A wider pathological network underlying breathlessness and respiratory failure in amyotrophic lateral sclerosis

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Neurophysiology studies in ALS may help us better understand breathlessness in primary respiratory disease http://ow.ly/ZkQLV

The adult-onset neurodegenerative disorder amyotrophic lateral sclerosis (ALS) is characterised by progressive dysfunction of upper motor neurons of the corticospinal tract, brainstem nuclear and lower motor neurons of the spinal cord anterior horns. There is clinicopathological and genetic overlap with frontotemporal dementia, and an emerging view of ALS as a syndrome [1]. The majority of patients present with either focal limb or bulbar muscle weakness, which then spreads at a variable rate to other body regions [2]. Median survival in ALS is 30 months from symptom onset, with most deaths associated with type II respiratory failure [3]. In the majority of ALS patients, respiratory failure emerges insidiously after a variable period of progressive limb or bulbar muscle weakness. Symptoms are highly variable, but include breathlessness, often with orthopnoea, sleep fragmentation (with nocturnal desaturations detectable on oximetry), daytime somnolence and other systemic symptoms associated with chronic hypercapnia.

The novel study by Georges *et al.* [4], in this issue of the *European Respiratory Journal*, studied higher cerebral activity in ALS patients with respiratory failure. The authors raise the possibility that cortically driven responses to diaphragm weakness, which are also associated with accessory muscle activation, might have the undesirable effect of increasing breathlessness. In a technically challenging study, a small group of ALS patients with respiratory failure underwent electroencephalography to detect pre-inspiratory potentials (PIPs), along with electromyography of inspiratory neck muscles, during both spontaneous breathing and when using noninvasive ventilation (NIV). The authors noted that NIV appeared to attenuate the PIPs found in more than half of patients during spontaneous breathing. These PIPs were identified in the Cz position, most probably reflecting brain activity in sensory and motor areas. NIV reduced the inspiratory neck muscle activity seen in all patients, and importantly, also their breathlessness.

NIV prolongs survival as well as improving the symptoms of respiratory insufficiency in ALS, including breathlessness [5]. Diaphragm weakness is assumed to be a principal driver of respiratory insufficiency in ALS, with orthopnoea very common in the advanced stages. An accurate measure of diaphragm strength using oesophageal pressure has been correlated with survival in ALS [6]. Other studies have shown that the use of accessory muscles is a sensitive and specific surrogate marker for diaphragm weakness [7], with a specific link to the electromyographic detection of denervation in paraspinal muscles [8]. Vital capacity is the commonly used surrogate to identify ALS patients developing respiratory failure in the clinic,

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although sniff nasal pressure has been shown to be more sensitive and is particularly useful for those with bulbar dysfunction [9].

ALS is associated with widespread cortical and brainstem pathology, but less is known about the relative contribution of the wider respiratory control network in ALS, with the suggestion that there may be compensatory neuronal plasticity [10]. Sleep disordered breathing is common in ALS and appears driven by central apnoeic events [11]. Lesions of the central pattern-generating neurons of the brainstem pre-Bötzinger complex produce similar deficits [12], although this region has not yet been the subject of dedicated study in ALS.

The authors are clear about the limitations of their study, principally the use of a small patient group with symptomatically advanced disease. The six patients in this study who did not show PIPs were generally more impaired, with longer disease duration and more severe respiratory impairment, but reported less breathlessness. The authors can only speculate whether this sub-group has decompensated, suffered an effect of more chronic NIV use or has an unrelated basis for what is increasingly recognised to be a clinically heterogeneous syndrome.

Cortical activity in relation to sleep disordered breathing in ALS is an obvious area in which this study offers new avenues for exploration, and potentially modulation. It has been suggested that the only licensed, modestly disease-modifying drug for ALS, namely riluzole, might have a specific beneficial role in modulating sleep disordered breathing based on effects on neuronal rhythmicity in rodent models [13].

The authors identify the need to explore the relationship of their findings with the expanding awareness of frontotemporal cognitive and behavioural cortical deficits inherent to this multisystem neurodegenerative disorder. Breathlessness is likely to worsen already impaired cognitive performance *via* reallocation of limited attentional resources [14]. Beyond ALS, this may have relevance to primary respiratory disorders. In chronic obstructive pulmonary disease (COPD) there is some evidence that pulmonary rehabilitation improves cognitive performance [15], which may be partly due to improvements in breathlessness. Therefore the link between breathlessness and cognitive dysfunction is particularly worthy of further investigation.

More broadly, there is increasing realisation that the sensation and impact of breathlessness is considerably more complex than simply increased neural traffic between the lungs and the sensory cortex [16–18]. Abnormal respiratory signalling is shaped by a variety of emotional and psychological processes in different parts of the brain, the interactions of which lead to the sensations of breathlessness. Drawing a parallel from COPD, there is mounting evidence that many of the beneficial effects of pulmonary rehabilitation derive from relieving anxiety about breathlessness rather than the physical sensations of breathlessness [19, 20]. Thus in the context of ALS a potential beneficial strategy may be to consider anxiety about breathlessness independently, especially once medical therapy is optimised [21]. Observations on breathlessness anxiety in COPD suggest that fear conditioning related to learned negative associations between everyday situations and dyspnoea exacerbate the downward spiral of breathlessness and inactivity. Neuroimaging studies testing this are starting to emerge [22, 23], and implicate emotional processes in the medial prefrontal cortex contributing to chronic breathlessness. Whether neurodegeneration in frontal and other emotion-processing brain regions specifically contributes to breathlessness in ALS remains unknown. In the present dataset, it is clear than NIV successfully attenuated the affective dimensions of breathlessness, presumably reducing the work of breathing to such an extent that the PIPs disappeared.

Measurements of the affective components of breathlessness combined with neurophysiology and neuroimaging have great potential to help individualise the treatment of breathlessness and have potential as a powerful stratification tool, whether it be in ALS, COPD, cancer or asthma. Notably, this study quantitatively examined the subjective impact of breathlessness. The authors used the recently developed Multidimensional Dyspnea Profile (MDP) [24], revealing measurable anxiety about breathlessness in both groups during spontaneous breathing, which was relieved by NIV. These findings echo those of a qualitative study [25].

Although the MDP has been designed primarily as a research tool [24], an alternative approach for clinical (and research) use is the Dyspnoea-12 (D-12) questionnaire [26]. The D-12 can be split into affective and physical components. The D-12 has been validated in clinical practice with a minimally clinically important difference of three units for the overall score [27]. A detailed comparison of the two instruments is discussed by Banzett *et al.* [24]. To fully evaluate how measuring the affective component of breathlessness will benefit patients, wider use of instruments such as these is now necessary in clinical practice, in conjunction with clinical research and quality improvement projects.

Future research using electroencephalography or functional neuroimaging [28] might specifically address the mechanisms by which emotions influence breathlessness processing in ALS, with the potential for

novel therapeutic or palliative strategies. Thus the study of Georges *et al.* [4] broadens our insight into the neural networks underpinning the respiratory control system, and may lead to a deeper understanding of the neurophysiology of breathlessness across a more diverse range of pathology.

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