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Experimental dyspnea interferes with locomotion and cognition: a randomised trial

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Abstract

Background: Chronic respiratory diseases are associated with cognitive dysfunction, but whether dyspnea by itself negatively impacts on cognition has not been demonstrated. Cortical networks engaged in subjects experiencing dyspnea are also activated during other tasks that require cognitive input and may provoke a negative impact through interference with each other.

Methods: This crossover randomised trial investigated whether experimentally-induced dyspnea would negatively impact on locomotion and cognitive function among 40 healthy adults. Crossover conditions were unloaded breathing or loaded breathing using an inspiratory threshold load. To evaluate locomotion, participants were assessed by the Timed Up and Go test. Cognitive function was assessed by categorical and phonemic verbal fluency tests, the Trail Making Test A and B (executive function), the CODE test from the WAIS-IV (processing speed), and by direct and indirect digit span (working memory).

Results: The mean time difference to perform the Timed Up and Go test between unloaded and loaded breathing was -0.752 sec (-1.012 to -0.492; $p<0.001$). Executive function, processing speed and working memory performed better during unloaded breathing, particularly for subjects starting first with the loaded breathing condition.

Conclusion: Our data suggest that respiratory threshold loading to elicit dyspnea had a major impact on locomotion and cognitive function in healthy adults.

Tweetable abstract@ERSpublication:

Acute experimental dyspnea can negatively impact on locomotion/cognition through shared neural substrates. There is a need for clinical interventions to improve non-respiratory symptoms of chronic respiratory diseases by focusing on alleviating dyspnea.

Introduction

Background

Chronic respiratory diseases, in particular chronic obstructive pulmonary disease (COPD), are associated with cognitive dysfunction [1, 2]. In parallel, gradual ageing of the general population strongly impacts on the prevalence of neurodegenerative and cerebrovascular conditions affecting cognition [3]. As the prevalence of COPD increases with age [4], it is important to understand whether older patients with symptomatic respiratory diseases present cognitive dysfunction due to ageing or if there is a true causal association between symptomatic respiratory diseases and cognitive function. Several hypotheses have been advanced to explain the underlying pathophysiology of cognitive dysfunction in COPD including modified arterial blood gases [5], persistent cigarette smoking, comorbid vascular diseases [6], loss of hippocampal volume and inflammatory mediator-related neuronal damage [7, 8]. An association between reduced lung function, impaired cognition and a greater risk of incident dementia has been also reported [9-11].

Dyspnea, the most common symptom of respiratory diseases, has been associated with disrupted brain activity [12], self-consciousness [13, 14] and gait control [15]. However, the effect of dyspnea itself, an "all-consuming and life changing" experience, on cognition is less well studied. A first set of studies have demonstrated that experimental dyspnea impairs affective picture processing [16], response inhibition [17] and memory and face recognition [18, 19], but more research is needed to study important aspects of dyspnea-cognition interactions, including the interaction with locomotion.

In healthy humans, normal breathing stems from automatic brainstem neural processes and does not give rise to conscious perception or require any motor or sensory cortical resources [13, 14, 20]. Under certain circumstances, such as voluntary respiratory movements or during speech, breathing can be operated by cortico-subcortical networks [21]. Cortically-driven breathing has also been described in reaction to changes in the mechanical properties of the respiratory system [20, 22]. Externally-applied inspiratory and expiratory constraints also give rise to respiratory-related motor cortical activities [20, 23]. The corresponding network involves the primary motor cortex, the supplementary motor area and corticospinal projections. In addition, recent evidence suggests that cortical activation, as demonstrated by an electroencephalogram, may make a significant contribution to quiet breathing in older age [24].

Similar to breathing, gait is considered to be an automatic function in young adults that should not depend on cognition [25]. However, in elderly patients and those suffering from neuropsychiatric conditions, gait control relies on cognitive function, particularly executive functions [26, 27], and shares similar cortical networks activated by a respiratory load [28, 29]. Thus, the cortical networks engaged in response to inspiratory loading are also activated during complex locomotor tasks that require cognitive input, such as gait. As a reliable measure of locomotion, the Timed Up and Go test (TUG) has been largely used in the elderly population [30] to identify poor clinical outcomes, such as cognitive impairment or dementia [31, 32]. More recently, an imaginary version of the TUG (iTUG) has been developed to evaluate the central control of locomotion [33].

In a preliminary study [15], we showed that progressive inspiratory threshold loading increased linearly the time to perform the TUG and suggested that a competition for cortical resources, among other mechanisms, may account for the observed breathing-locomotion interference. This study is designed to test the hypothesis that laboratory-induced dyspnea in healthy young subjects would impact on gait control and cognitive function.

Methods

Study design

This randomised, two-condition, two-period crossover study was conducted at Geneva University Hospitals (Geneva, Switzerland). The study was approved by the local ethics committee on research involving humans and registered on the Swiss national clinical trials portal (ID 2016-00807). All participants provided written informed consent in accordance with Swiss Federal Laws on Human Research and Clinical Trials Ordinance.

Subjects

Forty highly-educated subjects were recruited from the Geneva University campus. Individuals aged from 18-40 years old and of French mother tongue were eligible for study inclusion. Exclusion criteria were a physician's diagnosis of a respiratory, neurological or psychiatric disorder and pregnancy. Subjects were also excluded if considered unable to perform the TUG. During enrollment, all eligible participants underwent a medical examination by a physician and data were collected on past medical history, age, gender, body mass index (kg/m2), FEV_1, forced vital capacity, SpO2, sniff nasal inspiratory pressure (SNIP) and mouth inspiratory pressure (MIP) [34].

Experimental dyspnea

From February 2017 to May 2019, participant enrollment, randomisation and testing took place at the respiratory physiology laboratory of Geneva University Hospitals. Lung function parameters were assessed using a portable spirometer (Spirotel® with Winspiro PRO® software version 7.3, Rome, Italy). SNIP and maximal MIP were measured using a microRPM® device (CareFusion, Hoechberg, Germany) [34]. Dyspnea was induced by an inspiratory threshold load (POWERbreathe Classic©, PowerBreathe Ltd, London, UK) connected to a commercial comfortable orofacial mask (Resmed AcuCareTM F1-0, Sydney, Australia) designed for non-invasive ventilation. The inspiratory threshold load device provides an inspiratory pressure ranging from 10 to 170 cmH2O (9 predefined levels) that needs to be overcome by the study participant at every breath during the experimentally-induced dyspnea sequence of the trial. The inspiratory threshold device has in inbuilt one-way expiratory valve to prevent CO_2 rebreathing. Before the experiment started, the inspiratory load was progressively increased to a predefined dyspnea rating of 6/10 on a visual analog scale. Before and after each period of experimentally-induced dyspnea, subjects completed the Multidimensional Dyspnea Profile (MDP) questionnaire [35], which assesses dyspnea during a specific time or condition and is a proven valid instrument for clinical and laboratory research [36].

Locomotion

We used the TUG as described by Podsiadlo et al [30] and its imagined version validated by Beauchet et al [33] to assess locomotion. On command, the subject had to stand up from an armchair, walk 3 metres, then turn and sit down again on the chair. For the iTUG, on command, subjects had to imagine the TUG and signal to the investigator its mental completion. The difference in time (i.e. delta time) between TUG and iTUG conditions was calculated according to the following formula [(TUG − iTUG) / (TUG + iTUG / 2)] and was also used as an outcome variable. Cognitive status is strongly associated with TUG, iTUG and delta time [31, 33, 37, 38] as these tasks place additional cognitive challenges on brain function.

Cognition

Categorical and phonemic verbal fluencies tests [39], as well as the Trail Making Test (TMT) A and B [40], were used to assess executive functions. During categorical verbal fluency tests, subjects had 2 minutes to produce the maximum number of words from the “animal” category. For the phonemic verbal fluency test, the subjects had to produce the maximum number of words starting with the letter “P” during 2 minutes. For the TMT A, subjects had to connect numerated bullets as fast as possible in an increasing

manner. The same principle was applied for TMT B, except that the subject had to alternatively connect a number to a letter in an increasing way.

Processing speed was assessed by the CODE test from the Wechsler Adult Intelligence Scale (WAIS-IV) [41, 42] for which subjects had to copy in 2 minutes the maximum number of symbols associated with numbers on an answer sheet with numbers without the symbols.

Working memory was assessed by direct and indirect digit span [41, 42]. During the direct digit span, subjects had to repeat in the same order a series of numbers read by the examiner and in the indirect digit span, subjects had to repeat the series of number read by the investigator in reverse order.

Intervention

The randomisation sequence was computer-generated using the permuted block method with blocks of varying size (4 to 6). Using a sealed, opaque, envelope randomisation system, we assigned subjects in a 1:1 ratio to receive either the sequence "loaded breathing/unloaded breathing" or the sequence "unloaded breathing/loaded breathing" (figure 1). During the first period (either experimentally-loaded breathing or unloaded breathing), subjects had to complete the locomotion and cognitive tests in a fixed order. During the loaded breathing period, subjects wore the orofacial mask connected with the respiratory load at a predefined level of resistance. During the unloaded breathing period, subjects wore the same mask without the respiratory load. During the second period, subjects were switched to the complementary condition (either unloaded or loaded breathing) and the exact same tests in the same order were completed. Oxygen saturation was continuously monitored during both periods with pulse oximetry (Konica Minolta Pulsox-300i, Konica Minolta Sensing, Osaka, Japan).

Predetermination of study endpoints

The primary endpoint was the time to perform TUG and iTUG (measured in seconds). Secondary endpoints were the fluency tests (measured by the number of correct words), TMT A and B (measured in seconds), CODE test (measured by the number of correct associations) and digit span (measured by the number of correct sequence of numbers).

Statistical analysis

The study was designed to show a difference of 0.5 sec to perform TUG between the two experimental conditions with a standard deviation of the difference of 1 sec according to our previous findings [15]. To show this difference in a crossover design using a paired t-test with a two-sided significance level of 0.05 and a power of 0.8, enrollment of 36 subjects was required. The effect of dyspnea on each test was

assessed using a linear mixed-effects model with a random intercept for each participant. In addition to the experimental condition (loaded breathing vs unloaded breathing), each model also included the experimental sequence (starting the experiment with unloaded or loaded breathing) and the interaction between the experimental sequence and the experimental condition as fixed effects. The statistical significance of the interactions was assessed using the likelihood ratio test. All p-values were two-sided and statistical significance was set at a p-value of 0.05. All analyses were performed using R for Windows (version 3.6.1) [43] with the lme4 [44], emmeans Lenth [45]and tidyverse [46]packages.

Results

Forty healthy subjects were randomly assigned either to the sequence "loaded breathing/unloaded breathing" (n=20) or to "unloaded breathing/loaded breathing" (n=20). Baseline characteristics were similar between groups (table 1). Experimentally-induced dyspnea (self-rated intensity of 6/10 on a visual analog scale) was obtained in all subjects at a median threshold level of 4.75 (interquartile range [IQR] 3.00-7.62) on the inspiratory threshold device. Oxygen saturation was stable during the entire experiment with no drop during experimentally-induced dyspnea (SpO2 99%; IQR 98-100]). Differences of locomotion and neuropsychological tests performance between conditions are reported in Table 2. Mean estimated value ± SD for each test according to respiratory conditions are provided in Table S1 of the supplementary material.

Motor function

Mean time to perform TUG was 8.97 ±1.35 (sec) during unloaded breathing and 9.72 ±1.54 (sec) during loaded breathing, with an estimated difference of -0.75 (sec) (95% CI -1.01 to -0.49; p<0.001) between conditions (figure 2, panel A). An interaction between experimental conditions (unloaded or loaded breathing) and experimental sequences (starting the experiment with unloaded breathing or starting with loaded breathing) was demonstrated for the TUG (p=0.005) (figure 2, panel B). We did not observe a difference between conditions or an interaction for iTUG. Conversely, delta time increased with loaded breathing compared with unloaded breathing (estimated difference = -0.08 (sec); 95% CI -0.14 to -0.02; p=0.011), with no interaction between conditions and sequences.

Neuropsychological tests

Executive function: Categorical and verbal fluencies tests both demonstrated the same profile. While subjects were able to produce more words during unloaded compared to loaded breathing, the effect of the experimental condition was more pronounced for those who started the experiment with loaded

breathing as a result of an interaction between the experimental condition and the experimental sequence (p=0.003 for verbal fluency and p=0.004 for categorical fluency). For TMT A, although no differences in time to perform the test between experimental conditions were observed, subjects who started the experiment with loaded breathing much improved their time to perform it with unloaded breathing as a result of an interaction between the experimental condition and the experimental sequence (p<0.001). For TMT B, no differences in time to perform the test between experimental conditions were observed. As for TMT A, an interaction was found between the experimental condition and the experimental sequence (P<0.001) for TMT B. However subjects who started the experiment with the unloaded breathing performed better during the second condition compared to those who started with loaded breathing.

Processing speed: Overall, the number of correct associations performed during the CODE test seemed to be higher during unloaded compared to loaded breathing (difference of correct associations between conditions: 4.13; 95% CI -0.27 to 8.52; p=0.07). Furthermore, subjects who started the experiment with loaded breathing much improved their performance with unloading as a result of an interaction between the experimental condition and the experimental sequence (p<0.001).

Working memory: No differences between conditions were observed for both direct and indirect digit span. However, subjects who started the experiment with loaded breathing much improved their performance with unloading as a result of an interaction between the experimental condition and the experimental sequence (p=0.03 for direct digit span and p=0.008 for indirect digit span for both).

Discussion

In this randomised crossover trial of experimental dyspnea in healthy subjects, we found that experimental dyspnea to a predetermined intensity of 6/10 on a visual analog scale had a major impact on locomotion and cognitive function in a sample of highly educated younger adults. Our data support previous evidence of dyspnea-cognition interactions [15-18] and suggest a plausible causal association between dyspnea and brain function leading to altered locomotion and cognition. The crossover design also highlighted that alleviation of dyspnea has a positive effect on locomotion and cognition.

Among locomotion parameters, gait speed is considered as the “sixth vital sign” [47] and mainly depends on exercise capacity related to cardiorespiratory fitness, but also on the integrity of musculoskeletal, peripheral and central nervous systems. Reduced gait speed is associated with a poor clinical outcome in ageing and associated with mortality [48]. Only a few studies have focused on gait speed in respiratory

diseases as the 6-min walking test and the incremental shuttle walk are historically so important to quantify cardiorespiratory reserve and exercise tolerance in this field. However, gait speed, as measured by the 4-metre gait speed, correlates with exercise capacity, dyspnea and health-related quality of life [49] and is a predictor of hospital readmission for acute exacerbation of COPD [50]. The 4-metre gait speed is also responsive to pulmonary rehabilitation [51] and has been proposed as a promising functional assessment in COPD to inform the clinician about many functional aspects and overall outcome [52].

As suggested in a previous study of our group, but with no formal demonstration [15], dyspnea might independently impact on gait through shared neural networks with cognitive functions. In the present study, experimentally-induced dyspnea increased time to perform TUG and consistently impacted on cognition across all neuropsychological tests particularly for subjects starting the experiment with the loaded breathing condition. Indeed, dual-tasking experimental paradigms state that two tasks performed simultaneously may have a negative impact on each other when they both depend on similar cortical networks [53] as demonstrated here. The impact of dyspnea on the time to perform the TUG (+8.4% from baseline) and the neuropsychological tests in our trial is large, especially when considering that only highly educated young subjects were included. Recent evidence from a large cohort also suggests that challenging gait speed with a concurrent cognitive task may represent a sensitive marker in younger subjects to assess brain health and cognitive function. This calls for rethinking locomotion and gait speed not only as a geriatric index of frailty, but also as a surrogate marker of brain functioning in younger subjects or in patients with chronic respiratory diseases. For instance, developing a test to challenge gait speed with a respiratory load at hospital discharge in patients surviving an exacerbation of COPD could inform the clinician about which patient is more likely to present or to develop poor cognition that would place him/her at risk of poor adherence to medical treatment and thus at increased risk of readmission [54].

The current observations that dyspnea is associated with poor executive function, attention and processing speed are in line with previous findings showing that chronic respiratory diseases are associated with cognitive impairment. However, it has consistently been reported that other intermediate factors such as altered blood gases [5, 55], reduced lung function [11, 56], persistent cigarette smoking [57], vascular disease [10, 58, 59], loss of hippocampal volume and inflammatory mediator-related neuronal damage [60, 61] are responsible for this association with cognition. As lung dysfunction and disease severity do not fully explain the development of cognitive impairment, our

findings expand current knowledge by highlighting that dyspnea *per se* is independently associated with locomotion and cognition in a plausible causal relationship.

Alleviation of dyspnea consistently improved locomotion and cognition across all neuropsychological tests in our study, suggesting a possible learning effect. However, this observation also suggests that addressing chronic or persistent breathlessness as a syndrome with a specific treatment in addition to treating the underlying respiratory condition may also improve outcomes [62, 63].

The dyspnea-inactivity vicious circle model in COPD is now supported by real-life data that has bridged a gap of knowledge by identifying dyspnea as a major endpoint in a chain of events leading to disability [64, 65]. More research is needed to determine where cognitive dysfunction stands in this chain of events and if a specific intervention on dyspnea itself might reverse the vicious circle. At present, opiates are the only evidence-based pharmacologic treatment to target dyspnea. Immediate-release morphine has been shown to improve exercise-induced breathlessness and exercise endurance in a significant proportion of COPD patients with advanced disease [66]. Our findings may support that such a treatment would also have an impact on locomotion and cognition, while respiratory mechanics are unchanged, thus providing a definitive demonstration that dyspnea impacts on cognitive function, but further studies are needed (MORDYC trial: NCT02429050).

Our study has some potential limitations. First, we did not assess any modification of brain activity by electroencephalography or functional MRI, nor did we assess $PaCO_2$ (or a surrogate) during the experiment. Indeed, we considered that using a randomised trial of experimentally-induced dyspnea would provide sufficient evidence to infer that dyspnea impacts on cognition and locomotion. It is now firmly established that respiratory loading modifies respiratory-related cortical activity [67-71] and recent evidence suggests that such a modification is associated with impaired cognitive performance (VENTIPSY trial: NCT03095729; Prof. Thomas Similowski personal communication). Moreover, the respiratory system has a remarkable ability to fight externally applied mechanical loads to maintain alveolar ventilation within normal range [72]. Second, our findings cannot be generalized to an older population with chronic respiratory diseases, in which dyspnea at an intensity of 4/10 is already clinically relevant [73]. Indeed, we specifically focused on highly functioning young adults. Interestingly, it was easy to artificially induce cognitive impairment in young healthy brains with a simple method of respiratory loading and this should certainly open up research avenues devoted to exploring the interaction between dyspnea and cognition in older adults. Third, acute dyspnea was induced in a secured experimental setting and does not reflect the chronic condition associated with respiratory

diseases. Therefore, our results may not reflect the interactions among physiological, psychological, social and environmental factors involved in secondary physiological and behavioural responses to refractory dyspnea in the clinical setting.

Conclusions

Acute experimental dyspnea can negatively impact on locomotion and cognition in a reversible manner by challenging shared neural substrates. These findings challenge current understanding of non-respiratory symptoms of chronic respiratory diseases and will provide a rationale for future clinical interventions aiming to improve locomotion and cognition by focusing on alleviating dyspnea.

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TABLES

Table 1: Baseline characteristics of participants

*Plus–minus values are means ± standard deviation.

BMI, body mass index; FEV_1: forced expiratory volume in 1 s, FVC; forced vital capacity; MIP; minimum MIP: mouth inspiratory pressure; SNIP: sniff nasal inspiratory pressure.

Characteristics*	Unloaded breathing first (n= 20)	Loaded breathing first (n=20)	Total (n=40)
Age - yr	26.35 ± 4.94	26.60 ± 5.14	26.48 ± 4.98
Male sex - n (%)	11 (55)	13 (65)	24 (60)
BMI - kg/m^2	23.50 ± 4.00	22.98 ± 3.73	23.24 ± 3.82
FEV_1/FVC - predicted %	101.15 ± 6.23	102.45 ± 8.20	101.80 ± 7.22
FEV_1 - predicted %	100.40 ± 11.25	101.30 ± 12.45	100.85 ± 11.72
MIP - cmH2O	111.65 ± 24.34	106.65 ± 25.86	109.15 ± 24.92
SNIP - cmH2O	104.00 ± 25.02	86.75 ± 20.82	95.38 ± 24.34
Level of inspiratory load provided by Powerbreath® device (from 1 to 9)	5.92 ± 2.28	4.33 ± 2.52	5.12 ± 2.51

Table 2: Results summary

The first row (a) depicts the mean difference between loaded and unloaded breathing, regardless of the arm, and its confidence interval estimated by the linear mixed model (the p-value corresponds to the test of this difference being equal to 0). The second row (b) depicts the mean difference between loaded and unloaded breathing and its confidence interval estimated by the linear mixed model for the experimental sequence “unloaded breathing first”. The third row (c) shows the mean difference between loaded and unloaded breathing and its confidence interval estimated by the linear mixed model for the experimental sequence “loaded breathing first”. The p-values presented in the 2nd and 3rd rows correspond to the result of the interaction test.

Tests		Beta	Beta 95% CI	p-value
LOCOMOTION				
TUG (seconds)	Overall[a]	-0.752	-1.012 to -0.492	<0.0001
	Unloaded 1st[b]	-0.403	-0.736 to -0.070	0.005
	Loaded 1st[c]	-1.101	-1.435 to -0.768	
iTUG (seconds)	Overall[a]	0.022	- 0.396 to 0.441	0.915
	Unloaded 1st[b]	0.341	-0.235 to 0.916	0.121
	Loaded 1st[c]	-0.296	-0.871 to 0.279	
Delta TUG (seconds)	Overall[a]	-0.081	-0.141 to -0.020	0.011
	Unloaded 1st[b]	-0.094	-0.180 to -0.008	0.666
	Loaded 1st[c]	-0.068	-0.153 to 0.018	
EXECUTIVE FUNCTION				
Verbal Fluency (# word)				
Categorical	Overall[a]	3.700	1.347 to 6.053	0.003
	Unloaded 1st[b]	0.500	-2.505 to 3.505	0.004
	Loaded 1st[c]	6.900	3.895 to 9.905	
Lexical	Overall[a]	0.725	-1.226 to 2.676	0.457
	Unloaded 1st[b]	-2.050	-4.515 to 0.415	0.003
	Loaded 1st[c]	3.500	1.035 to 5.965	
Trail Making Test (seconds)				
A	Overall[a]	-0.235	-1.813 to 1.344	0.765
	Unloaded 1st[b]	2.488	0.617 to 4.358	<0.0001
	Loaded 1st[c]	-2.957	-4.827 to -1.087	
B	Overall[a]	0.389	-4.769 to 5.547	0.880
	Unloaded 1st[b]	9.563	3.534 to 15.591	0.0001
	Loaded 1st[c]	-8.785	-14.813 to -2.756	
TMT B-TMT A	Overall[a]	0.624	- 4.648 to 5.896	0.812
	Unloaded 1st[b]	7.075	0.195 to 13.955	0.011
	Loaded 1st[c]	-5.828	-12.708 to 1.053	
PROCESSING SPEED				
CODE (# correct association)	Overall[a]	4.125	-0.265 to 8.515	0.065
	Unloaded 1st[b]	-6.800	-10.612 to -2.988	<0.0001
	Loaded 1st[c]	15.050	11.238 to 18.862	
WORKING MEMORY				
Memory span (# correct sequence)				
Direct	Overall[a]	0.325	- 0.174 to 0.824	0.196
	Unloaded 1st[b]	-0.200	-0.866 to 0.466	0.030
	Loaded 1st[c]	0.850	0.184 to 1.516	
Indirect	Overall[a]	0.050	-0.581 – 0.681	0.874
	Unloaded 1st[b]	-0.750	-1.568 to 0.068	0.008
	Loaded 1st[c]	0.850	0.032 to 1.668	

Legends to the Figures

- **Figure 1: Study design***

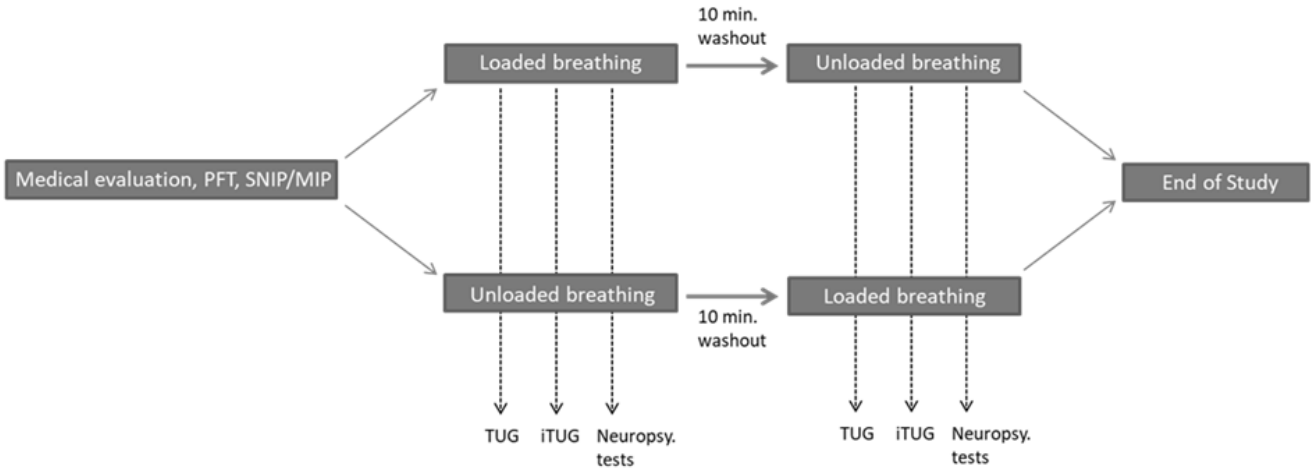
  *Randomized, open label, two-condition, two-period crossover design.
  PFT= Pulmonary function tests, SNIP = sniff nasal inspiratory pressure, MIP = maximal inspiratory pressure, TUG= Timed Up and Go, iTUG= Imagined Timed Up and Go

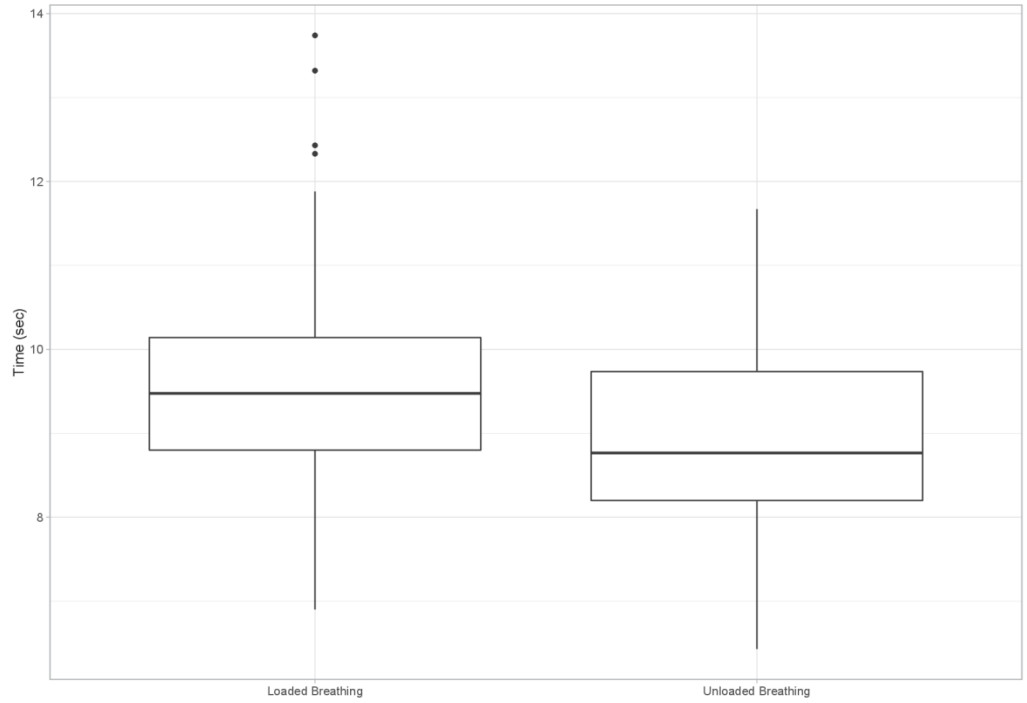
- **Figure 2: TUG Test results**

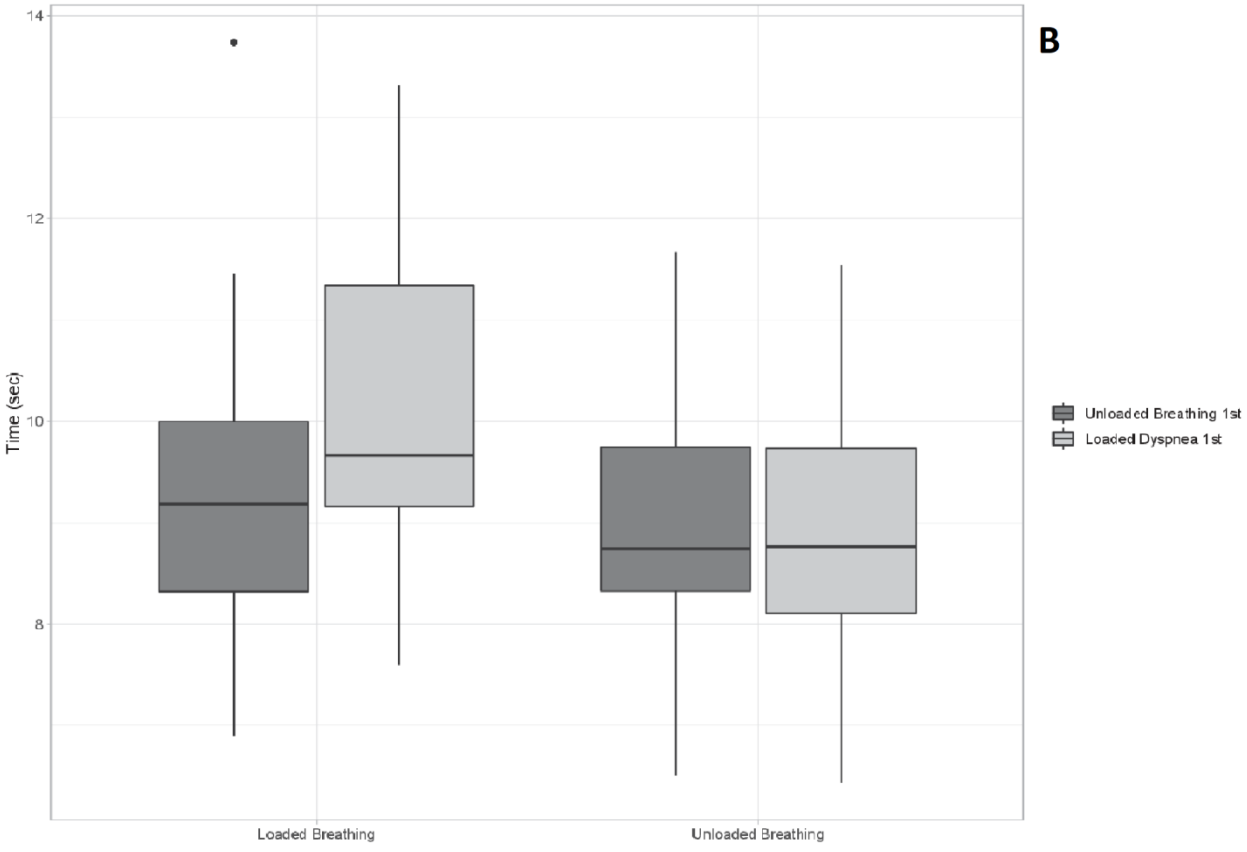
  Thick line within the box represents the median, the boundary of the box closest to zero indicates the 25^{th} percentile and the farthest from zero indicates the $75^{th,}$ percentile, whiskers above and below the box indicate the 10^{th} and 90^{th} percentiles, points above the upper whisker indicates outliers outside the 90^{th} percentiles.

  Panel A:
  Boxplots depicting subjects TUG test performance during the calm breathing phase compared to the experimentally induced dyspnea phase independently of experimental sequence.

  Panel B:
  Boxplots depicting subjects TUG test performance during the calm breathing phase compared to the experimentally induced dyspnea phase classified by experimental sequence.


Medical evaluation, PFT, SNIP/MIP
Loaded breathing
10 min.
washout
Unloaded breathing
Unloaded breathing
10 min.
washout
Loaded breathing
End of Study
TUG
iTUG
Neuropsy.
tests
TUG
iTUG
Neuropsy.
tests


A
14
12
10
8
Time (sec)
Loaded Breathing
Unloaded Breathing


B
14
12
10
8
Time (sec)
Loaded Breathing
Unloaded Breathing
Unloaded Breathing 1st
Loaded Dyspnea 1st

SUPPLEMENTARY MATERIAL

Experimental dyspnea interferes with locomotion and cognition: a randomised trial

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Table S1: Results summary

	Calm breathing		Experimental dyspnea	
TESTS *	**Loaded breathing first**	**Unloaded breathing first**	**Loaded breathing first**	**Unloaded breathing first**
LOCOMOTION				
TUG (seconds)	9.35 ± 1.50	8.95 ± 1.36	10.09 ± 1.53	8..99 ± 1.36
iTUG (seconds)	6.69 ± 2.23	7.03 ± 2.11	6.35 ± 1.55	6.05 ± 1.29
EXECUTIVE FUNCTION				
Verbal Fluency Test (# word)				
Categorical	34.9 ± 8.17	35.4 ± 8.34	29.80 ± 7.94	36.7 ± 8.04
Lexical	26.10 ± 6.58	24.05 ± 4.77	22.7 ± 7.77	26.20 ± 7.47
Trail Making Test (seconds)				
A	6.13 ± 3.10	18.61 ± 4.03	17.98 ± 4.56	15.02 ± 4.55
B	33.47 ± 10.81	43.04 ± 10.60	39.68 ± 12	30.90 ± 15.47
PROCESSING SPEED				
CODE (# correct association)	88.10 ± 14.81	81.3 ± 12.37	77 ± 15.42	92.05 ± 16.21
WORKING MEMORY				
Memory span (# correct sequence)				
Direct	10.5 ± 1.7	10.3 ± 1.3	9.3 ± 1.49	10.15 ± 1.63
Indirect	7.2 ± 2.24	6.45 ± 1.79	6.45 ± 1.88	7.3 ± 2.05

*Plus–minus values are means ± standard deviation.

TUG : Test Up and Go, iTUG : imagined Test Up and Go, TMT : Trail Making Test, CODE: CODE test