Cortical drive to breathe in amyotrophic lateral sclerosis: a dyspnoea-worsening defence?

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ABSTRACT Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease causing diaphragm weakness that can be partially compensated by inspiratory neck muscle recruitment. This disappears during sleep, which is compatible with a cortical contribution to the drive to breathe. We hypothesised that ALS patients with respiratory failure exhibit respiratory-related cortical activity, relieved by noninvasive ventilation (NIV) and related to dyspnoea.

We studied 14 ALS patients with respiratory failure. Electroencephalographic recordings (EEGs) and electromyographic recordings of inspiratory neck muscles were performed during spontaneous breathing and NIV. Dyspnoea was evaluated using the Multidimensional Dyspnea Profile.

Eight patients exhibited slow EEG negativities preceding inspiration (pre-inspiratory potentials) during spontaneous breathing. Pre-inspiratory potentials were attenuated during NIV (p=0.04). Patients without pre-inspiratory potentials presented more advanced forms of ALS and more severe respiratory impairment, but less severe dyspnoea. Patients with pre-inspiratory potentials had stronger inspiratory neck muscle activation and more severe dyspnoea during spontaneous breathing.

ALS-related diaphragm weakness can engage cortical resources to augment the neural drive to breathe. This might reflect a compensatory mechanism, with the intensity of dyspnoea a negative consequence. Disease progression and the corresponding neural loss could abolish this phenomenon. A putative cognitive cost should be investigated.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by progressive loss of upper and lower motor neurons, resulting in wasting of skeletal muscles, including the respiratory muscles. Respiratory muscle weakness impairs quality of life in relation to sleep-related respiratory disorders and dyspnoea [1], and respiratory failure is a prominent cause of ALS-related death [2, 3].

The ALS-related degenerative process involves all respiratory muscle groups, with ensuing inspiratory and expiratory muscle weakness. This reduces ventilatory capacity and deteriorates respiratory mechanics, mostly through the impairment of cough, which leads to airway mucus encumbrance and atelectasis. As a result, a load–capacity imbalance develops, with signs of diaphragmatic dysfunction a prominent feature of the disease. ALS patients with diaphragm weakness often exhibit intense inspiratory neck muscle recruitment during wakefulness [4, 5], which is interpreted as compensatory in nature. This activity decreases or disappears during sleep, leading to hypoventilation [6]. As in the case of other wakefulness-dependent respiratory phenomena, it can be hypothesised that inspiratory muscle recruitment during wakefulness proceeds from a cortical contribution to the neural drive to breathe. A similar hypothesis has been proposed to explain the maintenance of ventilation during wakefulness in patients with defective automatic breathing, such as patients suffering from congenital central alveolar hypoventilation due to a PHOX2B mutation [7]. In such patients, electroencephalographic recordings (EEGs) time-locked to the spontaneous ventilatory activity have evidenced specific pre-inspiratory potentials resembling those that are observed during the preparation and execution of voluntary movements [7]. In healthy people, there is normally no respiratory-related cortical activity during quiet breathing, which means that pre-inspiratory potentials cannot be detected in this condition. They appear in the presence of a mechanical inspiratory load [8, 9], and reflect the activation and subsequent automatisation of respiratory cortico-subcortical networks involving the supplementary motor area (SMA) [10]. In the context of intrinsic inspiratory loads, they have been observed during normal breathing in patients suffering from severe forms of the obstructive sleep apnoea syndrome [11], and have been interpreted as contributing to the absence of upper airway obstructive events during wakefulness.

We therefore hypothesised that some ALS patients with respiratory failure would exhibit a respiratory-related cortical activity in the form of pre-inspiratory potentials, an activity that would be abolished or attenuated by noninvasive ventilation (NIV). We anticipated heterogeneous findings because of ALS-related cortical degeneration as a possible confounding factor. Because the presence of pre-inspiratory potentials in reaction to respiratory loading bears a relationship with respiratory discomfort [8, 12], we also predicted that a putative respiratory-related cortical activity would influence dyspnoea.

Material and methods

Patients

This study was conducted in the home mechanical ventilation unit of the respiratory medicine department at a 1600-bed tertiary university hospital. This unit is part of the local reference ALS multidisciplinary centre. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was part of an experimental programme approved by the appropriate French regulatory and ethical authority (Comité de Protection des Personnes). Patients received detailed information about the methods used and provided written consent to participate. The exact purpose of the study was explained after completion of the measurement to ensure that participants were as naïve as possible and to avoid bias. The inclusion criteria were as follows: 1) a probable or definite diagnosis of ALS according to the revised El Escorial criteria [13]; 2) overt respiratory failure with clear recruitment of inspiratory neck muscles during quiet breathing, at least when supine; and 3) previously established NIV. The exclusion criteria were as follows: 1) coexistence of any other respiratory diagnosis; 2) cumulative tobacco consumption >10 pack-years; 3) history of acute respiratory symptoms during the past 6 weeks; 4) gross cognitive impairment; and 5) end-stage disease.

Given the exploratory nature of the study, no statistical power calculation was performed, and a convenience sample of 14 patients was studied (table 1). Two patients had an initial bulbar form of ALS and one had an initial respiratory form. All patients received 50 mg of riluzole twice daily. None were gastrostomised. NIV settings were as follows: positive inspiratory pressure 17 cmH_2O [14–20], positive expiratory pressure 8 cmH_2O [4–10] and back-up respiratory rate 14 bpm [12–16].

Experimental protocol

Patients were studied in a sitting position that provided full support to the back, arms, neck and head. During the entire experiment, they watched an emotionally neutral movie (*e.g.* animal documentary) or television show to distract their attention from the experimental set-up and from their breathing. They were instructed to relax but to keep their eyes open to avoid any risk of falling asleep and to minimise eye movements.

TABLE 1 Patient characteristics at the time of the study

	Overall population	Presence of PIPs	Absence of PIPs	p-value
Subjects	14	8	6	
Anthropometric data				
Age years	63 (57–66)	62 (55.5–67.5)	64 (57–66)	0.85
Body mass index kg·m^{-2}	22.14 (20.7–24.6)	21.78 (20.7–23.2)	25.11 (22.0–30.8)	0.08
Neurological assessment				
ALS-FRS-R score (out of 48)	21 (14–23)	22.5 (20.5–23.5)	13.5 (13–20)*	0.04
Norris bulbar score (out of 39)	37 (35–37.2)	37 (35–37.5)	35 (25.7–37.2)	0.28
Time since onset of first neurological symptoms months	44 (25–53)	28.5 (24–44)	53 (49–71)*	0.01
Time since initiation of NIV months	11 (6–23)	9 (5.5–21.5)	14 (7–48)	0.41
Respiratory assessment				
Sitting FVC % pred	45 (29.2–62.5)	50 (36–66)	36 (29–39)	0.19
Supine FVC % pred	35.5 (31–48)	38 (32.2–60)	25 (19.7–34.7)	0.12
P_{Imax} % pred	24.5 (14–32.5)	32 (22.2–39.5)	8 (4.2–21.5)	0.14
SNIP % pred	20.5 (16–34.5)	34 (21.7–38.5)	12 (6–18)*	0.04
mMRC dyspnoea score	4 (3–4)	4 (3.5–4)	3.5 (3–4)	0.76
Efficacy of NIV				
Morning P_{aCO_2} during spontaneous breathing	44 (42–49)	47.5 (43–49.5)	43 (42–44)	0.34
Morning P_{aCO_2} after 1 h of NIV	39 (36–41)	38 (36–42)	39 (36–40.5)	0.76
Night-time spent with S_{pO_2} <90% on NIV % of recording	0 (0–7.7)	1 (0–5.7)	2 (0–10)	0.63
Tidal volume	512.5 (440–640)	520 (410–615)	502.5 (440–640)	1.00
NIV hours·day^{-1}	11.5 (8–16)	8 (7.5–12.5)	15 (12–18)	0.05

Data are presented as n or median (interquartile range), unless otherwise stated. Forced vital capacity (FVC) was measured in sitting and supine positions using an EasyOne ultrasound spirometer (NDD Medical Technologies, Andover, MA, USA). Inspiratory muscle strength was evaluated by measuring the maximal inspiratory pressure at the mouth (P_{Imax}) and at the nostril (sniff nasal inspiratory pressure (SNIP)) using a Micro-RPM digital manometer (Micro Medical, Chatham, UK). One of the patients with an initial bulbar form of amyotrophic lateral sclerosis (ALS) did exhibit a pre-inspiratory potential (PIP) during resting breathing; the other did not. The patient with an initial respiratory form of ALS did exhibit a PIP during resting breathing. ALS-FRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; NIV: noninvasive ventilation; mMRC: modified Medical Research Council; P_{aCO_2}: arterial carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. *: p<0.05 for presence of PIPs *versus* absence of PIPs.

Ventilatory variables, electromyograms (EMGs) and EEGs were first recorded during spontaneous room air breathing and then on NIV (Stellar, spontaneous-timed pressure support mode; ResMed, Bella Vista, Australia). In each of these conditions, the first 10 min were discarded to allow for stabilisation, and the following 20 min were kept for analysis. There was ~5–10 min between the two recordings.

Measurements

Ventilatory variables

During spontaneous breathing, ventilatory airflow was recorded through a nasal cannula connected to a ±2 cmH_2O linear differential pressure transducer (DP-45-18; Validyne, Northridge, CA, USA). This approach was chosen to minimise both apparatus-related inspiratory loading and apparatus-related focusing on breathing, both factors being liable to give rise to artefactual respiratory-related cortical activity (see discussion in [12]).

During NIV, the subjects breathed through the same facemask as they used at home (in all cases a QuattroFX; ResMed) connected to their ventilator and attached in series to a low-resistance pneumotachograph connected to a ±2 cmH_2O linear differential pressure transducer (DP-45-18) to measure ventilatory airflow. Airway pressure was measured using a ±140 cmH_2O differential pressure transducer (DP 15-32; Validyne).

Dyspnoea

Dyspnoea was evaluated using the French version of the Multidimensional Dyspnea Profile (MDP) after each recording session (spontaneous breathing and NIV), the patients being asked to focus on the past 30 s in each case [14]. This questionnaire comprises 11 items: one item (A1) assesses the unpleasantness of dyspnoea on a 0–10 visual analogue scale (from "neutral" to "unbearable"); five items assess the sensory dimension of dyspnoea in terms of quality and intensity (0–10); and five items assess the affective dimension of dyspnea in terms of quality and intensity (0–10). We calculated an "immediate perception domain" score (S) as the sum of the A1 intensity and the intensities of the five sensory descriptors and an "emotional response domain" score (A2) as the sum of the five emotional descriptors [14, 15].

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Electroencephalographic activity

EEG was recorded using active surface electrodes placed at scalp positions Fp1, Fpz, Fp2, F3, Fz, F4, Fcz, C3, Cz, C4, P3 and P4 on the basis of the international 10–20 electrode placement system using a 12-electrode cap installed after application of a conductive gel (EasyCap; Brain Products, Gilching, Germany). Electrode impedances were monitored and maintained at <5 kΩ. The EEG signal was digitised at 2000 Hz, recorded using V-Amp software (Brain Products) and filtered (0.01–5 Hz). EEG data were stored for offline analysis.

Surface electromyographic recordings of inspiratory neck muscles

Surface recordings of the EMG activity of inspiratory neck muscles were obtained using a pair of silver cup electrodes placed over the anatomical landmark of the middle scalene, 2 cm above the clavicle. The EMG signal was fed to an amplifier (Neuropack electromyograph; Nihon Kohden, Tokyo, Japan) with a 2 kHz sampling rate and was filtered between 20 and 3000 Hz. EEGs were digitised at 2 Hz and stored for offline analysis (LabChart version 7.0; AD Instruments, Oxford, UK).

Signal processing

Electroencephalographic data

Offline, EEG signals were referenced to the average of the electrodes. The EEG was split into 3 s epochs extending from 2.5 s before to 0.5 s after the onset of inspiration, as determined from the flow trace. Based on previous experiments [16], we have determined that ~80 epochs must be averaged to clearly identify pre-inspiratory potentials, which requires the recording of ~120 epochs to account for rejection criteria. The EEG recording therefore lasted ⩾120 breaths at the end of the steady-state period. All epochs exhibiting EEG artefacts, spurious EEG activity exceeding 20% of the baseline background signal or intense electro-oculographic activity were discarded (median rejection rate 38% [21–39]). On the averaged tracings, a slow negative shift starting between 2 and 0.5 s before inspiration was identified as pre-motor activity based on visual inspection by two observers blinded to the recording condition. Discrepancies were resolved by a third observer, also blinded to the recording condition. When a pre-inspiratory potential was considered to be present, its slope, amplitude and area under the curve (AUC) were determined. Finally, patients were grouped according to the presence or absence of pre-inspiratory potentials during spontaneous breathing, and a point-by-point ensemble averaging procedure was conducted among these groups.

Electromyographic data

The root mean square (RMS) of the inspiratory neck muscle EMG, reflecting the electrical energy spent by muscle contraction was calculated numerically using fixed 1-ms windows. For each condition in each subject, the beginning of inspiration was identified from the flow signal. The continuous EMG RMS signal was truncated into as many epochs as there were inspiratory efforts, with each period starting 1 s before the beginning of the corresponding inspiratory effort and ceasing 2 s after it ended; the epochs therefore contained the full inspiratory-related EMG activity [17, 18]. A set of 70–80 EMG epochs were then ensemble averaged, resulting in a mean EMG RMS envelope that was used for subsequent analysis [17, 18]. The averaged EMG RMS was used to measure the maximum EMG activity, the EMG_{AUC} and the produce of EMG_{AUC} × respiratory rate (f_R).

Statistical analysis

Statistical analysis was performed using SigmaStat software (Systat Software Inc., San Jose, CA, USA). Because data distributions were generally non-normal (Kolmogorov–Smirnov test), the data were summarised by the median and interquartile range, and nonparametric tests were used. The occurrence of pre-inspiratory potentials during spontaneous breathing and NIV were compared using Fisher's exact test. Spontaneous breathing and NIV were compared in terms of the presence of pre-inspiratory potentials using a Wilcoxon signed-rank test. Patients exhibiting pre-inspiratory potentials and those not exhibiting pre-inspiratory potentials were compared using a Mann–Whitney U-test. The relationship between dyspnoea ratings and inspiratory neck muscle EMG values was examined using Spearman's correlation coefficient. Comparisons were considered significant when $p<0.05$.

Results

Respiratory-related EEG activity

Pre-inspiratory cortical potentials were present in the Cz derivation in eight patients during spontaneous resting breathing and absent in the remaining six patients (figs 1–3). Only two of these eight patients still exhibited pre-inspiratory potentials during NIV (OR 7.4, 95% CI 1.0–92.8; p=0.046) (figs 1 and 3). In these two cases, the persistent pre-inspiratory potentials had reduced amplitudes (2.13 μV during spontaneous breathing *versus* 1.43 μV during NIV in one case; 5.51 *versus* 1.45 μV in the other case). The area under the averaged EEG activity curve was also reduced (1601 *versus* 798 μV^2 and 3627 *versus* 865 μV^2, respectively),

as was the slope of the pre-inspiratory potentials (0.0024 *versus* 0.0015 $\mu V.s^{-1}$ and 0.0016 *versus* 0.0008 $\mu V.s^{-1}$, respectively).

Inspiratory neck muscle EMG activity

Phasic inspiratory activity was clearly visible in almost all EMG recordings during spontaneous breathing (13 out of 14 patients; electrical interferences prevented analysis in one case) (figs 1 and 2), which is generally not observed in healthy people. Inspiratory neck muscle EMG activity was completely or almost completely abolished during NIV (fig. 1 and table 2) in all patients, including the two patients who exhibited a pre-inspiratory potential during spontaneous breathing and in whom NIV was not associated with complete disappearance of this potential.

Dyspnoea

Ratings of the MDP components are described in fig. 4. The patients reported intense dyspnoea during spontaneous breathing; "air hunger" and "work or effort" being the sensory descriptors most frequently used, and "anxiety" being the affective descriptor most frequently used. NIV almost completely relieved dyspnoea (fig. 4 and table 3). Of note, most patients considered it pointless to answer the "affective" questions after NIV, hence the absence of pre/post data for these items (fig. 4).

In the overall study population, a significant correlation was observed between the NIV-related decrease in the A1 score of the MDP and the corresponding decrease in the $EMG_{AUC} \times f_R$ product (fig. 5). No other correlation was observed between any of the dyspnoea scores (and their changes) and inspiratory neck muscle EMG activity (and its changes).

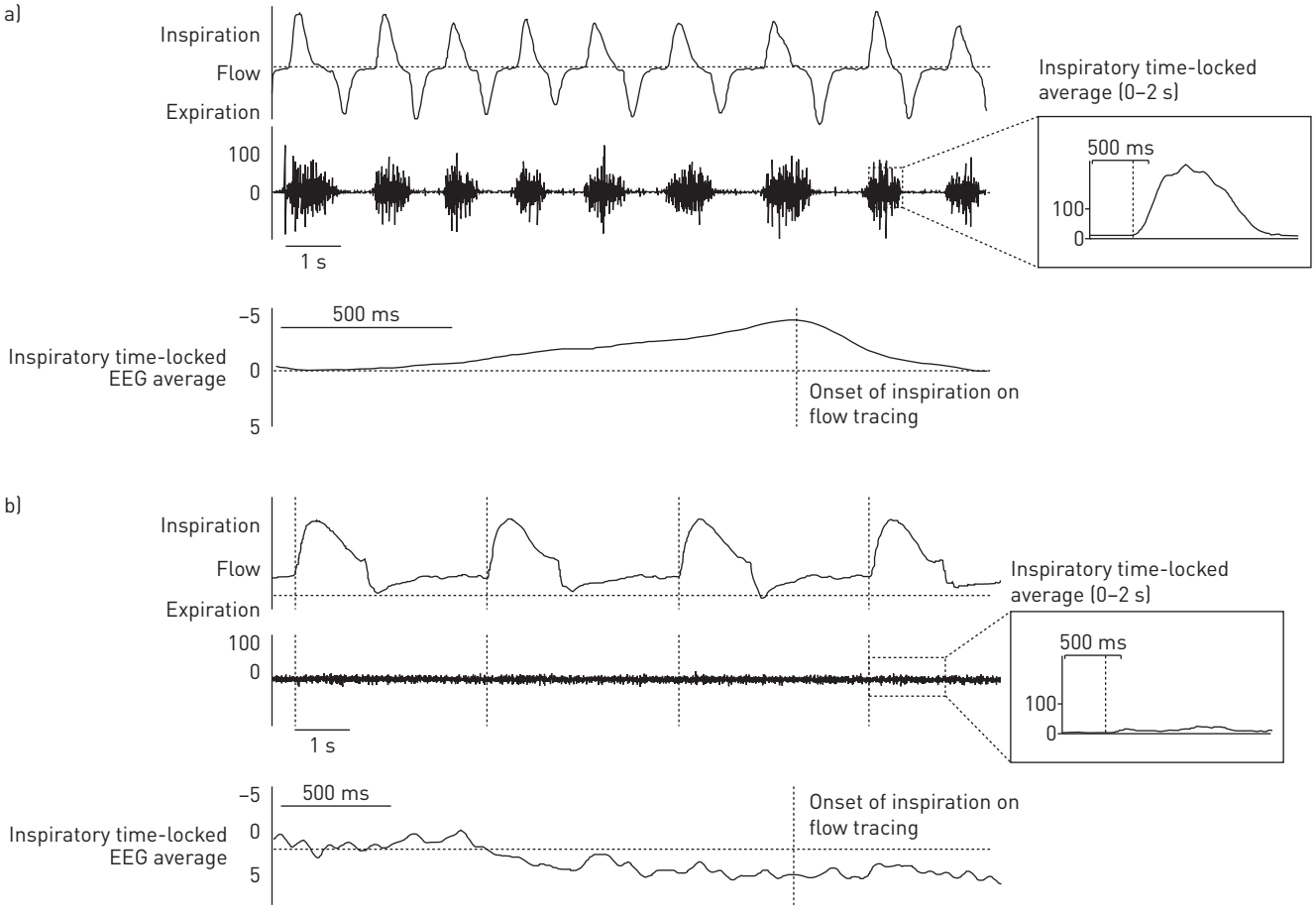

FIGURE 1 Inspiratory neck (scalene) muscle electromyogram (EMG) and electroencephalographic (EEG) detection of respiratory-related cortical activity in the form of pre-inspiratory potentials in one patient with amyotrophic lateral sclerosis during a) spontaneous breathing and b) noninvasive ventilation. Strong phasic inspiratory neck muscle EMG activity is clearly visible during spontaneous breathing, giving rise to a well-defined inspiratory envelope (right insert; the vertical dashed line indicates the onset of inspiration). This activity almost completely disappears on noninvasive ventilation. The inspiratory time-locked averaging of the EEG signal indicates a clearly visible pre-inspiratory potential during spontaneous breathing, while this type of potential is not observed during noninvasive ventilation. Note the dramatic decrease in respiratory frequency between spontaneous breathing and noninvasive ventilation.

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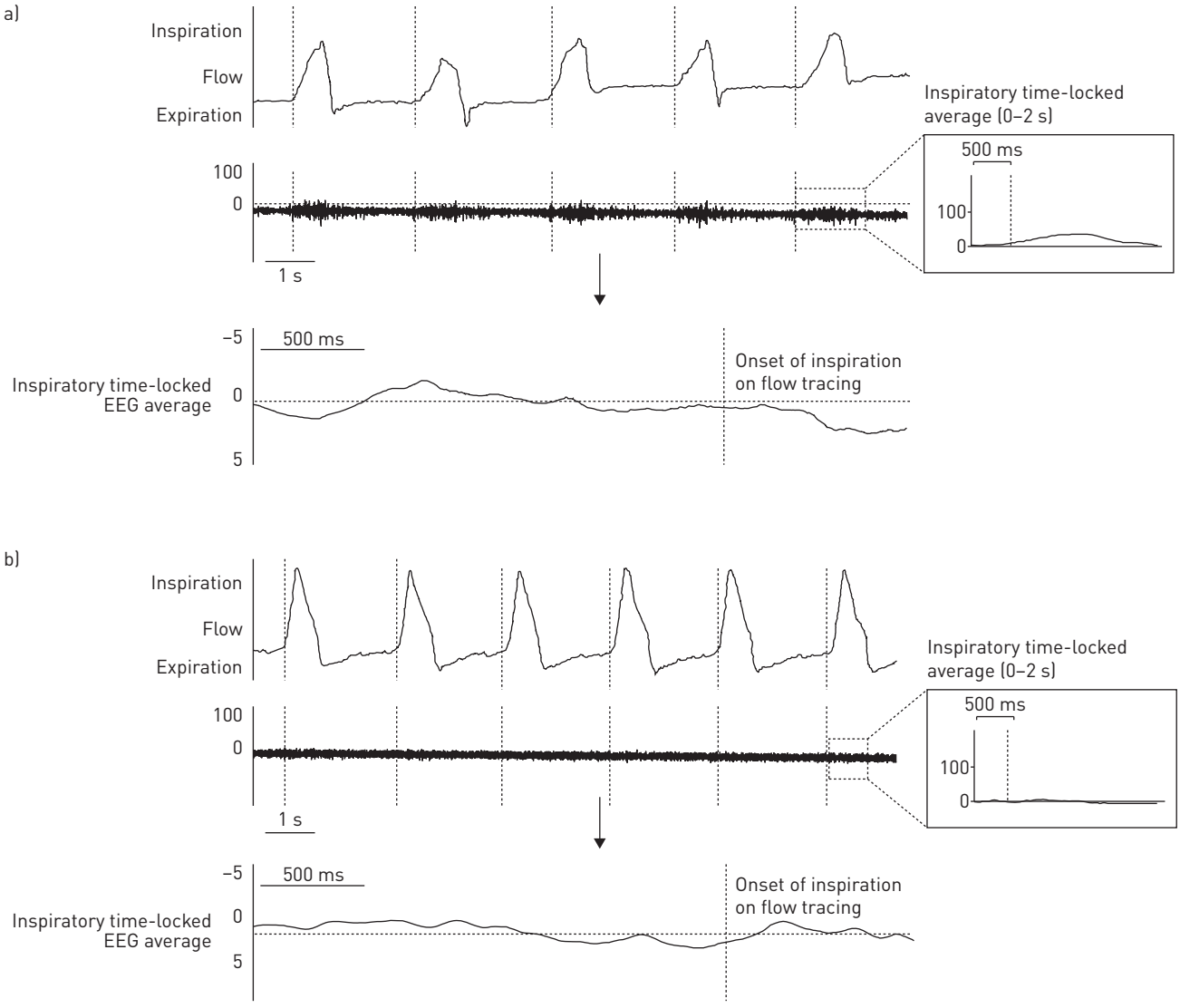

FIGURE 2 Inspiratory neck (scalene) muscle electromyogram (EMG) and electroencephalographic (EEG) detection of respiratory-related cortical activity in the form of pre-inspiratory potentials in one patient with amyotrophic lateral sclerosis not exhibiting this type of activity during a) spontaneous breathing and b) noninvasive ventilation. Phasic inspiratory neck muscle EMG activity is visible during spontaneous breathing, giving rise to a small inspiratory envelope (right insert; the vertical dashed line indicates the onset of inspiration). This activity almost completely disappears upon noninvasive ventilation. The inspiratory time-locked averaging of the EEG signal does not reveal any visible pre-inspiratory potential during either spontaneous breathing or noninvasive ventilation.

Comparison of patients with and without pre-inspiratory potentials during resting breathing

Patients who did not exhibit pre-inspiratory potentials during spontaneous breathing had a more advanced form of ALS (table 1). They had significantly longer disease duration and significantly lower ALS Functional Rating Scale-Revised scores and sniff nasal inspiratory pressures; additionally, they used NIV for longer daily durations.

Patients who exhibited a pre-inspiratory potential during spontaneous breathing had higher $EMG_{AUC} \times f_R$ values (a descriptor of the intensity of the drive to breathe) (table 2). These patients reported higher sensory dyspnoea ratings during spontaneous breathing, both for aggregated scores and "air hunger" and "work or effort" items considered separately. Emotional dyspnoea ratings were not significantly different between the two categories of patients (table 3).

Discussion

In line with our hypothesis, this study shows that ALS patients with respiratory failure can, in certain cases, exhibit respiratory-related cortical activity during resting breathing. This activity is associated with more intense dyspnoea, and disappears under NIV.

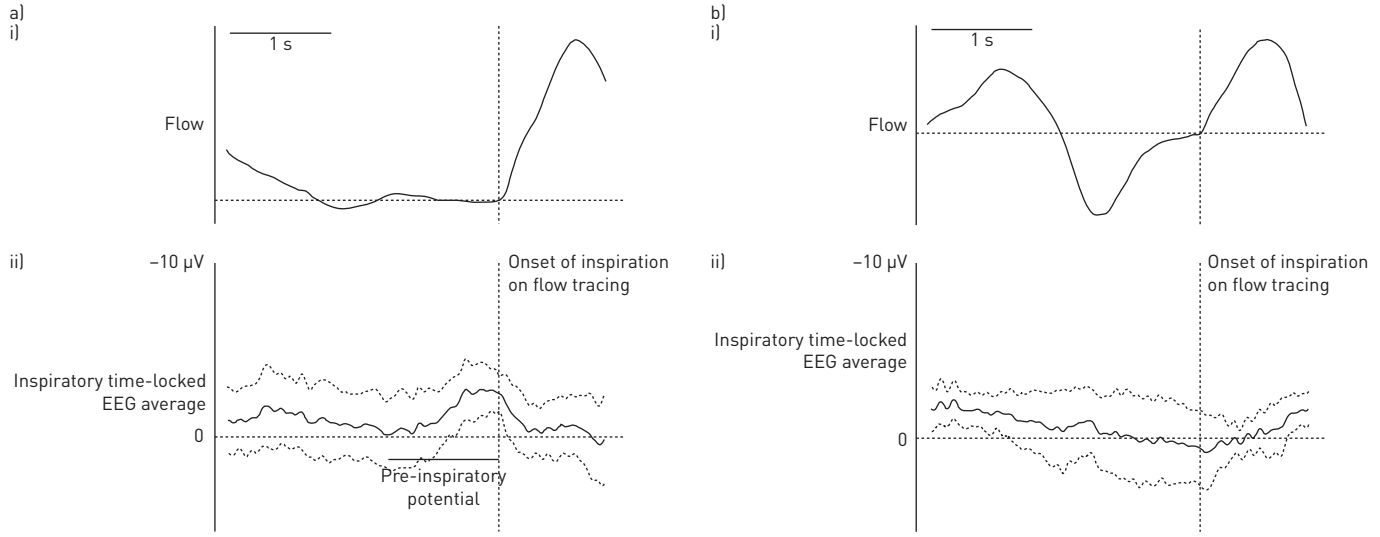

FIGURE 3 Ensemble averaging of the electroencephalographic (EEG) recordings obtained in a) the eight patients exhibiting pre-inspiratory potentials based on analysis of individual recordings: i) flow signal and ii) EEG signal; and b) the six patients not exhibiting pre-inspiratory potentials: i) flow signal and ii) EEG signal. EEG signal data are presented as mean±1 SD.

Analogy with inspiratory loading

Resting ventilation is normally under the control of brainstem automatic neural activities [19]. Cortico-subcortical networks allow disruption of ventilatory automatisms during voluntary apnoea [20], voluntary breathing [40, 41] or speech [42]. Experimental studies have shown that some of these networks, which comprise the SMA [10, 43], become active in response to an inspiratory [8, 10] or expiratory constraint [12] and involve cortical automatisms [10]. This leads to the concept of brainstem–cortex cooperation to sustain adequate ventilation. In patients with congenital central alveolar hypoventilation, it has been postulated that the cortical drive to breathe evidenced during wakefulness compensates for the deficient brainstem respiratory central pattern generators that contribute to the maintenance of ventilation during wakefulness [7]. In patients with severe obstructive apnoea, it has been postulated that the cortical drive to breathe contributes to overcome the increased upper airway resistance and thus explains the absence of upper airway collapse during wakefulness [11]. In patients suffering from ALS (this study), the cortical drive to breathe could compensate for diaphragm weakness through the recruitment of inspiratory muscles other than the diaphragm, and that would be cortically driven (at least in part). This is supported by the fact that those of our patients who exhibited pre-inspiratory potentials had higher inspiratory muscle activity than those who did not (table 2). More importantly, it is also supported by the fact that NIV abolished or markedly attenuated pre-inspiratory potentials when present (figs 1–3). This establishes causality regarding the respiratory origin of the observed cortical activity. Of note, while all patients exhibited inspiratory neck muscle recruitment, only eight out of 14 patients had pre-inspiratory potentials. This could indicate that our EEG approach was insufficiently sensitive to detect pre-inspiratory potentials in some cases or that other cortical mechanisms were at play. It could also mean that cortico-subcortical cooperation is only one of the possible pathways for compensatory respiratory neuroplasticity in ALS. Other possible pathways could involve brainstem plasticity, allowing increased output of preserved medullary premotor neurons to override the impact of decreased respiratory motor neuron numbers, or "redistribution" of the descending neural drive to extradiaphragmatic inspiratory muscles (*i.e.* neck muscles and intercostals) to compensate for the loss of phrenic motor neurons [44, 45].

Heterogeneity among patients

Pre-inspiratory potentials were present in eight of our patients and were absent in six. While this did not translate into a survival difference, those patients who did not exhibit pre-inspiratory potentials had more severe motor impairment, a longer disease duration and more severe respiratory muscle weakness (table 1). In these patients, the lack of respiratory-related cortical activity could be due to disease progression, resulting in the loss of previously established neuroplasticity. Abnormal recruitment of nonprimary motor regions, including the SMA, has been described in ALS patients during manual tasks [21–24, 46], but these changes are not observed in patients with more advanced forms of the disease. This has been attributed to motor neuron loss, which could extend beyond the primary motor cortex and involve the SMA. Similarly, electrophysiological substrates of movement preparation are altered in patients with

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TABLE 2 Inspiratory neck muscle electromyographic data

	Overall population	PIP^+	PIP^-	p-value (PIP^+ *versus* PIP^-)
Subjects n	14	8	6	
EMG_{max} mV				
Spontaneous breathing	12.3 (6.1–18.9)	13.8 (8.6–28.1)	5.7 (3.1–11.9)	0.06
NIV	1.2 (0.6–5.6)	1.6 (0.7–5.8)	0.6 (0.4–3.4)	0.11
p-value (spontaneous breathing *versus* NIV)	<0.001	0.02	0.06	
$EMG_{AUC} \times f_R$ $mV^2 \cdot min^{-1}$				
Spontaneous breathing $\times 10^5$	3.17 (1.0–4.4)	3.41 (2.2–7.1)	1.03 (0.6–2.8)	<0.001
NIV $\times 10^4$	2.1 (6.1–7.0)	2.5 (1.3–8.9)	6.4 (5.9–2.4)	0.20
p-value (spontaneous breathing *versus* NIV)	<0.001	0.02	0.06	

Data are presented as n or median (interquartile range), unless otherwise stated. PIP: pre-inspiratory potentials; EMG_{max}: peak value of the averaged inspiratory neck muscle electromyographic activity; NIV: noninvasive ventilation; EMG_{AUC}: area under the curve of the averaged inspiratory neck muscle electromyographic activity; f_R: respiratory frequency.

advanced ALS [25], and premotor potentials are more severely attenuated in ALS patients with intense spasticity [26]. In addition, our patients without pre-inspiratory potentials used NIV for longer daily durations (table 1). Mechanical ventilation has been shown to acutely depress diaphragm motor cortex excitability in healthy subjects [43] and in patients with chronic obstructive pulmonary disease [27]. It can be postulated that NIV itself could have had a long-term inhibitory effect on respiratory-related cortical activity in our patients. Finally, the presence or absence of pre-inspiratory potentials could reflect an EEG biomarker of ALS phenotypic heterogeneity [28].

Influence on dyspnoea

Figure 5 depicts a correlation between NIV-induced relief in dyspnoea and NIV-induced decrease in inspiratory neck muscle EMG activity. Such a relationship is expected based on experimental [29] and clinical [30] data. Here, it is mostly driven by data from patients exhibiting pre-inspiratory potentials. These patients experienced more severe dyspnoea than those without pre-inspiratory potentials (table 3), although their respiratory muscle strength was less severely altered and their neurological impairment less marked (table 1). This supports the idea that respiratory-related cortical activity may be among the determinants of dyspnoea, a concept that has already been proposed on the basis of experimental studies [8, 12]. The present data indicate that such a relationship can also exist in a clinical setting of dyspnoea. In this view,

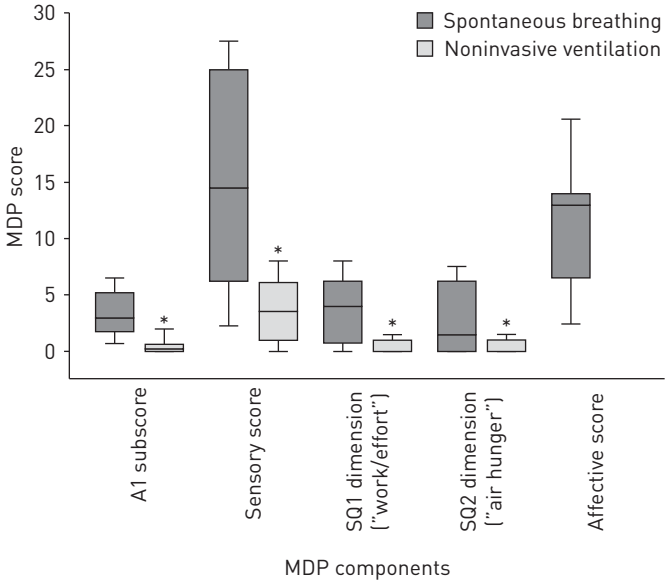

FIGURE 4 Assessment of dyspnoea using the Multidimensional Dyspnea Profile (MDP) during spontaneous breathing and noninvasive ventilation. For details, see the methods section and [14]. A1: immediate affective component of the score; SQ: sensory quality. *: p<0.05.

TABLE 3 Results of Multidimensional Dyspnea Profile during spontaneous breathing and noninvasive ventilation (NIV) according to the pre-inspiratory cortical activity

	Overall population	PIP$^+$	PIP$^-$	p-value (PIP$^+$ *versus* PIP$^-$)
Subjects n	14	8	6	
A1 score (out of 10)				
Spontaneous breathing	3 (1.7–5.2)	5 (3–6)	1.5 (0.9–2.7)	<0.01
NIV	0.25 (0–0.62)	0.25 (0–0.5)	0.25 (0–1.2)	0.85
p-value (spontaneous breathing *versus* NIV)	<0.001	0.008	0.031	
SQ1: muscle work or effort (out of 10)				
Spontaneous breathing	4 (0.75–6.25)	4.5 (4–7.7)	0.5 (0–3.7)	0.01
NIV	0 (0–1)	0.5 (0–1)	0 (0–0.2)	0.28
p-value (spontaneous breathing *versus* NIV)	<0.001	0.008	0.250	
SQ2: air hunger (out of 10)				
Spontaneous breathing	1.5 (0–6.2)	6 (2.5–7)	0 (0–1)	<0.01
NIV	0 (0–1)	0.5 (0–1)	0 (0–0)	0.14
p-value (spontaneous breathing *versus* NIV)	0.002	0.008	0.500	
Sensory score (out of 60)				
Spontaneous breathing	14.5 (6.2–25)	21 (14.2–26.5)	5.5 (2.4–12.2)	0.01
NIV	3.5 (1–6.1)	3.5 (1.2–5.62)	3 (0.7–6.87)	1.00
p-value (spontaneous breathing *versus* NIV)	<0.001	<0.01	0.03	
Emotional response score (out of 50)				
Spontaneous breathing	13 (6.5–14)	13 (7.75–18.5)	11 (6.5–12.5)	0.354
NIV	ND	ND	ND	ND
p-value (spontaneous breathing *versus* NIV)	ND	ND	ND	

Data are presented as n or median (interquartile range), unless otherwise stated. PIP: pre-inspiratory potentials; SQ: sensory quality; ND: not determined.

dyspnoea would appear as one of the negative consequences of the cortical compensation of diaphragm weakness. Those of our patients without pre-inspiratory potentials were less dyspnoeic, which would mean that the disappearance of dyspnoea with time would be of poor prognosis in ALS.

One possible interpretation of the relationship between dyspnoea and respiratory-related cortical activity relies on the "corollary discharge" theory of dyspnoea [31]. This theory involves an imbalance between the global motor respiratory output as "copied" to the cerebral cortex and respiratory afferents. From this perspective, it is interesting to note that the SMA, which is most probably involved in the genesis of pre-inspiratory potentials [10, 32], receives respiratory afferents [33, 34] and is involved in the prediction of the sensory consequences of movement [35]. Another possible interpretation involves connections between the SMA and the limbic cortex [36], which also receives respiratory afferents [37] and is markedly implicated in the pathogenesis of inspiratory

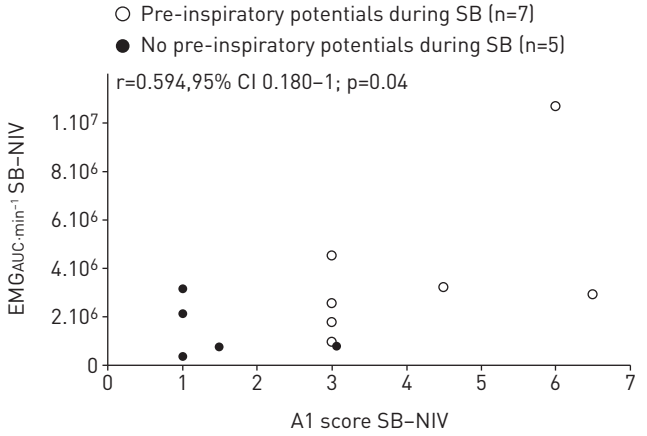

FIGURE 5 Correlation between the intensity of the noninvasive ventilation (NIV)-induced relief of dyspnoea (A1 score of the Multidimensional Dyspnea Profile) and the magnitude of the NIV-induced decrease in inspiratory neck muscle electromyogram (EMG) activity, as recorded by the neck surface electrode. SB: spontaneous breathing; SB–NIV: difference between the two conditions; $EMG_{AUC \cdot min^{-1}}$: area under the inspiratory neck muscle EMG envelope after signal processing (see the methods section).

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loading-related dyspnoea [38]. Of note, the increased activation of cortical areas involved in movement preparation has been described in ALS during manual tasks and interpreted as resulting from compensatory neuroplasticity (see earlier) [21–24, 46]. It has been associated with increased activity in the anterior insula [46].

Study limitations

The main limitations of this study are the small size of the population and its very specific nature (*i.e.* ALS patients with overt respiratory failure). We acknowledge that this may reduce the generalisability of our results. Further studies of the cortical contribution to the neural drive to breathe should therefore be conducted in patients with earlier forms of ALS. Additionally, longitudinal studies are necessary to provide a relevant picture, more clearly understand how this phenomenon can explain certain features of ALS-related respiratory failure and determine whether these findings have prognostic or practical implications (*e.g.* to guide NIV management). Meanwhile, we believe that our results have proof-of-concept value and can be hypothesis-generating.

Perspectives

This study provides novel information about breathing control in ALS-related respiratory failure, as it demonstrates a cortical contribution to the neural drive to breathe in some patients and suggests that this contribution plays a role in the pathogenesis of dyspnoea. In view of the cortical connectivity breakdown that is associated with sleep [39], these results are highly relevant to the respiratory-related alterations in sleep quality that are typical of ALS. They could also open innovative research avenues regarding ALS-related cognitive impairment. Firstly, certain forms of ALS-related cognitive impairment have recently been related to functional abnormalities within the dorsomedial and dorsolateral prefrontal cortices and in the SMA [47] with altered amygdala–SMA connectivity [48]. Secondly, a relationship between cognitive and executive performances and respiratory-related cortical activity and connectivity was documented in a patient with congenital central hypoventilation who exhibited pre-inspiratory potentials during wakefulness [7] and who obtained better results on psychometric testing during mechanical ventilation than during spontaneous breathing [49]. The need to mobilise the SMA to maintain ventilation may not only accentuate dyspnoea but may also interfere with cognitive performance in the presence of pre-existing ALS-related SMA dysfunction, or even more simply, with motor performance [50]. These hypotheses could be tested by assessing the effects of NIV on cognitive and motor performance.

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