The load of dyspnoea on brain and legs

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Cognitive impairments are common in patients with dyspnoea, associated with additional adverse health effects, but remain under-recognised and under-treated. Acute dyspnoea can worsen cognitive and locomotor performance, potentiating patient burden. https://bit.ly/3biHnAN

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Dyspnoea is the subjective experience of breathing discomfort that can vary in quality and intensity and lead to subsequent physiological and behavioural responses [1, 2]. It is a highly frightening experience for many patients worldwide and associated with severe disability and impaired functioning. Recurrent acute, as well as chronic, forms of dyspnoea cause significant loss of quality of life and can evolve into an overwhelming burden in all areas of life in affected patients, and also in their caregivers and families [3–5]. Dyspnoea is not only the cardinal symptom in respiratory and heart diseases, such as COPD [6], asthma [7] and heart failure [8], but is also prominent in various other prevalent diseases, including cancer and neuromuscular diseases, as well as mental disorders, such as anxiety, panic and psychosomatic disorders [2, 9–12]. The enormous relevance of dyspnoea is further reflected by estimations that up to 25% of the general population and up to 50% of severely ill patients are suffering from dyspnoea [2, 12]. Alarmingly, dyspnoea is often under-recognised and under-treated [13], despite the availability of respective diagnostic instruments and multidisciplinary treatment approaches [5, 14–16].

Notably, patients suffering from dyspnoea, for example due to COPD, asthma or heart failure, often present with varying forms of cognitive impairments, ranging from mild intensities to significant dementia [17–19]. For example, across studies the prevalence rates for cognitive impairments often exceed 40% in COPD patients [17] and vary between 25% and 75% in heart failure patients [19]. These impairments are typically attributed to several characteristics of the underlying primary or comorbid diseases, such as hypoxia, hypercapnia, inflammatory processes, impaired (cerebral) blood flow, medications, sleep fragmentation, depression and brain morphological changes [19, 20]. Surprisingly, the impairing effect of dyspnoea itself on cognitive functioning has not received much scientific attention, although it is often (and correctly) argued that dyspnoea is a leading cause for impairments in performance and the ability to function [1, 21, 22]. While this argument has been supported by impressive qualitative research [3, 23], controlled experimental studies examining specific categories of cognitive functioning have long been absent. Only recently, a first set of respective studies became available, suggesting that experimentally induced dyspnoea might indeed impair different domains of cognitive functioning. For example, Juravle *et al.* [24], demonstrated that resistive loaded breathing impairs the neural processing of affective pictures. Moreover, inspiratory threshold loading decreased the performance in a face recognition task and a locomotor task as suggested by Vinckier *et al.* [25] and Nierat *et al.* [26]. Similarly, Sucec *et al.* [27, 28] recently demonstrated that resistive load-induced dyspnoea impairs response inhibition and recognition memory [29]. Even the anticipation of upcoming dyspnoea was suggested to affect such cognitive

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processes [30, 31]. However, so far, the potential effects of acute experimental dyspnoea on other important domains of cognitive functioning, including locomotor performance, remain widely unknown.

In this issue of the *European Respiratory Journal*, Lawi *et al.* [32] present a study which closes this knowledge gap to a significant extent. In their crossover randomised trial, the authors examined whether acute experimental dyspnoea would interfere with several different cognitive functions in healthy adults. These functions included categorical and phonemic verbal fluency, executive functioning, processing speed and working memory, which were assessed with a battery of validated cognitive tests during breathing through an inspiratory threshold load or during unloaded breathing, respectively. In addition, locomotor performance was tested by a validated timed up and go test (TUG). Their results show dyspnoea-induced impairments across all tests, in particular for participants starting the tests during loaded breathing and subsequently repeating them during the unloaded control condition. This study first demonstrates in the same sample of participants that acute dyspnoea impairs functioning across a whole range of different cognitive domains in addition to locomotor performance. Moreover, it suggests that the relief from dyspnoea as operationalised as a second, unloaded breathing condition might be associated with improvements in cognitive and locomotor functioning. Together, these findings highlight that not only organic and disease-related factors (*e.g.* hypoxia, hypercapnia, inflammation), but acute dyspnoea *per se*, can lead to detriment of higher brain functions, which are crucially important in everyday life. In addition, and this is the good news, these impairments might be reversed if dyspnoea is successfully treated.

Of course, as correctly addressed by the authors, this study also has its limitations as inherent to most controlled experimental studies. For example, experimentally induced dyspnoea in safe laboratory environments might only partially mimic the threatening character of real-life dyspnoea. Similarly, cognitive and locomotor functioning in experimental tests might not fully reflect respective performance in more complex real-life situations. Furthermore, the observed dyspnoea-functioning interactions in healthy individuals might not fully mimic the physiological and behavioural responses to acute and chronic dyspnoea in patients suffering this symptom, which requires future replications in diverse patient samples. In this regard it is noteworthy that dyspnoea descriptors, which at least partly reflect different underlying pathophysiological mechanisms, are different in patients with heart failure and with respiratory disease, and also in healthy individuals when dyspnoea is induced by different stimuli [33–35]. Finally, it is worth mentioning that gender also plays a role in dyspnoea perception. Indeed, dyspnoea is more prevalent in women, both in heart failure and respiratory diseases, and women use dyspnoea descriptors that are different than those used by men [36–39]. Whether such differences in gender and dyspnoea descriptors are related to differences in cognitive and locomotor performance remains unknown from the present study and awaits future investigation.

Nevertheless, the present findings by Lawi *et al.* [32], together with those from previous studies [24–31], have several important implications. First, they highlight that dyspnoea *per se* changes important higher brain processes, above the level of the brainstem respiratory oscillator required for normal and usually unconscious breathing. Although not directly measured by Lawi *et al.* [32], several previous studies using different neuroimaging techniques have already demonstrated that experimentally induced dyspnoea activates brain networks, which are also involved in cognitive, affective and motor processing [40–42]. These activations during acute dyspnoea, especially if involving brain areas that are needed for both processing of dyspnoea as well as cognitive and motor functions, limit available brain processing capacities for simultaneous cognitive and locomotor performance [26, 29, 30]. This dyspnoea-cognition/locomotor interference is in line with previous findings on dual-task interference showing that the simultaneous engagement in two tasks diminishes performance in both tasks, especially when depending on shared brain networks [43, 44]. In addition, this dyspnoea-cognition/locomotor interference is most likely further influenced by other factors, for example negative affect. Dyspnoea as a threatening and highly salient sensation is strongly intertwined with negative affective states and personality traits, such as anxiety and depression, and elicits strong activations in respective affect-related brain networks [40, 41, 45]. This further limits the availability of overall brain capacities for cognitive functioning and locomotor performance. Notably, the mere fearful anticipation as well as observation of dyspnoea and dyspnoea-related stimuli has been shown to impact on higher brain processing [46–50] and to potentially interfere with cognitive processes such as error and picture processing [30, 31].

Moreover, the present study by Lawi *et al.* [32] calls for more clinical attention towards potential impairments in cognitive and locomotor functions in patients with dyspnoea. Next to the burden due to their primary disease symptoms, these impairments can additionally and substantially interfere with their functioning in daily life, including physical and social activities, job performance, mobility, communication and interpersonal relations, with further potential consequences for patient's families and caregivers [4, 17–19]. Importantly, impaired cognitive and locomotor functioning are associated with significant clinical implications, including worse health status and frequent falls as well as increased risk of

(longer) hospitalisation and even mortality [17–19, 51, 52]. This can partly be attributed to reduced abilities to adhere to prescribed treatments and less effective self-management, such as forgetting to correctly use the right medication, failure to initiate required behavioural changes (*e.g.* increases in physical exercise due to fear of falls, balance impairment and dyspnoea itself, dietary changes, smoking cessation) and limited adherence to scheduled clinical appointments [17, 51–53]. It doesn't take much to imagine how difficult it is to adequately perform all these procedures if the necessary cognitive functions and/or brain-leg coordination are impaired. Therefore, diagnostic screenings for these non-organic impairments should find their way into clinical routine assessments of patients with dyspnoea. Whether the hypothesised use of simple respiratory threshold loading together with locomotor gait speed tests such as the TUG might be of diagnostic or predictive value for cognitive impairment in these patients, and even in normally ageing controls [32], is an exciting thought that awaits future validation.

Finally, the results presented by Lawi *et al.* [32] encourage further examination of whether different available treatment options for dyspnoea as a symptom [54] would also show downstream effects on improving cognitive functioning and locomotor performance. As suggested by the authors, one potential option could be opioids, which have been shown to relieve dyspnoea without changing respiratory mechanics [55]. However, the use of opioids in acute and chronic heart failure has been associated with limited efficacy and frequent side-effects, which currently limits their long-term use in these conditions [56, 57]. Another option might be physical exercise training, ideally embedded in multidisciplinary treatment/rehabilitation contexts, which, together with improvements in other domains such as muscular, mechanical and psychological functioning, has been demonstrated to alleviate not only dyspnoea, but also cognitive and locomotor function [16, 58].

In summary, dyspnoea is still an under-recognised and under-treated major health problem in millions of patients worldwide. It is not only the mere sign of one of the various potentially underlying conditions, but as a threatening and "all-consuming" experience, dyspnoea itself induces additional significant burden to the patient, and their families and caregivers. Acute impairments in several domains of cognitive functioning and locomotion, as demonstrated by Lawi *et al.* [32], are one important example for this additional burden, which might potentiate ongoing, more chronic forms of cognitive malfunctioning due to the effects of underlying, primary disease processes. Next to the already existing strain due to these diseases, cognitive impairments are associated with additional serious adverse health effects in patients with dyspnoea, but are still not sufficiently recognised. Therefore, it is high time for increased interdisciplinary research and clinical efforts to improve the detection and treatment of cognitive and locomotor impairments in dyspnoeic patients in order to alleviate this additional load of dyspnoea on brain and legs.

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