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Early View

Research letter

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Opioids for breathlessness: Psychological and neural factors influencing response variability

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“Take home” message: Diminished opioid efficacy in the treatment of breathlessness was related to negative affect and anticipatory brain activity in the anterior cingulate and medial prefrontal cortex.

To the Editor:

Chronic breathlessness is a multidimensional and aversive symptom, which is often poorly explained by underlying pathophysiology (1). For many patients, breathlessness is refractory to maximal medical therapies that target disease processes (2). However, opioids are thought to be a possible therapeutic avenue to treat symptomology independently of disease (3). Importantly, research in chronic pain has demonstrated that qualities such as anxiety and depression (collectively termed *negative affect* here) can both exacerbate symptoms (4) and reduce opioid efficacy (5, 6). Therefore, it may be pertinent to consider such behavioural factors when contemplating the use of opioids for breathlessness.

According to the Bayesian Brain Hypothesis, perception (e.g., breathlessness) is the result of a delicate balance between the brain's set of expectations and beliefs (collectively known as *priors*), and incoming sensory information (7, 8). An individual's priors are shaped by previous experiences and learned behaviours. For example, if climbing a flight of stairs triggers severe breathlessness, an individual may "expect" to experience severe breathlessness during subsequent stair climbing. Negative affect may act as a moderator within this perceptual system (7-10), altering the balance between priors and sensory inputs to influence symptom perception. Therefore, the relative contribution of sensory inputs and priors (which are thought to be generated in several brain areas, including the anterior cingulate cortex (ACC)) to overall symptom perception may be important when considering opioid responsiveness for relief of breathlessness.

Abdallah et al. (3) demonstrated that 11 of 20 adults with advanced chronic obstructive pulmonary disease (COPD) reported clinically significant relief of exertional breathlessness (defined as a decrease by ≥1 Borg unit) following single-dose administration of immediate-release oral morphine. While the authors were unable to elucidate the physiological mechanisms underlying opioid response variability, they speculated that unmeasured differences in "*conditioned anticipatory/associative learning*" played a role. The aim of the present study was to test this hypothesis and to determine if there exists a relationship between physiological and behavioural measures of negative affect, neural activity of brain centers during anticipation of breathlessness, and opioid responsiveness for relief of breathlessness. We reanalysed data from 1) Abdallah et al. (3) and 2) a behavioural and functional neuroimaging dataset in healthy volunteers by Hayen et al. (11), where the perception of laboratory-induced breathlessness was manipulated with the opioid remifentanil. As with Abdallah et al. (3), Hayen et al. (11) observed variability in opioid responsiveness, with 9 of 19 subjects reporting a remifentanil-induced decrease in breathlessness by ≥10 mm on a 100-mm visual analogue scale (VAS). This parallel approach allowed us to verify associations observed in a clinical population in an independent sample that were free of the confounds of chronic disease.

For a complete description of the study design, data acquisition and analyses, please see the original manuscripts (3, 11), full details of methodology are permanently archived at the following web address: https://doi.org/10.1101/344523. In Abdallah et al.

(3), 20 participants with COPD completed two sessions, where physiological and perceptual parameters were measured during constant-load cardiopulmonary cycle exercise testing (morphine 0.1 mg/kg or saline placebo – randomized order). Intensity and unpleasantness of breathlessness were rated using Borg's modified 0-10 category ratio scale at rest and during exercise (12). In Hayen et al. (11), 19 healthy participants underwent two fMRI scans, wherein breathlessness was induced using inspiratory resistive loading combined with mild hypercapnia (remifentanil 0.7 ng/ml target controlled infusion or saline placebo – counterbalanced order). Participants also underwent a delay-conditioning paradigm before the scanning visits, wherein they learned associations between three visual cues presented on a screen, and three conditions: mild inspiratory load (approximately -3 cmH_20), strong load (approximately -12 cmH_20) and unloaded breathing. A cued anticipation period of 8 seconds preceded each loading condition. Participants rated the intensity and unpleasantness of their breathlessness using a VAS (0-100 mm). The change in all scores was calculated as: opioid minus placebo.

In both datasets, a hierarchical cluster analysis (MATLAB: 2013a, MathWorks Inc., Natick, MA, USA) was performed on questionnaires, breathlessness ratings, and physiological measures; all measures included are listed in **Fig. 1**. In the COPD dataset, the hierarchical cluster analysis supported the existence of three distinct clusters of variables, verified by the elbow method – a validated cluster threshold technique that determines the number of clusters in a dataset (see details in **Fig. 1** legend). **Cluster A** included items that predominantly represented responses to opioid administration,

breathlessness and affective measures, and was therefore designated as a **'response and state-trait affect'** cluster. Both **Clusters B and C** contained affective and subjective measures at rest and during the placebo condition and were designated as **'baseline'** clusters. See tables in **Fig.1** for the complete list of variables induced in each sub-cluster.

In the healthy volunteer dataset, the elbow method initially supported the existence of two distinct clusters (**Fig. 1**, solid lines). Upon visual inspection, the larger cluster could clearly split into two distinct and related clusters (**Fig. 1**, dashed lines). We designated **Cluster A** as a **'state-trait affect'** cluster, **Cluster B** a **'response'** cluster, and **Cluster C** a **'baseline'** cluster (see tables in **Fig.1**). In both datasets, the predominant 'state-trait affect' and 'response' clusters were more closely related to each other than to the 'baseline' cluster. Importantly, the association between the 'state-trait affect' and 'response' clusters indicated that worse affective scores corresponded to a smaller degree of opioid-induced relief of breathlessness.

These behavioral findings suggest that opioid responsiveness is inversely associated with the collective co-existing weight of affective moderators. This work aligns with previous findings in chronic pain, where it has been found that in addition to less effective analgesia, negative affective qualities are associated with dose escalation (13) and greater difficulty in reducing opioid medication use (14). Interestingly, the cluster structure revealed in the COPD participants was conceptually consistent with that found in the healthy volunteers. Free of the confounds of respiratory disease, the results in

these healthy individuals suggest that even subtle variations in affective traits may have measurable effects upon opioid responsiveness.

To extend these behavioural findings and further explore the potential influence of prior expectations, we then investigated how brain activity during anticipation of breathlessness (saline placebo condition) may relate to an individual's 'opioid efficacy' using the brain imaging data from Hayen et al. (11). This analysis revealed significant *anticipatory* brain activity that correlated with opioid unresponsiveness in the ACC and ventromedial prefrontal cortex (vmPFC) during both mild and strong loading; and in the caudate nucleus (CN) during mild loading only (**Fig. 1**). That is, the greater the activity in these brain regions during anticipation of breathlessness under placebo conditions, the smaller the degree of opioid-induced relief of breathlessness.

Interestingly, the ACC and vmPFC are thought to be part of a brain network, involved in generating predictions on emotional state and bodily awareness (8, 15). When anticipating breathlessness, individuals with greater brain activity in these regions were less likely to experience meaningful opioid-induced relief of breathlessness, and therefore were potentially more 'resistant' to opioid therapy. If this brain activity is related to negative affective properties, these might influence breathlessness perception by more heavily weighting the brain's perceptual system towards learned priors during anticipation of breathlessness (7). For example, in anticipation of climbing a set of stairs, an individual with high negative affect may have worse breathlessness expectations relative to an individual with less negative affect. In turn, and despite

receiving the same sensory afferent inputs when climbing the stairs, the individual with more negative affect may be less responsive to opioid therapy as their breathlessness perception is more rigidly attracted towards their breathlessness expectations (i.e., strong, precise priors).

Finally, whilst this neuroimaging work was completed in healthy volunteers, previous neuroimaging studies have evaluated the relationship between learned associations and relief of breathlessness in COPD. In contrast to our findings with opioids, Herigstad et al. (16) reported that baseline activity in the brain network responsible for generating predictions (e.g., ACC) correlated positively with changes in breathlessness following pulmonary rehabilitation in COPD. Pulmonary rehabilitation is thought to exert its benefits, in part, by re-shaping associations and modulating negative affect (16). The results of these studies suggest that individuals with strong learned associations (priors) and negative affective comorbidities may be more likely to benefit from treatments such as pulmonary rehabilitation than opioids for relief of breathlessness. It is also possible that individuals with these strong learned associations and negative affective comorbidities may require higher opioid doses to experience adequate relief of breathlessness, as previously demonstrated in pain (5, 13, 14).

This initial, explorative study is limited by its retrospective, cross-sectional nature and small sample sizes, and future work is required to specifically explore and accurately quantify the relationship between negative affective qualities and opioid responsiveness in health and disease. Nevertheless, the datasets by Abdallah et al. (3) and Hayen et al. (11) allowed us to investigate potential predictors of opioid responsiveness, and to

generate hypotheses based upon possible neurobiological mechanisms of action. Although additional research is necessary, our results are unique and support the hypothesis that opioids may be less effective for relief of breathlessness among individuals with higher levels of negative affect comorbidities and strong learned associations (priors).

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Figure Legends.

Figure. 1 – The hierarchical cluster analysis allowed us to explore the possible relationships between the magnitude of opioid-induced relief of breathlessness, behavioural measures and physiological traits. Variables were first aligned such that larger values represented more negative properties (via multiplication of relevant variables by -1). All measures were then individually normalised via Z-transformation, to allow accurate variable comparisons and distance calculations. The distance between neighboring branches indicates the relative similarity of two measures. Mathematically distinct clusters were determined via the 'elbow method', with a minimum intra-cluster correlation coefficient of 0.3 between the variables, and further cluster divisions were considered utilizing a-priori knowledge and visual inspection of the dendrogram structure. The elbow method is a validated clustering technique in which the percentage of explained variance is described as a function of the number of clusters. Considering the variable set as initially one large cluster, the algorithm then divides the variables into increasing numbers of clusters. With each additional cluster, the percentage of explained variance is expected to increase. While initially this increase is sharp, after a certain number of clusters the gain will become marginal. When this relationship is plotted, as the sum of intra-cluster distance against cluster number, the point at which additional clusters add only marginally to the explained variance can be seen as a sharp bend or elbow in the graph. The number of clusters corresponding to this elbow point is thus the number of most statistically distinct clusters in the dendrogram.

Top panel: Clustergram of physiological and behavioural variables in healthy volunteers and participants with COPD. Identified hard cluster boundaries (via 'elbow method') are denoted in solid black lines, whilst sub-clusters (via visual inspection) are denoted with dashed lines. Tables identify the physiological and behavioural variables induced in each of the sub-clusters. The change (Δ) in all scores was calculated as: opioid minus placebo. In the COPD dataset, physiological and perceptual responses

were evaluated during exercise at isotime - defined as the highest equivalent 2-min interval of exercise completed by each participant after oral morphine and placebo.

Bottom panel: We explored how brain activity associated with anticipation of breathlessness (during the saline placebo condition) may relate to an individual's 'opioid efficacy' for the treatment of breathlessness. This analysis allowed us to determine if there was an association between the activity of prior-rich brain regions and opioid responsiveness. The group of items that formed **Cluster B** within the hierarchical cluster analysis on the healthy volunteers were used to define overall 'opioid efficacy' (i.e., items that represented opioid-induced changes in physiological and subjective measures). We employed a principal component analysis (PCA; MATLAB 2013a) on this group of variables, and the resulting individual scores were included within a group FMRI analysis of the saline placebo condition only, using a general linear model ($Z > 2.3$, whole brain corrected $p < 0.05$). The resulting mean BOLD changes identified during anticipation of the mild and strong breathlessness challenge are presented in the left and right panels, respectively. The image consists of a colour-rendered statistical map superimposed on a standard (MNI 2x2x2) brain. Significant regions are displayed with a threshold $Z > 2.3$, using a cluster probability threshold of $p < 0.05$. Abbreviations: ACC, anterior cingulate cortex; CN, caudate nucleus; vmPFC, ventromedial prefrontal cortex.

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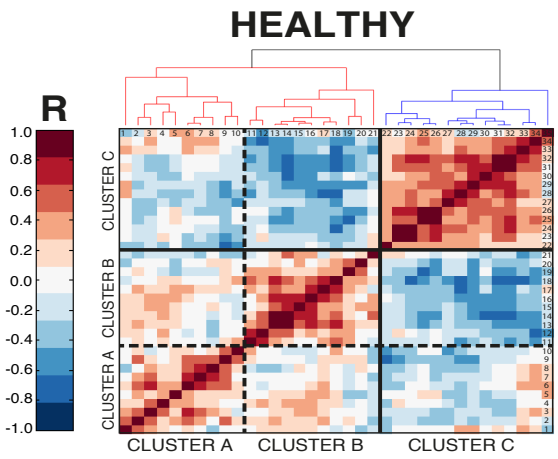
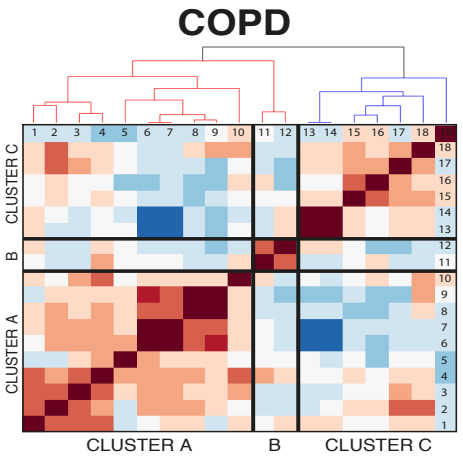
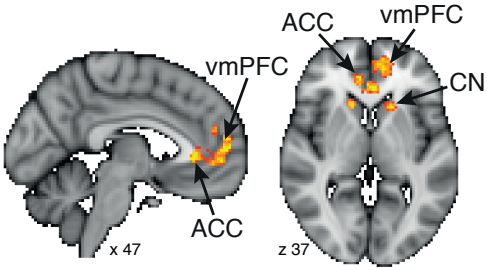




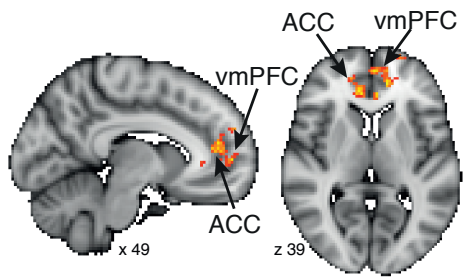
Cluster identifier	Variable number	Physiological variable
	1	Locus of control inventory – Chance control
	2	Locus of control inventory – Others in control
	3	The positive affect negative affect schedule – Negative affect
Cluster A	4	Δ Sedation
	5	The thought control questionnaire – Reappraisal
"State-trait affect cluster"	6	Spielberger state-trait anxiety inventory
	7	The revised center for epidemiological studies depression scale
	8	Locus of control inventory – Internal control
	9	The positive affect negative affect schedule – Positive affect
	10	The thought control questionnaire – Social control
	11	Δ Discontentment
	12	Δ Tension
	13	Δ Mouth pressure (mild load)
	14	Δ Anticipation mouth pressure (mild load)
Cluster B	15	Δ Anticipation mouth pressure (strong load)
	16	Δ Mouth pressure (strong load)
"Response cluster"	17	Δ Breathlessness intensity (strong load)
	18	Δ Breathlessness unpleasantness (strong load)
	19	Δ Breathlessness unpleasantness (mild load)
	20	Δ Breathlessness intensity (mild load)
	21	Sedation (saline)
	22	Sex
	23	Breathlessness intensity (strong load; saline)
	24	Breathlessness unpleasantness (strong load; saline)
	25	Breathlessness unpleasantness (mild load; saline)
	26	Breathlessness intensity (mild load; saline)
Cluster C	27	The thought control questionnaire – Worry
	28	Mouth pressure (strong load; saline)
"Baseline cluster"	29	Anticipation mouth pressure (strong load; saline)
	30	The defence style questionnaire – Neuroticism
	31	Anticipation mouth pressure (mild load; saline)
	32	Mouth pressure (mild load; saline)
	33	Discontentment (saline)
	34	Tension (saline)
	35	Anxiety sensitivity index

Cluster identifier	Variable number	Physiological variable
	1	COPD assessment test – Breathlessness item
	2	Hospital anxiety and depression scale – Depression subscale
	3	COPD assessment test activity – Activity limitation item
Cluster A	4	Oxygen cost diagram
	5	Sex
"Response and state-trait affect cluster"	6	Δ Isotime breathlessness intensity
	7	Δ Isotime breathlessness unpleasantness
	8	Δ breathing frequency
	9	Δ tidal volume
	10	Modified medical research council scale
Cluster B	11	Isotime tidal volume (placebo)
"Baseline cluster"	12	Isotime breathing frequency during the (placebo)
	13	Isotime breathlessness unpleasantness (placebo)
Cluster C	14	Isotime breathlessness intensity (placebo)
	15	Plasma morphine
"Baseline cluster"	16	Forced expiratory volume in 1-second
	17	Hospital anxiety and depression scale – anxiety subscale
	18	Plasma morphine-6-glucuronide
	19	Cigarette smoking history (pack years)

ANTICIPATION OF MILD BREATHLESSNESS



ANTICIPATION OF STRONG BREATHLESSNESS



Z score 2.3 3.0 correlation with unresponsiveness to opioid administration