Age-related changes in the neural gating of respiratory sensations in humans

Wen-Pin Chang [1,8], Kai-Jie Liang [2,3,8], Chia-Hsiung Cheng [2,4,5], Chia-Yih Liu [4,6], Andreas von Leupoldt [7] and Pei-Ying S. Chan [2,4]

[1]Department of Occupational Therapy, University of Texas Rio Grande Valley, Edinburg, TX, USA. [2]Department of Occupational Therapy, College of Medicine, Chang Gung University, Taoyuan, Taiwan. [3]Department of Occupational Therapy, College of Medical Science and Technology, Chung Shan Medical University, Taichung, Taiwan. [4]Department of Psychiatry, Chang Gung Memorial Hospital at Linkuo, Taoyuan, Taiwan. [5]Brain Imaging and Neural Dynamics Laboratory, College of Medicine, Chang Gung University, Taoyuan, Taiwan. [6]Department of Psychiatry, New Taipei City Municipal Tucheng Hospital, New Taipei City, Taiwan. [7]Research Group Health Psychology, Faculty of Psychology and Educational Sciences, University of Leuven, Leuven, Belgium. [8]These authors contributed equally.

Corresponding author: Pei-Ying S. Chan (chanp@cgu.edu.tw)

Shareable abstract (@ERSpublications)
Ageing has an impact on the neural gating of respiratory sensations in healthy adults. Higher age is associated with reduced neural processing of the first stimulus in a pair, resulting in poorer gating function. https://bit.ly/3TPFvc4

Cite this article as: Chang W-P, Liang K-J, Cheng C-H, *et al*. Age-related changes in the neural gating of respiratory sensations in humans. *ERJ Open Res* 2024; 10: 00821-2023 [DOI: 10.1183/23120541.00821-2023].

Received: 27 Oct 2023
Accepted: 19 Dec 2023

Abstract

Background Neural gating of respiratory sensations (NGRS) characterises the brain's ability to filter out repetitive respiratory sensory stimuli. This mechanism plays a crucial role in the neural processing of respiratory stimuli. However, whether ageing affects NGRS in healthy adults is still unclear. Therefore, we aimed to measure the effect of age on NGRS as well as the corresponding S1 and S2 components of the respiratory-related evoked potentials (RREPs).

Methods Three age groups of healthy adults participated in this study: a young group (YG; age 20–39 years), a middle-aged group (MG; age 40–59 years) and an old group (OG; age ⩾60 years). NGRS was measured by the RREPs in the electroencephalogram in response to short-paired respiratory occlusion stimuli (S1 and S2). The S2/S1 ratio of the RREP N1 amplitude (the negative deflection of the RREP at ∼85–135 ms) was used to characterise NGRS.

Results The results showed a significantly smaller N1 S2/S1 ratio in the YG than in the MG (p=0.01) and OG (p=0.03). Further analysis showed that the S1 N1 amplitude was larger for the YG compared with the MG (p=0.03) and OG (p=0.007). Moreover, age was significantly correlated with the N1 S2/S1 ratio (r=0.43), with higher age relating to higher N1 S2/S1 ratios.

Conclusions The greater N1 S2/S1 ratios observed in older adults suggest that ageing has a negative impact on the NGRS. This might contribute to increased experiences of respiratory sensations such as dyspnoea in ageing adults.

Introduction

Healthy humans actively inhale and passively exhale constantly and rhythmically at rest [1]. The process of respiration is fundamentally vital in maintaining homeostasis in the body by regulating the exchange of oxygen and carbon dioxide, and typically occurs automatically without reaching consciousness. According to the neural gating hypothesis of respiratory sensations [2, 3], a neural filter mechanism (*i.e.* neural gating of respiratory sensations (NGRS)) prevents the brain from being overloaded by repetitive respiratory sensations. By gating-out such unnecessary sensory information, NGRS allows sufficient neural processing capacities for other daily living tasks [3, 4]. However, in several situations, respiration can be sensed deliberately (*e.g.* during meditation) or due to increased respiratory demand (*e.g.* during dyspnoea) [5, 6]. Such circumstances result in the transmission of respiratory information to higher brain centres, which

causes the allocation of attentional resources to the respiratory process and brings respiratory sensations into consciousness, *i.e.* gating-in [4]. The pathophysiology of respiratory and some psychological diseases is significantly influenced by the presentation of respiratory sensations [7–9]. Impairments in NGRS have been suggested to contribute to increased experiences of respiratory sensations such as dyspnoea [10] and generalised anxiety disorder [7].

Moreover, previous studies have shown that higher age is associated with changed experiences of respiratory sensations such as breathlessness or dyspnoea [11–14]. For example, Hegendörfer and Degryse [12] indicated that the prevalence of breathlessness ranged from 25% to 36% in older adults, and the prevalence increased with age. On the other hand, Battaglia *et al*. [11] indicated that ageing is associated with blunted feelings of dyspnoea. Nevertheless, Olsson *et al*. [13] suggested that older adults who experienced breathlessness may develop coping mechanisms over time, resulting in a U-shape phenomenon in their reported breathlessness experiences. Similarly, Petersen *et al*. [14] found that although older adults generally presented with lower lung functions, their subjective experience of respiratory discomfort was not necessarily higher compared with younger adults.

Given these contrasting findings, testing the ageing effect on the underlying neural processing of respiratory sensations, such as NGRS, can potentially contribute to a better understanding of changes in dyspnoea experiences in older age. To date, it has been established that earlier developmental phases may affect NGRS [15]; however, it remains unknown whether older age can influence NGRS as well.

Therefore, the present study aimed to investigate potential age-related changes in NGRS in healthy adults using the paired respiratory-related evoked potential (RREP) paradigm. In previous studies, the paired-occlusion paradigm was found to result in decreased amplitudes of the RREP components to the second stimulus (S2) in contrast to the first stimulus (S1) in healthy young adults, hence it is thought to reflect NGRS [2, 16]. The N1 (physiological measurement of attention) S2/S1 ratio is a frequently used index for quantifying NGRS, with a typical ratio in healthy adults nearing 0.5 [2]. We hypothesised that NGRS would gradually decline as age increases, as represented by increased RREP N1 S2/S1 ratios.

Methods

Participants

A total of 57 healthy nonsmokers were enrolled in the study and divided into three age groups: a young group (YG; n=20, age 20–39 years), a middle-aged group (MG; n=20, age 40–59 years) and an old group (OG; n=17, age ⩾60 years). All participants self-reported the absence of neurological, cardiovascular or pulmonary conditions. The Institutional Review Board Committee of the Chang Gung Medical Foundation (Taoyuan, Taiwan) approved the study protocol (#201902211B0C103).

Respiratory apparatus

A detailed description of the measurement setup was provided in Chan and Davenport [17]. Briefly, the participant was instructed to sit in an armed chair and breathed through an occasionally closed two-way nonrebreathing valve (Hans Rudolph, Kansas City, MO, USA) with their nose clipped. The valve was connected to a customised occlusion valve (Hans Rudolph), which was further controlled by a solenoid connected to a pressured air tank *via* reinforced tubing. The mouth pressure was recorded with a differential pressure transducer that was connected to a pneumotachograph amplifier (1110 series; Hans Rudolph) and a PowerLab AD converter (ADInstruments, Bella Vista, Australia). Closure of the occlusion valve was manually controlled by the experimenter with a customised trigger box. The participants were familiarised with the experience of the paired inspiratory occlusions before the actual experiment. With a 40-channel EEG device (NuAmps; Compumedics Neuroscan, Charlotte, NC, USA), the continuous EEG was measured at 1 kHz, with an additional notch filter (60 Hz), and referenced to the bilateral mastoids. The impedance of each electrode was kept below 5 kΩ. The EEG recording software (Neuroscan 4.5; Compumedics Neuroscan) received parallel markers for occlusion presentations from an external trigger box. The start of the occlusion-induced mouth pressure change was used as the onset of occlusions during the RREP analyses (LabChart version 7; ADInstruments).

Experimental procedure

All participants were provided with a detailed informed consent form explaining the nature of the study before the experiment. Thereafter, participants performed a pulmonary function test (PFT) to assure adequate baseline lung function with forced spirometry (Cardinal Health, Dublin, OH, USA) based on the guidelines of the American Thoracic Society and European Respiratory Society [18]. After the PFT, participants completed the self-reported respiratory symptom questionnaire. Specifically, we adapted the St George's Respiratory Questionnaire (SGRQ) [19] to measure respiratory symptoms in healthy adults by

adopting and modifying the second section of the original SGRQ to include items regarding daily living activities. These items are better suited for healthy individuals without respiratory problems. This modification served as the foundation of our respiratory questionnaire. The questionnaire comprised 38 questions on a 4-point rating system (0=never, 3=always). Higher total scores, which range from 0 to 114, indicated more respiratory problems.

After completing the questionnaire, participants were seated in an armed chair with back support. The experiment consisted of two blocks of 100 trials each, during which inspiratory occlusion pairs were presented while the subjects were instructed to attend to occluded breaths mentally. Respiratory occlusion pairs (duration ∼150 ms) with a 500-ms interstimulus interval were presented at the onset of inspiration every second to fourth breath. Following each block, the participants used a visual analogue scale (VAS) to rate their subjective breathlessness intensity and breathlessness unpleasantness (0=not breathless/not unpleasant at all, 100=most breathless/unpleasant).

Data analyses

The amplitudes of RREP peaks were determined individually for the S1 and S2 RREPs. Specifically, the N1 peak was identified from 85 to 135 ms following the occlusion-induced mouth pressure change for the S1 and S2 RREPs. Both the baseline-to-peak and peak-to-peak methods were utilised for quantifying the N1 peak amplitudes. For the peak-to-peak method, the differences in peak amplitudes were measured from the preceding P1 peak to the subsequent N1 peak. The P1 peak was defined as the maximum positive peak between 40 and 100 ms post-occlusion. After determining the peak amplitudes, S2/S1 ratios for each N1 peak were calculated. The normality assumptions were checked using the Shapiro–Wilk test. Baseline demographics and N1 S2/S1 ratios were compared between groups using Welch's or Kruskal–Wallis ANOVA based on the data distribution. Categorical data were examined using the Chi-squared test. If a significant effect was found in Welch or Kruskal–Wallis one-way ANOVA, the post-hoc analyses were conducted using the Games–Howell or DSCF (Dwass–Steel–Critchlow–Fligner) comparison [20, 21], respectively. PFT performance as well as the self-reported data were also compared between the three groups using Welch or Kruskal–Wallis one-way ANOVA followed by post-hoc analysis. For amplitudes of single S1 and S2 RREP components, a 3 (Group)×2 (Stimuli) repeated measures ANOVA was performed. Significant interaction effects were followed up with post-hoc t-tests with Bonferroni correction. In addition, Pearson or Spearman correlation analyses were performed to determine the relationship between age and N1 S2/S1 ratios as well as the RREP N1 peak amplitudes. All statistics were performed using JAMOVI version 2.3.28 (www.jamovi.org) and the p-value threshold was set at $p<0.05$.

Results

The demographics, PFT results and self-reported questionnaire scores for the three age groups are shown in table 1. The mean±SD ages for the YG, MG and OG were 28.95±6.20, 47.95±6.37 and 67.24±5.12 years, respectively. For the PFT results, there was no significant difference between the three groups in percentage predicted forced expiratory volume in 1 s ($p=0.21$). For the self-reported questionnaire, there was no significant difference in terms of self-reported respiratory symptoms scores between the three groups (9.65±13.24 for YG, 11.80±9.24 for MG and 7.06±7.14 for OG; $p=0.23$).

Figure 1 shows the bar graphs for N1 S2/S1 ratios using the peak-to-peak and baseline-to-peak analyses, respectively. There was a significant difference between the three age groups in terms of peak-to-peak N1

TABLE 1 Demographic characteristics, lung function and questionnaire results of the study participants

	YG (20–39 years)	MG (40–59 years)	OG (⩾60 years)	p-value[#]	Post-hoc test
Subjects	20	20	17		
Age (years)	29±6	48±6	67±5	<0.001	YG<MG<OG
Sex (male/female)	7/13	6/14	9/8	0.33	
FEV_1 % pred	84.90±5.71	88.45±9.78	90.24±14.65	0.21	
Respiratory questionnaire score	10±13	12±9	7±7	0.23	
VAS Breathlessness intensity	34.95±27.00	30.71±24.16	27.94±28.21	0.65	
VAS Breathlessness unpleasantness	41.37±31.13	30.58±27.53	27.53±29.30	0.35	

Data are presented as n or mean±SD, unless otherwise stated. YG: young group; MG: middle-aged group; OG: old group; FEV_1: forced expiratory volume in 1 s; VAS: visual analogue scale. [#]: across the three groups.

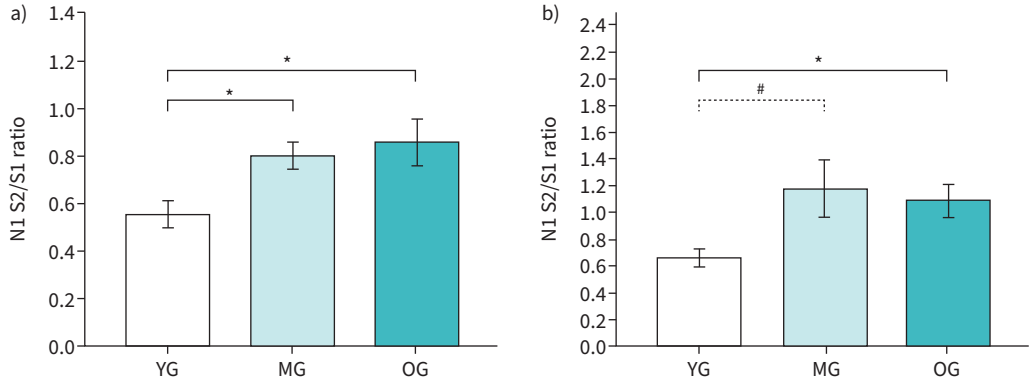

FIGURE 1 Group averaged respiratory-related evoked potential N1 peak S2/S1 ratio at the Cz electrode for the young group (YG), middle-aged group (MG) and old group (OG) by using the a) peak-to-peak method and b) baseline-to-peak method. Error bars represent standard error. *: p<0.05; #: p<0.06.

S2/S1 ratios (0.55±0.24 for YG, 0.79±0.25 for MG and 0.86±0.40 for OG; p=0.005). The post-hoc test showed that the YG had significantly smaller N1 S2/S1 ratios than the MG and OG (p=0.01 and p=0.03, respectively), but the ratios between the MG and OG were not significantly different (p=0.82). Similar ANOVA results were obtained using the baseline-to-peak method with a significant difference in N1 S2/S1 ratios between groups (0.65±0.26 for YG, 1.18±0.92 for MG and 1.08±0.50 for OG; p=0.03). Corresponding post-hoc comparisons showed significantly smaller N1 S2/S1 ratios for the YG compared with the OG (p=0.01) and as a trend when compared with the MG (p=0.06). However, the ratios for the MG and OG were not significantly different (p=0.90).

Figure 2 shows the group averaged RREP waveforms measured at the Cz (midline central) electrode for S1 and S2 RREPs for all three age groups. The two-way repeated measures ANOVA for Stimuli (S1 and S2 N1 peak-to-peak amplitudes) and Group (YG, MG and OG) showed a significant Stimuli×Group interaction (F=9.56, p<0.001). The post-hoc analyses showed that the S1 N1 amplitude for the YG (−13.05±5.09 µV) was significantly larger than for the MG (−8.95±2.60 µV; p=0.03) and OG (−8.11±3.99 µV; p=0.007). However, N1 amplitudes for the MG and OG were not significantly different (p=0.74). In contrast, there was no significant difference for the S2 N1 amplitudes between the three groups (−6.95±2.99, −6.91±2.69 and −6.29±3.09 µV for YG, MG and OG, respectively; p=0.77).

Finally, the correlational analyses showed that higher age was significantly correlated with higher N1 S2/S1 ratios (Spearman's ρ=0.43, p<0.001) (figure 3a). There was also a significant relationship between higher age and smaller S1 N1 amplitudes (Spearman's ρ=0.47, p<0.001) (figure 3b). There was no significant relationship between the reported respiratory symptoms and the N1 amplitude S2/S1 ratios or between the VAS scores and the N1 S2/S1 ratios.

Discussion

The present study demonstrated that ageing was associated with reduced NGRS in healthy adults, where the youngest adults (YG) showed the lowest N1 S2/S1 ratios, followed by the older groups (MG and OG). Moreover, age was significantly positively correlated with the N1 S2/S1 ratio as well as the S1 N1 amplitudes.

This finding of decreased NGRS (represented by increased N1 amplitude S2/S1 ratios) in the OG group indicates that older adults' neural gating of repeated respiratory inputs is less effective than that of young adults. This finding is comparable to a previous neural gating study in healthy older adults in other somatosensory domains [22]. Specifically, Terrasa *et al.* [22] probed 20 healthy young adults and 20 older adults and showed reduced N1 sensory gating (*i.e.* larger N1 S2/S1 ratio) in older individuals than young adults in response to pneumatic stimuli.

To better understand the factors contributing to the ageing effect resulting in differences in the NGRS, we performed additional analyses comparing the N1 amplitudes of S1 and S2 between the three groups. Our analyses showed that older adults had a smaller N1 amplitude for S1 than the young adults but not for S2, indicating that the deficient NGRS in older adults compared with young adults was mainly due to a smaller response to the first of the paired stimuli. This finding is consistent with the results obtained in a

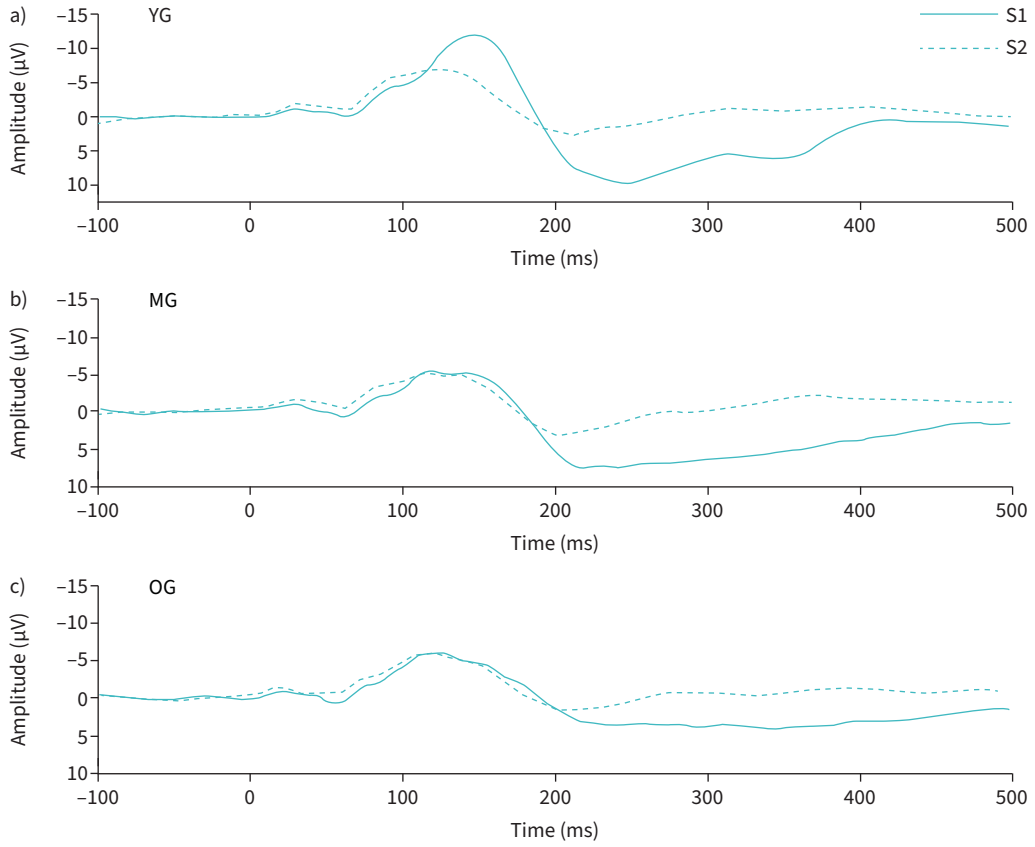

FIGURE 2 Group averaged waveforms for the S1 and S2 respiratory-related evoked potentials measured at the Cz electrode: a) young group (YG), b) middle-age group (MG) and c) old group (OG).

study by Epiu *et al*. [23] using a single-occlusion paradigm, which observed a greater N1 amplitude in young adults compared with older adults. Our current findings imply that a diminished neural respiratory sensory gating function in older adults is more closely associated with a reduced reaction to the initial, novel stimulus (S1) than to a reduced response to the second, redundant stimulus (S2). This suggests that a diminished response to the initial respiratory stimulus may be the primary cause of respiratory sensory gating in older persons, which is also supported by our observation of a significant relationship between reduced N1 amplitudes of S1 and older age.

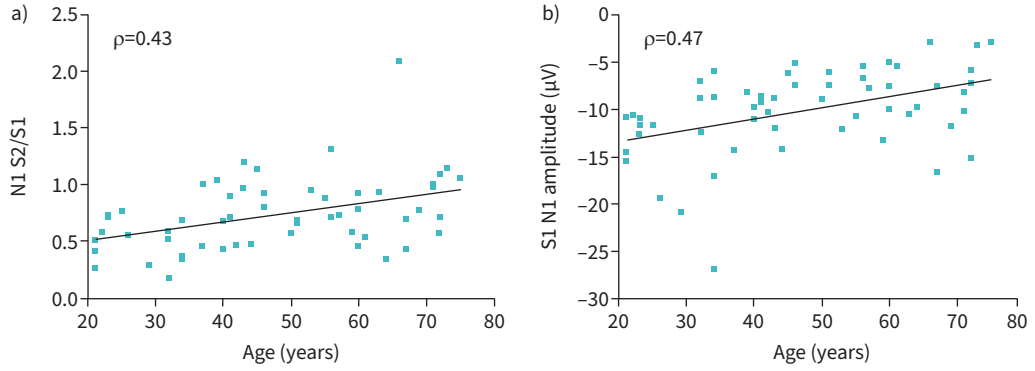

FIGURE 3 Scatter plots for the correlations of a) N1 S2/S1 ratio (peak-to-peak method) and b) S1 N1 amplitude (peak-to-peak method) and age for all participants across the three groups (n=57).

Interestingly, Reijnders *et al*. [9] delineated how middle-aged to older-aged patients with COPD perceived and processed respiratory stimuli, and they observed that the mean amplitudes of the RREP components were larger in COPD patients, who also described the occlusions as more intense, unpleasant and attention-demanding than healthy controls. However, whether ageing poses an effect on the NGRS in populations with diseases such as COPD needs further investigation, especially since other studies suggested that older adults do not always report more subjective respiratory discomfort, even with low lung function [14].

Generally, the N1 component is thought to indicate a physiological measure of attention, and according to Näätänen and Picton [24], it appears to be generated within the secondary somatosensory cortex and is mostly dispersed over frontocentral areas. The somatosensory gating study by Terrasa *et al*. [22] and the auditory gating study by Zhang *et al*. [25] both showed that older adults had less activation and involvement of the anterior cingulate cortex and medial frontal gyrus than young adults during gating. These regions have been linked to attention and self-related processing [26]. Additionally, Seeley *et al*. [27] indicated that the anterior cingulate cortex participates in a salience network that detects relevant stimuli. Therefore, regardless of the sensory modality used, the decreased activity over these brain areas may contribute to the age-related deficit in older adults at the attentional component of sensory gating and may also underlie the specific reductions in the N1 amplitudes to S1 observed in our study. Future studies are encouraged to examine changes in terms of neural activation levels of different brain areas in respiratory sensation in relation to age with neuroimaging techniques such as functional magnetic resonance imaging.

We also tested whether the experienced respiratory symptoms in daily life were related to potential age-related reductions in the NGRS. Despite the age-related change of the N1 gating ratio found in our study, there was no relationship between the self-reported symptoms and the N1 S2/S1 ratios nor age-related differences in experienced symptoms. This may be due to the fact that the symptoms reported in our study from exclusively healthy adults were overall very low, presumably resulting in a floor effect. Alternatively, a discrepancy may exist between subjective respiratory symptoms and objective N1 S2/S1 ratio measures, as several previous studies failed to find a direct correlation between subjective respiratory symptoms and objective respiratory sensory gating measures, both in healthy populations or in patients with anxiety [16, 28]. One exception was the study by Herzog *et al*. [10], where different levels of inspiratory loads were used to elicit increasing dyspnoea during parallel RREP measurements in healthy volunteers. Here, neural gating decreased as dyspnoea increased. Such contrasting findings once again suggest that the subjective perception of respiratory sensations may vary significantly between individuals and, therefore, it remains difficult to test the relationship between an objective measure of brain activations and subjective ratings of respiratory symptoms within a bigger sample. However, it may be more feasible to test these relationships after the objective and subjective parameters undergo some “standardisation”, such as in the experimental design used by Herzog *et al*. [10] to compare different conditions within the same individual. This may also mitigate the impact of overall low symptom reporting in healthy samples, which potentially influenced the results of the correlation analyses in the present study.

Notably, we used two metrics to determine the N1 S2/S1 ratio by utilising the baseline-to-peak and peak-to-peak methods to measure RREP amplitudes. Using the traditional baseline-to-peak analysis, we discovered potential problems of different baseline drift issues between the S1 and S2 peak amplitudes, especially in the MG and OG. Similar issues were also mentioned by Chenivesse *et al*. [29], who tested the effect of negative emotional stimulation on NGRS. The peak-to-peak method utilised in the current study was useful in dealing with the potential errors that baseline-to-peak amplitude readings may have caused. This peak-to-peak measure may, therefore, be recommended for use in future investigations of RREPs, especially in paired-occlusion paradigms.

There are some limitations in the present study. First, only healthy nonsmoking participants were included, and the numbers of males and females were unequal, potentially influencing the result. However, explorative post-hoc analyses comparing male and female participants in all variables, including N1 amplitude and N1 S2/S1 ratio, did not reveal any significant differences between two sexes. Second, the sample size was not big enough to allow examination of the age effect on the NGRS in a more fine-graded manner using 10-year age intervals per group. A future study with a larger sample size and sex-matched participants within each age group is warranted. Lastly, a small number of subjects reported having frequent nasal allergies; therefore, we cannot rule out the possibility that processes related to allergies could have impacted the NGRS.

In summary, our study demonstrates an ageing effect such that healthy older adults exhibit reduced NGRS, as shown by greater RREP N1 S2/S1 ratios and a positive correlation between higher age and higher N1

S2/S1 ratios. This reduction in the gating function resulted mainly from a smaller N1 amplitude of S1, reflecting reduced neural processing of the first, novel stimulus of the pair. Further research is required to determine the factors contributing to this pattern of brain processing of respiratory information in the older adult population.

Provenance: Submitted article, peer reviewed.

Ethics statement: The Institutional Review Board Committee of the Chang Gung Medical Foundation (Taoyuan, Taiwan) approved the study protocol (#201902211B0C103).

Conflict of interest: None declared.

Support statement: The project received financial support from the following grants: MOST109-2320-B-182-008-MY3 and NSTC112-2320-B-108-010-MY3 from the National Science and Technology Council, and BMRPB96 from the Chang Gung Memorial Hospital at Linko in Taiwan. A. von Leupoldt was supported by grants from the Research Foundation Flanders (FWO), Belgium (GOA3718N; G0C1921N), by an infrastructure grant from the FWO and the Research Fund KU Leuven, Belgium (AKUL/19/06; I011320N), and by a research grant from the Research Fund KU Leuven, Belgium (C16/23/002). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Fleming S, Thompson M, Stevens R, *et al.* Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet* 2011; 377: 1011–1018.
2 Chan PYS, Davenport PW. Respiratory-related evoked potential measures of respiratory sensory gating. *J Appl Physiol* 2008; 105: 1106–1113.
3 Chan PYS, Davenport PW. Respiratory-related-evoked potential measures of respiratory sensory gating in attend and ignore conditions. *J Clin Neurophysiol* 2009; 26: 438–445.
4 O'Donnell DE, Banzett RB, Carrieri-Kohlman V, *et al.* Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 2007; 4: 145–168.
5 Burki NK, Lee LY. Mechanisms of dyspnea. *Chest* 2010; 138: 1196–1201.
6 Gigliotti F. Mechanisms of dyspnea in healthy subjects. *Multidiscip Respir Med* 2010; 5: 195–201.
7 Chan PYS, Cheng CH, Hsu SC, *et al.* Respiratory sensory gating measured by respiratory-related evoked potentials in generalized anxiety disorder. *Front Psychol* 2015; 6: 957.
8 Manning HL, Schwartzstein RM. Respiratory sensations in asthma: physiological and clinical implications. *J Asthma* 2001; 38: 447–460.
9 Reijnders T, Troosters T, Janssens W, *et al.* Brain activations to dyspnea in patients with COPD. *Front Physiol* 2020; 11: 7.
10 Herzog M, Sucec J, Van Diest I, *et al.* Reduced neural gating of respiratory sensations is associated with increased dyspnoea perception. *Eur Respir J* 2018; 52: 1800559.
11 Battaglia S, Sandrini MC, Catalano F, *et al.* Effects of aging on sensation of dyspnea and health-related quality of life in elderly asthmatics. *Aging Clin Exp Res* 2005; 17: 287–292.
12 Hegendörfer E, Degryse J. Breathlessness in older adults: what we know and what we still need to know. *J Am Geriatr Soc* 2023; 71: 2082–2095.
13 Olsson M, Currow DC, Johnson MJ, *et al.* Prevalence and severity of differing dimensions of breathlessness among elderly males in the population. *ERJ Open Res* 2022; 8: 00553-2021.
14 Petersen S, von Leupoldt A, Van den Bergh O. Geriatric dyspnea: doing worse, feeling better. *Ageing Res Rev* 2014; 15: 94–99.
15 Chan PYS, Cheng CH, von Leupoldt A. The effect of development in respiratory sensory gating measured by electrocortical activations. *Neural Plast* 2015; 2015: 389142.
16 Chan PYS, Cheng CH, Jhu YJ, *et al.* Being anxious, thinking positively: the effect of emotional context on respiratory sensory gating. *Front Physiol* 2016; 7: 19.
17 Chan PYS, Davenport PW. Respiratory related evoked potential measures of cerebral cortical respiratory information processing. *Biol Psychol* 2010; 84: 4–12.
18 Miller MR, Crapo R, Hankinson J, *et al.* General considerations for lung function testing. *Eur Respir J* 2005; 26: 153–161.
19 Jones P. Quality of life measurement for patients with diseases of the airways. *Thorax* 1991; 46: 676.
20 Douglas CE, Michael FA. On distribution-free multiple comparisons in the one-way analysis of variance. *Commun Stat Theory Methods* 1991; 20: 127–139.
21 Lee S, Lee DK. What is the proper way to apply the multiple comparison test? *Korean J Anesthesiol* 2018; 71: 353–360.

22 Terrasa JL, Montoya P, González-Roldán AM, *et al.* Inhibitory control impairment on somatosensory gating due to aging: an event-related potential study. *Front Hum Neurosci* 2018; 12: 280.
23 Epiu I, Gandevia SC, Boswell-Ruys CL, *et al.* Respiratory-related evoked potentials in chronic obstructive pulmonary disease and healthy aging. *Physiol Rep* 2022; 10: e15519.
24 Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 1987; 24: 375–425.
25 Zhang F, Deshpande A, Benson C, *et al.* The adaptive pattern of the auditory N1 peak revealed by standardized low-resolution brain electromagnetic tomography. *Brain Res* 2011; 1400: 42–52.
26 Qin P, Northoff G. How is our self related to midline regions and the default-mode network? *Neuroimage* 2011; 57: 1221–1233.
27 Seeley WW, Menon V, Schatzberg AF, *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 2007; 27: 2349–2356.
28 Jelinčić V, Torta DM, Van Diest I, *et al.* Cross-modal relationships of neural gating with the subjective perception of respiratory and somatosensory sensations. *Psychophysiology* 2021; 58: e13710.
29 Chenivesse C, Chan PY, Tsai HW, *et al.* Negative emotional stimulation decreases respiratory sensory gating in healthy humans. *Respir Physiol Neurobiol* 2014; 204: 50–57.