Opioids for breathlessness: Psychological and neural factors influencing variability in response

Sara J. Abdallah*[1] (sara.abdallah@mail.mcgill.ca)

Olivia K. Faull*[2,] (faull@biomed.ee.ethz.ch)

Vishvarani Wanigasekera[2] (vishvarani.wanigasekera@ndcn.ox.ac.uk)

Sarah L. Finnegan[2] (sarah.finnegan@ndcn.ox.ac.uk)

Dennis Jensen[1] (dennis.jensen@mcgill.ca)

Kyle Pattinson[2] (kyle.pattinson@nda.ox.ac.uk)

*Co-first authors

[1]Clinical Exercise & Respiratory Physiology Laboratory, Department of Kinesiology & Physical Education, McGill University, Montréal, QC, Canada.

[2]Wellcome Centre for Integrative Neuroimaging and Nuffield Division of Anaesthetics, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK.

Corresponding author: Kyle Pattinson, Nuffield Department of Clinical Neuroscience, West Wing Level 6, John Radcliffe Hospital, Oxford, OX3 9DU, UK. E-mail: kyle.pattinson@nda.ox.ac.uk

"Take home" message: Diminished opioid efficacy in the treatment of breathlessness is related to negative affect and anticipatory brain activity in the anterior cingulate and medial prefrontal cortex, areas known to be moderated by negative affect.

ABSTRACT

There is considerable inter-individual variability in the efficacy of opioids for treating chronic breathlessness. Studies in pain, another aversive symptom, have demonstrated that negative affective qualities (e.g., anxiety, depression) can exacerbate pain and diminish opioid efficacy. We questioned whether such mechanisms may also be relevant for breathlessness.

Methods. We first investigated the relationship between opioid efficacy and physiological/behavioural qualities. We utilised two existing opioid datasets: a clinical study in chronic obstructive pulmonary disease, and a functional magnetic resonance brain imaging study of breathlessness in healthy volunteers, employing hierarchical cluster analyses to determine the relationship between physiology, behaviour and opioid responsiveness. We then investigated how opioid efficacy relates to anticipatory brain activity using linear regression in the healthy volunteers.

Results. Consistent across both datasets, reduced opioid efficacy was more closely associated with negative affect than with baseline physiology and self-reported breathlessness scores. Furthermore, in healthy individuals, brain activity in anterior cingulate and ventromedial prefrontal cortices during anticipation of breathlessness was inversely correlated with opioid effectiveness.

Conclusion. Diminished opioid efficacy for relief of breathlessness may be associated with high negative affective and is correlated with the magnitude of brain activity during anticipation of breathlessness. **Clinical implications**. Negative affect may influence perceptual systems to become less responsive to opioid therapy.

INTRODUCTION

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 targeting disease processes (2). Due to the potential distress caused by chronic refractory breathlessness, opioids are thought to be a possible therapeutic avenue (3, 4) to treat symptomology independently of disease. However, it is known from research in other aversive symptoms such as chronic pain, that qualities such as anxiety and depression (collectively termed *negative affect* here) can both exacerbate symptoms (5) and reduce opioid efficacy (6, 7). Therefore, it may also be pertinent to consider such behavioural factors when considering the use of opioid therapy for breathlessness.

In the context of modern neuroscientific understanding, perception (e.g., breathlessness) is considered to be the result of a delicate balance between the brain's set of expectations and beliefs (collectively known as *priors*), and incoming sensory information (8, 9). 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 will "expect" to experience severe breathlessness during subsequent stair climbing. Negative affect is thought to act as a moderator within the brain's perceptual system (8-11), altering the balance between priors and sensory inputs to influence our perceptions of internal sensations such as breathlessness.

In a recent clinical study, Abdallah et al. (4) demonstrated that 11 out of 20 (55%) adults with advanced chronic obstructive pulmonary disease (COPD) reported clinically significant relief of exertional breathlessness following single-dose administration of immediate-release oral morphine. The authors were unable to elucidate the mechanisms underlying the variability in response to opioids (i.e., responders vs. non-responders); although they speculated that differences in "*conditioned anticipatory/associative learning*" might play a role.

Therefore, the aim of the present study was to better understand potential mechanisms underlying variability in opioid responsiveness for the relief of breathlessness. To this end, we have reanalysed data from Abdallah et al. (4), in conjunction with a reanalysis of a behavioural and brain neuroimaging dataset in healthy volunteers (12), where the perception of laboratory-induced breathlessness was manipulated with the opioid remifentanil. 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, and to shed light on associated changes in brain activity with opioid efficacy. Furthermore, the healthy volunteer dataset allowed us to test the hypotheses presented in Abdallah et al. (4) regarding how differences in conditioned anticipatory/associative learning might influence variability in the effect of opioids upon breathlessness.

METHODS

A brief overview of the study methods is provided here. For full details, please see the supplementary material and the original manuscripts (4, 12).

COPD exercise study:

Twenty participants with severe COPD (mean±SD forced expiratory volume in 1 sec % predicted (FEV_1%predicted): 35±9) completed two sessions (morphine 0.1 mg/kg or placebo – randomized order and double-blinded), where physiological and perceptual parameters were measured during constant-load cardiopulmonary cycle exercise testing at 75% of peak power output. Intensity and unpleasantness of breathlessness were rated using Borg's modified 0-10 category ratio scale at rest and during exercise (13). Data were analyzed at isotime, defined as the highest equivalent 2-min interval of exercise completed by a given participant during each of the constant-load cardiopulmonary exercise tests. The change in all scores was calculated as opioid minus placebo (see **Fig. 1** for details). Participants were characterized using questionnaires listed in **Fig. 1**.

FMRI study in healthy volunteers:

In the original study (14), 19 healthy participants underwent two FMRI scans (3T Siemens Trio scanner), on two separate visits (remifentanil 0.7 ng/ml target-controlled infusion or saline placebo – counterbalanced order, randomised and double-blinded) wherein breathlessness was induced using inspiratory resistive loading. Participants underwent a psychological delay-conditioning paradigm before the scanning visits in

which they learned associations between three visual cues (shapes) presented on a screen, and three conditions: mild breathlessness, strong breathlessness and no breathlessness (unloaded breathing). A cued anticipation period of 8 seconds then preceded each resistive load, and participants rated the intensity and unpleasantness of their breathlessness using a visual analogue scale (VAS:0-100 mm). The change in all scores was calculated as opioid minus placebo (see **Fig. 1** for details). Participants were characterized using questionnaires listed in **Fig. 1**.

Hierarchical cluster analyses:

Variables were first aligned such that larger values represented more negative properties, this was achieved through the multiplication of relevant variables by -1 (e.g., FEV_1% predicted was multiplied by -1 as a larger FEV_1%predicted value reflects less severe disease). All measures were then individually normalised via Z-transformation, to allow accurate variable comparisons and distance calculations.

A hierarchical cluster analysis (MATLAB: 2013a, MathWorks Inc., Natick, MA, USA) was then performed on the questionnaires, breathlessness ratings, and physiological measures from each of the two datasets. Hierarchical cluster models reorder variables based on their correlation strengths so that groups of related measures sit closer to each other than non-related measures. This allows natural relationships to be easily visualised. This modeling process formalizes not only the relationship between pairs of variables, but also the manner by which shared variance can be described as part of larger, related clusters. The clustering algorithm initially considers pairs of variables in

terms of their similarity or “distance”. Linked pairs are then incorporated into larger clusters with the goal of minimizing a cost function (distance to be bridged), a process that can be thought of as minimizing the dissimilarity within clusters. As pairs become clusters, a cluster tree or dendrogram is created. The distance between neighboring branches indicates the relative similarity of two measures, while advancing up the hierarchical cluster tree moves further away in terms of link distance, and therefore similarity.

A threshold of relatedness can then be applied to the hierarchical cluster tree, to formally separate clusters of variables thought to be statistically distinct from one-another. Various cluster pruning and division methods exist, where the most mathematically distinct cut point needs to be considered together with the most biologically relevant information, given an a-priori hypothesis. Here we applied a typical cluster forming technique of the ‘elbow method’ (for a full description please see the supplementary material) to identify the most mathematically distinct clusters, before considering further cluster divisions utilizing a-priori knowledge and visual inspection of the dendrogram structure. This analysis allowed us to explore natural ‘groupings’ within the recorded measures, and the relationship of these groupings to each other. Clusters were defined by higher-order variable groupings denoted by the hierarchical clustering structure, with a minimum intra-cluster correlation coefficient of 0.3 between the variables.

FMRI analysis of opioid efficacy:

In the present study, the FMRI data from the healthy volunteers was further investigated to determine the relationship between brain activity and opioid efficacy. We undertook a linear regression analysis of the brain activity during the saline placebo condition, to investigate how brain activity associated with breathlessness anticipation and perception may indicate the effectiveness of opioid treatment for breathlessness in an individual. As multiple subjective and physiological factors could be considered to represent 'opioid efficacy', we undertook the data reduction technique of a principal component analysis (PCA; MATLAB 2013a) on the group of variables that formed the 'response' cluster within the hierarchical cluster analysis, 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 $p < 0.05$).

RESULTS

Hierarchical cluster analysis. The hierarchical cluster analysis of the COPD group supported the existence of three distinct clusters of variables which were verified by the elbow method (**Fig. 1,** and **Supplementary Fig. 3**). These clusters consisted of variable groupings that largely represented: (1) an 'affect' cluster of psychological affective measures; (2) a 'response' cluster, reflecting physiological and subjective responses to opioid administration; and (3) a 'baseline' cluster of predominantly physiological and psychological variables measured at baseline and during the placebo condition.

In the COPD dataset (**Fig. 1**), The **'affect' cluster** included the: hospital anxiety and depression scale (HADS) depression subscale; the COPD assessment test breathlessness and activity-limitation items (15); and the oxygen cost diagram (16). The **'response' cluster** included: the opioid-induced changes in isotime breathing frequency, tidal volume, breathlessness intensity and breathlessness unpleasantness; and sex. The **'baseline' cluster** included: isotime breathing frequency, tidal volume and breathlessness intensity and unpleasantness (placebo); cigarette smoking history; FEV_1%predicted; the modified medical research council scale (17); and the HADS anxiety subscale (18).

In the healthy volunteer dataset, the elbow method initially supported the existence of two distinct clusters (**Fig. 1**, solid lines; and **Supplementary Fig. 3**). One of these consisted of a coherent **'baseline' cluster** composed of physiological and subjective measures at rest and during the saline placebo condition. These consisted of sex;

breathlessness intensity and unpleasantness in the strong and mild conditions (saline); mouth pressure during anticipation and breathlessness in both strong and mild conditions (saline); discontentment and tension as defined by the Bond-Lader scale (19) during the saline placebo condition; the Thought Control Questionnaire – Worry subscale (20); the Defence Style Questionnaire – Neuroticism subscale (21); and Anxiety sensitivity index (22).

The second, larger cluster, could upon visual inspection be clearly split further into two distinct and related clusters that aligned with results from the COPD dataset (**Fig. 1**, dashed lines): (1) an **'affect' cluster** of psychological affective measures; and (2) a **'response' cluster**, reflecting physiological and subjective responses to opioid administration. This **'affect' sub-cluster** included the Levenson Multidimensional Locus of Control Inventory (23) – Chance Control, Others in control, Social Control, Reappraisal and Internal Control subscales; Positive and Negative affect schedules – positive and negative affect subscales (24); the Spielberger State-Trait Anxiety Inventory (25); the revised Center for Epidemiological Studies Depression Scale (26); and opioid-induced change in sedation (19). The '**response' sub-cluster** included change in mouth pressure during anticipation and perception of mild and strong breathlessness; change in subjective breathlessness unpleasantness and breathlessness intensity scores during mild and strong breathlessness; change in tension and discontentment, and baseline sedation in the saline placebo condition.

In both datasets, the association (smaller distances between respective clusters) between the 'affect' and 'response' clusters indicated that worse affective scores corresponded to a smaller degree of opioid-induced relief of breathlessness (i.e. variables were aligned such that larger values represented more negative properties).

FMRI analysis. The FMRI analysis revealed significant *anticipatory* brain activity correlating with opioid unresponsiveness (i.e., greater brain activity correlated with a smaller 'response' score from the principle component of the response cluster) in the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC) during both mild and strong breathlessness. Additionally, significant *anticipatory* brain activity corresponding to opioid unresponsiveness was observed in the caudate nucleus (CN) in the mild breathlessness condition only (**Fig. 2**). During mild breathlessness, significant brain activity corresponding to opioid unresponsiveness was observed in the medial thalamus and CN (**Fig. 3**); that is, the greater the activity in these brain regions during anticipation (i.e., ACC, vmPFC) and perception (i.e., thalamus) of breathlessness, the smaller the degree of opioid-induced relief of breathlessness. There was no significant brain activity corresponding to opioid unresponsive during perception of strong breathlessness.

DISCUSSION

The key findings of this study are that diminished opioid efficacy for breathlessness was more closely associated with negative affect than other physiological and behavioural properties (e.g., baseline breathlessness) in both the COPD and healthy volunteer datasets. Furthermore, functional neuroimaging findings of the healthy volunteer study revealed that the magnitude of opioid-induced relief of breathlessness was inversely associated with brain activity in the ACC and vmPFC during saline placebo infusion. These findings suggest that opioid efficacy for breathlessness may be associated with broader negative affective qualities within an individual and may be directly related to brain activity during conditioned responses to breathlessness stimuli.

Our findings from the behavioral data in both studies suggest that opioid responsiveness is inversely associated with the collective co-existing weight of affective moderators (**Fig. 1**). That is, individuals with high vs. low negative affect are less likely to experience opioid-induced relief of breathlessness. These results align with previous work in chronic pain, where it has been found that in addition to less effective analgesia, negative affective qualities are associated with dose escalation (27) and greater difficulty in reducing opioid medication use (28); factors that increase the potential for adverse opioid-related side effects (29). Interestingly, the hierarchical cluster analysis revealed a less tightly correlated ‘baseline’ cluster in COPD compared to the healthy volunteers. These results support the view that in COPD, breathlessness is a multifactorial symptom that is likely influenced by variables other than baseline pulmonary function.

Strikingly, the cluster structure revealed in the COPD participants was consistent with that found in the healthy volunteers. Free of the confounds of respiratory disease and chronic breathlessness, the results in these healthy individuals suggest that even subtle variations in affective traits may have measurable effects upon opioid responsiveness. Furthermore, our results suggest that baseline affective traits, and not breathlessness *per se*, may contribute towards the magnitude of opioid responsiveness.

Opioid-induced changes reflected in the ‘response’ cluster were directly related to *anticipatory* brain activity towards an upcoming breathlessness stimulus under baseline (placebo) conditions. Interestingly, the ACC and vmPFC are part of the brain network involved in evaluating the relevance of a stimulus and its associated value (i.e., reward processing and the ‘stimulus valuation network’) and are thought to be involved in generating predictions on emotional state and bodily awareness (i.e., interoception) (9, 30). Individuals with greater brain activity in these regions have a diminished breathlessness-related response to opioids and therefore potentially more ‘resistant’ to opioid therapy. In particular, associated negative affective properties might thus influence breathlessness perception by more heavily weighting the brain's perceptual system towards learned associations during anticipation of breathlessness (8). For example, in anticipation of climbing a set of stairs, an individual with worse affective traits may have greater breathlessness expectations (e.g., via ‘catastrophizing’ the severity of breathlessness during previous experiences of stair climbing) relative to an individual with more ‘normal’ affective traits. In turn, and despite receiving the same

sensory afferent inputs in anticipation of stair climbing, the individual with worse affective traits may be less responsive to opioid therapy as his/her breathlessness perception is more heavily weighted on previous expectations (i.e., strong priors) relative to the individual with 'normal' affective traits.

In contrast to opioid therapy, Herigstad et al. (31) 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, at least in part, by re-shaping associations and modulating negative affect (31-33). Collectively, the results of these studies suggest that individuals with strong learned associations (priors) and negative affective comorbidities may be more likely to benefit from pulmonary rehabilitation than opioids for relief of breathlessness. Furthermore, it is possible that individuals with these strong associations and negative affective comorbidities may thus require higher opioid doses to experience adequate relief of breathlessness, as previously demonstrated in individuals with pain (6, 27, 28).

Finally, opioid responsiveness negatively correlated with activity in the medial thalamus during mild, but not strong breathlessness. The medial thalamus is an early relay sensory structure known to be connected to the prefrontal regions correlated with opioid responsiveness during anticipation of breathlessness (i.e., ACC) (34). It is possible that the perceptual expectations produced in anticipation of breathlessness may inform and thus alter the activity in the medial thalamus during perception of breathlessness. This

information may be important during perception of ambiguous stimuli, when prior expectations may be more heavily weighted in the model. For example, during a mild breathlessness challenge (e.g., walking briskly on the level in COPD), incoming afferent sensory signals may be vague, resulting in breathlessness perception that is weighted more heavily towards expectations. In contrast, during a strong breathlessness challenge (e.g., stair climbing in COPD), strong afferent sensory signals may overwhelm any perceptual expectations to allow less ambiguous sensory processing.

Methodological considerations. Interpretation of behavioural findings are limited by sample sizes. Given a larger sample size we would suggest the utilisation of a confirmatory factor analysis, which could provide additional statistical confidence in the interpretation of the hierarchical cluster model. Confirmatory factor analysis allows the researcher to propose and fit a formal model to the data to investigate the relationship between variables, and to establish whether an underlying shared construct exists via a description of the full variance of the data and a number of fit statistics. However, although in this project the hierarchical cluster model revealed several clear clusters that would easily feed into a confirmatory factor analysis, it is generally accepted that in order to create a stable model the number of samples should be at least 5 times greater than the number of investigatory variables (35). This would limit us to a model consisting of 4 variables, which we believe does not accurately or wholly describe the clusters identified by the hierarchical model. Therefore, in this work we selected the elbow method as a cluster threshold technique, which proposed 2 or 3 clusters for the healthy population and 3 clusters for the COPD population and was validated and

refined visually. Additional subject numbers, would likely improve the stability of these cluster estimates, but would be unlikely to alter cluster identity.

Despite these statistical considerations, our results demonstrated a consistent message across two independent datasets. These datasets allowed us to explore potential predictors of opioid responsiveness, and to generate hypotheses based upon potential neurobiological mechanisms of action without subjecting a new set of individuals to unnecessary opioid administration. Indeed, our results provide strong justification for future studies to specifically explore and accurately quantify the relationship between negative affective qualities and opioid responsiveness in health and disease, as these have potentially important clinical implications. Our neuroimaging data suggested that brain areas thought to be intricately involved in generating perceptual expectations (i.e., ACC, vmPFC) may be more active during anticipation of breathlessness in more opioid resistant individuals. These results provide clues towards opioid mechanisms of action, which could be tested in future prospective and longitudinal studies.

Conclusions. The efficacy of opioids for relieving chronic breathlessness is of great importance as we move toward individualized, safe and targeted symptom management. Our results mirror those from the study of chronic pain, which suggest that opioids may be less effective for the treatment of breathlessness among individuals with higher levels of negative affective comorbidities and strong learned associations.

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Figure Legends.

Figure. 1 – 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. The change (∆) 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.

In healthy participants (left), the **'affect'** sub-cluster included: 1: Locus of Control Inventory – Chance Control; 2: Locus of Control Inventory – Others in control; 3: Negative affect (The Positive Affect Negative Affect Schedule); 4: ∆ Sedation; 5: The Thought Control Questionnaire – Reappraisal; 6: Spielberger State-Trait Anxiety Inventory; 7: The revised Center for Epidemiological Studies Depression Scale; 8: Locus of Control Inventory – Internal control; 9: Positive affect (The Positive Affect Negative Affect Schedule); 10: The Thought Control Questionnaire – Social Control. The **'response'** sub-cluster included: 11: ∆ Discontentment; 12: ∆ Tension; 13: ∆ Mouth pressure mild condition; 14: ∆ Anticipation mouth pressure mild condition; 15: ∆ Anticipation mouth pressure strong condition; 16: ∆ Mouth pressure strong condition; 17: ∆ Breathlessness intensity strong condition; 18: ∆ Breathlessness unpleasantness strong condition; 19: ∆ Breathlessness unpleasantness mild condition; 20: ∆ Breathlessness intensity mild condition; and 21: Sedation (saline). The **'baseline'** cluster included: 22: Sex; 23: Breathlessness intensity strong condition (saline); 24: Breathlessness unpleasantness strong condition (saline); 25: Breathlessness unpleasantness mild condition (saline); 26: Breathlessness intensity mild condition (saline); 27: The Thought Control Questionnaire – Worry; 28: Mouth pressure strong condition (saline); 29: Anticipation mouth pressure strong (saline); 30: The Defence Style Questionnaire – Neuroticism; 31: Anticipation mouth pressure mild (saline); 32:

Mouth pressure mild condition (saline); 33: Discontentment (saline); 34: Tension (saline); and 35: Anxiety sensitivity index.

In COPD participants (right), the **'response'** cluster included: 36: Sex; 37: Δ Isotime breathlessness intensity; 38: Δ Isotime breathlessness unpleasantness; 39: Δ Isotime tidal volume; and 40: Δ Isotime breathing frequency. The **'affect**' cluster included: 41: COPD Assessment Test – activity limitation item; 42: Hospital Anxiety and Depression Scale – depression subscale; 43: COPD Assessment Test – dyspnea item; and 44: Oxygen Cost Diagram. Lastly, the '**baseline**' cluster included: 45: Modified Medical Research Council Scale; 46: Cigarette smoking history (pack years); 47: Forced expiratory volume in one second; 48: Hospital Anxiety and Depression Scale – anxiety subscale; 49: Isotime breathlessness intensity (placebo); 50: Isotime breathlessness unpleasantness (placebo); 51: Isotime breathing frequency (placebo); and 52: Isotime tidal volume (placebo).

Figure. 2 – Mean BOLD changes identified during anticipation of the mild (left panel) and strong breathlessness (right panel) challenge. 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 $p < 0.05$. ACC, anterior cingulate cortex; CN, caudate nucleus; vmPFC, ventromedial prefrontal cortex.

Figure. 3 – Mean BOLD changes identified during perception of mild breathlessness challenge. 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 $p < 0.05$. CN, caudate nucleus; mThal, medial thalamus.

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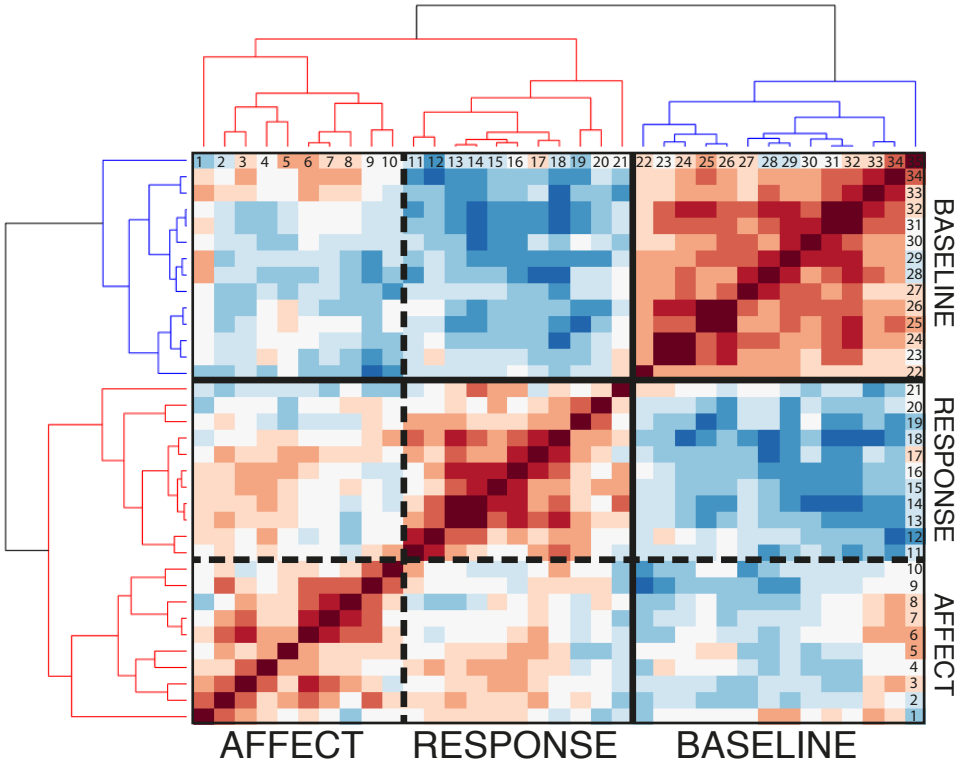
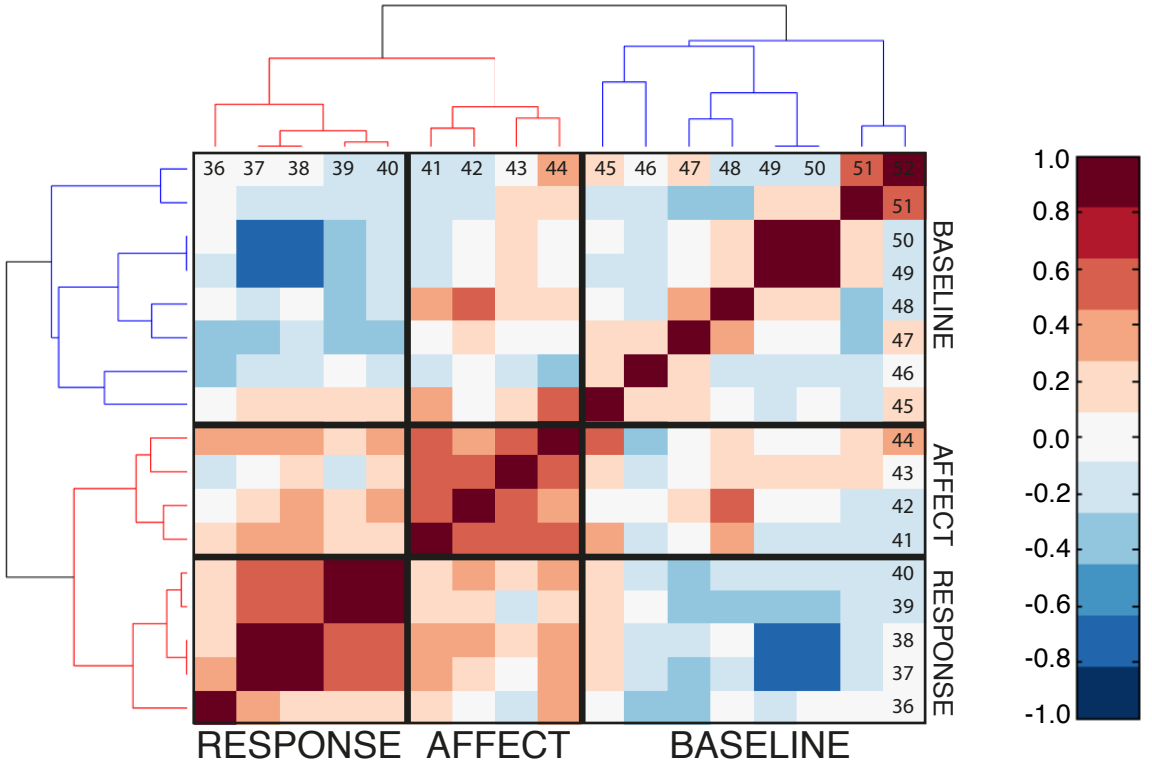
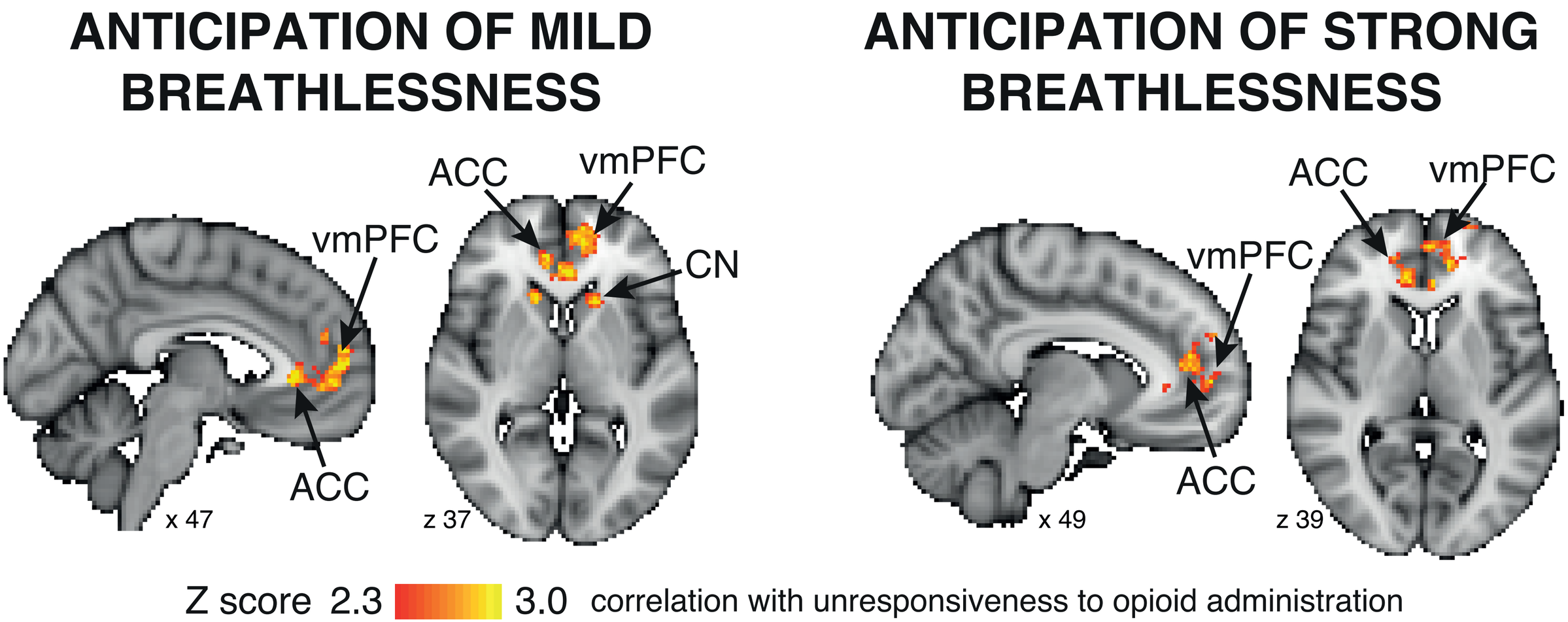
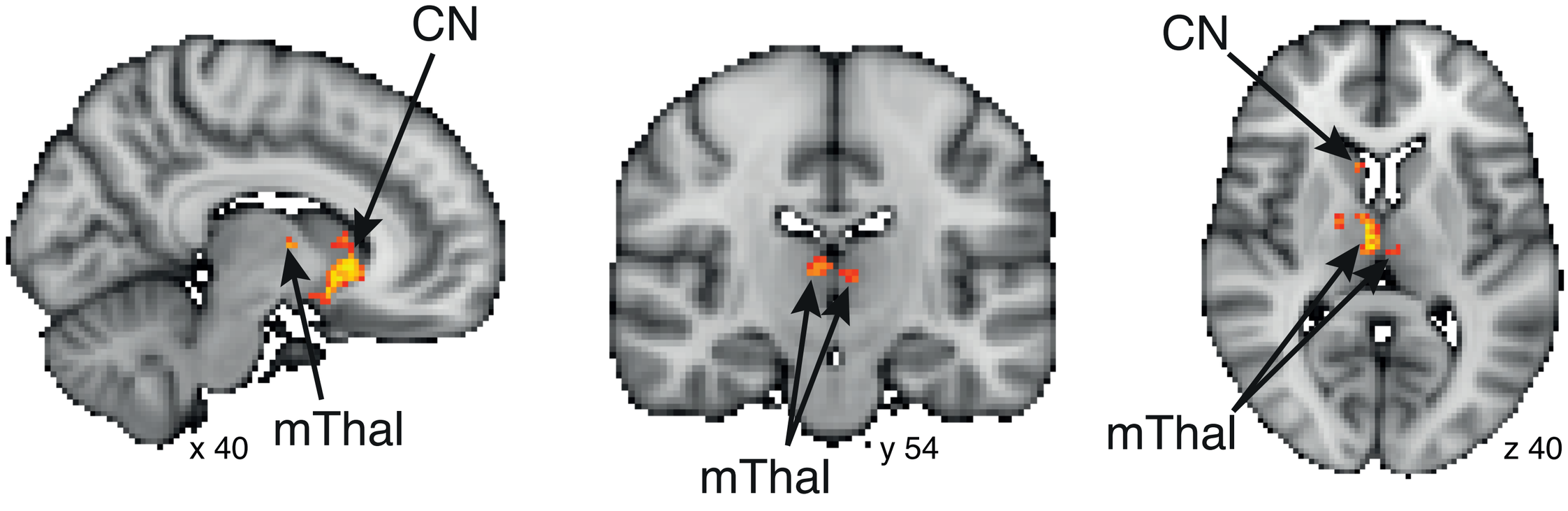


COPD




ANTICIPATION OF MILD BREATHLESSNESS
ANTICIPATION OF STRONG BREATHLESSNESS
ACC
vmPFC
vmPFC
CN
ACC
x 47
z 37
ACC
vmPFC
vmPFC
ACC
x 49
z 39
Z score 2.3
3.0
correlation with unresponsiveness to opioid administration

PERCEPTION OF MILD BREATHLESSNESS



Z score 2.3 3.0 correlation with unresponsiveness to opioid administration