REVIEW

Dyspnoea and the brain

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Summary
Chronic dyspnoea is a devastating symptom that debilitates millions of people worldwide. It causes a large burden on both patient and carer, and significant costs to society and health services. Treatment options are limited. Much effort has been directed at optimising lung function and improving exercise capacity, however, the brain mechanisms underlying dyspnoea perception have received less attention.

In this review, we focus on cognitive and affective aspects of dyspnoea and discuss how novel neuroimaging methods can provide quantitative measures of these subjective sensations. We draw parallels with the more advanced field of chronic pain, and explain some of the challenges faced when imaging dyspnoea.

To date, brain mechanisms of dyspnoea have been investigated in a handful of studies by a limited number of authors. These have found consistent activation in the insular cortex, the anterior cingulate cortex and the amygdala. Novel neuroimaging methods and an improved understanding of perceptual mechanisms underlying dyspnoea now position us to transform dyspnoea research. Future research should investigate how brain regions associated with dyspnoea interact, as well as accurately correlate this neuronal activation with reliable behavioural measures.

A better understanding of the brain processes underlying dyspnoea perception will lead to new therapies that will improve quality of life for a very large group of patients.

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Introduction

Dyspnoea is the uncomfortable breathlessness suffered by millions of patients with illnesses as diverse as cardiac failure, cancer and chronic obstructive pulmonary disease (COPD). Few sensations can match dyspnoea for unpleasantness, and even with an artificial dyspnoea stimulus delivered under controlled laboratory conditions, subjects have reported a feeling of impending death.\(^1\) In COPD, dyspnoea is an independent predictor of mortality as well as a cause for morbidity.\(^2\) For simplicity, dyspnoea is often described in terms of air hunger, chest tightness, respiratory effort or a combination of these,\(^3\) although the clinical state is in fact more complicated. Air hunger is the conscious sensation of being starved of air,\(^4\) respiratory effort is frequently described in terms of work\(^5\) and chest tightness appears to be associated with bronchoconstriction.\(^6\) These can be independently manipulated in an experimental model of dyspnoea.\(^7\)

Most healthy individuals will experience breathlessness, for example during physical exercise or conscious hyperventilation. These transient, reversible sensations are likely to be qualitatively different from the sensations of breathlessness experienced by dyspnoeic patients, which are, by their very nature, associated with threat to survival and linked to disease-related fear and anxieties. Terms such as ‘rewarded’ breathing (respiratory effort is matched by ventilation) and ‘unrewarded’ breathing (respiratory effort is not matched by ventilation, leading to an unpleasant sensation) may be used to differentiate between the normal breathlessness experienced by healthy individuals and the breathlessness suffered by patients.

The symptoms of dyspnoea vary between patients and are not fully explained by differences in disease severity (e.g. spirometric measures of lung function). Patients may exhibit low disease severity but report high levels of dyspnoea,\(^7\) or vice versa.\(^6\) Indeed, in idiopathic hyperventilation, no lung abnormalities are identified.\(^9\) This suggests that the perception of dyspnoea is not necessarily linearly related to the sensory input, but is modulated by cognitive and affective factors.\(^10\) Cognitive factors include attention, expectation and catastrophising, and affective factors include depression, anxiety and short-lasting moods.

Up until recently, most research into dyspnoea has focused on the lungs and muscles, while the cognitive and affective aspects have been less investigated.\(^11\) In this paper, we will outline our current understanding of cognitive and affective factors in dyspnoea, and address how neuroimaging may provide objective measures of brain mechanisms in dyspnoea.

Addressing the multidimensionality of dyspnoea

A growing body of literature, including consensus statements from the American Thoracic Society\(^12\) and the American College of Chest Physicians,\(^13\) supports the view that chronic dyspnoea has a cognitive and affective dimension that is (partly) separate from the sensory intensity of breathlessness,\(^10,14,15\) i.e. a multidimensional model (Fig. 1). However, our understanding of the cognitive and affective dimension remains limited.

Chronic dyspnoea has been linked to depression and anxiety,\(^16,17\) and may be exacerbated by negative emotions,\(^18,19\) including worry and fear.\(^6\) Negative emotions and anxiety have also been linked to the perception of dyspnoea in healthy volunteers.\(^20\) In COPD patients, high depression scores are consistently associated with poor exercise performance,\(^21\) although the causal relationship has yet to be determined. Distraction may improve exercise tolerance in COPD patients,\(^22,23\) suggesting a role for attention in the modulation of dyspnoea perception. Furthermore, expectation and affective factors may provide a possible explanation for variation in symptom perception that cannot be explained by severity of physical symptoms (reviewed by Jansson et al.\(^15\)). Studies using electroencephalography (EEG) during brief inspiratory occlusions (less than 1 s) demonstrate that attention\(^14,24,25\) and affective states\(^26\) may modulate respiratory-related evoked potentials (RREP), specifically the P300/P3 peak of the RREP. This further supports the importance of attention and affective states in respiratory perception.

Pulmonary rehabilitation is a therapy that successfully alleviates the feeling of dyspnoea in patients suffering from COPD, yet does not affect lung function. A 2007 Cochrane review, taking into account 31 randomised controlled trials, found no significant change in maximal exercise capacity following pulmonary rehabilitation, but reported significant reduction in perception of dyspnoea and fatigue, and improvements in functional exercise capacity that were less striking.\(^27\) More importantly, Carrieri-Kohlman et al.\(^28\) have found that an exercise programme (one component of pulmonary rehabilitation) lowers dyspnoea-related anxiety to a greater extent than the dyspnoea itself. If the improvements seen with pulmonary rehabilitation were solely due to muscle training, then one would expect an equal decrease in dyspnoea intensity and dyspnoea-related...
dyspnoea and pain are closely linked to chronic and often severe dyspnoea in a similar fashion for COPD.

Pulmonary rehabilitation may reduce symptom perception, and cognitive behavioural therapy lowers anxiety levels and reduces symptom perception. However, while negative emotions may increase perceived pain, positive emotions may reduce pain perception.

Comparing pain and dyspnoea has recently garnered attention, including comparing the multidimensionality of pain and dyspnoea.

Anxiety in these patients. Exercise programmes have also been linked to improvements in cognitive function in COPD patients and in the performance of COPD patients.

In addition, pulmonary rehabilitation includes cognitive and behavioural treatment paradigms, such as providing coping strategies, giving information and undertaking group therapy, which are components also found in cognitive behavioural therapy, an established treatment for chronic pain.

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As a therapy for chronic pain, cognitive behavioural therapy lowers anxiety levels and reduces symptom perception, without altering the underlying disease process. Pulmonary rehabilitation may reduce dyspnoea in a similar fashion for COPD.

Borrowing ideas from pain research

Comparing pain and dyspnoea has recently garnered attention, including comparing the multidimensionality of dyspnoea with the more established multidimensional pain model. Pain, like dyspnoea, is a highly subjective sensation, often associated with negative emotions. Both dyspnoea and pain are closely linked to chronic and often severe conditions and the sensory intensity level in both conditions may vary irrespective of disease state. While studies on dyspnoea to date have largely focussed on anxiety and depression, the multidimensional pain model has grown to distinguish between and incorporate several centrally mediated components. Expectation and threat perception may heighten the pain experience (and also anxiety levels), and pain-related fear is a better predictor for disability than the sensory intensity itself. Positive emotions may reduce while negative emotions may increase perceived pain, similar to what has been observed in dyspnoea.

Attention may modulate pain perception i.e. distraction may reduce the perception of pain intensity and vice versa. In pain, attention may alter both neural activation and its functional integration, and this modulation has been linked to activation in the periaqueductal grey (PAG) of the brainstem.

Addressing cognitive and affective factors that are well known in the pain field could provide further insight into the morbidity of chronic dyspnoea. Indeed, the novel dyspnoea-12 questionnaire specifically includes items on the affective dimension of dyspnoea.

Studies on asthmatic patients have recently begun to incorporate assessments of catastrophic thinking in addition to anxiety assessments, and the role of attention states has also garnered some interest. Furthermore, based on the role of anxiety in the treatment of COPD using pulmonary rehabilitation, it is reasonable to expect that previous experiences and expectations (i.e. memory and learning) are important to a similar extent in dyspnoea as has been shown in pain.

Indeed, studies using conditioning paradigms, such as different odours coupled with various respiratory challenges, have shown that previous experiences can subsequently alter respiratory responses and perception.

While pain and dyspnoea certainly share some common features, it would be equally interesting to explore the brain mechanisms by which pain and dyspnoea differ, by addressing the factors that are unique to dyspnoea. Some of these differences have already been outlined in an earlier review.

To fully understand the cognitive and affective dimension of dyspnoea, we should investigate the brain mechanisms underlying these factors rather than treating the brain as a black box, and to do this, neuroimaging is one of our best bets.

Neuroimaging of dyspnoea

To date, neuroimaging studies on dyspnoea are rare. Early neuroimaging studies have demonstrated the importance of the insular cortex and also implied a role for the anterior cingulate cortex and the amygdala in experimental dyspnoea (Table 1).

It is difficult to draw solid conclusions based on these results due to both the limited number of studies and to the great variation in experimental methods used in these studies (for the studies listed in Table 1, no less than three different types of respiratory stimuli have been employed). For example, while it is possible that the activation of the anterior cingulate reported by Evans et al. may have been a consequence of using a constantly changing stimulus, it is equally possible that the absence of activation in the same region observed by Von Leupoldt et al. could have been

Figure 1 Schematic illustrating factors that influence afferent respiratory signalling to affect the perception of dyspnoea and respiratory drive.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Neuroimaging Studies on Dyspnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Brain Region(s)</td>
</tr>
<tr>
<td>Evans</td>
<td>Insular cortex, anterior cingulate cortex, amygdala</td>
</tr>
<tr>
<td>Von Leupoldt</td>
<td>Insular cortex</td>
</tr>
</tbody>
</table>

### Table 1  Brain regions identified in neuroimaging studies of dyspnoea.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Brain region activations reported</th>
<th>Method</th>
<th>Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liotti et al.</td>
<td>2001</td>
<td>Amygdala/periamygdala</td>
<td>PET</td>
<td>Hypercapnia, CO$_2$ baseline raised from 41.0 mmHg to 66.1 mmHg for ~3 min</td>
</tr>
<tr>
<td>Brannan et al.</td>
<td>2001</td>
<td>Anterior insula/claustrum</td>
<td>PET</td>
<td>Hypercapnia, $P_{ETCO}_2$, constant at 44.0 mmHg and high and low tidal volume for 210 s</td>
</tr>
<tr>
<td>Parsons et al.</td>
<td>2001</td>
<td>Bilateral anterior temporal poles</td>
<td>PET</td>
<td>Inspiratory and expiratory resistive loads, 13.3 cmH$_2$O for 90 s</td>
</tr>
<tr>
<td>Banzett et al.</td>
<td>2002</td>
<td>Mid/anterior insula</td>
<td>PET</td>
<td>Mechanical ventilation, $P_{ETCO}_2$, constant at 41.0 mmHg and high and low tidal volume for 60 s</td>
</tr>
<tr>
<td>Peiffer et al.</td>
<td>2008</td>
<td>Anterior cingulate cortex</td>
<td>PET</td>
<td>Inspiratory and expiratory resistive loads, 19.4 cmH$_2$O for 100 s</td>
</tr>
<tr>
<td>Von Leupoldt et al.</td>
<td>2008</td>
<td>Amygdala</td>
<td>BOLD</td>
<td>Inspiratory resistive load, 13.3 cmH$_2$O for 24 s</td>
</tr>
<tr>
<td>Von Leupoldt et al.</td>
<td>2009</td>
<td>Insula</td>
<td>BOLD</td>
<td>Inspiratory resistive load, 13.3 cmH$_2$O (patients) and 12.2 cmH$_2$O (controls) for 24 s</td>
</tr>
<tr>
<td>Von Leupoldt et al.</td>
<td>2009</td>
<td>Periaqueductal gray</td>
<td>BOLD</td>
<td>Inspiratory resistive load, 12.2 cmH$_2$O for 24 s</td>
</tr>
</tbody>
</table>

(PET, Positron Emission Tomography; BOLD, Blood Oxygen Level Dependent; FMRI, Functional Magnetic Resonance Imaging, $P_{ETCO}_2$, end-tidal PCO$_2$).

* Deactivation.
* Associated with relief from dyspnoea.
* Associated with perceived unpleasantness of dyspnoea.

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due to a type 2 error (perhaps physiological noise). As such, we may still only speculate on the role of the anterior cingulate in dyspnoea. Interpretation of results is further complicated as these experimental methods may to various degrees also cause changes in neural control of breathing that is not specific to dyspnoea. Last but certainly not least, all neuroimaging studies to date have investigated acute experimental dyspnoea in healthy volunteers, but no studies have yet looked at chronic dyspnoea. Acute experimental dyspnoea induced in healthy volunteers is likely to be qualitatively very different from the chronic dyspnoea experienced by patients, since the former is experienced in a safe, experimental setting while the latter is often influenced by disease-related fear and anxiety. This is an area that requires further study.

There have also been a few neuroimaging studies investigating brain mechanisms of control of respiration other than dyspnoea. Brainstem activation has been observed both during volitional control of breathing (breath hold, voluntary hyperpnoea, Valsalva manoeuvre) and during automatic or unconscious control of breathing (chemo-stimulated ventilation). Studies of volitional breathing have suggested the involvement of a range of cortical areas involved in breathing, of which some, including the insular cortex and caudate nucleus, have also been identified in dyspnoea. Similarly, neuroimaging studies on chemo-stimulated increases in ventilation have shown activation in the basal ganglia, parietal cortex, cerebellum, midbrain, occipital lobe, the frontal cortex and the limbic system. While not addressing dyspnoea directly, imaging studies on respiratory control may assist in identifying and separating the brain regions that are involved in other breathing responses from those that are unique for dyspnoea.

Pain research as a roadmap

Whereas neuroimaging of dyspnoea is in its infancy, these techniques have revolutionised our understanding of mechanisms underlying chronic pain perception. Neuroimaging has led to the identification of what has (perhaps unfortunately) been termed the pain matrix, which includes the thalamus and the primary and secondary somatosensory, insular, anterior cingulate and prefrontal cortices. These brain regions are associated with, but not unique to, pain, and comprise a network which activation may be altered depending on the factors involved in pain perception. Furthermore, several modulatory networks that may control nociceptive processing in the central nervous system have also been identified. The most extensively investigated of these is the descending pain modulatory system, which is thought to underlie the analgesia observed during flight-or-flight responses and includes the hypothalamus, the frontal lobe, anterior cingulate cortex, insula, amygdala, PAG, nucleus cuneiformis and the rostral ventromedial medulla.

In light of the similarities between dyspnoea and pain, it is not surprising that the brain regions that so far have been associated with dyspnoea (the insular cortex, anterior cingulate cortex and the amygdala) have also been implicated in pain perception. The insula plays a central role in the conscious awareness of body state and is important in pain perception. The anterior cingulate cortex, which is involved in emotional processing, has been widely implicated in cognitive and affective pain processing. The amygdala, which has a well-established involvement in emotion processing and conditioning, is thought to be central to the modulation of pain, possibly through attention. Interactions between brain regions are central to most sensory perception, and identifying networks that govern higher-order functions is therefore crucial to further our understanding of dyspnoea. One could reasonably speculate that the brain regions associated with dyspnoea are part of a complex network that is shared in part with other types of sensations, including pain. Indeed, early observational studies have shown some commonalities in brain activation between pain and dyspnoea, highlighting the insular cortex, anterior cingulate cortex, amygdala, PAG and thalamus. To better address the clinical aspects of dyspnoea, this line of investigation may be continued using longer, more realistic, dyspnoea stimuli as well as sophisticated methods for physiological noise correction. Intervention studies that carefully link brain imaging results to reliable behavioural measures may also improve our current understanding of dyspnoea. This would generate a well-controlled, more detailed picture of the brain mechanisms involved in dyspnoea specifically, and assist in disentangling these from brain areas that are merely generally associated with unpleasant sensations.

It is our opinion, however, that dyspnoea is not merely a carbon copy of pain. Patients suffering from dyspnoea often have very different pathologies, and it is likely that the psychological components of these conditions are also not identical. As such, blindly copying pain research will most likely not be fruitful in dyspnoea research. Nevertheless, considering the commonalities between dyspnoea and pain, using the more advanced pain field as a roadmap for dyspnoea research might be a reasonable strategy, using the more advanced pain field as a roadmap for dyspnoea research.

The challenges and potential of imaging

Magnetic resonance imaging (MRI) may be crucial to the further identification of brain mechanisms in dyspnoea. Two techniques in particular are considered to hold a lot of potential; blood oxygen level dependant (BOLD) functional MRI (fMRI) and arterial spin labelling (ASL). BOLD fMRI is an indirect measure of changes in cerebral blood flow, while ASL is a measure of cerebral blood flow in absolute units using an endogenous tracer (magnetically labelled water protons). BOLD fMRI offers high spatial resolution. future developments may include improved temporal resolution and higher spatial resolution, which could improve the accuracy of identifying the brain regions involved in dyspnoea. However, interpreting fMRI results is challenging due to the complexity of the respiratory system and the difficulty in controlling for physiological noise. ASL, on the other hand, offers high spatial resolution and improvement in temporal resolution, but the use of an endogenous tracer can introduce variability and bias. Future improvements are necessary for both techniques to provide more reliable and accurate results. Despite these challenges, the potential of imaging in dyspnoea research is promising, and further developments may lead to a more detailed understanding of the brain mechanisms involved in dyspnoea.
resolution, but has limited sensitivity for low-frequency tasks and cannot be used to measure a tonic state, such as chronic dyspnoea. ASL does not share this limitation, and may therefore be important to further investigations of chronic conditions. Compared with BOLD FMRI, ASL has certain drawbacks such as smaller spatial coverage, relatively low signal-to-noise ratio (which in turn introduces a need for more subjects and/or longer imaging time), however, novel acquisition schemes are addressing these limitations, making ASL a much more attractive imaging technique.

The successful further investigation of brain mechanisms underlying dyspnoea depends on several factors. Firstly, it is important to use a realistic dyspnoea stimulus that is compatible with FMRI. Physiological noise relating to respiration degrades MR image quality and minor alterations in blood gases may affect the interpretation of the FMRI signal. Satisfactorily addressing these challenges is crucial to future dyspnoea research. Secondly, it is important to look beyond experimentally induced dyspnoea. This, however, introduces practical concerns such as the reduced ability of some patients to be supine for an extended period of time. Furthermore, some patients suffer primarily from exertion-related dyspnoea, which may be difficult to induce in a manner that is compatible with FMRI. Finally, it is highly important that future research uses appropriate experimental paradigms in order to accurately correlate neuronal activation with reliable behavioural measures. Future research should therefore employ predictive, and thus testable, models of brain function (e.g.), rather than aimlessly search for static "blobs" of activation.

Measuring electrical activity in the brain with magnetoencephalography (MEG) and EEG also holds great potential for investigating dyspnoea mechanisms. Synaptic transmission creates an electrical current in the brain (measured by EEG), which in turn generates magnetic field variations (measured by MEG). As such, MEG and EEG are direct measures of synaptic transmission in the brain, unlike FMRI, which is indirect due to its haemodynamic nature. MEG and EEG have very high temporal resolution (i.e. milliseconds), are non-invasive and can be conducted in an upright position, which may be of benefit when studying patients suffering from severe orthopnoea. MEG is less susceptible to signal loss across the skull than EEG and displays better spatial resolution, but is more expensive than EEG by far. However, both MEG and EEG are ill equipped to measure subcortical activation and cannot provide structural information.

With the advent of even more sophisticated acquisition schemes, such as more powerful MRI scanners (3T and above), neuroimaging will become even more central to dyspnoea research.

Conclusions

Dyspnoea research lags years behind pain research. In light of the similarities between chronic dyspnoea and chronic pain, a number of concepts successfully used in the study of pain might reasonably be applied to guide the future approaches to dyspnoea research. However, one should be careful not to automatically assume similarities between the two conditions. It is highly important for the future of dyspnoea research and, ultimately, dyspnoea treatment, to invest time and effort into identifying and addressing factors that are unique to dyspnoea. These factors must be seen in the context of dyspnoea as a multidimensional disease, in which there may often be a mismatch between disease severity and symptom perception. Cognitive and affective factors, including how threat and disease-related anxiety affect symptom perception, are thus crucial to our understanding of dyspnoea and should be incorporated in future research. Investigating brain mechanisms underlying dyspnoea perception is likely to aid the development of novel therapies. This includes identifying new drug targets, building the capacity to non-invasively measure responses to novel treatments, i.e. making quantitative measures of hitherto subjective sensations, and also paving the way for individualised treatments. In order to identify novel treatments, the cognitive and affective dimension of dyspnoea must be better understood, building both on clinical observations and on new neuroimaging techniques.

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Conflict of interest

None.

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