5 (74.3, 81.5)
FER (%Pred)	98.0 (92.3, 101.3)
FRC (L BTPS)	3.3 (3.3, 3.8)
FRC (% Pred)	95.5 (81.8, 101.5)
TLC (L BTPS)	7.2 (6.4, 7.9)
TLC (% Pred)	107.5 (102.0, 113.5)
RV (L BTPS)	1.7 (1.6, 2.0)
RV (%Pred)	90.5 (81.5, 96.5)
Raw (cmH₂O·L⁻¹·s)	
Oral route	2.1 (1.6, 2.3)
Nasal route (Pre-decongest)	4.2 (3.3, 5.7)
Nasal route (Post-decongest)	3.2 (2.8, 4.5)
Nasal (Pre-decongest) – oral route	1.6 (1.4, 3.6)

Values are median (inter-quartile range). Abbreviations: BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; AHI: Apnoea Hypopnoea Index derived using AASM Chicago hypopnoea definition (AASM, 1999); %TST < 90%SpO₂: % of total sleep time with oxygen saturation less than 90%; FEV1: forced expiratory volume in 1 s; FER: forced expiratory ratio; FVC: forced vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity. Raw: airway resistance measured using body box plethysmography; % Pred: percent predicted; BTPS: body temperature and pressure, saturated.

contribute to the ensemble average.

Participant characteristics of the remaining 10 participants are shown in Table 1.

3.2. Stimulus characteristics

The mean number of stimulus presentations contributing to each ensemble average was 57 ± 13 . There were no significant differences between detected and undetected resistive loads in pre-stimulus circuit resistance, stimulus ΔR , or $\Delta R/R_0$ (Weber fraction) (Table 2). There was a small but statistically significant difference in pre-stimulus Pmask (P_{mask_0}) and Pepi ($Pepi_0$) between detected and undetected loads (Table 2; Fig. 1). However stimulus Pmask change (ΔP_{mask}), $\Delta P_{mask}/P_{mask_0}$, stimulus Pepi change ($\Delta Pepi$) and $\Delta Pepi/Pepi_0$ were not significantly different between detected and undetected loads (Table 2; Fig. 1).

3.3. Conscious detection threshold

The mean conscious detection threshold was $2.22 (0.76) \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$ and was within the range of presented resistive loads for the 10 participants. When expressing the ΔR as a Weber fraction, accounting for R_0 , the conscious detection threshold was $0.44 (0.25)$.

Table 2
Comparison of stimulus conditions between detected and undetected loads.

	Detected	Undetected	Difference	P-value
Resistance (R)				
Baseline (cmH ₂ O·L ⁻¹ ·s)	1.96 (0.12)	2.00 (0.13)	0.03 (0.06)	0.095
Δ (cmH ₂ O·L ⁻¹ ·s)	2.26 (0.42)	2.24 (0.42)	-0.01 (0.04)	0.402
Δ/R ₀	0.44 (0.18)	0.44 (0.19)	0.00 (0.01)	0.255
Pmask				
Baseline (cmH ₂ O)	-1.08 (0.22)	-1.03 (0.21)	0.05 (0.06)	0.017
Δ (cmH ₂ O)	-0.79 (0.20)	-0.76 (0.20)	0.03 (0.07)	0.176
Δ/Pmask ₀	0.74 (0.20)	0.75 (0.18)	0.00 (0.06)	0.887
Pepi^a				
Baseline (cmH ₂ O) ^a	-2.85 (1.77)	-2.57 (1.61)	0.28 (0.29)	0.021
Δ (cmH ₂ O) ^a	-0.42 (0.44)	-0.49 (0.41)	-0.07 (0.10)	0.072
Δ/Pepi ₀ ^a	0.23 (0.21)	0.29 (0.22)	0.05 (0.07)	0.073

Notes: Values are mean (SD). Baseline values are prior to stimulus presentation. Abbreviations: Δ: Change; R₀: Background resistance incorporating circuit plus airway resistance measured using plethysmography. Pmask: Mask pressure; Pmask₀: Baseline mask pressure; Pepi: Epiglottic pressure; Pepi₀: Baseline epiglottic pressure. P-values derived using paired t-tests.

Note: Bold values are the statistically significant results ($P < 0.05$).

^a n = 9.

3.4. RREP component amplitudes

3.4.1. Nf

There was a statistically significant difference in baseline-to-peak Nf

Table 3
RREP component amplitudes (μV).

Component	Control	Undetected	Detected	Occlusion	P-value
Baseline-to-peak					
Nf @ F _Z	-0.75 (1.01)	-1.61 (1.09)	-1.96 (1.48) *	-2.77 (1.16) *	0.003
P1 @ C _Z	1.82 (1.22)	2.26 (1.25)	2.61 (1.68)	3.15 (1.91)	0.215
N1 @ C _Z	-0.30 (1.45)	0.06 (0.98)	-0.54 (1.73)	-1.80 (2.54)	0.068
P3 @ P _Z	3.17 (1.75)	3.08 (0.99)	5.48 (2.14) * †	8.35 (3.09) *	< 0.001
Peak-to-peak					
P1@C _Z - Nf@C _Z	2.36 (0.81)	3.67 (1.27) *	3.86 (1.45)*	5.50 (2.12) *	< 0.001
P3@P _Z -N1@ P _Z	3.69 (1.46)	3.33 (0.98)	5.91 (1.54) * †	9.07 (2.15) *	< 0.001

Values are mean (SD). P-values are from one-way repeated measures ANOVA. Symbols: * $P < 0.05$ from planned comparison vs. control load. † $P < 0.05$ from planned comparison vs. undetected load.

Note: Bold values are the statistically significant results ($P < 0.05$).

amplitude between stimulus conditions (Table 3). Planned contrasts revealed that the baseline-to-peak Nf amplitude was significantly more negative for detected resistive loads ($P = 0.023$) and occlusion ($P = 0.002$) but not for undetected loads ($P = 0.081$), when compared to the zero load control. Baseline-to-peak Nf amplitudes were not significantly

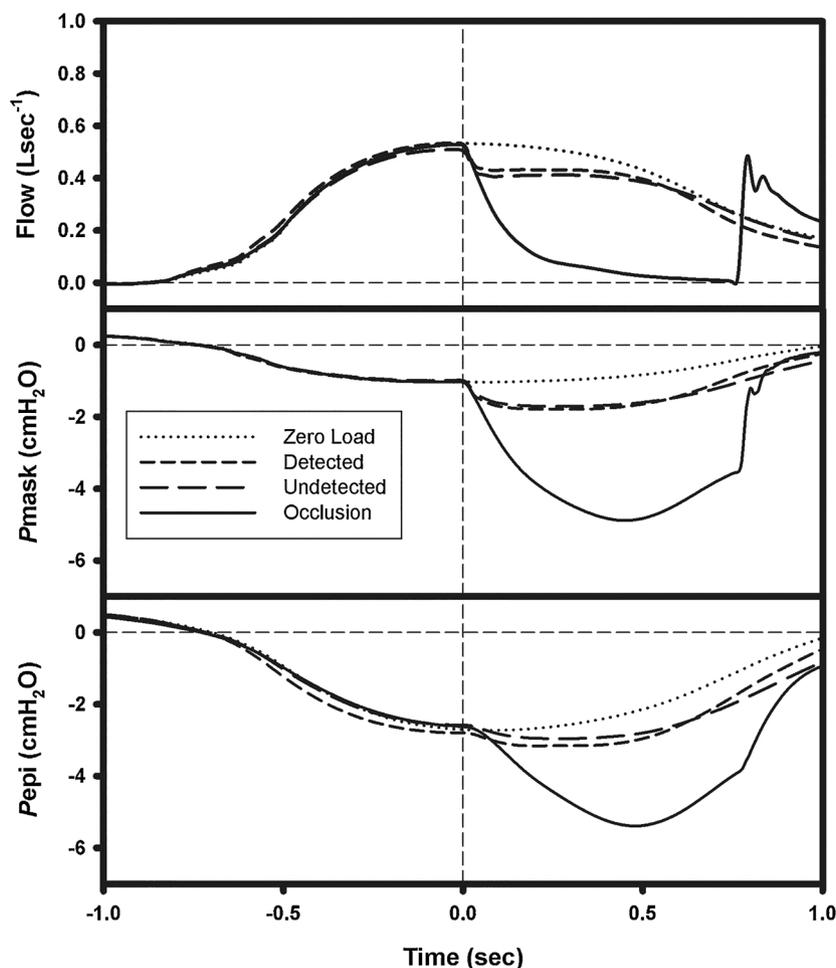


Fig. 1. Stimuli presented in the study.

Panels from top to bottom are: (i) Flow, (ii) mask pressure, and, (iii) epiglottic pressure. Traces are the grand average (n = 10 for Pmask and flow; n = 9 for Pepi), with the various stimulus conditions overlaid on each other. Abbreviations: Pmask: mask pressure; Pepi: epiglottic pressure.

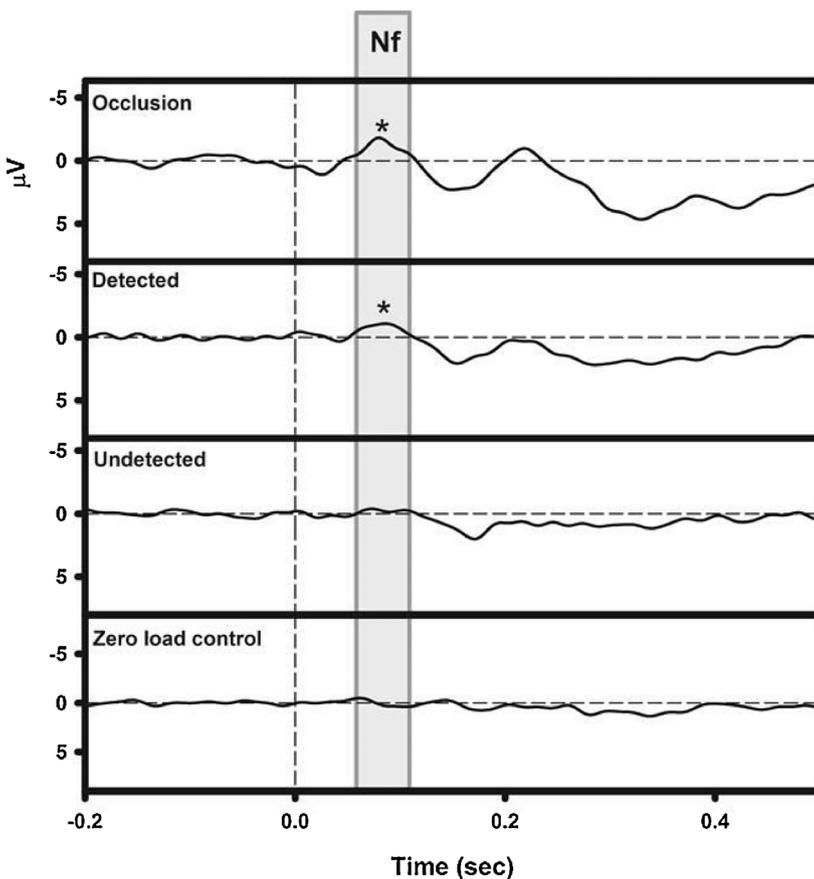


Fig. 2. Grand average ($n = 10$ participants) RREPs from F_z electrode site.

Horizontal panels represent responses to occlusion, detected loads, undetected loads and the zero load control. Grey vertical panel represents the 50 ms component detection window for Nf, defined by the latency of Nf in response to the occlusion stimulus. Symbols: * = Baseline-to-peak measurement significantly different ($P < 0.05$) from zero load control.

different between detected and undetected loads ($P = 0.248$). Visual inspection of the grand averaged RREP at F_z , suggested Nf was present for occlusion and detected loads but not undetected loads or the zero load control (Fig. 2).

3.4.2. P1

There was no statistically significant difference in baseline-to-peak P1 amplitude between stimulus conditions (Table 3). However, there was a significant difference in peak-to-peak P1 amplitude between stimulus conditions. Planned contrasts revealed that the peak-to-peak P1 amplitude was significantly greater for detected resistive loads ($P = 0.020$), undetected loads ($P = 0.001$) and occlusion ($P = 0.001$), when compared to the zero load control. Peak-to-peak P1 amplitudes were not significantly different between detected and undetected loads ($P = 0.372$). Visual inspection of the grand average RREP at C_z , suggested P1 was present for the occlusion, detected and undetected loads but not the zero load control (Fig. 3).

3.4.3. N1

There was no statistically significant difference in baseline-to-peak N1 amplitude between stimulus conditions (Table 3).

3.4.4. P3

There was a statistically significant difference in baseline-to-peak P3 amplitude at P_z between stimulus conditions (Table 3). Planned contrasts revealed that the baseline-to-peak amplitude in the P3 component detection window was significantly greater for detected resistive loads ($P = 0.006$) and occlusion ($P < 0.001$) but not undetected loads ($P = 0.431$), when compared to the zero load control. Baseline-to-peak P3 amplitudes were significantly greater for detected compared to undetected loads ($P < 0.001$). There was also a significant difference in peak-to-peak P3 amplitude between stimulus conditions (Table 3). Similar to the baseline-to-peak measurements, planned contrasts revealed

that the peak-to-peak P3 amplitude was significantly greater for detected resistive loads ($P < 0.001$) and occlusion ($P < 0.001$), but not undetected loads ($P = 0.189$) when compared to the zero load control. Peak-to-peak P3 amplitudes were significantly greater for detected compared to undetected loads ($P < 0.001$). Visual inspection of the grand averaged RREP at P_z , indicated P3 was present for occlusion and detected loads but not undetected loads or the zero load control (Fig. 4).

3.5. RREP component latencies

There were no statistically significant differences between stimulus conditions in the latency from stimulus onset of any component peaks (Nf, P1, N1, and P3) (Table 4).

4. Discussion

In this study a unique methodology was used to examine the relationship between the RREP and conscious detection of respiratory loads. Respiratory loads spanning the conscious detection threshold were separated into those that were consciously detected and those that were not, then separate ensemble averages were created from these two groups of stimulus presentations that were matched for stimulus intensity and number of stimulus presentations. In opposition to the hypothesis that predicted that RREP components would not be produced in response to undetected loads, the findings from this study suggest that undetected loads may produce early but not late RREP components. The detected loads that were matched for intensity, however, elicited early components and late components. There was no difference in latency of any component between detected and undetected loads.

In the present study, the peak-to-peak measurements and visual inspection of grand average RREPs (Fig. 2) suggest that the P1 component is present for both detected and undetected resistive loads. Thus

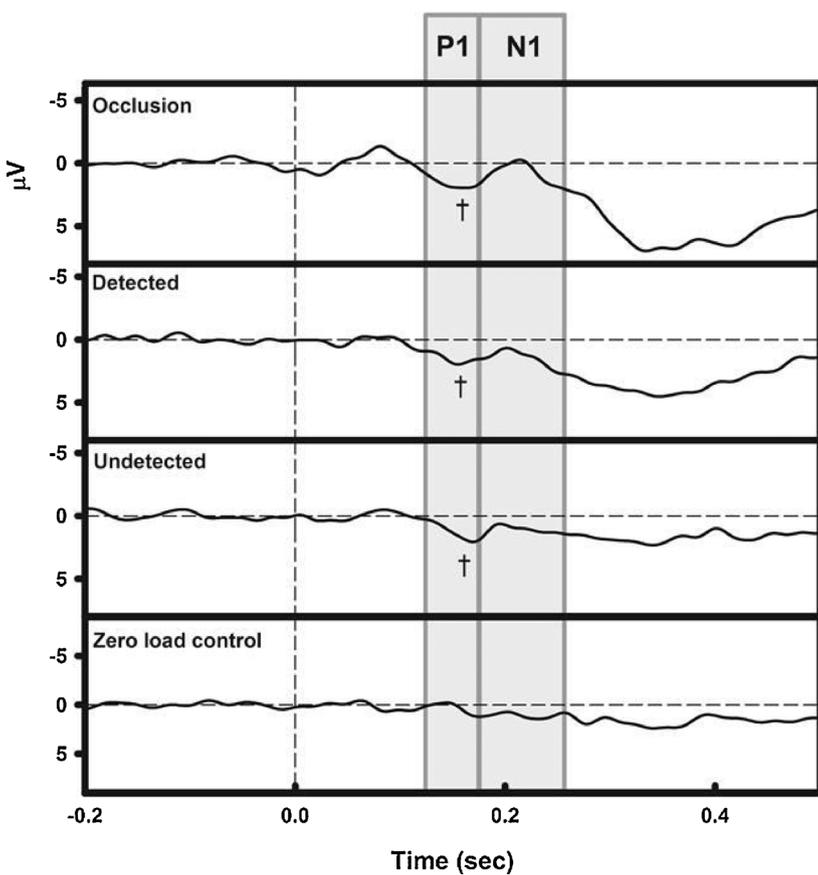


Fig. 3. Grand average ($n = 10$) RREPs from C_z electrode site. Horizontal panels represent responses to occlusion, detected loads, undetected loads and the zero load control. Grey vertical panel represents the 50 ms and 80 ms component detection window for P1 and N1 respectively, defined by the latency of components in response to the occlusion stimulus. Symbols: † = Peak-to-peak P1 measurements significantly different ($P < 0.05$) from zero load control.

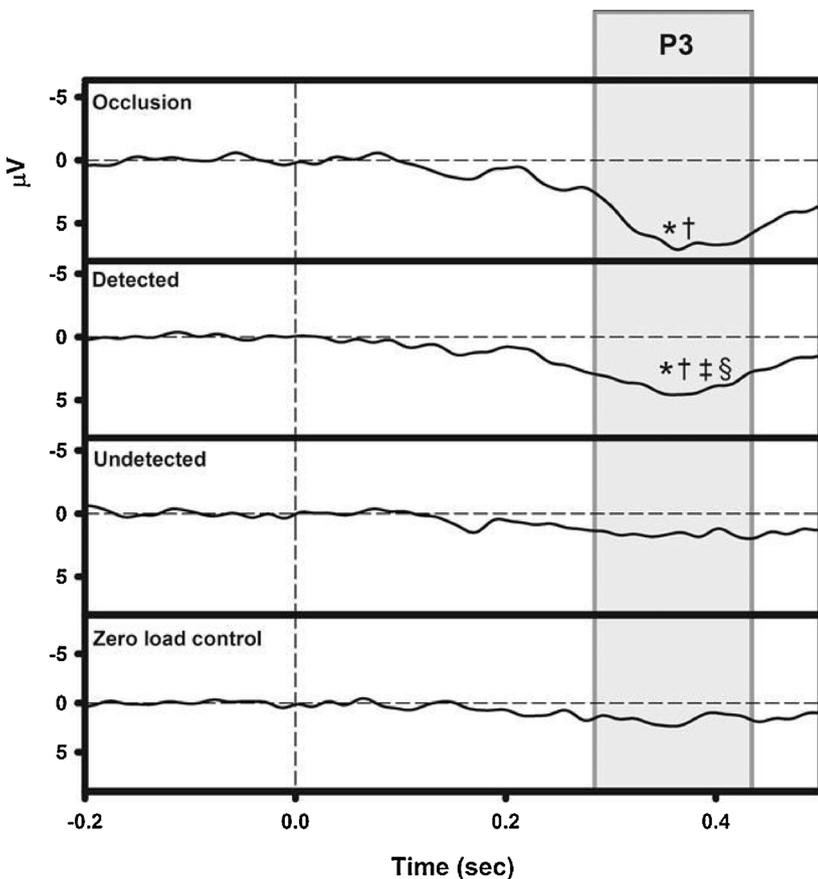


Fig. 4. Grand average ($n = 10$) RREPs from P_z electrode site. Horizontal panels represent responses to occlusion, detected loads, undetected loads and the zero load control. Grey vertical panel represents the 150 ms component detection window for P3, defined by the latency of P3 in response to the occlusion stimulus. Symbols: * = Baseline-to-peak P3 measurements significantly different ($P < 0.05$) from zero load control; † = Peak-to-peak P3 measurements significantly different from zero load control; ‡ = Baseline-to-peak detected P3 measurements significantly different from undetected P3 measurements; § = Peak-to-peak detected P3 measurements significantly different from undetected P3 measurements.

Table 4
RREP peak latencies (ms).

Component	Undetected	Detected	Occlusion	P-value
Nf @ F _z	87 (26)	85 (14)	90 (16)	0.710
P1 @ C _z	166 (15)	166 (20)	158 (22)	0.392
N1 @ C _z	228 (26)	204 (27)	212 (21)	0.196
P3 @ P _z	378 (54)	373 (37)	384 (31)	0.877

Values are mean (SD). Values are the latency from stimulus onset to the maximal RREP amplitude measured within the component detection window of interest. P-values are from one-way repeated measures ANOVA.

load-related sensory information may reach the somatosensory cortex for undetected loads close to the conscious detection threshold, but is not cognitively processed. Previous studies have suggested P1 peak is only elicited for respiratory loads above the conscious detection threshold (Chou and Davenport, 2007; Davenport et al., 2007). However, the P1 peak may not have been elicited by sub-threshold loads in previous studies as they were considerably below the conscious detection threshold at approximately 30–50% of its value (Chou and Davenport, 2007; Davenport et al., 2007). It should be noted however that for baseline-to-peak P1 measurements no significant differences were found between stimulus conditions. Given the peak-to-peak P1 amplitude results, and considering that there was no difference in baseline-to-peak P1 amplitude between the occlusion stimulus and the zero load control, this finding likely indicates a substantial influence of prior components, or that the study was insufficiently powered to detect baseline-to-peak P1 amplitude differences.

For the Nf component, baseline-to-peak amplitude for detected resistive loads was larger compared to the zero load control, but this was not the case for undetected loads. In combination with visual inspection of the grand averages, this may suggest the presence of an Nf component in response to detected but not undetected loads. Casting some doubt on this interpretation, it must be noted that there was no statistically significant difference in baseline-to-peak Nf amplitude between detected and undetected loads. Additionally there was a trend for greater Nf amplitude in response to the undetected load compared to the control load, with the mean undetected Nf amplitude being approximately 2 times that of the control load. The role of Nf in the sensory processing of respiratory stimuli is not known and so the significance of this finding is uncertain. However because of its early latency and localisation being consistent with a supplementary motor cortex source (Logie et al., 1998) it has been suggested that the Nf peak may reflect a predictive process in cognitive functioning (Chan and Davenport, 2010) or some form of preparatory motor response (Webster and Colrain, 2000a). While the results of this study do not elucidate the role of Nf, the fact that P1 and Nf may respond differently in the current study may suggest different gating mechanisms for these components, and is consistent with the dipole modelling study of Logie et al. (1998) which proposes that P1 and Nf are likely generated by separate radial dipoles.

The most robust finding from this study was that detected resistive loads produced the P3 component of the RREP whereas undetected loads did not. This finding was observed when baseline-to-peak and peak-to-peak measurements were made, and was clearly evident on visual inspection of the grand average RREPs (Fig. 4). This result is consistent with previous studies suggesting that only loads above the conscious detection threshold produce a P3 component (Davenport et al., 2007). Additionally, our results suggest that P3 may act as an index of the perceptual detection of increased airflow resistance, and add to the evidence that the P3 peak is related to the cognitive processing of respiratory stimuli. Other observations supporting the proposal that P3 is related to cognitive processing include: (i) P3 amplitude is related to attention; it is diminished or absent if attention is not directed to the stimulus (Davenport et al., 2007; Harver et al., 1995; Webster and Colrain, 2000b), (ii) P3 amplitude is influenced by

emotion (von Leupoldt et al., 2011, 2013; von Leupoldt et al., 2010b), (iii) P3 amplitude is influenced by stimulus context, for example larger amplitudes are observed with smaller stimulus probability (Webster et al., 2002), (iv) P3 amplitude has a direct correlation with stimulus magnitude estimation (Webster and Colrain, 2000a), and, (v) P3 is dampened in both healthy and asthmatic poor perceivers (Webster and Colrain, 2002).

The observed results have implications on theories relating to threshold gating of respiratory stimuli. Gating of respiratory stimuli has been proposed by Davenport and colleagues (Chan et al., 2016, 2012; Chan and Davenport, 2008, 2009; Chenivresse et al., 2014; Chou and Davenport, 2007; Davenport and Vovk, 2009; O'Donnell et al., 2007), where the “gate” is considered as a filter of sensory stimuli. If current data is interpreted to indicate that Nf and P3 peaks are absent in response to undetected loads but present in response to detected loads then this is consistent with a proposed subcortical threshold gating process (Chan and Davenport, 2008; Chou and Davenport, 2007; Davenport and Vovk, 2009; O'Donnell et al., 2007), whereby if stimulus magnitude is sufficient the subcortical gate allows respiratory information to be transmitted to the cortex. In contrast, the P1 data from the current study suggest that the P1 component is present in response to detected and undetected loads close to the detection threshold, which is more supportive of a cortical gating mechanism. This is supported by the observation that P1 to undetected loads was not substantially altered compared to detected loads. The mean peak-to-peak P1 amplitude in response to undetected loads was close to 100% of the mean P1 amplitude in response to detected loads. This is in contrast to the frequency gating study of Chan et al. (Chan and Davenport, 2008) which examined the RREP response to paired 150 ms occlusions in a single breath, separated by a 500 ms interval. That study reported peak Nf, P1 and N1 amplitudes for the second presentation that were approximately 80–85%, 60–65%, and 45% of the first presentation respectively, suggested by the authors to indicate attenuation of signals arriving in the somatosensory cortex (Chan and Davenport, 2008).

It has been suggested that N1 peak may be important in the gating process, linking the primary sensory neural information and the attention related cognitive processes (Chan et al., 2016, 2012; Chan and Davenport, 2008, 2010; Chan and Davenport, 2009; Chenivresse et al., 2014; Davenport et al., 2007; Davenport and Vovk, 2009). This suggestion is related to its dependence on attention (Davenport et al., 2007; Webster and Colrain, 2000b) and its temporal location. Chan et al. (Chan and Davenport, 2008) emphasised the importance of the N1 peak in frequency gating, highlighting that it was attenuated to a greater degree than other peaks. Whilst in the present study a trend for increasing N1 amplitude was observed, from undetected to detected to occlusion stimuli, there was no statistically significant difference from the zero load control for any stimulus condition. There is a possibility the N1 result is a type-II error, however the P1 and N1 results in the present study taken together suggests a distinction between threshold gating of respiratory stimuli and frequency gating.

More generally, the observation in the current study that P1 is present in response to undetected loads but not other components, may suggest that different processes are involved in the gating of the different components and therefore that respiratory sensory gating is a multi-stage (cortical and sub-cortical) and multi-component process. This is similar to proposals for other sensory modalities (Boutros and Belger, 1999).

The methodology of the present study allowed a close matching of stimulus intensity and the number of stimulus presentations contributing to the RREPs in response to detected and undetected loads. While the stimuli were closely matched they were not identical, with very small (and of questionable physiological significance) but statistically significant differences observed, possibly providing insight into the process of stimulus detection. Although the R₀ and ΔR were well matched, detected loads had slightly more negative baseline P_{mask} and P_{epi} and therefore greater inspiratory flow, suggestive of greater

ventilatory drive prior to stimulus presentation. This observation is consistent with the findings of Burdon et al. (1982) which showed increased magnitude estimation with increased ventilatory drive induced by exercise, hypercapnia, and hypoxia. In that study the authors proposed that the close relationship between magnitude estimation and mouth pressure was indicative of an important role of inspiratory muscle force in sensing respiratory loads.

Some caution should be exercised in interpretation of the results from the present study. The analysis used 10 of 17 healthy control participants who were part of a larger study comparing OSA patients to healthy controls in their threshold RREP response to inspiratory resistive loads (Ruehland et al., 2017). The Ruehland et al. (2017) study aimed to target loads around the conscious detection threshold but not necessarily at the conscious detection threshold. This meant that for the current study analysis participants were excluded if presented loads were not sufficiently close to the conscious detection threshold. The reduced number of included participants may have contributed to the inability to find significant baseline-to-peak P1 and N1 amplitude differences between stimulus conditions. It is also recognised that this study may have benefited by increasing the number of number of load presentations and therefore increasing the signal-to-noise ratio of the RREP, which in turn would reduce the number of excluded participants. Increasing the number of load presentations however, was not feasible given the already lengthy and monotonous task assigned to participants and because signal-to-noise ratio only increases as a function of the square root of the number of trials (Luck, 2005). Nevertheless, future studies using similar methodology may benefit by specifically targeting resistive loads at or very close to the conscious detection threshold. This could be achieved using a threshold tracking procedure similar to that described by Zechman and Burki (1976), and would serve to maximise the number of peri-threshold stimulus presentations.

A caveat should also be made about the gender of participants who were recruited for the current research. As previously mentioned the analysis used 10 of 17 healthy control participants who were part of a larger study comparing OSA patients to healthy controls (Ruehland et al., 2017). Although it was not intentional, in that study the selection criteria, which combined severe OSA with a restricted BMI, resulted in a sampled OSA population, and therefore a group of matched controls, that included male but not female participants. Given that there are known gender differences regarding respiratory sensation and dyspnoea (Gui et al., 2014; Schaeffer et al., 2014), further work is required to confirm the current results are applicable to both genders.

In this study there was no reliance on subjective RREP peak detection. Instead an automated process was utilised, measuring peak amplitudes in a predefined component detection window, based on a large stimulus, occlusion, to guide where components would be expected to occur. This was possible as component latency does not change with stimulus magnitude (Davenport et al., 2007; Webster and Colrain, 2000a). Using a control stimulus accounted for any noise within the ensemble average and for any deflections not related to presentation of the stimulus. The importance of zero load control is highlighted by the grand average RREP at P_z which demonstrated a small positive deflection which may be related to the detection task required for participants in this study (Fig. 4).

Creating component detection windows was also important as our components were later compared to previous studies. In the present study and our past study (Ruehland et al., 2017), P1 latencies were reported at approximately 160 ms, whereas mean P1 latencies have previously been reported in the range of ~60–145 ms (Davenport et al., 2007; Gora et al., 2002; Tapia et al., 2015; Webster and Colrain, 2000a). As has been previously suggested (Gora et al., 2002; Ruehland et al., 2017), it is proposed that this was a result of the nature of the stimulus, in particular the rate of pressure change, which is a function of the apparatus used to deliver the stimulus, as well as respiratory drive. Indeed, Davenport et al. (Davenport et al., 1986) noted that individuals with reduced rate of pressure change had longer component

latencies and that mouth pressure change at 0.1 s was inversely correlated with the latency of the RREP P1 peak. To assess this contention, three control participants attended on a separate occasion to the main experimental testing and a comparison was made between RREP responses to occlusion of our apparatus with and without the loading manifold in circuit. Removing the loading manifold resulted in maximal rate of pressure change increase in the order of $70 \text{ cmH}_2\text{O}\cdot\text{s}^{-1}$ and a reduction in P1 latency in the order of 60 ms on average. Thus longer RREP peak latencies may be due to a delay between stimulus onset and respiratory mechanoreceptor activation. Importantly, the faster rate of pressure change only reduced component latency and did not change the pattern of components observed.

In the current study there was no significant difference between detected, undetected loads and occlusion in the latency of any of the RREP components. Our latency findings are consistent with previous observations that latency of components is not influenced by stimulus magnitude (Davenport et al., 2007; Webster and Colrain, 2000a), although one must consider that latencies were constrained by component detection windows in the current study.

5. Conclusion

Using a novel methodology, this study examined the relationship between conscious detection of respiratory loads and the RREP. The study tested the notion that only loads above the conscious detection threshold produce RREP components (Chou and Davenport, 2007; Davenport et al., 2007) by comparing ensemble averages from detected and undetected loads close to the conscious detection threshold, matched for stimulus intensity and number of stimulus presentations. The results from the present study indicate that the P1 component of the RREP, but not other components, may be present in response to undetected loads. Considering that P1 is thought to reflect arrival of somatosensory information at the cortex, and P3 is thought to reflect cognitive processing, this result suggests that normal load-related sensory information reaches the somatosensory cortex for sub-threshold loads near the detection threshold, but is not cognitively processed. If replicated in future studies, this observation has implications for the threshold gating of respiratory stimuli, indicating involvement of sub-cortical and cortical mechanisms and suggesting multi-stage and multi-component processes.

Author contributions

This study was performed at the Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia.

WRR, PDR, and FJO'D contributed to study design. Data collection, analysis and manuscript preparation were performed by WRR. WRR, PDR, JAT, JS, and FJO'D contributed to results interpretation, manuscript revision and editing. Additionally, all authors:

- approved the final version of the manuscript
- agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
- qualify for authorship, and agree that all those who qualify for authorship are listed

Competing interests

The authors declare no conflicts of interests.

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