Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation.

Supplementary material.

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Supplementary Methods

Participants

We recruited 44 (16 F, mean age 68+/-8 years) patients with COPD from the pulmonary rehabilitation services in Oxfordshire, UK. In the present study, we report findings from the 31 patients (21 male, mean age 68 +/-(SD) 9) who completed pulmonary rehabilitation.

Some of the findings have already been published [1] in a study that compared baseline (pre-rehabilitation) FMRI findings with a healthy control group. A more detailed description of the development and validation of the word-cue task has also been published [2].

Patients were studied on two separate occasions; in the two weeks prior to commencement of pulmonary rehabilitation and subsequently in the four weeks after its completion. All participants gave written, informed consent and the study was approved by Oxfordshire Research Ethics Committee A.

MRI data acquisition

Imaging was performed at the University of Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Scans were always done in the same order. Participants undertook two separate FMRI scans. Each FMRI scan lasted 8 minutes and 20 seconds, with a break between scans allowing participants a chance to cough. The break was no longer than 1 minute in duration.

Scanner: MRI was performed with a 3 T Siemens Tim Trio scanner, with 40 mT/m gradient strength and a 12 channel receive, single channel transmit head coil (Nova Medical).

BOLD scanning: A T2*-weighted, gradient echo EPI was used for functional scanning. The field of view (FOV) covered the whole brain and comprised 45 slices (sequence parameters: TE, 30 ms; TR, 3 s; flip angle, 87°; voxel size, 3 x 3 x 3 mm; field of view,192 x192 mm; (GRAPPA factor, none) echo spacing, 0.49 ms), with 168 volumes (scan duration, 8 mins 20s) for the task fMRI.

Structural scanning: A T1-weighted structural scan (MPRAGE, sequence parameters: TE, 4.68 ms; TR, 2040 ms; flip angle, 8°; voxel size, 1 x 1 x 1 mm; field of view, 200 mm; inversion time, 900 ms; bandwidth; 130 Hz/Px) was acquired. This scan was used for registration of functional images.

Additional scanning: Fieldmap scans (sequence parameters: TE1, 5.19 ms; TE2, 7.65 ms; TR, 488.0 ms; flip angle,60°; voxel size, 3.5 x 3.5 .3.5 mm) of the B_0 field were also acquired to assist distortion-correction.

FMRI task. The FMRI task comprised a set of randomised breathlessness-related cues that were presented as white text on a black background for 7 seconds. Full details of the task (and its development) can be found in previous publications [1, 2]. Patients were instructed to rate each cue on a visual analogue scale (VAS) scale (range: 0-100; anchors: 'Not at all' and 'Very much', 7 seconds), first answering the question "How breathless would this make you feel?" (wB) and second "How anxious would this make you feel?" (wA), for each given scenario. Patients were trained to reliably do the task immediately prior to the scan.

As part of the validation of the word-cue test we took care to include words that were generally relevant for most people [1]. This was done by iterative testing of the word cue set, which led to the exclusion of certain word-cues. These were mostly related to gender-specific tasks such as "housework", "laundry", "shopping". All subjects viewed the same set of words during both sessions although the order of presentation was randomised.

A control task to assess potential differences in baseline BOLD responsiveness between groups was employed in the form of random letter strings which were presented after every third word cue. These were not followed by any ratings and participants were instructed to ignore them. Participants were instructed to keep their eyes open for the full duration of the BOLD sequences.

MRI physiological measurements. Heart rate (HR) and pulse oximetry (SpO_2, multigas monitor, model 9500, MR Equipment), respiration (respiratory bellows around the chest) and end-tidal partial pressures of oxygen ($P_{ET}O_2$)

and carbon dioxide ($P_{ET}CO_2$; Datex, Normocap, nasal cannula (Salter Labs)) were continuously measured during the scan. All physiological data were sampled at 50Hz and recorded along with triggers for the scan volumes via PowerLab 8 (ADinstruments), using Chart5 (ADinstruments).

Psychological measurements

Self-report questionnaires: We chose a variety of self-reported questionnaires to comprehensively capture psychological constructs associated with COPD and with breathlessness. The following self-report questionnaires were completed and scored according to their respective manuals:

- **Center for Epidemiologic Studies Depression Scale (CES-D)** (3). This is a brief self-report questionnaire that asks 20 questions about symptoms of depression. It is widely used in clinical care and in research.
- **State-Trait Anxiety Inventory** (4). This questionnaire comprises two sections (state, trait anxiety) each of 20 questions. State anxiety relates to "how anxious do you feel now" whereas trait anxiety asks about "how anxious do you generally feel".
- **Fatigue Severity Scale** (5). Fatigue is highly prevalent in COPD, and has well-reported negative impact on quality of life. This is a 9-point self-report questionnaire that was developed to facilitate research into fatigue.
- **St George's Hospital Respiratory Questionnaire** (SGRQ) (6). This is a 50-item self report questionnaire that was developed and validated for use in COPD and asthma. The questionnaire is designed to measure the impact on overall health, daily life, and well-being.
- **Medical Research Council (MRC) breathlessness scale** (7). This is a scale that measures perceived respiratory difficulty on a scale of 1 to 5. It was designed for epidemiological studies, although is often used in clinical practice.
- **Dyspnoea-12 (D-12) questionnaire** (8). This is a 12-item questionnaire designed to measure the severity of breathlessness in

clinical populations. It was developed from patient-derived descriptors of breathlessness using hierarchical methods.

- **Catastrophic Thinking Scale in Asthma** (modified by substituting the word “breathlessness” for the word “asthma") (9). This is a 13-point questionnaire that measures catastrophic thinking, which is well known to play a role in the emotional exacerbation of symptoms.
- **Pain Awareness and Vigilance Scale**, (modified by substituting the word “breathlessness” for the word “pain”) (10). This is a 16-point scale which measures how much someone focuses their attention on their breathlessness.
- **Behavioral Inhibition System/Behavioral Activation System scale** (11). This questionnaire examines motivation and reward sensitivity. It may relate to activity of the endogenous opioid system. We included this questionnaire based on reports suggesting opioid activation during exercise in COPD (33).

The Catastrophic Thinking Scale in Asthma [9] and Pain Awareness and Vigilance Scale [10], were modified for breathlessness (see [2]), as no suitable breathlessness-specific questionnaires were available at the time of study. A later study has validated the Catastrophic Thinking Scale for COPD [12], and the resulting questionnaire is very similar, although not identical, to our questionnaire.

Spirometry and exercise testing

Patients undertook spirometry (FEV_1 and FVC, performed by a trained respiratory nurse) and an exercise test (Modified Shuttle Walking Test (MSWT), performed twice). HR and SpO_2 were measured every minute (pre-exercise to 10 min post-exercise) using a non-invasive fingertip pulse oximeter (GO_2, Nonin Medial Inc.). Immediately before and after the MSWT, breathlessness ratings were obtained using the modified Borg scale [13].

Analysis of behavioural data

Questionnaires were scored by hand according to their respective manuals, with comparisons made using Student's t-test and Spearman's rank correlation coefficient. VAS scores were averaged and used for the FMRI analysis. For spirometry, the measurement associated with the highest FEV_1 was used. For MSWT, the measurement associated with the largest distance was used.

Full correlation matrices were calculated for all behavioural and physiological measures at baseline and for the change with pulmonary rehabilitation, using MATLAB (R2013a, The Mathworks, Natick, MA). **Partial correlation matrices** were calculated on correlated variables, defined as $p < 0.05$ (uncorrected).

Mediation analysis. To explore the relationship between the fMRI task measures (wB and wA) the D12 questionnaire (our clinical measure of breathlessness) and other behavioural measures, we conducted a mediation analysis using the CANlab mediation toolbox [14-16].

Mediation incorporates variables that may potentially mediate a correlation (X←→Y), calculating the correlation between both variables (XM and MY). If the combination of these correlations is significant, then a variable may be deemed a potential mediator. The residuals of the regressions (XM and MY) can then be regressed to indicate whether the direct (unmediated) relationship still stands.

FMRI Data Analysis

Preprocessing: Image processing was performed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FMRIB, Oxford, UK; FSL version 5.0.8; http://www.fmrib.ox.ac.uk/fsl/). The following preprocessing methods were used prior to statistical analysis:

motion correction and motion parameter recording (MCFLIRT [17, 18]), removal of the non-brain structures (skull and surrounding tissue) (BET [19]), spatial smoothing using a full-width half-maximum Gaussian kernel of 5 mm, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting; 100 s). B_0 field unwarping was conducted with a combination of FUGUE and BBR (Boundary-Based-Registration; part of FEAT: FMRI Expert Analysis Tool, version 6.0[20]. Data denoising was conducted using a combination of independent components analysis (ICA) and retrospective image correction (RETROICOR) [21-25]. Timepoints in the dataset subject to large, rapid motion artefacts were detected using FSL.

Image registration: After preprocessing, the functional scans were registered to the MNI152 (1x1x1mm) standard space (average T1 brain image constructed from 152 normal subjects at the Montreal Neurological Institute (MNI), Montreal, QC, Canada) using a two-step process: 1) Registration of subjects' whole-brain EPI to T1 structural image was conducted using BBR (6 DOF) with (nonlinear) fieldmap distortion-correction [20] and 2) Registration of the subjects' T1 structural scan to 1 mm standard space was performed using an affine transformation followed by nonlinear registration (FNIRT)[26].

Functional voxelwise and group analysis: Functional data processing was performed using FEAT (FMRI Expert Analysis Tool), part of FSL. The first-level analysis in FEAT incorporated a general linear model [27], with explanatory variables (EVs) at the first (individual) level for word presentation, and two EVs modelling the variability in VAS responses to the breathlessness and anxiety cues presented during scanning. Modelling this way meant that the word presentation EV was normalised, and this normalised EV was the primary measure used to examine inter-individual variability in brain responses to pulmonary rehabilitation.

Functional voxelwise analysis incorporated HRF modeling using three FLOBS regressors to account for any HRF differences caused by slice-timing delays, differences between the brainstem and cortex, or between individuals [28, 29]. Time-series statistical analysis was performed using FILM, with local autocorrelation correction [30]. The second and third waveforms were orthogonalised to the first to model the 'canonical' HRF, of which the

parameter estimate was then passed up to the group analysis.

Higher level analyses: Group analyses were conducted using a mixed-effects analysis in FLAME 1+2 (FMRIB's Local Analysis of Mixed Effects [31]). Z statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p < 0.05$.

Higher level analysis 1 - Assessing variability of response to pulmonary rehabilitation: A middle level, fixed-effects analysis was conducted to calculate the difference in cope images from pre-rehab to post-rehab for each subject. These difference images were then taken up into a third, highest level, where EVs were included for mean BOLD activity, change in the VAS scales relating to "*How breathless would this make you feel?*"(wB) and "*How anxious would this make you feel?*" (wA).

Higher level analysis 2 – Baseline factors associated with improved breathlessness following pulmonary rehabilitation: The cope images corresponding for each subject prior to rehabilitation were taken up into a higher level analysis, where EVs were included for mean BOLD activity, pre-rehab wB, pre-rehab wA, pre-post rehab change in wB and pre-post rehab change in wA.

All FMRI data processing was carried out within FEAT (FMRI Expert Analysis Tool) Version 6.0, part of FSL (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library, version 5.0 www.fmrib.ox.ac.uk/fsl). The cluster Z threshold was set to 2.3 and the corrected cluster significance threshold to p=0.05 [32].

Images were registered to the MNI152 standard space using an affine registration (FMRIB Linear Image Registration Tool) between the EPI and T1 structural scan and a nonlinear registration (FMRIB NonLinear Image Registration Tool) between T1 structural scans and the MNI standard brain.

Further methodological considerations

The level of baseline BOLD, and BOLD activation to a standard stimulus is variable between people. Therefore, BOLD FMRI is analysed in a way that

identifies areas of consistent activation across subjects representing those areas where activation to a stimulus consistently outweighs between-subject variability. Furthermore, by relating these patterns of activity to the magnitude of subjective behavioural scores, we are able to identify where variations in BOLD activity may be related to the magnitude of these scores across subjects.

The strength of combining the word-cue task with a VAS is that it allows us to model the VAS rating in the FMRI analysis. This accounts for the individual cues being associated with differing levels of breathlessness and breathlessness anxiety across individuals. We could thus normalise BOLD responses by the individual trial-by-trial ratings, and thus the analysis becomes insensitive to the specific word cue.

Brain areas where activity is outweighed by inter-individual variability in BOLD would therefore not be identified as "active". It is also important to note that a linear change in BOLD activity across people does not necessarily equate to a linear change in breathlessness. This is due the multidimensional and complex nature of the symptom, and the way different people rate on a VAS. This observation holds true for all FMRI (including the vast FMRI literature exploring the neural basis of pain, anxiety, depression etc.). However, what we can infer from our data is that the brain areas identified are those that most consistently scale with the behavioural measures (wB, wA) across our population, and the directionality of the scaling.

To reduce inter-individual variability in BOLD response, we have employed techniques during the data acquisition and analysis to minimise and account for physiological noise [21-23]. Physiological noise can either increase signal variability (thus reduce the signal to noise ratio) or alternatively introduce erroneous signal (e.g. when the noise is correlated with the FMRI stimulus of interest).

We did not observe a relationship between baseline BOLD activity and behavioural scores across individuals at baseline (as discussed above). Instead, we investigated the BOLD activity at baseline that reflected the

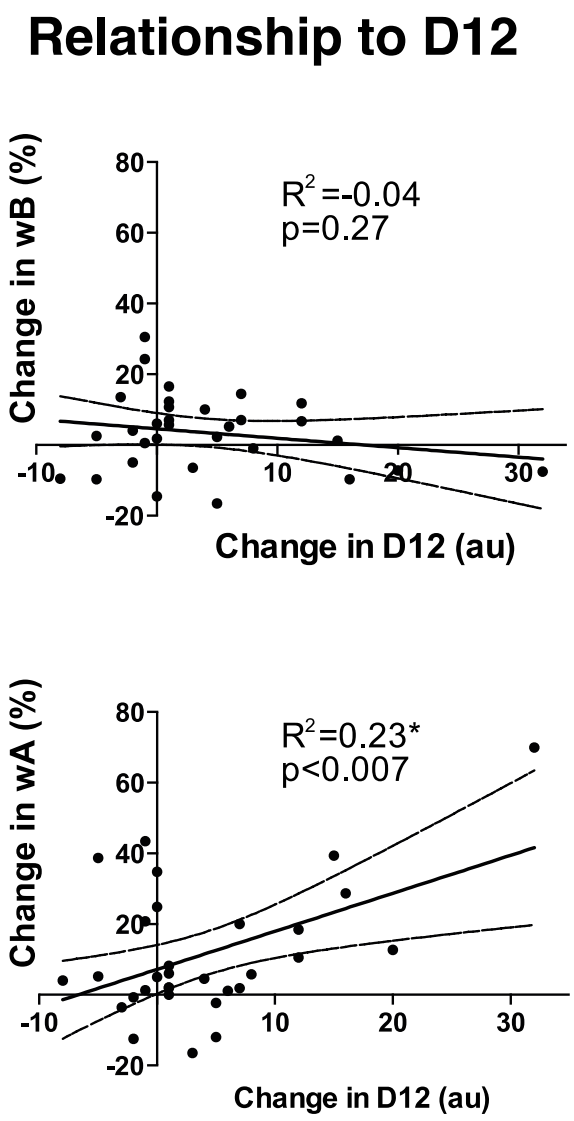
magnitude of change in an individual's behavioural score, without assuming that global BOLD activity and breathlessness perceptions are directly reflective of one another.

It is possible that the positive correlation between the level of activation/perception at baseline and the reduction in activation/perception post rehabilitation may reflect those with the 'largest room' for improvement following pulmonary rehabilitation. Therefore, we included the baseline breathlessness scores (as well as the change in breathlessness score across pulmonary rehabilitation) as regressors of no interest in our analysis model, to separate the effects of baseline score from change in score across pulmonary rehabilitation.

We saw no significant BOLD activation before pulmonary rehabilitation that correlated with baseline VAS scores (wB, wA). Inferring how absolute subjective scores relate to baseline levels of BOLD activity patterns across individuals is unlikely to produce tangible results for such a complex phenomenon as breathlessness. Each person comes to their own subjective perception based on a multitude of disease experiences and psychological constructs. Therefore, expecting a linear relationship between scores from different individuals is not realistic from what we know about breathlessness. Instead, what we have done is to consider where the BOLD activity in an individual best reflects the subsequent magnitude of change in that individual, and where this pattern is consistent across subjects.

ADDITIONAL RESULTS SECTION

Full and partial correlations are listed in supplementary tables 1 and 2 below.



Supplementary Figure 1. Correlations between change in D12 with changes in wB and wA over the course of pulmonary rehabilitation

PULMONARY REHABILITATION DETAILS

Pulmonary rehabilitation was delivered by an experienced community pulmonary rehabilitation team. The full course ran for 6 weeks, with two sessions per week including an hour of exercises and an hour of education, as part of a standard pulmonary rehabilitation programme. Patients had been referred to pulmonary rehabilitation as part of their standard management. As pulmonary rehabilitation courses vary in duration and content we briefly describe the course that the patients in this study undertook. The Oxfordshire pulmonary rehabilitation programme is a cohort course which consists of two-hour sessions performed twice weekly for six weeks in an outpatient setting, that is currently (December 2016) being run by Oxford Health NHS Foundation Trust.

Outpatient settings were non-medical facilities with the appropriate exercise equipment available, e.g. sports halls. Each session consisted of one hour of exercise (under supervision) and one hour of education.

Exercise sessions included both aerobic and strength exercises, tailored to the individual's ability. Aerobic exercises could include step-ups, walking (on the spot or treadmill) and exercising on a cycle ergometer. Strength exercises were conducted in sets (usually 3) of ten, and included sit-to-stand exercises, biceps curls, upright row and leg extensions.

Education sessions included items such as ‘introduction to rehabilitation’, ‘management of breathlessness’, ‘airway clearance’, ‘understanding your lung condition’, ‘home exercises’, medicine management’, ‘staying healthy’, ‘stress and relaxation’, ‘pacing and energy conservation’, ‘smoking cessation’, ‘continuing support’, ‘sexual function’ and ‘advanced care plans’. Supervised modified shuttle walking tests were used to measure patients’ improvement throughout the programme.

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Full Correlation Matrix for pre vs post rehabilitation scores

Correlation coefficients (r)

wA		0.03	0.48	0.63	0.57	0.15	0.45	0.43	0.02	0.36	-0.30	-0.17	0.26
wB	0.03		-0.20	0.01	-0.11	0.22	-0.03	0.04	-0.05	0.22	0.21	-0.30	0.10
D12	0.48	-0.20		0.38	0.70	0.41	0.79	0.42	0.20	0.23	0.15	0.28	0.40
St G	0.63	0.01	0.38		0.45	0.25	0.48	0.56	0.26	0.54	0.36	0.29	0.26
Cat	0.57	-0.11	0.70	0.45		0.47	0.63	0.57	0.05	0.27	0.20	0.16	0.30
Vig	0.15	0.22	0.41	0.25	0.47		0.47	0.31	0.05	0.07	-0.07	-0.05	0.09
Dep	0.45	-0.03	0.79	0.48	0.63	0.47		0.58	0.37	0.26	0.12	0.24	0.36
T Anx	0.43	0.04	0.42	0.56	0.57	0.31	0.58		0.65	0.47	0.36	0.25	0.17
S Anx	0.02	-0.05	0.20	0.26	0.05	0.05	0.37	0.65		0.32	0.40	0.12	0.05
Fat	0.36	0.22	0.23	0.54	0.27	0.07	0.26	0.47	0.32		0.55	0.07	-0.05
BisBas	0.30	0.21	0.15	0.36	0.20	-0.07	0.12	0.36	0.40	0.55		-0.10	0.22
Spir	0.17	-0.30	0.28	0.29	0.16	-0.05	0.24	0.25	0.12	0.07	-0.10		0.12
MSWT	0.26	0.10	0.40	0.26	0.30	0.09	0.36	0.17	0.05	-0.05	0.22	0.12	
	wA	**wB**	**D12**	**St G**	**Cat**	**Vig**	**Dep**	**T Anx**	**S Anx**	**Fat**	**BIS BAS**	**Spir**	**MSWT**

Statistical significance (p value) (uncorrected)

	wA	**wB**	**D12**	**St G**	**Cat**	**Vig**	**Dep**	**T Anx**	**S Anx**	**Fat**	**BIS BAS**	**Spir**	**MSWT**
wA		0.88	0.01	0.00	0.00	0.44	0.01	0.02	0.91	0.05	0.10	0.36	0.16
wB	0.88		0.27	0.96	0.56	0.24	0.87	0.82	0.80	0.24	0.25	0.10	0.61
D12	0.01	0.27		0.03	0.00	0.02	0.00	0.02	0.27	0.22	0.42	0.12	0.03
St G	0.00	0.96	0.03		0.01	0.17	0.01	0.00	0.15	0.00	0.05	0.11	0.16
Cat	0.00	0.56	0.00	0.01		0.01	0.00	0.00	0.80	0.14	0.28	0.39	0.10
Vig	0.44	0.24	0.02	0.17	0.01		0.01	0.09	0.79	0.70	0.71	0.78	0.61
Dep	0.01	0.87	0.00	0.01	0.00	0.01		0.00	0.04	0.16	0.53	0.19	0.05
T Anx	0.02	0.82	0.02	0.00	0.00	0.09	0.00		0.00	0.01	0.05	0.17	0.37
S Anx	0.91	0.80	0.27	0.15	0.80	0.79	0.04	0.00		0.08	0.03	0.51	0.79
Fat	0.05	0.24	0.22	0.00	0.14	0.70	0.16	0.01	0.08		0.00	0.71	0.79
BisBas	0.10	0.25	0.42	0.05	0.28	0.71	0.53	0.05	0.03	0.00		0.60	0.24
Spir	0.36	0.10	0.12	0.11	0.39	0.78	0.19	0.17	0.51	0.71	0.60		0.51
MSWT	0.16	0.61	0.03	0.16	0.10	0.61	0.05	0.37	0.79	0.79	0.24	0.51	

Abbreviations: **wA** visual analogue scale relating to "How anxious would this make you feel?", **wB** visual analogue scale relating to "How breathless would this make you feel?", **D12** Dyspnoea-12 score, **St G** St Georges Respiratory Questionnaire, **Cat** Breathlessness catastrophising score, **Vig** Breathlessness vigilance scale, **Dep** Center for Epidemiological Studies Depression Scale, **T Anx** Trait Anxiety, **S Anx** State Anxiety, **Fat** Fatigue Severity Scale, **Spir** Spirometry (FEV1/FVC)(multiplied by minus 1, for display purposes in Figure 3), **MSWT** Modified Shuttle Walk Test (multiplied by minus 1, for display purposes in Figure 3)

Partial Correlation Matrix for pre vs post rehabilitation scores

Partial correlation coefficients (r)

wA		0.08	0.02	0.30	0.05	0.22
D12	0.08		0.65	0.42	-0.25	0.06
Cat	0.02	0.65		-0.01	0.40	-0.08
Dep	0.30	0.42	-0.01		0.33	-0.09
T Anx	0.05	-0.25	0.40	0.33		0.38
Fat	0.22	0.06	-0.08	-0.09	0.38	
	wA	**D12**	**Cat**	**Dep**	**T Anx**	**Fat**

Statistical significance (p value) (uncorrected)

wA		0.68	0.91	0.13	0.82	0.28
D12	0.68		0.00	0.03	0.21	0.77
Cat	0.91	0.00		0.98	0.04	0.70
Dep	0.13	0.03	0.98		0.09	0.66
T Anx	0.82	0.21	0.04	0.09		0.05
Fat	0.28	0.77	0.70	0.66	0.05	
	wA	**D12**	**Cat**	**Dep**	**T Anx**	**Fat**

Abbreviations: **wA** visual analogue scale relating to "How anxious would this make you feel?", **D12** Dyspnoea-12 score, **Cat** Breathlessness catastrophising score, **Dep** Center for Epidemiological Studies Depression Scale, **T Anx** Trait Anxiety, **Fat** Fatigue Severity Scale