



HAL
open science

Short-term cognitive loading deteriorates breathing pattern and gas exchange in adult patients with congenital central hypoventilation syndrome

Jessica Taytard, Marie-Cécile Niérat, Camille Gand, Sophie Lavault, Capucine Morélot-Panzini, Maxime Patout, Laure Serresse, Nicolas Wattiez, Laurence Bodineau, Christian Straus, et al.

► To cite this version:

Jessica Taytard, Marie-Cécile Niérat, Camille Gand, Sophie Lavault, Capucine Morélot-Panzini, et al.. Short-term cognitive loading deteriorates breathing pattern and gas exchange in adult patients with congenital central hypoventilation syndrome. ERJ Open Research, 2023, 10.1183/23120541.00408-2022]. . hal-04035158

HAL Id: hal-04035158

<https://hal.science/hal-04035158>

Submitted on 17 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License



Short-term cognitive loading deteriorates breathing pattern and gas exchange in adult patients with congenital central hypoventilation syndrome

Jessica Taytard^{1,2}, Marie-Cécile Niérat ¹, Camille Gand¹, Sophie Lavault^{1,3}, Capucine Morélot-Panzini^{1,3}, Maxime Patout ^{1,4,5}, Laure Serresse^{1,6}, Nicolas Wattiez¹, Laurence Bodineau ¹, Christian Straus^{1,7,8} and Thomas Similowski^{1,3,8}

¹Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France. ²AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Armand-Trousseau, Service de Pneumologie Pédiatrique, Paris, France. ³AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Département R3S, Paris, France. ⁴AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service des Pathologies du Sommeil (Département R3S), Paris, France. ⁵AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Centre de référence maladie rare “hypoventilations centrales congénitales” (Département R3S), Paris, France. ⁶AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Paris, France. ⁷AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service d’Exploration Fonctionnelles de la Respiration, de l’Exercice et de la Dyspnée (Département R3S), Paris, France. ⁸These authors contributed equally.

Corresponding author: Thomas Similowski (thomas.similowski@upmc.fr)



Shareable abstract (@ERSpublications)

In adult CCHS patients, acute cognitive loads disorganise breathing and induce oxygen desaturation during unassisted breathing but not ventilatory support. Ventilatory support should be considered in this setting, to avoid repeated hypoxia. <https://bit.ly/3Mlp0yH>

Cite this article as: Taytard J, Niérat M-C, Gand C, *et al.* Short-term cognitive loading deteriorates breathing pattern and gas exchange in adult patients with congenital central hypoventilation syndrome. *ERJ Open Res* 2023; 9: 00408-2022 [DOI: 10.1183/23120541.00408-2022].

Copyright ©The authors 2023

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 15 Aug 2022
Accepted: 5 Oct 2022

Abstract

Question Human *PHOX2B* mutations result in life-threatening sleep-related hypoventilation (congenital central hypoventilation syndrome, CCHS). Most patients retain ventilatory activity when awake through a respiratory-related cortical network. We hypothesised that this need to mobilise cortical resources to breathe would lead to breathing-cognition interferences during cognitive loading.

Patients and methods Seven adult CCHS patients (five women; median age 21) performed standard neuropsychological tests (paced auditory serial addition test – calculation capacity, working memory, sustained and divided attention; trail making test – visuospatial exploration capacity, cognitive processing speed, attentional flexibility; Corsi block-tapping test – visuospatial memory, short-term memory, working memory) during unassisted breathing and under ventilatory support. Ventilatory variables and transcutaneous haemoglobin oxygen saturation were recorded. Cortical connectivity changes between unassisted breathing and ventilatory support were assessed using electroencephalographic recordings (EEG).

Results Baseline performances were lower than expected in individuals of this age. During unassisted breathing, cognitive loading coincided with increased breathing variability, and decreases in oxygen saturation inversely correlated with an increasing number of apnoeic cycles per minute ($\rho = -0.46$, 95% CI -0.76 to -0.06 , $p = 0.01$). During ventilatory support, cognitive tasks did not disrupt breathing pattern and were not associated with decreased oxygen saturation. Ventilatory support was associated with changes in EEG cortical connectivity but not with improved test performances.

Conclusions Acute cognitive loads induce oxygen desaturation in adult CCHS patients during unassisted breathing, but not under ventilatory support. This justifies considering the use of ventilatory support during mental tasks in CCHS patients to avoid repeated episodes of hypoxia.

Introduction

Human *PHOX2B* mutations result in various autonomic disorders including defective breathing control leading to life-threatening sleep-related hypoventilation (congenital central hypoventilation syndrome



(CCHS), 1 per 50–200 000 births [1]). Most patients retain normal or subnormal alveolar ventilation when awake, suggesting a cortical contribution to the neural drive to breathe. In adult patients with CCHS, electroencephalographic recordings show the activation of a respiratory-related cortical network during quiet unassisted breathing [2]. This network is normally silent in healthy individuals [2]. Functional neuroimaging in a patient with CCHS showed reduced respiratory-related cortical activity and reduced cortex-brainstem connectivity under mechanical ventilation, further supporting a cortical contribution to the neural drive to breathe [3]. The mobilisation of cortical resources to maintain ventilation could lead to breathing-cognition interference, since the simultaneous performance of a cognitive task and of a motor task can lead to a deterioration of one or both when they involve a shared neural network (dual-task framework, see review in LEONE *et al.* [4]). In the above neuroimaging observation, the reduction in respiratory-related cortical activity associated with mechanical ventilatory assistance has been shown to be associated with improved cognitive performance (freeing the cerebral cortex from the burden of breathing) [3]. Reciprocally, cognitive loading in CCHS patients could interfere with the cortical drive to breathe and therefore result in alveolar hypoventilation. No systematic assessment of this phenomenon has been conducted in adult CCHS patients. We therefore tested the primary hypothesis that acute cognitive loading during unassisted resting breathing in patients with CCHS would disrupt breathing pattern and possibly result in alveolar hypoventilation hence oxygen haemoglobin desaturation. We predicted that such changes would not occur during acute cognitive loading under ventilatory support, given the controlled ventilatory modes routinely used by the patient. We also tested the secondary hypothesis that performing neuropsychological tests under ventilatory support would be associated with improved test performances.

Methods

Ethics

This single-centre study was part of a larger programme (NCT03095729). It was conducted in compliance with the Declaration of Helsinki. It was approved by the appropriate ethics committee (*Comité de Protection des Personnes Sud-Ouest et Outre-Mer IV*, CPP17-005a/2A01660-51). All participants provided written consent to participate.

Patients with CCHS

Adult patients (≥ 18 years) with *PHOX2B* mutations were eligible. Non-inclusion criteria were: 1) ventilator dependency during wakefulness; 2) respiratory abnormalities other than related to CCHS; 3) acute respiratory issues during the last 6 weeks; and 4) a formal diagnostic of cognitive impairment or patent cognitive disorders. Patients were asked not to consume alcohol or psychotropic drugs during the 24 h preceding the study.

Study protocol

Evaluations were conducted on the same day for each patient. To limit the impact of a learning effect on the overall results, the patients were randomised to perform the neuropsychological tests either first during unassisted resting breathing or first during ventilatory support, at random (figure 1). Given the size of the population, the data from the resulting groups were then pooled: no between-group comparisons were conducted. Also to limit the impact of learning effect, two versions of the paced auditory serial addition test (PASAT) were performed according to a XYYX plan (unassisted breathing – ventilatory support – ventilatory support – unassisted breathing) [5]. Under ventilatory support, the patients used their usual ventilatory support devices and settings (controlled mode in all cases; noninvasive ventilation in pressure control mode in six patients, volume-controlled ventilation through a tracheotomy in one patient). All the patients confirmed being familiar with the corresponding mode of mechanical ventilation during wakefulness. Because CCHS patients exhibit a respiratory-related cortical activity during unassisted breathing [2] that decreases during ventilatory support [3] and because changes in a respiratory-related cortical activity have been shown to occur concomitantly with changes in cognitive performances during inspiratory loading in normal humans [5], electroencephalogram (EEG) recordings were acquired during the first and last 10 min of the evaluations (figure 1). The aim of these recordings was to document that ventilatory support was associated with changes in brain activity.

Ventilatory variables

Ventilatory flow was measured with a low resistance ($< 1 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$) low dead space ($\sim 40 \text{ mL}$) pneumotachograph (3700A series; Hans Rudolf, Shawnee, KS, USA) connected to a differential pressure transducer ($\pm 5 \text{ cmH}_2\text{O}$, DP45-18; Validyne, Northridge, CA, USA) and linked to an analogue digital converter (Powerlab 16/35; AD Instruments, Bella Vista, Australia). Pulse oximetry was measured continuously. Tidal volume (V_T) was calculated by integration of the flow signal. Inspiratory time (t_I), expiratory time (t_E), respiratory period (T_T) and breathing frequency (f_B) were measured using LabChart 7.3 (AD Instruments). The breath-by-breath variability of ventilatory variables was described by calculating

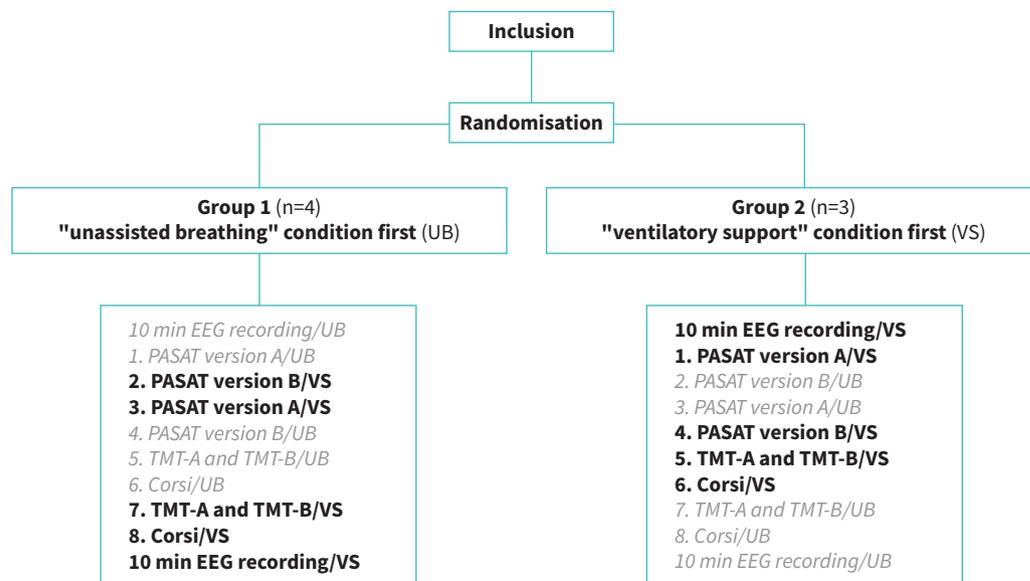


FIGURE 1 Experimental plan of the study. Tests performed during unassisted breathing (UB) are shown in the gray italic typeface, and tests performed during ventilatory support (VS) are shown in bold black typeface. EEG: electroencephalogram; PASAT: paced auditory serial addition test; TMT: trail making test; Corsi: Corsi block-tapping test.

their coefficients of variation. Apnoeic cycles (t_E above 3 standard deviations of the corresponding value measured during unassisted resting breathing [6, 7]) were counted.

Electroencephalographic (EEG) data

EEG activity was recorded by four active scalp electrodes (Cz, Fz, FP1, FP2) connected to a V-Amp amplifier (Brain Products, Gilching, Germany; digitisation 256 Hz, bandwidth 0.05–5 Hz), the patients being asked to limit body and eye movements as much as possible to reduce artefacts. Changes in brain activity related to breathing condition were identified using the Riemannian evaluation of cortical connectivity previously described [8–11]. EEG classifying performance was evaluated by a cross-validation process: the reference period of the “unassisted breathing” condition was divided into 10 equal EEG segments, and comparisons between nine of these segments and the data from the “ventilatory support” condition were repeated nine times to take all combinations into account. The results were plotted as receiver operating characteristic curves. A prediction area under the curve (AUC) of 1 and 0.5 indicated perfect and random discrimination, respectively, and an $AUC \geq 0.7$ indicated satisfactory discrimination.

Neuropsychological tests

Among the many existing neuropsychological tests, we chose three on which the impact of changes in respiratory-related cortical activation has been studied before [5]. The participants underwent:

- 1) The PASAT version A and B [12], during which patients were given a number from 0 to 9 every 3 s and asked to recall the two most recent numbers (3-min fixed duration); the PASAT evaluates calculation capacity, working memory, sustained and divided attention; respiratory-related brain activation has been associated with PASAT deterioration in healthy subjects [5].
- 2) The trail making test (TMT) A and B [13–15], during which patients were asked to connect a set of dots as quickly and as accurately as possible (TMT duration varied from 15–20 s for version A to 60–90 s for version B); the TMT evaluates visuospatial exploration capacity, and cognitive processing speed (version A), plus attentional flexibility (version B); attentional flexibility alone was evaluated by subtracting TMT-B time from TMT-A time; respiratory-related brain activation has been associated with deterioration of TMT-A without effect on TMT-B in healthy subjects [5].
- 3) Corsi block-tapping test (Corsi) [16], during which patients were asked to mimic an operator tapping a progressively increasing sequence of up to nine identical cubes either forwards or backwards (Corsi duration up to 5 min); the Corsi evaluates visuospatial memory, short-term memory (forward) and working memory (backward). Corsi span was defined as the length of the last successfully reproduced series. The total crude score corresponded to the sum of the forward and backward spans;

respiratory-related brain activation has been associated with maintained Corsi performances in healthy subjects [5].

The PASAT, but not the TMT or Corsi test, included discrete and brief verbal responses (numbers). Instructions were provided before each test, and a trial was performed to ensure good understanding of the instructions and to limit the learning effect.

Statistical analysis

Statistical analyses were performed using Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA). The variables were expressed as median and interquartile range (Q1–Q3). All analyses were performed using nonparametric tests (Wilcoxon for paired comparisons, Spearman for correlations). Oxygen saturation measured by pulse oximetry (S_{pO_2}) data were compared in a “before–after” manner (end of neuropsychological test *versus* beginning). Breathing pattern was continuously recorded during the experiments. Breathing pattern data were compared between baseline conditions (in the absence of cognitive tasks) and cognitive loading conditions. The recordings obtained during the whole duration of the cognitive tests were used for analysis and compared to 10 min of baseline recordings. The two-stage step-up method of BENJAMINI *et al.* [17] was used to control the false discovery rate (FDR), which was set up at 5%. Comparisons were considered statistically significant when FDR adjusted p-values, as reported in Results, were <0.05 .

Complementary study in healthy subjects

We compared the effects of acute cognitive loading on breathing pattern and S_{pO_2} in our CCHS patients with the corresponding effects in healthy individuals who had participated in a previously published study following the same general methodology [5] and in whom S_{pO_2} data were available.

Results

Patients

Seven patients with CCHS (five women, two men) bearing *PHOX2B* mutations (20/25 alanine expansion, $n=2$; 20/26, $n=3$; 20/27 expansion, $n=2$) were studied. Median age was 21 years (range 18 to 39). Median body mass index was $21.5 \text{ kg}\cdot\text{m}^{-2}$ (range 19.2 to 27.8). The ventilatory support interface was a face mask (six patients) and a tracheotomy (one patient). None of the patients had diaphragm pacing. Two patients were hypercapnic during unassisted resting breathing at baseline (arterial carbon dioxide tension (P_{aCO_2}) 52 and 49 mmHg, respectively; these two patients had declined). One patient had a cardiac pacemaker, one had Hirschsprung disease and one had strabismus. No patient had evidence of pulmonary artery hypertension on cardiac ultrasound. There were no other significant comorbidities. The patients all had low anxiety levels (State-Trait Anxiety Inventory median state score 26 (23–39.5); median trait score 32 (30–33)). Although not identified as suffering from cognitive impairment, one patient failed to understand and master the PASAT (PASAT results therefore pertain to six patients only). Four patients performed the neuropsychological tests first during unassisted breathing, while three started with the tests under mechanical ventilation.

Baseline neuropsychological performances

The baseline neurocognitive performances of our patients are provided in table 1. They appeared lower than the performances of normal subjects of comparable age studied in a similar manner [5] (median PASAT score 36.5 in this study *versus* 52 in healthy individuals; median TMT-B time 78 s *versus* 44 s; total Corsi score 14 *versus* 21).

Breathing-cognition interferences during unassisted resting breathing

During unassisted resting breathing at baseline, all patients had normal S_{pO_2} (97% (95–98)) in spite of low V_T and minute ventilation (V'_E) (V_T : 220 mL (150–320)/4 mL·kg⁻¹ (3–6); V'_E : 4.50 L·min⁻¹ (2.86–7.52)/80 mL·min⁻¹·kg⁻¹ (50–90)). A significant drop in S_{pO_2} was noted between the beginning and the end of each neuropsychological test (PASAT, TMT and Corsi) (figure 2):

- PASAT (A and B pooled, two tests per patient): 97% (96.25–98) to 95% (92–98), $p=0.028$ (S_{pO_2} decrease in eight out of 12 tests);
- TMT (A and B pooled): 96% (95–98) to 94% (92–96), $p=0.028$ (S_{pO_2} decrease in six out of seven patients).
- Corsi: 97% (94.75–98) to 93.5% (91–95.75), $p=0.035$ (missing data in one patient; S_{pO_2} decrease in five out of six patients).

Breathing pattern analysis did not detect statistically significant changes in median V_T , f_B , t_I or t_E , and T_T (except for a shorter t_I during TMT-A, $p=0.040$). In contrast, significant increases in breath-by-breath variability were observed (figure 3):

TABLE 1 Comparison of neuropsychological tests performed under the unassisted breathing condition and during ventilatory support

	Unassisted breathing	Ventilatory support	p-value
PASAT (n=6) (number of correct answers, /60)			
Version A	35 (23–50)	38 (27–44)	0.43
Version B	39 (29–47)	38 (28–51)	0.27
Versions A and B	36 (23–52)	38 (25–51)	0.29
TMT (n=7) (in seconds)			
Version A	46 (26–49)	34 (29–47)	0.38
Version B	78 (59–123)	87 (55–110)	0.46
B – A	46 (19–74)	53 (13–71)	0.39
CORSI (n=7) (score: number of correct series; span: number of tapped cubes tapped during the last successful series)			
Direct score (forward memory)	10 (9–10)	9 (6–11)	0.23
Indirect score (backward memory)	6 (4–8)	8 (5–9)	0.14
Direct span (forward memory)	6 (6–7)	5 (4–6)	0.5
Indirect span (backward memory)	3 (2–4)	4 (3–6)	0.07
Total	14 (12–18)	18 (11–20)	0.26

Data presented as median (interquartile range). n: number of patients. PASAT: paced auditory serial addition test; TMT: trail making test; Corsi: Corsi block-tapping test.

- increased t_I variability during PASAT A and PASAT B ($p=0.028$ in both cases);
- increased t_E variability during PASAT A and B ($p=0.028$ in both cases), during TMT-B ($p=0.008$) and during Corsi ($p=0.028$);
- increased f_B variability during PASAT A and B ($p=0.028$ in both cases) and during TMT-B ($p=0.028$).

The number of apnoeic cycles per minute was significantly higher during the neuropsychological tests (except for TMT-A) than at baseline (PASAT A and B, $p=0.035$; TMT-B, $p=0.028$; Corsi, $p=0.04$; figure 4). With a few exceptions, apnoeic cycles were not preceded by sighs. There was a significant correlation between the number of apnoeic cycles during the neuropsychological tests and the magnitude of the S_{pO_2} decreases observed during the corresponding tests (pooled data; $\rho=-0.46$, $p=0.010$; figure 5).

Breathing-cognition interferences under ventilatory support

All patients had normal S_{pO_2} under ventilatory support at baseline. In contrast with the observations made during unassisted breathing, no decreases in S_{pO_2} were observed between the beginning and the end of the neuropsychological test. As predicted, given the use of controlled ventilatory assistance modes, no significant changes in ventilatory variables, breathing variability or the number of apnoeas were detected between baseline and cognitive loading conditions.

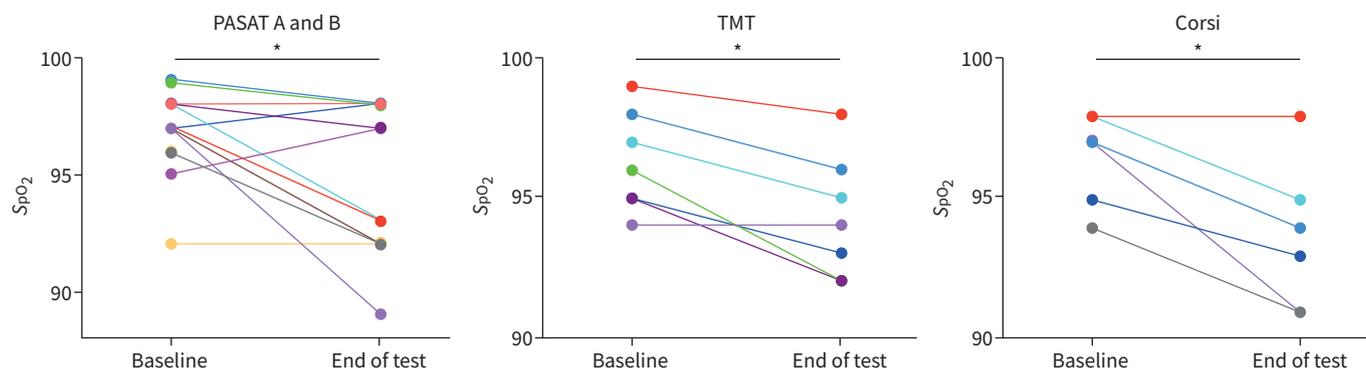


FIGURE 2 Oxygen saturation (S_{pO_2}) at the beginning and end of neuropsychological tests during unassisted breathing. PASAT: paced auditory serial addition test (six patients performed the test; A and B pooled, $n=12$); TMT: trail making test ($n=7$); Corsi: Corsi block-tapping test (all patients performed the test, but S_{pO_2} measurement failed in one case; $n=6$). *: $p < 0.05$.

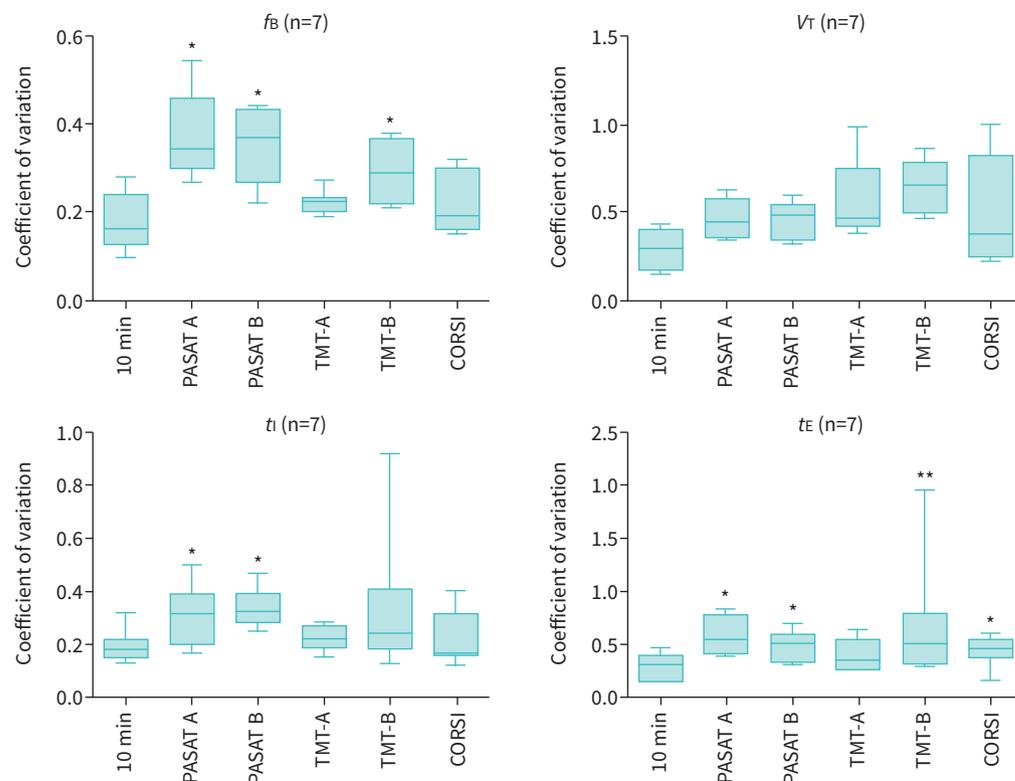


FIGURE 3 Breath-by-breath variability (coefficients of variation) of ventilatory variables during unassisted breathing in baseline condition (10-min recording) and during neuropsychological tests (totality of the recording). The boxes represent the 25–75th percentile of the data with indication of the median, and the whiskers depict the full range of the data. f_b : breathing frequency; V_t : tidal volume; t_i : inspiratory time; t_e : expiratory time. “10 min”: baseline value; PASAT: paced auditory serial addition test, versions A and B; TMT: trail making test, versions A and B; Corsi: Corsi block-tapping test. *: $p < 0.05$ versus baseline; **: $p < 0.01$ versus baseline.

The results of the neuropsychological tests performed under ventilatory support did not significantly differ from the results obtained during unassisted breathing (table 1).

Of note, and compatible with the contribution of cortical resources to ventilation in adult CCHS patients during unassisted breathing [2], the analysis of the EEG recordings showed changes in brain connectivity between unassisted breathing and ventilatory support, with a median prediction AUC of 0.82 (0.75–0.96) (prediction AUC above 0.7 in six out of seven patients, AUC 0.48 in one).

Healthy subjects

S_{pO_2} data were available in 10 of the subjects having participated in a previously published study using the same methodology [5]. The characteristics of this subgroup were similar to those of the patients with CCHS (five men, five women; age 22 years (range 20–26); body mass index $22.2 \text{ kg}\cdot\text{m}^{-2}$ (range 20.9–23.3)). S_{pO_2} during resting breathing was 98% (97–98). No change was observed at the end of the PASAT tests (98% (97–98)), the TMT (98% (98–98)) or the Corsi (97% (97–98)).

Discussion

Breathing-cognition interferences at the expense of breathing

In line with our primary hypothesis, this study showed that acute cognitive loading during unassisted resting breathing in adult CCHS patients resulted in breathing pattern disruption, with increased breath-by-breath variability and, most notably, an increased occurrence of apnoeic cycles leading to oxygen desaturation. This highlights an interference between cognition and breathing at the expense of breathing. It is highly suggestive of a dual-tasking phenomenon [4] and confirms that the respiratory-related cortical activity previously described [2] does drive breathing in adult CCHS patients. Integrating published evidence leads us to believe that, rather than acting on a breath-by-breath basis (“Ondine’s curse”, which would be contradictory with overlearning-associated cortical automatization

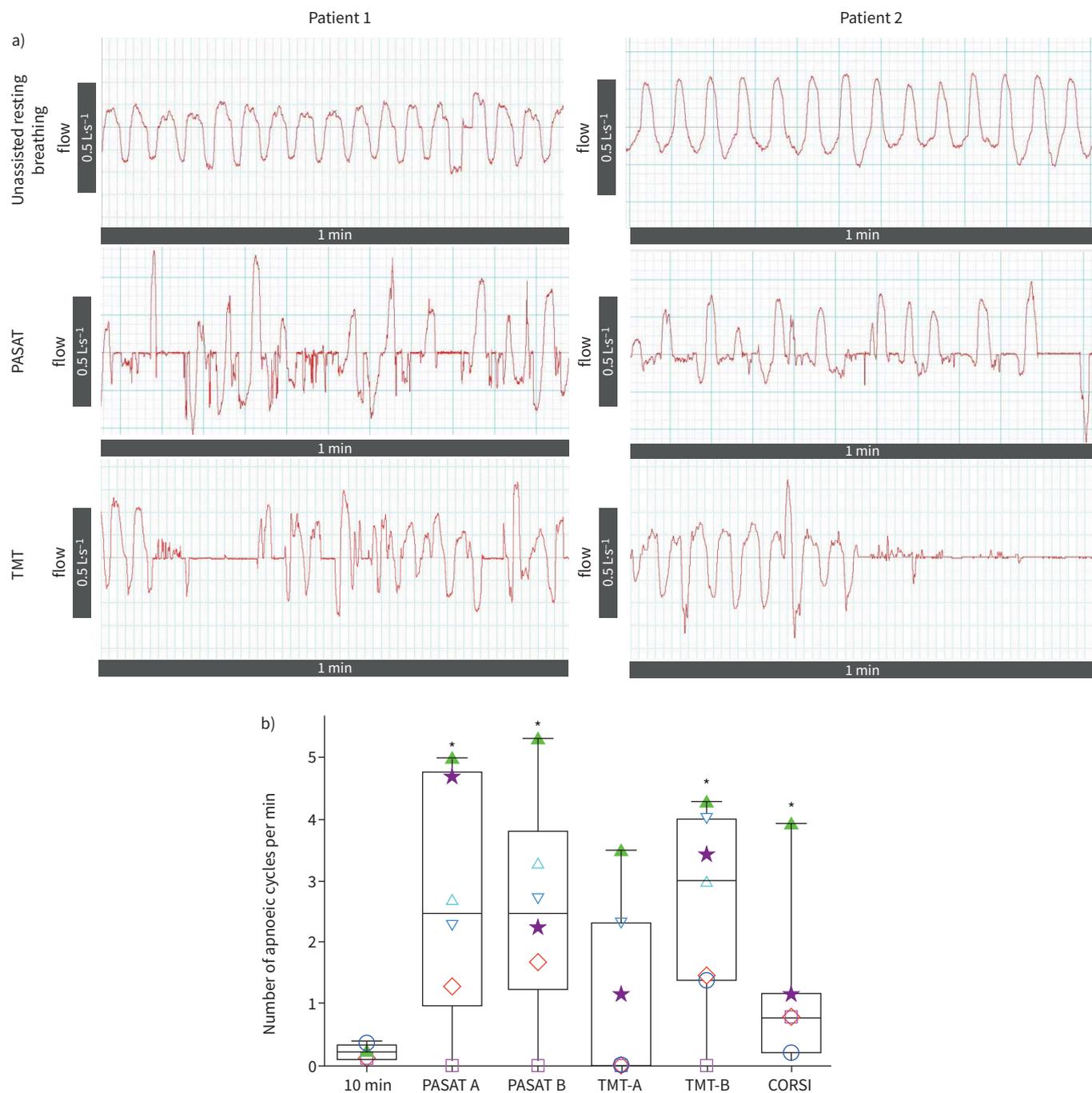


FIGURE 4 a) Example of ventilatory flow recordings in two selected patients (Patient #1 and Patient #2) during unassisted resting breathing at baseline (top trace), during the performance of a PASAT test (middle trace) and during the performance of a TMT test (bottom trace), illustrating breathing irregularities and the occurrence of apnoeic cycles. b) Frequency of apnoeas during unassisted breathing in baseline condition (10-min recording) and during neuropsychological tests (totality of the recording) (apnoeas were defined as breathing cycles with an expiratory time (t_E) above the mean t_E measured during unassisted breathing augmented by 3 standard deviations). The boxes represent the 25–75th percentile of the data with indication of the median, and the whiskers depict the full range of the data. “10 min”: baseline value; PASAT: paced auditory serial addition test, versions A and B; TMT: trail making test, versions A and B; Corsi: Corsi block-tapping test. *: $p < 0.05$ versus baseline.

[18]), this cortical drive consists of tonic excitatory corticospinal inputs depolarising phrenic motoneurons and facilitating their response to the oscillatory bulbospinal drive [19] (figure 6). Facilitation and disfacilitation at the spinal level play key roles in the interplay between subcortical and cortical breathing commands [20–22]. In the context of CCHS, an excitatory descending cortical drive [2] would facilitate

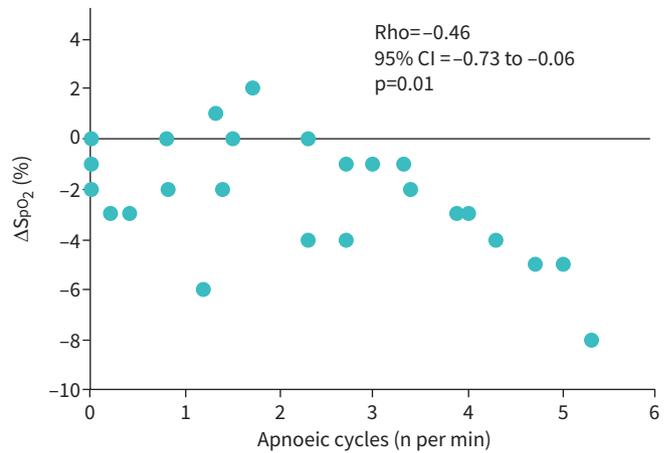


FIGURE 5 Correlation between decreases in oxygen saturation measured by pulse oximetry (S_{pO_2}) from baseline to the end of neuropsychological tests and number of apnoeas per minute during tests completion (pooled data: PASAT A n=6, PASAT B n=6, TMT-A and TMT-B in sequence n=7, Corsi n=6–7 patients performed the test, but S_{pO_2} failed in one case). PASAT: paced auditory serial addition test; TMT: trail making test; Corsi: Corsi block-tapping test.

the spinal motoneuronal response to the defective bulbar drive and allow ventilation to be maintained during wakefulness. Sleep-related disfacilitation would then result in hypoventilation, as would interfering with the cortical drive through dual-tasking (figure 6). The fact that cognitive loading did not disrupt breathing under ventilatory support, namely in a situation where a cortical contribution to breathing is not needed to maintain ventilation, supports the above interpretations, as does the absence of oxygen desaturation during cognitive loading in normal subjects. It is interesting to note that the residual ventilation present in *PHOX2B* mutant mice at birth is characteristically irregular with an abundance of central apnoeas [23, 24]. This irregularity decreases with development in conditional *PHOX2B* mutant mice [24]. If the cortical contribution to breathing shown in humans also existed in mice, this decrease in breathing irregularity could relate to the growth-related maturation of corticospinal pathways [25–27].

Our observations regarding the effects of cognitive tasks on breathing pattern diverge from those in healthy adults, which show that acute cognitive loading tends to accelerate breathing and increase ventilation, possibly in relation with task-induced stress [28]. Our observations also diverge to those reported by SHEA *et al.* [29] in five children with CCHS that did not show breathing-cognition interference; however, this study, which predates gene discovery, is difficult to interpret because of insufficient power to conclude on a negative result and because it used nonstandard mental tasks for which the results were not reported. In contrast, the abnormal respiratory response to cognitive loading in our patients is reminiscent of the response observed in normal children during emotionally neutral video gaming, consisting of prolonged t_E and slowed-down breathing [30]. Hypothetical explanations for our findings could include maturation-related factors and/or a low sensitivity to task-induced stress, in line with the low trait anxiety levels in our patients.

Lack of improvement in cognitive performances under ventilatory support

Our secondary hypothesis, *i.e.*, that cognitive performance would improve under ventilatory support (as reported by SHARMAN *et al.* [3]) is not supported by our overall results. One possible explanation could be that ventilatory support failed to free the necessary cortical resources. In view of the connectivity changes evidenced by the EEG analyses, we believe that this is unlikely. Another explanation would be that our patients had fixed neurocognitive impairments that they could not improve upon (ceiling effect). Such a mechanism would be in line with the low test scores that our patients exhibited at baseline, most likely in line with the known association of CCHS with neurocognitive deficits affecting a wide range of functions including processing speed and working memory [31–34]. Of note, some of our patients did perform markedly better under mechanical ventilation than during unassisted breathing (improved PASAT in two patients: from 38 to 53 and 50 to 59; improved Corsi in two patients: from 12 to 20 and from 11 to 18). This raises the possibility of individual differences with respect to the breathing-cognition interactions. In other words, breathing and cognition may interfere at the expense of the breathing pattern, cognitive performance, or both, depending on the priority given to one or the other activity. This priority could differ between patients and could also vary over time in a given patient.

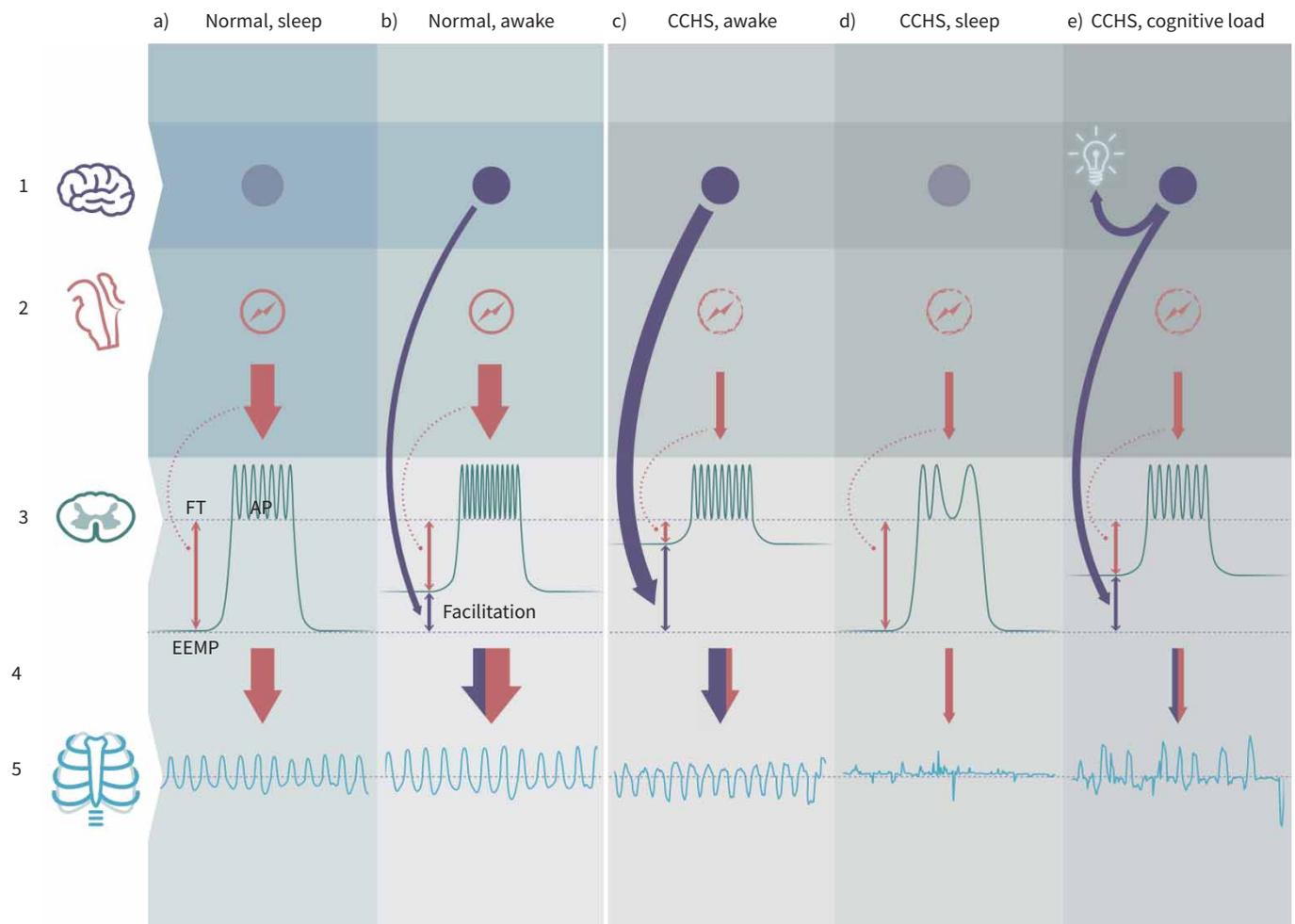


FIGURE 6 Schematic representation of the cortical facilitation theory of the neural drive to breathe, depicting the interactions between bulbospinal and corticospinal inputs on spinal respiratory motoneurons during: **a)** sleep in normal humans; **b)** wakefulness in normal humans; **c)** wakefulness in patients with central congenital hypoventilation syndrome (CCHS); **d)** sleep in patients with CCHS; **e)** acute cognitive load in patients with CCHS. From top to bottom, the horizontal bands correspond to 1: activation of respiratory-related cortical networks and intensity of corticospinal respiratory output (purple arrows); 2: status of the respiratory central pattern generators in the brainstem (normal: solid circle; defective: blurred circle) and intensity of the bulbospinal respiratory output (red arrow); 3: membrane potential (FT: firing threshold; EEMP: end-expiratory membrane potential) and firing rate (AP: action potentials) of respiratory spinal motoneurons; 4: net neural drive to breathe (bulbospinal contribution in red, corticospinal contribution in purple); 5: breathing pattern. In band 3, the vertical red double arrows represent the difference between end-expiratory membrane polarity and firing threshold that must be cancelled by the bulbospinal respiratory output for inspiration to occur (red dotted line). The vertical purple double arrows depict the effects of cortical facilitation. The presence of a corticospinal input to spinal respiratory motoneurons raises their membrane potential closer to the firing threshold, making a given bulbospinal output more efficient at producing ventilation (facilitation; column b versus a). In patients with CCHS during wakefulness (column c), the decreased bulbospinal output resulting from the *PHOX2B* mutation deleterious impact on central respiratory pattern generators is “compensated” by increased activation of a respiratory-related cortical network [1]. The absence of this corticospinal input during sleep (column d) can explain (and in any case contributes to) sleep-related hypoventilation. According to this cortical facilitation theory of the neural drive to breathe, the observations of the present study (breathing pattern disorganisation during cognitive loading, with correlation to desaturations) could relate to cognitive loading reducing the cortical resources available for breathing through a dual-tasking effect (column e).

Study limitations

The main limitation of our study is the small number of patients, reflecting the very rare nature of the disease and the relative complexity of the experimental setup. The patient population in this research represents one third of the known adult CCHS population nationwide at the time of the study in France. The study must therefore be considered a pilot, and more data will need to be collected using simpler designs. In particular, we could not study putative relationships between breathing-cognition interferences and genotypic and phenotypical characteristics (*e.g.* severity of hypoventilation or chemosensitivity blunting), which warrants further investigation. As a second limitation, we only assessed changes in

alveolar ventilation through changes in S_{pO_2} . It was indeed impossible to measure the end-tidal partial pressure in carbon dioxide during unassisted breathing in our setup; the time dynamics involved would have made transcutaneous measures unreliable, and arterial puncture would not have been acceptable for the patients. The impact of breathing pattern disruptions on S_{pO_2} that we observed could appear surprising, but our patients had very low V_T s (median of $4 \text{ mL}\cdot\text{kg}^{-1}$), which is consistent with paediatric data, and, consequently, high dead space volume (V_D) to V_T ratios (V_D/V_T). Owing to the hyperbolic nature of the P_{aCO_2} - V_D/V_T relationship, small falls in V_T lead to sharp rises in P_{aCO_2} when V_D/V_T is high: the alveolar gas equation indicates that this should be associated with corresponding decreases in oxygenation. A third limitation is the lack of definitive mechanistic explanations, in the absence of functional magnetic resonance imaging data similar to that provided by SHARMAN *et al.* [3]. Nevertheless, the change in the breathing-cognition interaction under ventilatory support as compared to unassisted breathing, and concomitant EEG connectivity changes, supports a dual-task mechanism.

Implications and perspectives

The aetiology of neurocognitive deficits in CCHS is largely unknown and may relate to genetic factors (even though PHOX2B is not expressed above the pons nor in the cerebellum) or to ventilation-related factors [34]. Acute experimental hypoxia severely impairs performance and task learning across several neurocognitive domains [35], and the hypoxia-reoxygenation induced systemic oxidative stress can be deleterious [36]. Our study suggests that such hypoxia-reoxygenation episodes could be very frequent in CCHS patients, would they occur each time that cognitive resources have to be mobilised. This could result in, or worsen, cognitive deterioration. Starting in infancy, this phenomenon could result in, or worsen, neurodevelopmental impairment.

For these reasons, we believe that our study is clinically relevant. Indeed, the occurrence of arterial oxygen desaturation during acute cognitive loading in adult CCHS patients breathing unassisted and the lack of such events when cognitive loading takes place under ventilatory support justify considering the use of ventilatory support during mental tasks in CCHS patients who otherwise do not receive mechanical ventilation during wakefulness. This ventilatory support can be personalised through an evaluation of breathing-cognition interactions during neuropsychological testing, a possibility that we have introduced at our centre.

We acknowledge the study limitations and the need for corroboration and more mechanistic knowledge. Meanwhile, in clinical practice, it appears reasonable to propose that adult patients with CCHS check their S_{pO_2} during prolonged and intense cognitive tasks and seek medical advice regarding ventilatory assistance in the event of related desaturations. This message is crucial to convey to the CCHS community, particularly in view of the additional burden for patients with CCHS and their families that would result from ventilator support during cognitive tasks.

Provenance: Submitted article, peer reviewed.

Data availability: Raw data will be communicated by the authors for research purposes upon reasonable request.

Conflict of interest: The study did not involve any conflict of interest, financial or otherwise.

Support statement: The study was funded in part by *Association Française pour le Syndrome d'Ondine*. Andrew Lane (Lane Medical Writing) provided editorial assistance and was funded by Sorbonne Université, Paris. Funding information for this article has been deposited with the Crossref Funder Registry.

References

- 1 Bardanzellu F, Pintus MC, Fanos V, *et al.* Neonatal congenital central hypoventilation syndrome: why we should not sleep on it. Literature review of forty-two neonatal onset cases. *Curr Pediatr Rev* 2019; 15: 139–153.
- 2 Tremoureux L, Raux M, Hudson AL, *et al.* Does the supplementary motor area keep patients with Ondine's curse syndrome breathing while awake? *PLoS One* 2014; 9: e84534.
- 3 Sharman M, Gallea C, Lehongre K, *et al.* The cerebral cost of breathing: an fMRI case-study in congenital central hypoventilation syndrome. *PLoS One* 2014; 9: e107850.
- 4 Leone C, Feys P, Moumdjian L, *et al.* Cognitive-motor dual-task interference: a systematic review of neural correlates. *Neurosci Biobehav Rev* 2017; 75: 348–360.
- 5 Taytard J, Gand C, Nierat MC, *et al.* Impact of inspiratory threshold loading on brain activity and cognitive performances in healthy humans. *J Appl Physiol (1985)* 2022; 132: 95–105.

- 6 Nakayama H, Smith CA, Rodman JR, *et al.* Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. *Am J Respir Crit Care Med* 2002; 165: 1251–1260.
- 7 Rodman JR, Curran AK, Henderson KS, *et al.* Carotid body denervation in dogs: eupnea and the ventilatory response to hyperoxic hypercapnia. *J Appl Physiol (1985)* 2001; 91: 328–335.
- 8 Gosselin F, Navarro-Sune X, Raux M, *et al.* CARE-rCortex: a Matlab toolbox for the analysis of Cardio-REspiratory-related activity in the Cortex. *J Neurosci Methods* 2018; 308: 309–316.
- 9 Hudson AL, Navarro-Sune X, Martinerie J, *et al.* Electroencephalographic detection of respiratory-related cortical activity in humans: from event-related approaches to continuous connectivity evaluation. *J Neurophysiol* 2016; 115: 2214–2223.
- 10 Navarro-Sune X, Hudson AL, De Vico Fallani F, *et al.* Riemannian geometry applied to detection of respiratory states from EEG signals: the basis for a brain-ventilator interface. *IEEE Trans Biomed Eng* 2017; 64: 1138–1148.
- 11 Raux M, Navarro-Sune X, Wattiez N, *et al.* Adjusting ventilator settings to relieve dyspnoea modifies brain activity in critically ill patients: an electroencephalogram pilot study. *Sci Rep* 2019; 9: 16572.
- 12 Tombaugh TN. A comprehensive review of the Paced Auditory Serial Addition Test (PASAT). *Arch Clin Neuropsychol* 2006; 21: 53–76.
- 13 Reitan RM. The relation of the trail making test to organic brain damage. *J Consult Psychol* 1955; 19: 393–394.
- 14 Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, *et al.* Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc* 2009; 15: 438–450.
- 15 Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. *J Clin Psychol* 1987; 43: 402–409.
- 16 Berch DB, Krikorian R, Huha EM. The Corsi block-tapping task: methodological and theoretical considerations. *Brain Cogn* 1998; 38: 317–338.
- 17 Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. *Biometrika* 2006; 93: 491–507.
- 18 Raux M, Tyvaert L, Ferreira M, *et al.* Functional magnetic resonance imaging suggests automatization of the cortical response to inspiratory threshold loading in humans. *Respir Physiol Neurobiol* 2013; 189: 571–580.
- 19 Laviolette L, Nierat MC, Hudson AL, *et al.* The supplementary motor area exerts a tonic excitatory influence on corticospinal projections to phrenic motoneurons in awake humans. *PLoS One* 2013; 8: e62258.
- 20 Davey NJ, Murphy K, Maskill DW, *et al.* Site of facilitation of diaphragm EMG to corticospinal stimulation during inspiration. *Respir Physiol* 1996; 106: 127–135.
- 21 Mehiri S, Straus C, Arnulf I, *et al.* Responses of the diaphragm to transcranial magnetic stimulation during wake and sleep in humans. *Respir Physiol Neurobiol* 2006; 154: 406–418.
- 22 Straus C, Locher C, Zelter M, *et al.* Facilitation of the diaphragm response to transcranial magnetic stimulation by increases in human respiratory drive. *J Appl Physiol (1985)* 2004; 97: 902–912.
- 23 Dubreuil V, Ramanantsoa N, Trochet D, *et al.* A human mutation in Phox2b causes lack of CO₂ chemosensitivity, fatal central apnea, and specific loss of parafacial neurons. *Proc Natl Acad Sci USA* 2008; 105: 1067–1072.
- 24 Ramanantsoa N, Hirsch MR, Thoby-Brisson M, *et al.* Breathing without CO₂ chemosensitivity in conditional Phox2b mutants. *J Neurosci* 2011; 31: 12880–12888.
- 25 Namikawa T, Kikkawa S, Inokuchi G, *et al.* Postnatal development of the corticospinal tract in the Reeler mouse. *Kobe J Med Sci* 2015; 61: E71–E81.
- 26 Uematsu J, Ono K, Yamano T, *et al.* Development of corticospinal tract fibers and their plasticity. II. Neonatal unilateral cortical damage and subsequent development of the corticospinal tract in mice. *Brain Dev* 1996; 18: 173–178.
- 27 Uematsu J, Ono K, Yamano T, *et al.* Development of corticospinal tract fibers and their plasticity I: quantitative analysis of the developing corticospinal tract in mice. *Brain Dev* 1996; 18: 29–34.
- 28 Grassmann M, Vlemincx E, von Leupoldt A, *et al.* Respiratory changes in response to cognitive load: a systematic review. *Neural Plast* 2016; 2016: 8146809.
- 29 Shea SA, Andres LP, Paydarfar D, *et al.* Effect of mental activity on breathing in congenital central hypoventilation syndrome. *Respir Physiol* 1993; 94: 251–263.
- 30 Denot-Ledunois S, Vardon G, Perruchet P, *et al.* The effect of attentional load on the breathing pattern in children. *Int J Psychophysiol* 1998; 29: 13–21.
- 31 Zelko FA, Stewart TM, Brogadir CD, *et al.* Congenital central hypoventilation syndrome: broader cognitive deficits revealed by parent controls. *Pediatr Pulmonol* 2018; 53: 492–497.
- 32 Charnay AJ, Antisdell-Lomaglio JE, Zelko FA, *et al.* Congenital central hypoventilation syndrome: neurocognition already reduced in preschool-aged children. *Chest* 2016; 149: 809–815.
- 33 Macdonald KT, Mosquera RA, Yadav A, *et al.* Neurocognitive functioning in individuals with congenital central hypoventilation syndrome. *BMC Pediatr* 2020; 20: 194.
- 34 Trang H, Bourgeois P, Cheliout-Heraut F. Neurocognition in congenital central hypoventilation syndrome: influence of genotype and ventilation method. *Orphanet J Rare Dis* 2020; 15: 322.

- 35 Turner CE, Barker-Collo SL, Connell CJ, *et al.* Acute hypoxic gas breathing severely impairs cognition and task learning in humans. *Physiol Behav* 2015; 142: 104–110.
- 36 Degl’Innocenti D, Becatti M, Peruzzi M, *et al.* Systemic oxidative stress in congenital central hypoventilation syndrome. *Eur Respir J* 2018; 52: 1801497.