Expectation and dyspnea: The neurobiological basis of respiratory nocebo effects

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Take home message:

A neural dyspnea nocebo effect was found; expectations of dyspnea increase the central neural processing of dyspnea and respiratory effort as seen by activation of the periaqueductal gray and deactivation of the rostral anterior cingulate cortex.

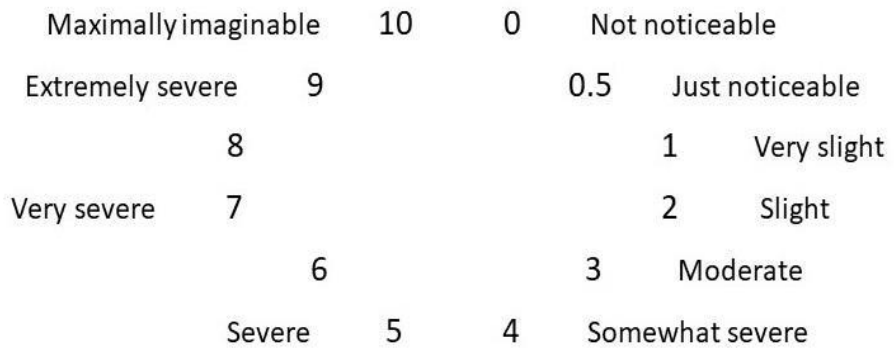
Supplementary Materials

Supplementary Results

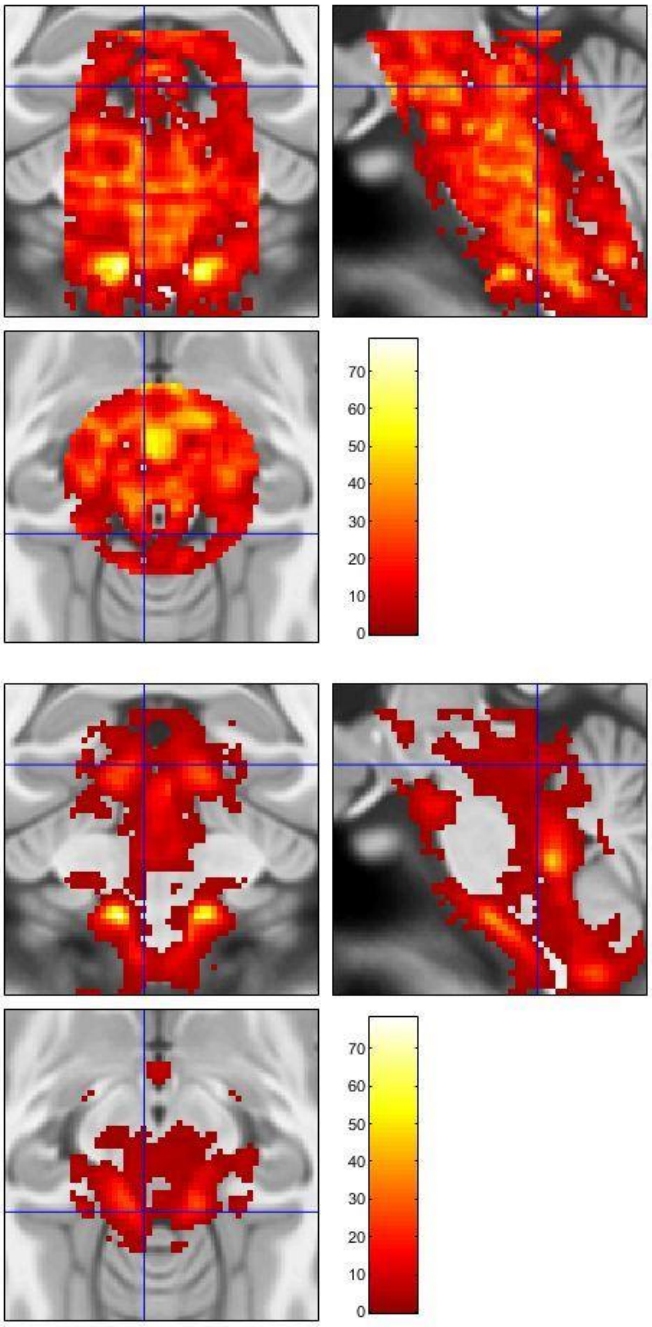
Phase by Condition interaction effect

To test for the differences between the experimental phases we additionally performed a Phase by Condition interaction analysis. For the whole insula a ROI analysis showed a significant interaction ($t(33)=2.83$; $p=0.004$). In addition to the planned analysis in the insula we estimated whole brain effects for this interaction using TFCE and observed significant effects in the dmPFC (peak x,y,z: -14, 38, 51mm, TFCE = 1714, $p=0.032$ corrected) and rACC (peak x,y,z: -6, 60, -2 mm, TFCE = 1562, $p=0.042$ corrected; peak x,y,z: -8, 50, -11 mm, TFCE = 1508; $p = 0.046$, corrected) (see Supplementary Figure S**4** for a whole brain panel). The activation, highlighting a significant difference in activations between the *Experience* and the *Expectation* phase largely overlapped with the main effects (Supplementary Figure S**5**).

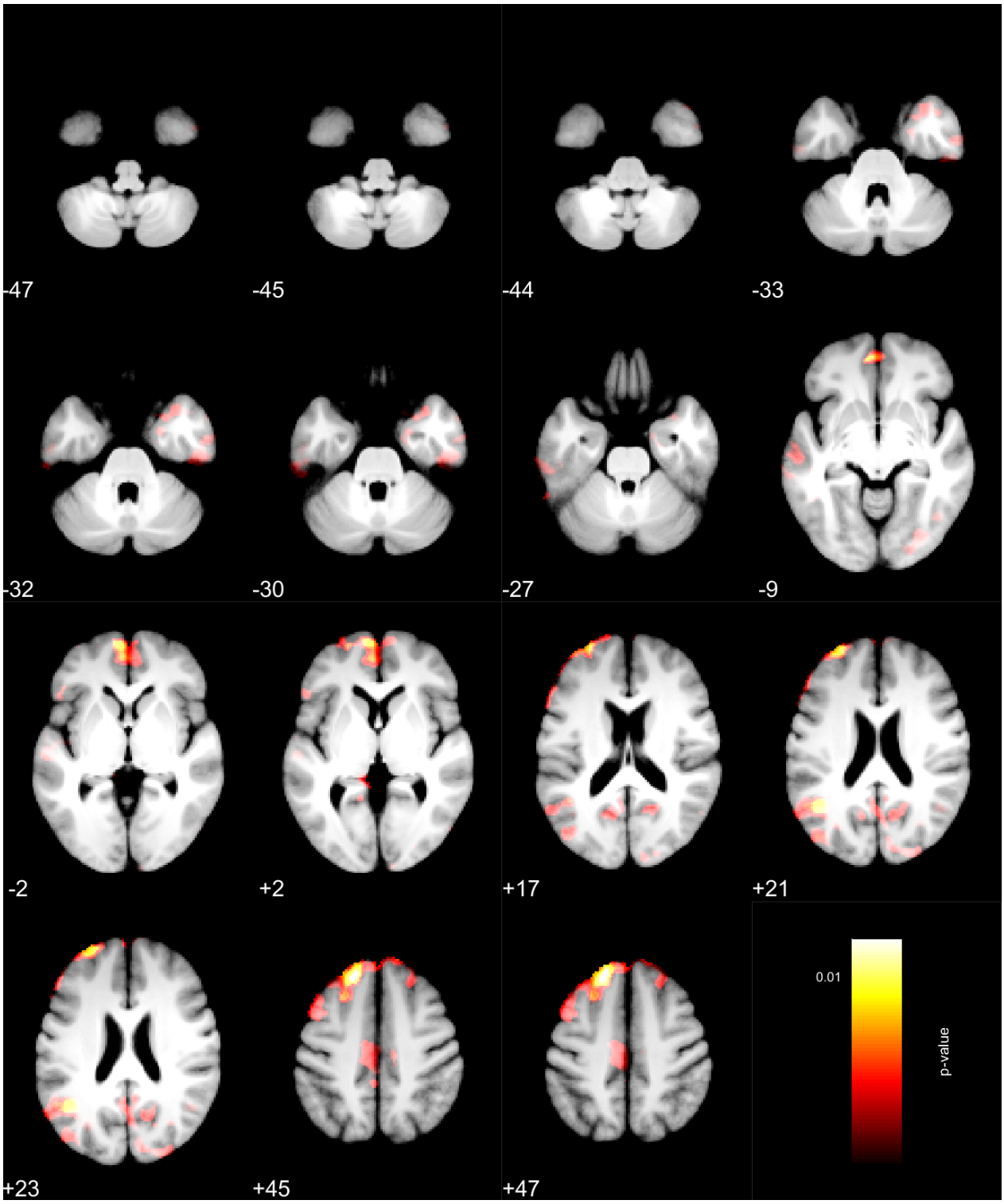
Supplementary Figures



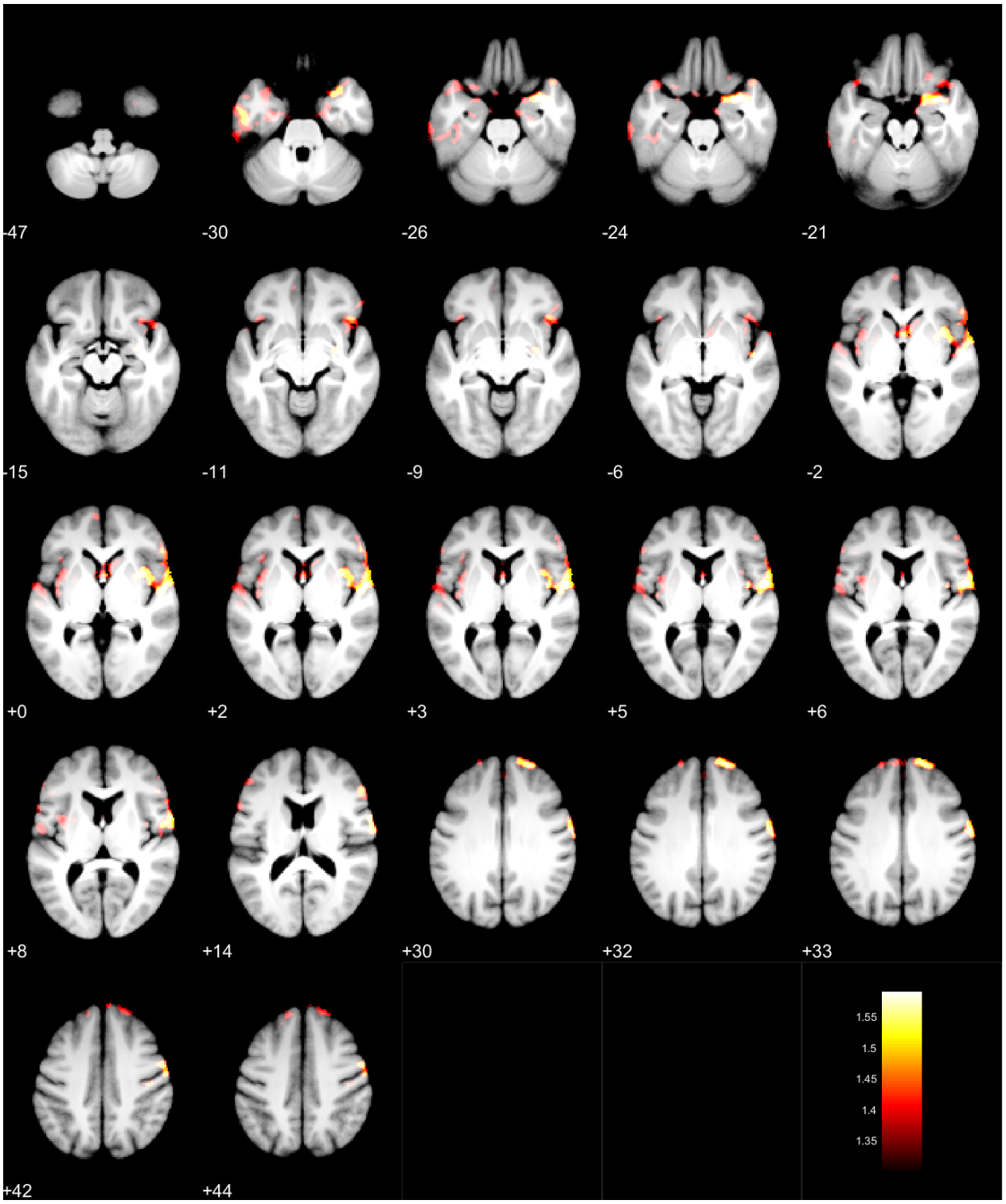
Supplementary Figure S1. Circular BORG scale. Subjects were asked to rate their dyspnea on this circular rating scale. A circular scale with a random start item and continuous clock- or counter-clockwise selection effectively orthogonalises motor activity from dyspnea rating.



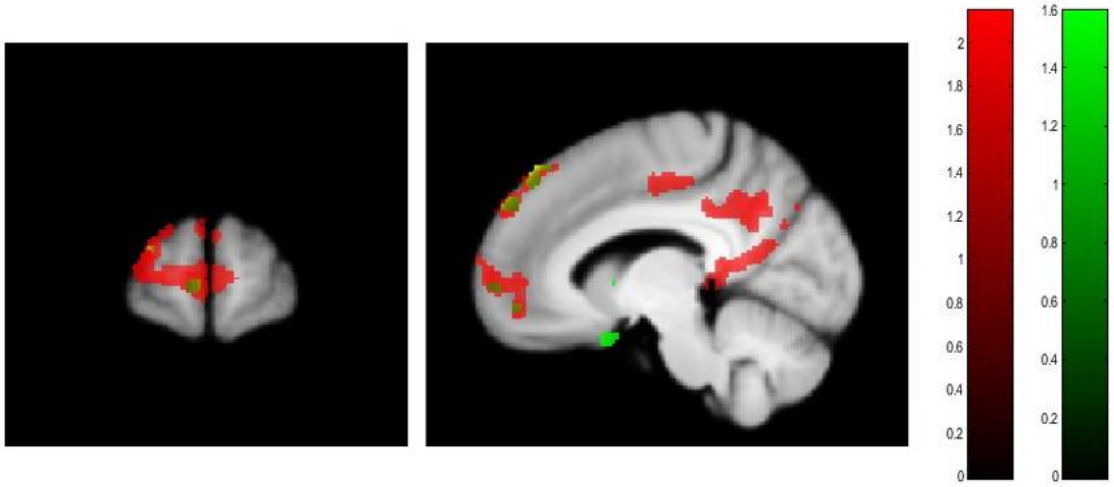
Supplementary Figure S2. Effect of modelling movement and physiological noise. (Top) Map of F statistics showing where movement parameters (3 translations 3 rotations) explain a significant amount of variance in the BOLD signal. (Bottom) Map of F statistics showing where respiratory and cardiac signals as modelled by RETROICOR (3R4C1X i.e. 3 cardiac, 4 respiratory sine and cosine harmonics and 1 interaction term) explain a significant amount of variance in the BOLD signal. petCO2 did not explain additional variance at $p<0.001$. Colourbar denotes F value. Overlays on an anatomical template thresholded at $p<0.001$ (uncorrected). Crosshair depicts peak voxel of the activation observed in the PAG. It can clearly be seen that movement, cardiac and respiratory signals contribute to the measured BOLD signal in this voxel and that this variance can be modelled by our physiological noise correction model.



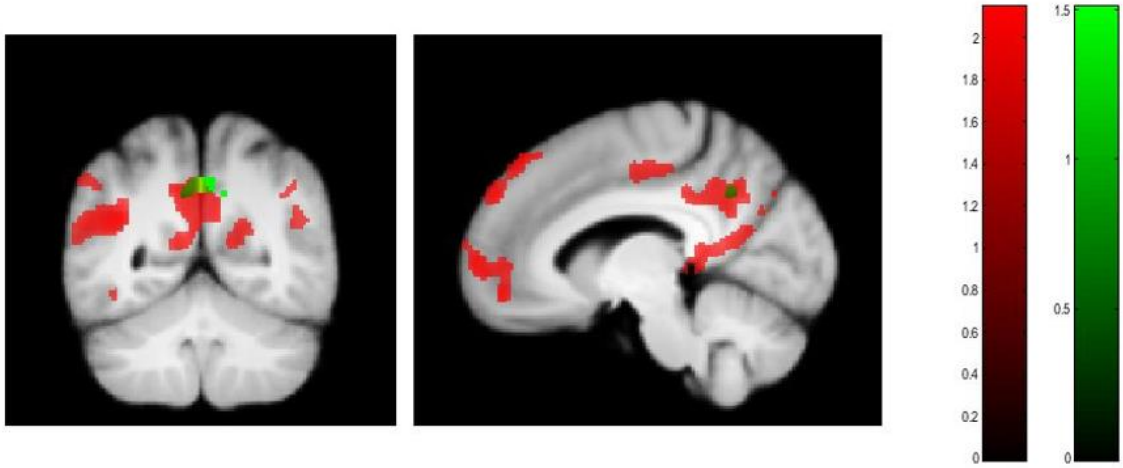
Supplementary Figure S3. BOLD signal differences during loaded breathing comparing the *Histarinol* to the *Control* condition in the *Expectation* phase. Activations are overlaid on a mean T1 weighted image and colour coded by p-value. The threshold was set at p<0.05 (corrected).



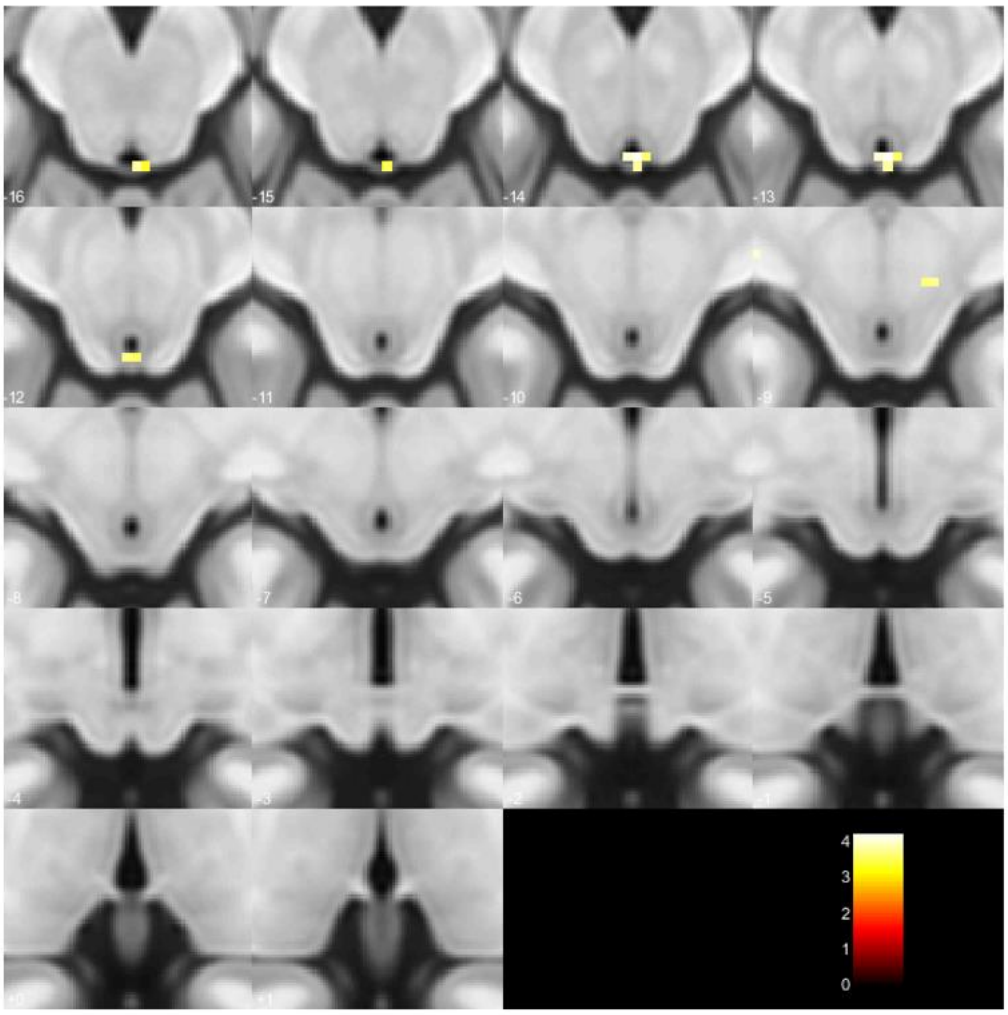
Supplementary Figure S4. BOLD signal differences during loaded breathing comparing the *Histarinol* to the *Control* condition between the *Expectation* and *Experience* phase (i.e. Condition [*Histarinol* vs. *Control*] by phase [*Experience* vs *Expectation*] interaction). Activations are overlaid on a mean T1 weighted image and colour coded by p-value. The threshold was set at $p<0.05$ (corrected).



Supplementary Figure S5. Overlap of fMRI signal differences comparing expected dyspnea to expected control during the load phase (red). The interaction (green) showing significant fMRI signal differences between the *Experience* and *Expectation* phase largely overlap with the main effect. Colourbars indicate –log10(p-value). The threshold was set at p<0.05 (corrected).



Supplementary Figure S6. Overlap of fMRI signal differences comparing expected dyspnea to expected control during the load phase (red) and the correlation of rating differences between both conditions with fMRI signal differences (green). Colourbars indicate –log10(p-value). The threshold was set at p<0.05 (corrected).



Supplementary Figure S7. Main effect for *Histarinol* versus *Control* in the brainstem overlaid on an anatomical template and thresholded at p<0.001 (uncorrected).

Supplementary Instructions

Nocebo instructions provided to participants, translated to English from German

"The aim of this study is to examine the regulation of breathing during acute respiratory distress. To do so, we will administer Histarinol®, a substance that causes shortness of breath.

Histarinol® has a specific odour, which, however, quickly fades. Shortly after inhaling, you will experience shortness of breath. Shortness of breath is associated with more difficult breathing and therefore requires more effort to breathe. If you inhale Histarinol®, you will first notice the odor and then you will notice shortness of breath.

We will test Histarinol® in comparison with a control substance in order to examine differences in breathing. You will immediately recognize Histarinol® by its specific odour. In order to control the odour effect of Histarinol®, a fragrance was also added to the control substance. This allows you to differentiate between the two substances. The control substance usually has no effect on breathing. When the administration of the substance starts, concentrate on your breathing and assess the intensity of your shortness of breath.

The exact process will now be demonstrated with a test trial. [The experimenter shows a test trial to demonstrate the visual information provided on the screen while in the scanner, and to explain the use of the button box.]

First, you will be informed via the display whether you are receiving Histarinol® or the control substance. At that moment, the administration of the substance takes place. When you inhale Histarinol®, you will first recognize the specific odour of Histarinol® and then you will experience shortness of breath: breathing becomes harder and requires more effort. If you inhale the control substance, you will recognize the specific odour of the control substance and you will usually not experience any shortness of breath.

At the end of the administration of the substance, please indicate how intense the dyspnea was on average during the last dose. When this scale appears, you can rate the intensity of your shortness of breath. [The circular borg scale is presented to the participants.] Use the left and right button to select a value on the scale. With the right mouse button you go clockwise, and with the left mouse button you go counter clockwise. Zero means no shortness of breath, 10 means maximum possible shortness of breath. Click the top button to confirm your answer.

When the administration of Histarinol® or the control substance has ended, there is a short break. If you have inhaled Histarinol®, the shortness of breath will quickly go away and your breathing will quickly return to normal. After the break, the intensity assessment will be repeated to ensure that your breathing has fully returned to normal. This is then followed by the next administration and the same procedure is repeated.

Please familiarize yourself with the scale now. [Participants practice the use of the button box.]

There will be four blocks: 2 blocks of 8 administrations of Histarinol® and 2 blocks of 8 administration of the control substance. During the entire experiment, you lie down and breathe through a mask. [The experimenter shows the mask.] The mask is necessary to administer Histarinol® and the control substance, and to monitor effects on your breathing. After each block, you fill out a short questionnaire.

Don't be anxious, your breathing will be closely monitored throughout the experiment. Therefore you will feel a click in the mask with every breath. Please don't let that bother you, this is due to the equipment monitoring your breathing. Please concentrate on your breathing and the assessment of the shortness of breath."