Experimental dyspnoea interferes with locomotion and cognition: a randomised trial

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Acute experimental dyspnoea 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 focussing on alleviating dyspnoea. https://bit.ly/2wGHcjW

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ABSTRACT

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

Methods: This randomised, crossover trial investigated whether experimentally-induced dyspnoea 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 (TUG) test. Cognitive function was assessed by categorical and phonemic verbal fluency tests, the Trail Making Tests (TMTs) A and B (executive function), the CODE test from the Wechsler Adult Intelligence Scale (WAIS)-IV (processing speed) and by direct and indirect digit span (working memory).

Results: The mean time difference to perform the TUG test between unloaded and loaded breathing was −0.752 s (95% CI −1.012 to −0.492 s) (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 dyspnoea had a major impact on locomotion and cognitive function in healthy adults.

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Introduction

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].

Dyspnoea, the most common symptom of respiratory disease, has been associated with disrupted brain activity [12], self-consciousness [13, 14] and gait control [15]. However, the effect of dyspnoea, itself an "all-consuming and life-changing" experience, on cognition is less well studied. A first set of studies have demonstrated that experimental dyspnoea 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 dyspnoea–cognition interaction, 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] and externally-applied inspiratory and expiratory constraints can 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 function [26, 27] and shares similar cortical networks to those 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 (TUG) test has largely been 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 test, the imagined Timed Up and Go (iTUG) test, has been developed to evaluate the central control of locomotion [33].

In a preliminary study [15], we showed that progressive inspiratory threshold loading linearly increased the time to perform the TUG test and suggested that, among other mechanisms, a competition for cortical resources may account for the observed breathing–locomotion interference. This study is designed to test the hypothesis that laboratory-induced dyspnoea would, in healthy young subjects, 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 to 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 test. During enrolment, all eligible participants underwent a medical examination by a physician and data were collected on past medical history, age, gender, body mass index (BMI, in $kg \cdot m^{-2}$), forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), oxygen saturation measured by pulse oximetry (S_{pO_2}), sniff nasal inspiratory pressure (SNIP) and maximal inspiratory pressure (MIP) [34].

Experimental dyspnoea

Participant enrolment, randomisation and testing took place from February 2017 to May 2019 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; Medical International Research, Rome, Italy). SNIP and MIP were measured using a respiratory muscle testing device (microRPM; CareFusion, Hoechberg, Germany) [34]. Dyspnoea was induced by an inspiratory threshold load device (POWERbreathe Classic; POWERbreathe Ltd, London, UK) connected to a comfortable commercial orofacial mask (AcuCare F1-0; Resmed, Sydney, Australia) designed for noninvasive ventilation. The inspiratory threshold load device provides an inspiratory pressure ranging from 10 to 170 cmH_2O (with nine predefined levels) that needs to be overcome by the study participant at every breath during the experimentally-induced dyspnoea sequence of the trial. It also has an inbuilt one-way expiratory valve to prevent carbon dioxide rebreathing. Before the experiment started, the inspiratory load was progressively increased to a predefined dyspnoea rating of six out of 10 on a visual analogue scale. Before and after each period of experimentally-induced dyspnoea, subjects completed the Multidimensional Dyspnoea Profile (MDP) questionnaire [35]. This assesses dyspnoea during a specific time or condition and is a proven valid instrument for clinical and laboratory research [36].

Locomotion

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

Cognition

Categorical and phonemic verbal fluency tests [39], as well as the Trail Making Tests (TMTs) A and B [40], were used to assess executive function. During the categorical verbal fluency test, the subjects had 2 min to produce the maximum number of words from the "animal" category; while for the phonemic verbal fluency test, they had 2 min to produce the maximum number of words starting with the letter "P". For the TMT A, subjects had to connect numerated bullets as fast as possible in an increasing manner. The same principle was applied for the TMT B, except that the subjects 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], where subjects had 2 min in which to copy the maximum number of symbols from a sheet where they are associated with numbers to an answer sheet containing numbers without symbols.

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

Intervention

The randomisation sequence was computer-generated using the permuted block method with blocks of varying size (four to six). Using a sealed, opaque, envelope randomisation system, we assigned subjects in a one to one 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 were completed in the same order. Oxygen saturation was monitored continuously 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 the TUG and iTUG tests (measured in seconds). Secondary endpoints were the fluency tests (measured by the number of correct words), the TMTs A and B (measured in seconds), the CODE test (measured by the number of correct associations) and the digit span tests (measured by the number of correct sequences of numbers).

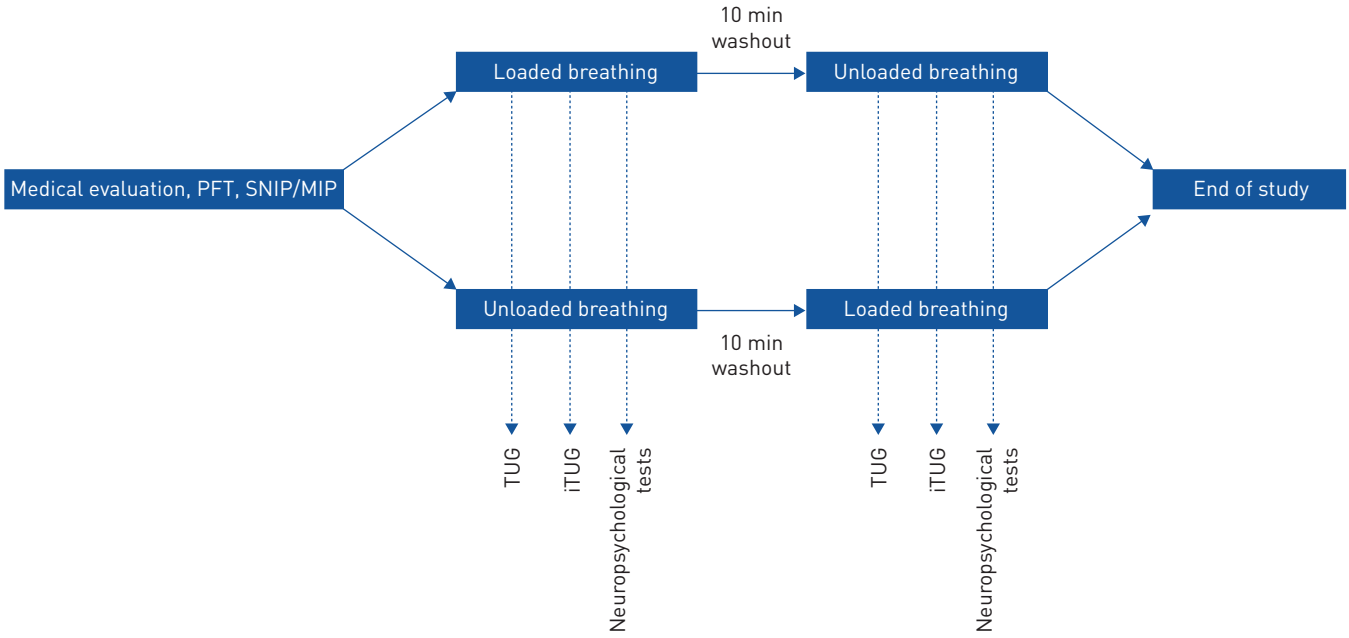

FIGURE 1 Design of the randomised, open-label, two-condition, two-period crossover study. PFT: pulmonary function test; SNIP: sniff nasal inspiratory pressure; MIP: maximal inspiratory pressure; TUG: Timed Up and Go; iTUG: imagined Timed Up and Go.

Statistical analysis

The study was designed to show a difference in time to perform the TUG test of 0.5 s between the two experimental conditions, with a standard deviation (SD) of the difference of 1 s 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, enrolment of 36 subjects was required. The effect of dyspnoea 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 *versus* unloaded breathing), each model also included as fixed effects the experimental sequence (starting the experiment with unloaded or loaded breathing) and the interaction between the experimental sequence and the experimental condition. 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 p=0.05. All analyses were performed using R for Windows (version 3.6.1) [43] with the lme4 [44], emmeans [45] and tidyverse [46] packages.

Results

Forty healthy subjects were randomly assigned either to the sequence "loaded breathing/unloaded breathing" (n=20) or to the sequence "unloaded breathing/loaded breathing" (n=20). Baseline characteristics were similar between groups (table 1). Experimentally-induced dyspnoea (with a self-rated

TABLE 1 Baseline characteristics of participants

Characteristics	Unloaded breathing first (n=20)	Loaded breathing first (n=20)	Total (n=40)
Age years	26.35±4.94	26.60±5.14	26.48±4.98
Male sex	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 cmH_2O	111.65±24.34	106.65±25.86	109.15±24.92
SNIP cmH_2O	104.00±25.02	86.75±20.82	95.38±24.34
Inspiratory load#	5.92±2.28	4.33±2.52	5.12±2.51

Data are presented as n (%) or mean±SD. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MIP: maximal inspiratory pressure; SNIP: sniff nasal inspiratory pressure; SD: standard deviation. #: level of inspiratory load provided by the Powerbreathe® device (from 1 to 9).

intensity of six out of 10 on a visual analogue 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 dyspnoea (S_{pO_2} 99%, IQR 98–100%). Differences in locomotion and neuropsychological test performance between conditions are reported in table 2. Mean estimated values±SDfor each test according to respiratory conditions are provided in supplementary table S1.

Motor function

The mean time to perform the TUG test was 8.97 ±1.35 s during unloaded breathing and 9.72±1.54 s during loaded breathing, with an estimated difference of −0.75 s (95% CI −1.01 to −0.49 s) (p<0.001) between conditions (figure 2a). An interaction between experimental conditions (unloaded or loaded

TABLE 2 Results summary

Tests		β	95% CI	p-value
Locomotion				
TUG s	Overall[#]	−0.752	−1.012 to −0.492	<0.0001
	Unloaded 1st[¶]	−0.403	−0.736 to −0.070	0.005
	Loaded 1st[+]	−1.101	−1.435 to −0.768	–
iTUG s	Overall[#]	0.022	−0.396 to 0.441	0.915
	Unloaded 1st[¶]	0.341	−0.235 to 0.916	0.121
	Loaded 1st[+]	−0.296	−0.871 to 0.279	–
Δ TUG s	Overall[#]	−0.081	−0.141 to −0.020	0.011
	Unloaded 1st[¶]	−0.094	−0.180 to −0.008	0.666
	Loaded 1st[+]	−0.068	−0.153 to 0.018	–
Executive function				
Verbal fluency (number of words)				
Categorical	Overall[#]	3.700	1.347 to 6.053	0.003
	Unloaded 1st[¶]	0.500	−2.505 to 3.505	0.004
	Loaded 1st[+]	6.900	3.895 to 9.905	–
Lexical	Overall[#]	0.725	−1.226 to 2.676	0.457
	Unloaded 1st[¶]	−2.050	−4.515 to 0.415	0.003
	Loaded 1st[+]	3.500	1.035 to 5.965	–
TMT s				
A	Overall[#]	−0.235	−1.813 to 1.344	0.765
	Unloaded 1st[¶]	2.488	0.617 to 4.358	<0.0001
	Loaded 1st[+]	−2.957	−4.827 to −1.087	–
B	Overall[#]	0.389	−4.769 to 5.547	0.880
	Unloaded 1st[¶]	9.563	3.534 to 15.591	0.0001
	Loaded 1st[+]	−8.785	−14.813 to −2.756	–
TMT B–TMT A	Overall[#]	0.624	−4.648 to 5.896	0.812
	Unloaded 1st[¶]	7.075	0.195 to 13.955	0.011
	Loaded 1st[+]	−5.828	−12.708 to 1.053	–
Processing speed				
CODE (number of correct associations)	Overall[#]	4.125	−0.265 to 8.515	0.065
	Unloaded 1st[¶]	−6.800	−10.612 to −2.988	<0.0001
	Loaded 1st[+]	15.050	11.238 to 18.862	–
Working memory				
Memory span (number of correct sequences)				
Direct	Overall[#]	0.325	−0.174 to 0.824	0.196
	Unloaded 1st[¶]	−0.200	−0.866 to 0.466	0.030
	Loaded 1st[+]	0.850	0.184 to 1.516	–
Indirect	Overall[#]	0.050	−0.581 to 0.681	0.874
	Unloaded 1st[¶]	−0.750	−1.568 to 0.068	0.008
	Loaded 1st[+]	0.850	0.032 to 1.668	–

CI: confidence interval; TUG: Timed Up and Go; iTUG: imagined Timed Up and Go; TMT: Trail Making Test. [#]: depicts the mean difference between loaded and unloaded breathing, regardless of the arm, as well as its CI estimated by the linear mixed model (the p-value corresponds to the test of this difference being equal to zero); [¶]: depicts the mean difference between loaded and unloaded breathing and its CI estimated by the linear mixed model for the experimental sequence "unloaded breathing first" (the p-value corresponds to the result of the interaction test); [+]: depicts the mean difference between loaded and unloaded breathing and its CI estimated by the linear mixed model for the experimental sequence "loaded breathing first" (the p-value corresponds to the result of the interaction test).

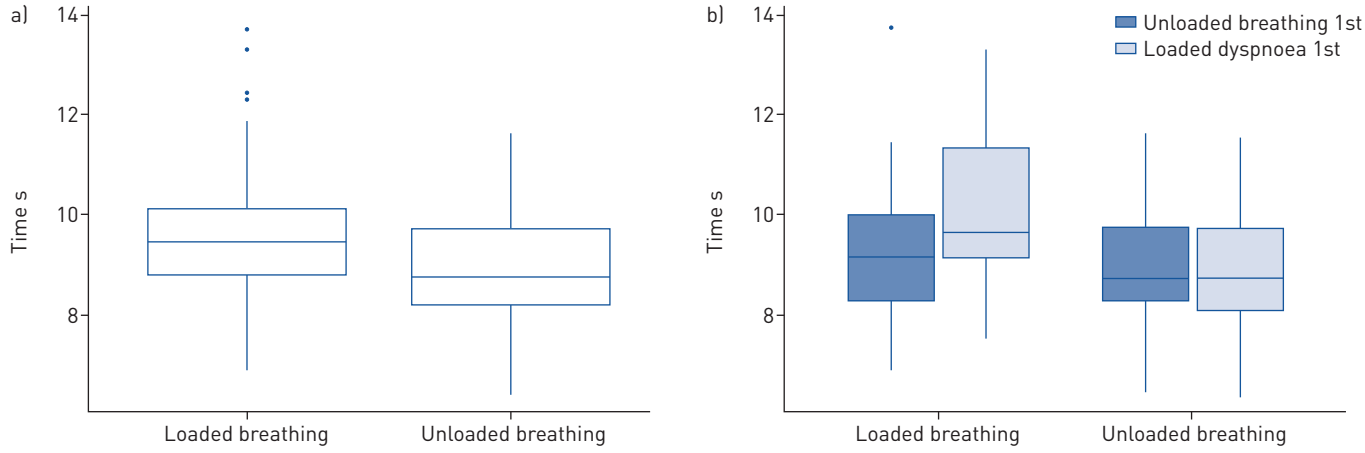

FIGURE 2 Timed Up and Go (TUG) test results. The thick line within a box plot represents the median, the boundary of the box closest to zero indicates the 25th percentile and that furthest from zero the 75th percentile. The whiskers above and below the box indicate the 10th and 90th percentiles, while points above the upper whisker indicate outliers outside the 90th percentile. a) Boxplots depicting subjects' TUG test performance during the calm breathing phase compared to the experimentally-induced dyspnoea phase, independent of experimental sequence. b) Boxplots depicting subjects' TUG test performance during the calm breathing phase compared to the experimentally-induced dyspnoea phase, classified by experimental sequence.

breathing) and experimental sequence (starting the experiment with unloaded breathing or starting it with loaded breathing) was demonstrated for the TUG test (p=0.005) (figure 2b). We did not observe a difference between conditions or an interaction for the iTUG Test. Conversely, Δ time increased with loaded breathing compared to unloaded breathing (estimated difference=−0.08 s, 95% CI −0.14 to −0.02 s) (p=0.011), with no interaction between conditions and sequences.

Neuropsychological tests

Executive function

Categorical and verbal fluency tests both demonstrated the same profile. While subjects were able to produce more words during unloaded breathing compared to loaded breathing, the effect of the experimental conditions was more pronounced for those who started the experiment with loaded breathing, as a result of an interaction between the experimental conditions 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 were observed between experimental conditions, subjects who started the experiment with loaded breathing had much improved performance times with unloaded breathing, as a result of an interaction between the experimental conditions and the experimental sequence (p<0.001). For TMT B, no differences in time to perform the test were observed between experimental conditions and, as for TMT A, an interaction was found between the experimental conditions and the experimental sequence (p<0.001). However, subjects who started the experiment with 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 breathing compared to loaded breathing (difference in 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 had much improved performance with unloading breathing, as a result of an interaction between the experimental conditions 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 had much improved performance with unloading breathing, as a result of an interaction between the experimental conditions and the experimental sequence (p=0.03 for direct digit span and p=0.008 for indirect digit span).

Discussion

In this randomised, crossover trial of experimental dyspnoea in healthy subjects, we found that experimental dyspnoea (to a predetermined intensity of six out of 10 on a visual analogue scale) had a major impact on locomotion and cognitive function in a sample of highly educated, younger adults. Our

data support previous evidence of dyspnoea–cognition interactions [15–18] and suggest a plausible causal association between dyspnoea and brain function leading to altered locomotion and cognition. The crossover design also highlighted that alleviation of dyspnoea had a positive effect on locomotion and cognition.

Among locomotion parameters, gait speed is considered as the "sixth vital sign" [47] and mainly depends upon exercise capacity related to cardiorespiratory fitness (but also the integrity of the musculoskeletal, peripheral and central nervous systems). Reduced gait speed is associated with a poor clinical outcome in ageing and is associated with mortality [48]. Only a few studies have focussed on gait speed in respiratory disease, as the 6-min walk test and the incremental shuttle walk are historically so important in quantifying cardiorespiratory reserve and exercise tolerance in this field. However, gait speed (as measured by the 4-m gait speed) correlates with exercise capacity, dyspnoea and health-related quality of life [49] and is a predictor of hospital readmission for acute exacerbation of COPD [50]. The 4-m gait speed is also responsive to pulmonary rehabilitation [51] and has been proposed as a promising functional assessment tool in COPD in order to inform the clinician about many functional aspects and overall outcome [52].

As suggested in a previous study by our group, albeit with no formal demonstration [15], dyspnoea might independently impact on gait through sharing of neural networks with cognitive functions. In the present study, experimentally-induced dyspnoea increased time to perform the TUG test 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 dyspnoea on the time to perform the TUG test (+8.4% from baseline) and on 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 function in younger subjects or in patients with chronic respiratory disease. For instance, in patients surviving an exacerbation of COPD, the development of a test to challenge gait speed with a respiratory load at hospital discharge could inform the clinician about those patients more likely to present with or to develop poor cognition. The clinician would thus be aware of which patients would be at risk of poor adherence to medical treatment and thus would be at increased risk of readmission [54].

The current observations that dyspnoea 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 been consistently 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 dyspnoea *per se* is independently associated with locomotion and cognition in a plausible causal relationship.

Alleviation of dyspnoea 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 dyspnoea–inactivity vicious circle model in COPD is now supported by real-life data that has bridged a gap in our knowledge by identifying dyspnoea 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 whether a specific intervention on dyspnoea itself might reverse the vicious circle. At present, opiates are the only evidence-based pharmacologic treatment to target dyspnoea. 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 the notion that such a treatment would also have an impact on locomotion and cognition while respiratory mechanics are unchanged, thus providing a definitive demonstration that dyspnoea impacts on cognitive function.

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 arterial carbon dioxide tension (P_{aCO_2}) or a surrogate thereof during the experiment. Indeed, we considered that using a randomised trial of experimentally-induced dyspnoea would provide sufficient evidence to infer that dyspnoea 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. T. 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]. Secondly, our findings cannot be generalised to an older population with chronic respiratory diseases, in which dyspnoea at an intensity of four out of 10 is already clinically relevant [73]. Indeed, we specifically focussed on high functioning young adults. Interestingly, it was easy to artificially induce cognitive impairment in young healthy brains with the simple method of respiratory loading and this should certainly open up research avenues devoted to exploring the interaction between dyspnoea and cognition in older adults. Thirdly, acute dyspnoea was induced in a secured experimental setting and does not reflect the chronic condition associated with respiratory disease. Therefore, our results may not reflect the interactions between physiological, psychological, social and environmental factors involved in secondary physiological and behavioural responses to refractory dyspnoea in the clinical setting.

Conclusions

Acute experimental dyspnoea 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 disease and will provide a rationale for future clinical interventions aimed at improving locomotion and cognition by focussing on alleviating dyspnoea.

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