Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare neuro-respiratory disorder associated with several possible mutations of the PHOX2B gene [1]. Animal models have shown that these mutations result in major alterations in the development of the parafacial region of the brainstem that is instrumental to respiratory chemosensitivity [2]. Patients with these mutations experience hypoventilation when sleeping, resulting in sleep-related ventilator-dependency [1]. They lack ventilatory and perceptual responses to hypercapnia or hypoxia [1]. However, most CCHS patients have normal or subnormal resting ventilation when awake. The dramatic discrepancy between sleep and wake suggests the contribution of cortical mechanisms [3], but the precise nature of these mechanisms is currently unknown.

Ventilation of the lungs results from phasic contractions of respiratory muscles in response to a so-called “neural drive to breathe” that is relayed to the muscles by spinal respiratory motoneurons. The net output of spinal respiratory motoneurons
depends on the various inputs that they receive not only from automatic brainstem central pattern generators but also from various suprapontine circuits that are responsible for emotional breathing modulations, voluntary breathing control and the interplay between respiration and nonrespiratory processes of cortical origin, primarily speech and voluntary movements [4,5,6]. Consequently, ventilatory behaviour at any given moment reflects the integration of voluntary and involuntary rhythmic and non-rhythmic central drives, further modulated by respiratory and nonrespiratory afferents [4].

In humans, the contribution of cortical processes to the overall drive to breathe is phenomenologically illustrated by certain particularities of breathing control. For example, decreasing carbon dioxide partial pressure in the blood by passive hyperventilation (ventilator-induced hypocapnia) is associated with apnoea during sleep, but rarely while awake [7,8]. Similarly, when breathing difficulties are induced experimentally in sleeping individuals by inspiratory loading, ventilation tends to decrease [9]. In contrast, awake humans faced with such loads compensate or overcompensate for the inspiratory burden and tend to hyperventilate [10,11]. Load compensation is accompanied by electroencephalographic (EEG) signs of activation of the supplementary motor area (SMA) in the form of slow EEG negativities recorded at the vertex that precede inspiration [12,13]. These “pre-inspiratory potentials” (PIPs) resemble the premotor potentials that accompany movement preparation [Bereitschaftspotential] and are thought to originate in the SMA (Shibasaki, 2006). Transcranial magnetic stimulation studies have also established connections between the SMA and phrenic motoneurons [14,15]. In addition, it has been shown that the SMA exerts a tonic facilitatory influence on phrenic motoneurons in humans, via the primary motor cortex [16].

Therefore, we hypothesized that resting ventilatory activity in awake CCHS patients would be associated with respiratory-related EEG signs of SMA activity, i.e. pre-inspiratory potentials. Such a respiratory-related cortical activity is normally not observed in healthy individuals.

Methods

Ethics statement

The study was conducted according to the principles expressed in the Declaration of Helsinki. Participants were informed about the general study procedure, the methods used and the absence of any associated risks, and gave their written consent to participate. The exact study objectives were only revealed to the subjects post hoc in order to limit bias. The study was approved by the appropriate local legal and ethics authority (Comité de Protection des Personnes Ile-de-France 6, Pitié-Salpêtrière, Paris).

Patients and controls

Index group. CCHS patients with documented PHOX2B mutations, followed at the adult section of the French national CCHS reference centre, were systematically considered for inclusion. Exclusion criteria were: partial pressure of oxygen in arterial blood (PaO2) while breathing room air less than 80 mmHg; daytime dependence on the time of study, this index group represented the majority of the arterial blood (PaO2) while breathing room air less than inclusion. Exclusion criteria were: partial pressure of oxygen in CCHS reference centre, were systematically considered for mutations, followed at the adult section of the French national

Experimental conditions and protocol

The participants were asked to abstain from alcohol, avoid sleep deprivation and refrain from taking any psychotropic medication for 24 hours prior to the experimental sessions. Study participants were studied whilst seated comfortably in a chair that fully supported their neck, legs and arms. During the experimental sessions, they were distracted from their laboratory surroundings by listening to music of their choice. The investigators and recording equipment were placed out of their view.

The experimental protocol comprised 5 study conditions. “Control 1” (condition #1) consisted of resting ventilation with minimal constraints, during which the participants only wore a respiratory inductance plethysmography vest (see below). “Control 2” (condition #2) also consisted of resting ventilation, but the participants breathed through a respiratory measurement apparatus (see below). “Chemostimulation” (condition #3) involved breathing a gas mixture of either 5–7% CO2 in oxygen for 20 minutes — 10 minutes stabilisation of the PEEP followed by 10 minutes of recording —. “Loading” (condition #4) involved breathing through an inspiratory threshold load with a 23 cmH2O load for 10 minutes. “Control 3” (condition #5) was identical to “Control 2”. Heart rate (HR) and transcutaneous pulse oximetry (SpO2) were monitored continuously as a safety measure.

Respiratory measurements

Respiratory inductance plethysmography. Rib cage and abdomen displacements were recorded by two coils placed in a sleeveless jacket, only allowing circumferential stretching of the wires (Visuresp®, RBI, Meylan, France). The signal was digitised at 40 Hz and processed to provide a measurement of ventilatory flow (V1pp, for “inductance plethysmography”), as previously described [18].

Expired CO2. During “Control 2”, “Chemostimulation”, “Loading” and “Control 3”, the subjects wore a facial mask (Ultra Mirage®, ResMed Corp Poway, CA, USA) that gave access to expired air sampling for the measurement of end-tidal partial CO2 pressure (PetCO2). This was achieved with an infrared gas analyzer connected to the mask (CO2 pump flow 150 cm3.min-1, IR1505, Servomex, Plaine Saint Denis, France). PetCO2 was only used to monitor the stability of the hypercapnic stimulations.

Electroencephalography

Surface scalp electroencephalographic signal (EEG) was recorded using a 12-electrode cap installed after rubbing and cleaning with alcohol and application of a conductive gel (EasyCap, Brain Products GmbH, Germany). Active electrodes were placed in equidistant positions (ActiCap, Brain Products GmbH, Germany) according to the conventional “10–20” topographic system. The
earth electrode was positioned at AFz. The EEG signal was digitised at 2000 Hz and recorded using V-Amp® software (Brain Products GmbH, Germany) for subsequent processing, which was performed according to the method previously described [12,19] (Figure 1. Offset, EEG signals were referenced to linked earlobe electrodes. In each of the study conditions, eighty 4-second EEG epochs (from 2.5 s before to 1.5 s after onset of inspiration defined as the point of zero flow) on the V1p signal were created. The EEG signal was filtered between 0.01 and 5 Hz. EEG epochs with clear artefacts (EEG gradient greater than 5 µV.m⁻¹.s⁻¹; EEG amplitude greater than 50 µV) or EEG consistent with eye movements were discarded and the remaining epochs were ensemble averaged. Averaged tracings were examined for the presence of an inspiratory premotor activity in the form of a slow upward shift of the EEG signal starting between 2 and 0.5 s before inspiration. When this activity was observed, a first-order least-squares regression equation was fitted to the corresponding segment of EEG. A pre-inspiratory potential was considered to be present when and only when the slope of this equation was positive and significantly different from zero according to the F-test for equality of variance. The latency of the pre-inspiratory potential, if present, was defined as the interval in ms between the negativity and the start of inspiration. The amplitude of the pre-inspiratory potential corresponded to the potential measured in µV between baseline and the “zero flow” point.

Statistical analysis
All statistics were performed using Prism 4® software (GraphPad Software, Inc., CA, USA). The normality of the distribution of the results was tested using a Shapiro-Wilk test. As the hypothesis of normality was not verified for all variables, continuous variables are expressed as their median and 95% confidence intervals (CI95). Between group comparisons of dichotomous variables (presence or absence of a PIP) were performed using Fisher’s exact test. Latencies and amplitudes were compared between groups only in the “Load” condition in which all subjects of both groups exhibited a PIP (see below, results). This comparison was performed using a Mann-Whitney test. Differences were considered significant when the probability P of a type I error was less than 5%.

Results
Control group
All subjects in the control group participated in all sessions. PIPS were inconsistent during spontaneous breathing (“Control 1”, “Control 2”, “Control 3”) and during “Chemostimulation”, as one subject exhibited a PIP during “Control 1”, 3 during “Control 2”, 1 during “Control 3”. PIPS were also inconsistent during “Chemostimulation” (2 out of 8 subjects). In contrast, PIPS were systematically present during “Loading” (8 out of 8 subjects). PIPS were clearly visible in the Cz derivation and none of the other ones. Figure 2 provides an example of the EEG tracings obtained in one subject in the various conditions.

Patients
Two patients dropped out of the study following “Chemostimulation” due to CO₂-induced headache. One patient only participated in “Control 1”, “Chemostimulation” and “Load”. All patients exhibited PIPS in all study conditions in which they participated. PIPS were clearly visible in the Cz derivation and none of the other ones. Figure 3 provides an example of the tracings obtained in one subject in the various conditions.

Consequently, PIPS were significantly more frequent in patients than healthy control subjects during all control conditions (“Control 1”, P = 0.001; “Control 2”, P = 0.031; “Control 3”, P = 0.01) and during “Chemostimulation” (P = 0.006). No significant difference was observed during “Loading” (P = 1.000).

During “Loading”, the median latency of PIPS was 1.8 s [1.1–2.0] in patients vs. 1.6 s [1.4–2.2] in controls (no statistically significant difference). The corresponding values for median amplitude were 5.9 µV [2.1–14] and 3.7 µV [2.1–8.9], respectively (no statistically significant difference). Of note, although statistical comparison of amplitudes and latencies was not possible in the other conditions due to the very small sample sizes, the amplitudes of PIPS inconsistently observed in controls were always much lower (5- to 10-fold) than those of the PIPS observed in patients. PIP latencies were also much shorter (2- to 4-fold) in controls.

Discussion
This study shows that awake, spontaneously breathing adult CCHS patients exhibit a respiratory-related cortical activity that is normally absent during resting ventilation in healthy subjects.

Methodological considerations
Available data predict that PIPS should generally not be detected during resting breathing, not be detected during exercise and not be detected during CO₂-stimulated breathing in normal individuals; they also predict that PIPS should consistently be present in response to inspiratory threshold loading [12,13,19,20,21]. This was mostly the case in our control subjects, but “unexpected” PIPS were observed. Similar observations have been made in previous studies conducted by our group (one subject out of ten in [12]; one subject out of nine in [13]; two subjects out of seven in [19]). In this study as in the previous ones, and despite the various precautions taken (see methods), we cannot exclude the possibility that some subjects focused on their respiratory activity, as suggested by the higher rate of PIPS during “Control 2” (breathing through a face mask) than during “Control 1” (minimally constrained breathing, with only a respiratory inductive plethysmography vest). This could also account for the higher rate of resting breathing PIPS during “Control 3”, i.e. at a point of the experimental protocol at which the subjects would have realized that their breathing was being manipulated. It is also possible that some CCHS patients also had a PIP due to the experimental setting rather than to physiological reasons. Yet the comparison of our CCHS group with a control group of similar size was sufficient to evidence a statistically significant difference in the incidence of PIPS during spontaneous breathing and during CO₂-stimulated breathing. This incidence was higher in the CCHS patients than in the normal individuals, and the levels of significance of the control-CCHS differences were at their highest in the two conditions where the comparison was the most important, namely the “control 1” condition (room air quiet breathing with minimal respiratory apparatus, p = 0.001) and the “CO₂ stimulated breathing” condition (p = 0.006). When PIPS were present in the normal subjects, they were several folds smaller than in the CCHS subjects. We therefore do not think that the small size of the control group (and the fact that the two groups were not exactly gender matched) compromises the physiological validity of our observations.

Neurophysiological considerations
SMA activity and “cortical drive to breathe” in CCHS. Studies using transcranial magnetic stimulation have
demonstrated a direct connection between the SMA and phrenic motoneurones [15] and that the SMA can modulate the pathway from the primary motor cortex to the phrenic motoneurones in both an inhibitory and an excitatory manner [16,21]. These studies suggest that the SMA is implicated in the cortical control of breathing in healthy subjects. Moreover, EEG and functional imaging studies have demonstrated SMA activation during voluntary inspirations [22,23] and during the non-volitional response to inspiratory constraints [12,24]. Therefore, the results of the present study suggest the SMA is involved in wake-related maintenance of rhythmic breathing in CCHS. However, the nature of this involvement has yet to be elucidated. Breath-by-breath “cortical control” of breathing could be postulated, [6,25], but its neurophysiological basis remains to be established (see below, “cortical automatization and interferences”). Alternatively, a “cooperative” mechanism involving facilitation at the level of spinal respiratory motoneurons could be proposed, as follows. Spinal respiratory motoneurons integrate various voluntary and involuntary rhythmic and non-rhythmic respiratory central drives [4,5,26]. These descending inputs interfere with one another: how spinal respiratory motoneurons react to a given input depends on how other prior inputs have modified their membrane polarity. For example, tidal inspiration during eucapnic resting breathing facilitates the diaphragm response to transcranial magnetic stimulation [27]. Increasing the bulbospinal ventilatory drive by CO₂ stimulation also strongly facilitates the response of the diaphragm to corticospinal inputs generated by transcranial magnetic stimulation [28,29]. The site of this facilitation appears to be spinal [29,30]. Also, that the inspiratory output from parasternal intercostal motoneurones is altered by voluntary trunk rotation (presumably due to corticospinal projections that decrease motoneurone threshold) [31], but that the same postural contraction has no effect on phrenic inspiratory motoneurone output [32] provides further evidence of the integration of different descending drives at the respiratory interneurones and motoneurones at the spinal cord. It could be postulated that, in awake CCHS patients, the SMA-phrenic input described in this study may be sufficient to make phrenic motoneurons responsive to the
“residual” automatic ventilatory command present in many of these patients. According to this hypothesis, the loss of intracortical connectivity characteristic of sleep [33] would contribute to sleep-related hypoventilation in CCHS. Fragmentary observations from our group suggest that some CCHS patients exhibit abnormally rapid diaphragm responses to TMS during relaxation (unpublished data), which would be consistent with a “facilitatory tone”. Of note, the fact that CCHS patients with certain Phox2B mutations have no residual ventilatory activity even awake is an argument against the hypothesis of a cortical “ectorhythm” [6] and in favour of the spinal facilitation mechanism described above.

Cortical automatization and interferences. A respiratory-related motor cortical activity does not necessarily mean that “each breath is taken voluntarily”. There are numerous examples of automatized voluntary motor actions that can be performed “without attention being clearly directed toward the details of the movement” [34]. Another characteristic of the automatization of a learned movement is that “performance does not deteriorate if another task is performed simultaneously” [35]. Breathing while awake in CCHS patients has been purported to satisfy these two criteria by Shea et al. [36] who reported that mental activities, such as reading, arithmetic, or video gaming, were not associated with hypoventilation in children with CCHS. However, conflicting observations have been reported [37]. They may be difficult to interpret because healthy children can also exhibit decreased ventilatory activity in relation to attentional load and its emotional content [38]. Of note, the SMA belongs to cortical structures believed to be involved in automatization processes [34]: data from our group suggests that respiratory automatization rapidly occurs during inspiratory loading, with a strong SMA involvement [24].

Irrespective of the previous observations, all made in children, our findings raise the question of putative “competition” for cortical resources in adult CCHS patients. In other words, can their respiratory-related cortical activity have an impact on their motor and/or cognitive performances? Voluntary breathing control disturbs simple motor tasks [39,40], but whether or not this remains the case when voluntary breathing becomes automatic has not been clearly elucidated. Patients with chronic obstructive pulmonary disease (COPD), who by nature perma-

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Figure 2. Average pre-inspiratory EEG tracings in one of the control subjects. In each of the panels, the top trace depicts the Cz-EEG signal, and the bottom trace depicts ventilatory flow. The vertical line indicates the onset of inspiration. In the three “control condition” panels (control 1: resting ventilation with minimal constraint, namely a respiratory inductance plethysmography vest only; control 2: resting ventilation while breathing through a pneumoatchograph; control 3: as control 2, but during the washout period following inspiratory loading), inspiration is not preceded by any change in the EEG signal (absence of pre-inspiratory potentials). In the “CO2 stimulated breathing” panel, inspiration is also not preceded by any change in the EEG signal (absence of pre-inspiratory potentials). In contrast, in the “inspiratory threshold loading” panel, inspiration is preceded by a shift upward of the EEG trace (horizontal double arrowed red line) that is characteristic of a pre-inspiratory potential. This pattern exactly corresponds to what is expected in normal individuals [12].

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nently fight an abnormal respiratory load, have normal manual tracking performances [41]. It could even be hypothesized that a sustained respiratory-related cortical activity could be beneficial on certain functions, because voluntary breathing enhances the response of nonrespiratory muscles to corticospinal inputs [42]: this could facilitate the execution of motor tasks. Of interest, some adult CCHS patients followed at our reference center anecdotally report that they concentrate more aptly on demanding intellectual tasks when under mechanical ventilation than when spontaneously breathing (one patient reported being used to put herself on her ventilator during academic exams). Specific studies will therefore need to determine whether or not the cortically driven breathing characteristic of awake CCHS patients negatively impacts neuromotor or cognitive performances.

Conclusion

In conclusion, we have evidenced that pre-inspiratory potentials are present during resting ventilatory activity in awake CCHS patients, which suggests that SMA activation is required for maintenance of breathing in this setting. It is likely that this activation facilitates the response of spinal motoneurones to the residual bulbospinal drive to breathe. Further studies are needed to fully characterize the mechanisms of “cortical breathing” in CCHS, and to determine the clinical implications of these findings. Whether or not inducing spinal facilitatory plasticity through pharmacological or nonpharmacological interventions could have therapeutic benefits will also have to be evaluated.

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Author Contributions

Conceived and designed the experiments: MR CS TS. Performed the experiments: LT AR MR. Analyzed the data: LT MR ALH CS TS. Wrote the paper: LT MR ALH CS TS.
References

1. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loughnane DA, et al. (2010) An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med 181: 626–644.

2. DuBreuil V, Ramanantsoa N, Trochet D, Vaubourg V, Amiel J, et al. (2008) A human mutation in Phox2b causes lack of CO2 chemosensitivity, fatal central apnea, and specific loss of parafacial neurons. Proc Natl Acad Sci U S A 105: 10702–10707.

3. Shea SA (1997) Life without ventilatory chemosensitivity. Respir Physiol 110: 199–210.

4. Shea SA (1996) Behavioural and arousal-related influences on breathing in normal men. J Appl Physiol 81: 1–26.

5. Hudson AL, Gandevia SC, Butler JE (2011) Control of human inspiratory motoneurons during voluntary and involuntary contractions. Respir Physiol Neurobiol 179: 23–35.

6. Haouzi P (2001) Initiating inspiration outside the medulla does produce eugonic breathing. J Appl Physiol 100: 854–856.

7. Corfield DR, Morrell MJ, Guz A (1995) The nature of breathing during hypocapnia in awake man. Respir Physiol 101: 145–159.

8. Datta AK, Shea SA, Horner RL, Guz A (1991) The influence of induced hypocapnia and sleep on the endogenous respiratory rhythm in humans. J Physiol 440: 17–33.

9. Wiegand L, Zovilich CW, White DP (1988) Sleep and the ventilatory response to resistive loading in normal men. J Appl Physiol 64: 1186–1195.

10. Axen K, Haas SS, Haas F, Gaudino D, Haas A (1983) Ventilatory adjustments during sustained mechanical loading in conscious humans. J Appl Physiol 55: 1211–1218.

11. Yanos J, Banner A, Stanko R, Gentry S, Greenawalt K (1990) Ventilatory responses to inspiratory threshold loading in humans. J Appl Physiol 68: 2511–2520.

12. Raux M, Straus C, Redolfi S, Morelot-Panzini C, Couturier A, et al. (2007) Electroencephalographic evidence for pre-motor cortex activation during inspiratory loading in humans. J Physiol 578: 569–578.

13. Tremourelx L, Raux M, Jutand J, Similowski T (2010) Sustained preinspiratory cortical potentials during prolonged inspiratory threshold loading in humans. J Appl Physiol 108: 1217–1313.

14. Raux M, Viganou M, Similowski T, Koski L (2010) Facilitatory conditioning of the supplementary motor area in humans enhances the corticospinal responsiveness to transcranial magnetic stimulation. J Appl Physiol 108: 39–46.

15. Sharshar T, Hopkinson NS, Jonville S, Prigent H, Carlier R, et al. (2004) Demonstration of a second rapidly conducting cortico-diaphragmatic pathway in humans. J Physiol 560: 897–908.

16. Lavandette I, Nierat MC, Hudson AL, Raux M, Allard E, et al. (2013) The supplementary motor area exerts a tonic excitatory influence on corticospinal projections to phrenic motoneurons in awake humans. PLoS One 8: e62250.

17. Straus C, Similowski T (2011) Congenital central hypoventilation syndrome and desogestrel: a call for caution: addendum to “C. Straus, H. Trang, M.H. Breccqman, P. Touraine, T. Similowski, Chemosensitivity recovery in Ondine’s curse syndrome under treatment with desogestrel” (Respir. Physiol. Neurobiol. 171 [2010] 171–174). Respir Physiol Neurobiol 178: 357–358.

18. Eberhard A, Calabrèse P, Bacoussier P, Benchetrit G (2001) Comparison between the respiratory inductance plethysmography signal derivative and the airflow signal. Adv Exp Med Biol 499: 409–419.

19. Raux M, Ray P, Prella M, Duguet A, Demoule A, et al. (2007) Cerebral cortex activation during experimentally induced ventilator fighting in normal humans receiving noninvasive mechanical ventilation. Anesthesiology 107: 746–755.

20. Jutand L, Tremourelx L, Fichon A, Delpech N, Denjean A, et al. (2012) Ventilatory response to exercise does not evidence electroencephalographical respiratory-related activation of the cortical premotor circuitry in healthy humans. Acta Physiol (Oxf) 205: 356–362.

21. Raux M, Tremourelx L, Couturier A, Hug F, Similowski T (2010) Simplified recording technique for the identification of inspiratory premotor potentials in humans. Respir Physiol Neurobiol 171: 67–70.

22. Colebatch JG, Adams L, Murphy K, Martin AJ, Lammersma AA, et al. (1991) Regional cerebral blood flow during volitional breathing in man. J Physiol 443: 91–103.

23. McKay LG, Evans KC, Frackowiak RS, Corfield DR (2003) Neural correlates of voluntary breathing in humans. J Appl Physiol 95: 1170–1178.

24. Raux M, Tyvaert L, Ferreira M, Kandier F, Morelot-Panzini C, et al. (2013) Automatization-like changes in brain activity in response to sustained inspiratory loading in conscious humans: a fMRI study. Respir Physiol Neurobiol in press.

25. Haouzi P, Bell HJ (2009) Control of breathing and volitional respiratory rhythm in humans. J Appl Physiol 106: 904–910.

26. Aminoff MJ, Sears TA (1971) Spinal integration of segmental, cortical and breathing inputs to thoracic respiratory motoneurones. J Physiol 215: 537–575.

27. Mehiri S, Strauss C, Arnulfi I, Antal V, Zelter M, et al. (2006) Responses of the diaphragm to transcranial magnetic stimulation during wake and sleep in humans. Respir Physiol Neurobiol 154: 406–418.

28. Murphy K, Mier A, Adams L, Guz A (1990) Putative cerebral cortical involvement in the ventilatory response to inhaled CO2 in conscious man. J Physiol 420: 1–18.

29. Strauss C, Locher C, Zelter M, Derenne JP, Similowski T (2004) Facilitation of the diaphragm response to transcranial magnetic stimulation by increases in human respiratory drive. J Appl Physiol 97: 902–912.

30. Davey NJ, Murphy K, Maskell DW, Guz A, Ellaway PH (1996) Site of facilitation of diaphragm EMG to corticospinal stimulation during inspiration. Resp Physiol 106: 127–135.

31. Hudson AL, Butler JE, Gandevia SC, De Troyer A (2010) Interplay between the inspiratory and postural functions of the human parasternal intercostal muscles. J Neurophysiol 103: 1622–1629.

32. Hudson AL, Butler JE, Gandevia SC, De Troyer A (2011) Role of the diaphragm in trunk rotation in humans. J Neurophysiol 106: 1622–1628.

33. Massimini M, Ferrarelli F, Huber R, Escol S, Singh H, et al. (2005) Breakdown of cortical effective connectivity during sleep. Science 309: 2228–2232.

34. Wu T, Kangaku K, Hallet M (2004) How self-initiated memorized movements become automatic: a functional MRI study. J Neurophysiol 91: 1690–1698.

35. Guilleminault C, McQuitty J, Ariagno RL, Challamel MJ, Korobshi K, et al. (1982) Congenital central alveolar hypoventilation syndrome in six infants. Pediatrics 70: 694–694.

36. Denot-Ledunois S, Vardon G, Perruchet P, Gallego J (1998) The effect of attentional load on the breathing pattern in children. Int J Psychophysiol 29: 13–25.

37. Guilleminault C, McQuitty J, Ariagno RL, Challamel MJ, Korobshi K, et al. (1982) Congenital central alveolar hypoventilation syndrome in six infants. Pediatrics 70: 694–694.

38. Denet-Ledunois S, Vardon G, Perruchet P, Gallego J (1998) The effect of attentional load on the breathing pattern in children. Int J Psychophysiol 29: 13–25.

39. Gallego J, Perruchet P (1993) The effect of voluntary breathing on reaction time. J Psychosom Res 37: 63–70.

40. Datta AK, Shea SA, Horner RL, Guz A (1991) Life without ventilatory chemosensitivity. Respir Physiol 110: 854–856.

41. Cohen E, Murphy K, Adams L, Guz A, Benchetrit G (1995) Is voluntary control of nonrespiratory finger muscles. J Neurophysiol 105: 512–521.