Breathlessness: *F*unctional MRI, *F*easibility and *F*indings

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Outline

- Background
  - why fMRI?
- fMRI feasibility study
  - local experience
- Next steps
- Discussion

Background

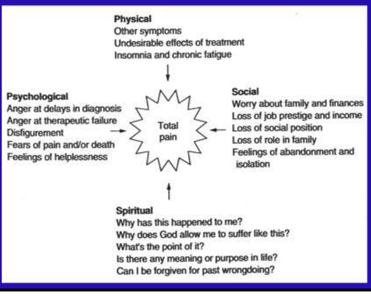
In palliative care, we:

- aim to relieve symptoms
- see that symptoms vary between people in:
  - intensity
  - unpleasantness or distress
  - impact.

Background

In palliative care, we:

- use a model of 'total pain'
  - can be extend to any symptom



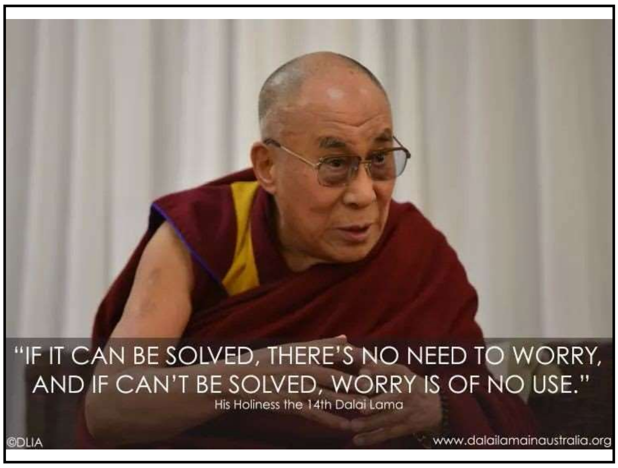
Background

In palliative care, we:

- see that symptoms are modulated by other factors, e.g.:
  - cognitive (attention, expectation, catastrophizing)
  - affective (negative/positive emotions and moods)
- often support patients coping with unpleasant emotions/moods as a consequence of their symptoms/situation.

Palliative care & emotion

- problem-focused coping is not generally possible; incurable progressive disease, outcome not good, out of the patients control
- a better approach is emotion-focused coping processes, which attempt to regulate the patient's emotional response to illness and its treatment.



Why fMRI?

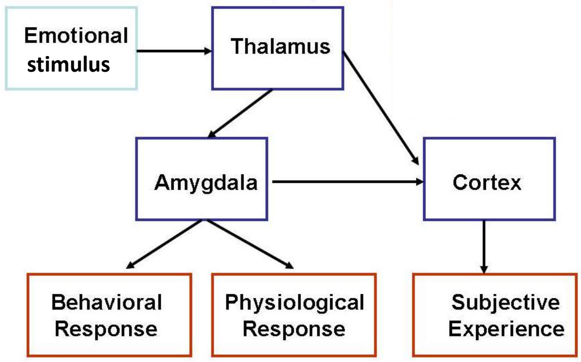
- greater understanding of the central processes involved in emotion generation in response to a unpleasant stimulus/symptom (e.g. anxiety related to breathlessness) may help develop more effective approaches
- fMRI is a tool that may help with this.

Progress in affective neuroscience

Identifying brain structures and systems that mediate:

- affective, or emotional, functions such as experiencing, perceiving, and expressing emotional feeling states
- initial focus on fear.

Neural basis of fear

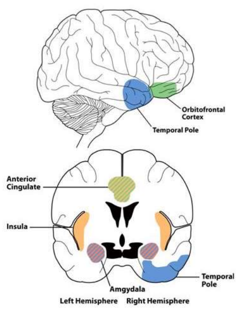


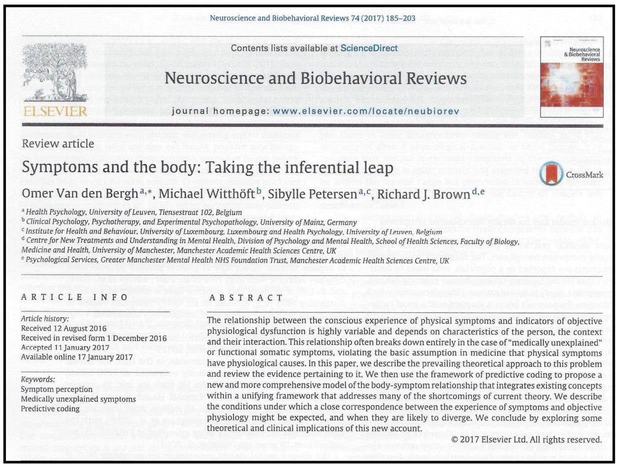
27 positive & **negative** emotions

Awe
Confusion
Joy
Boredom
Fear
Aesthetic Appreciation
Calmness
Anger
Sadness
Interest
Anxiety
Nostalgia
Relief
Disgust
Horror
Adoration
Satisfaction
Excitement
Amusement
Craving
Romance
Awkwardness
Sexual Desire
Admiration
Empathic Pain
Entrancement

Other emotions & centres

- Amygdala
- Orbitofrontal Cortex
- Anterior Cingulate Gyrus
- Nucleus Accumbens
- Insula





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Review article

Symptoms and the body: Taking the inferential leap

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ABSTRACT

The relationship between the conscious experience of physical symptoms and indicators of objective physiological dysfunction is highly variable and depends on characteristics of the person, the context and their interaction. This relationship often breaks down entirely in the case of "medically unexplained" or functional somatic symptoms, violating the basic assumption in medicine that physical symptoms have physiological causes. In this paper, we describe the prevailing theoretical approach to this problem and review the evidence pertaining to it. We then use the framework of predictive coding to propose a new and more comprehensive model of the body-symptom relationship that integrates existing concepts within a unifying framework that addresses many of the shortcomings of current theory. We describe the conditions under which a close correspondence between the experience of symptoms and objective physiology might be expected, and when they are likely to diverge. We conclude by exploring some theoretical and clinical implications of this new account.

Van den Bergh et al, 2017

- review focusing on 'medically unexplained symptoms'
- proposes a new model of body-symptom relationship
- explains how experience of symptoms and objective physiology may diverge
- also explains poor correlation between symptoms and objective disease measures in patient groups, e.g. in COPD:
  - poor correlation between breathlessness and FEV1 (r≤0.36)
  - trait negative affect, negative emotions and/or depression better predictors.

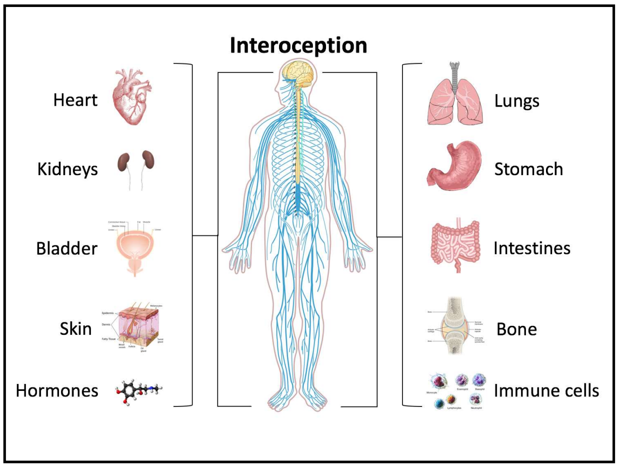
Model of symptom perception

- central principle is that physical symptoms, as felt and expressed by patients, are not a direct record of bodily activity (i.e. not a stimulus-response relationship)
- instead an inference based on implicit predictions about interoceptive information, based on prior knowledge
- thus, symptoms can result from an 'inferential leap' resulting in an experience that is coupled only loosely or not at all with dysfunctional physiology.

Model of symptom perception

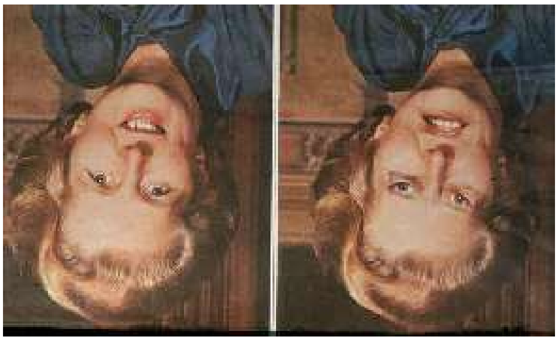
Brain generates sensations based on expectations learnt from past experiences (priors) which are then checked against incoming afferent signals.

Various factors act as moderators; they may alter priors, change relative attention towards incoming sensory information, or alter comparisons between priors and sensations, leading to more variable interpretation of an equivalent afferent input.



Interoception as an inference

- brain constantly bombarded by stimuli
- most used by subcortical regulation systems and not consciously perceived
- needs to regulate those that are perceived
- proposed brain achieves this through inferential processing, by creating probabilistic models (priors) about the causes of current inputs to the system, based on prior knowledge

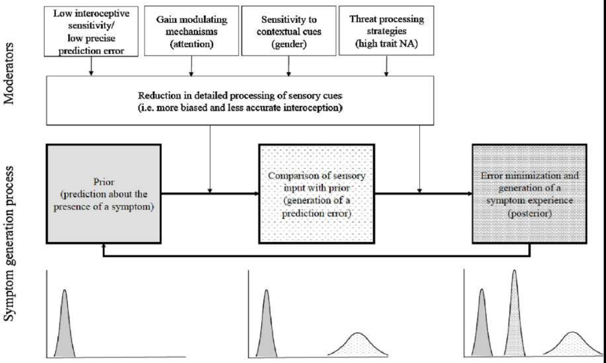


The Thatcher illusion

Interoception as an inference

- typically priors have less influence and are more subject to revision when processing involves units expecting precise information from the sensorium (e.g. vision in the light)
- conversely, priors have more of an influence on perception, and are more resistant to updating, when noisy, imprecise sensory input is expected (e.g. vision in the dark)
- thus, when inputs are predicted to be imprecise, perception may be biased towards a precise but inaccurate prior

Predictive coding approach to symptom perception



Neurobiology of interoception

- interoception is largely a construction of beliefs that are kept in check by the actual state of the body rather than vice versa.

Neurobiology of interoception

- Vagus nerve afferents major source of interoceptive information
- deliver visceral and somatic sensory information to the brain via the nucleus tractus solitarius (NTS) and ascending projections to brainstem, limbic and cortical structures

Neurobiology of interoception

Anterior insula cortex:

- central role in constructing a multimodal representation of the internal state of the body, integrating hormonal, immunological, metabolic, thermal, autonomic, visceromotor, proprioceptive, exteroceptive, motivational and cognitive sources of information
- source of visceromotor predictions and in matching prediction errors with predictions

Neurobiology of interoception

Anterior insula cortex:

- through close connections to *anterior cingulate cortex*, these multimodal representations also involve affective-motivational components and approach-avoidance tendencies
- consistent with close connection between interoceptive inference about bodily states and feelings and emotions.

Neurobiology of interoception

Other structures processing affective value of interoceptive stimuli are:

- orbitofrontal and ventromedial prefrontal cortex; together with parts of the cingulate cortex, these constitute a *stimulus valuation network* that engages behavioural control systems when physiological regulation fails (e.g. gasping for air/opening the window when breathless).

Interoception inference and symptom perception

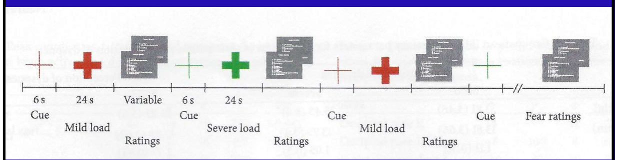
In summary:

- symptom experiences may correspond to varying degrees with peripheral somatic input
- depends on interplay between prediction errors, priors and their relative precisions
- modulated by various contextual and individual factors (see paper).

Interoception, expectations & sense of self

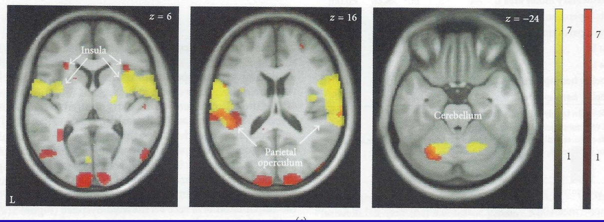
- conceptualizing interoception as inference blurs distinction between perceptions and beliefs/expectations
- indeed, same areas of brain are activated regardless of whether symptoms are produced by expectancy manipulations or elicited by peripheral stimulation

Breathless anticipation activates brain areas involved in breathlessness perception



Stoeckel MC et al., (2016)

Breathless anticipation (red) activates brain areas involved in breathlessness perception (yellow)



Anticipatory changes (right insula + ACC) correlated with levels of anticipatory fear; neural substrate for later avoidance behaviour and negative functional spiral.

Stoeckel MC et al., (2016)

Breathless anticipation reduced by opioids

- HV, similar cues prior to inspiratory loading
- saline vs. remifentanil
- opioid reduced unpleasantness but not intensity

Hayen A et al. (2017)

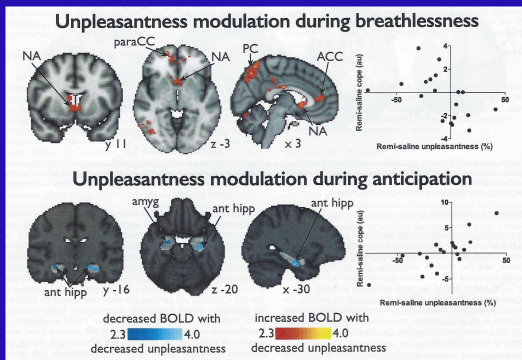
Breathless unpleasantness reduced by opioids

Reductions in unpleasantness:

- *during anticipation* correlated with reduced activity in amygdala and hippocampus
- *during breathlessness* correlated with increased activity in a network of areas including ACC and nucleus accumbens = *components of endogenous opioid system*.

Hayen A et al. (2017)

Breathless unpleasantness reduced by opioids



Hayen A et al. (2017)

Breathless unpleasantness reduced by opioids

Thus, effects of opioids, may help decrease unpleasantness of breathlessness via:

- endogenous opioid system (ACC/NA)
- interfering with neural function in brain areas that regulate emotional and memory functions related to breathlessness anticipation (amygdala/hippocampus).

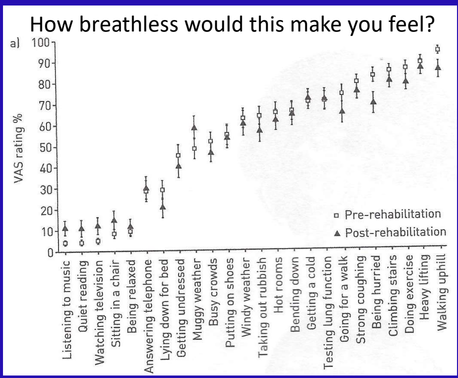
Hayen A et al. (2017)

Breathlessness ‘priors’ reduced by rehabilitation?

- patients with COPD
- underwent pulmonary rehabilitation
- fMRI before and after, exploring responses to breathlessness–related word-cue task

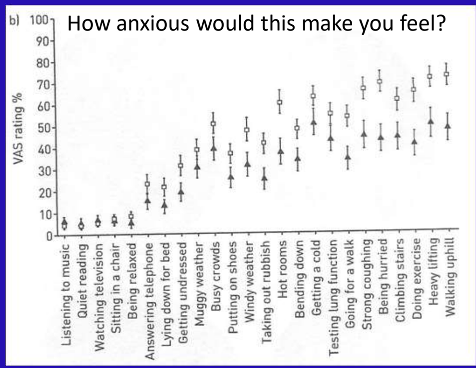
Herigstad M et al. (2017)

Rehabilitation effect on intensity



Herigstad M et al. (2017)

Rehabilitation effect on anxiety



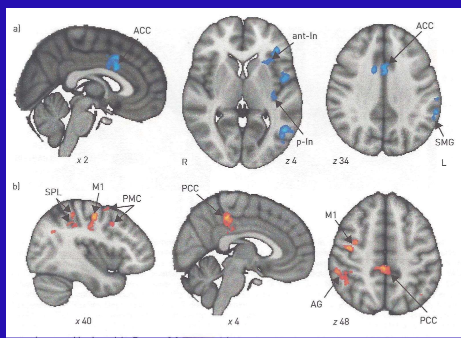
Herigstad M et al. (2017)

Brain changes with rehabilitation

- reduction in breathlessness-anxiety negatively correlated with activity in the attention regulating networks
- i.e. lower anxiety with greater activity in attention regulating networks

Herigstad M et al. (2017)

Brain changes with rehabilitation associated with reduced breathlessness intensity (a) and anxiety (b)



Herigstad M et al. (2017)

Benefit of rehabilitation

- repeated exposure to exercise/breathlessness in a ‘safe environment’
- changes associative learning; updates brain’s set of breathless related-priors
- improves objective perceptual processing
- lowers anxiety that acts as a perceptual moderator
- less dependent upon learned associations, reducing ‘over-perception’ of symptoms.

Herigstad M et al. (2017)

Conclusions

fMRI beginning to:

- identify how the brain responds to the anticipation and experience of a symptom
- identify mechanisms of benefit that will allow improved/targeted approaches

Further reading

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- Pattinson K (2015) Functional brain imaging in respiratory medicine. Thorax. 70:598-600.

Is functional MRI feasible and acceptable to people with chronic breathlessness?

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Background

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MRI and Nottingham

fMRI and breathlessness

When setting out:
- limited patient data
  - mostly healthy volunteers/experimental SOB
  - some patients with (stable) asthma
- reflects challenge of asking a breathless person to lie flat in a confined space
- also ideally want to compare conditions +/- stimulus
  - limited scope to apply exercise in a standardized way to stimulate breathlessness.

fMRI and breathlessness

- from DM work, some patients not breathless at rest, but became so on lying flat:
  - ? could this group tolerate fMRI
  - ? could lying flat alone be sufficient stimulus
- would worry about exercise issue after seeing if can/can't tolerate scanner
- thus, this feasibility study
- funded by NUH Charity pump-priming award
- National Research Ethics Service Committee East Midlands – Nottingham (15/EM/0322).

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Methods

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fMRI feasibility study

Research question
- Primary: Is functional MRI feasible and acceptable to people with chronic refractory breathlessness?
- Secondary: Are functional brain changes related to breathlessness intensity/distress in patients with chronic refractory breathlessness from various causes?

fMRI feasibility study

Recruitment:
- maximum of 12 months
- from outpatient, day care and community-based services
- adults with cancer, COPD, idiopathic pulmonary fibrosis (IPF)
- on optimal treatment, stable for the previous week
- modified MRC dyspnoea scale grade 2–4
- prognosis of ≥2 months.

The Modified Medical Research Council (MMRC) Dyspnoea Scale

Grade of dyspnoea	Description
0	Not troubled by breathlessness except on strenuous exercise
1	Shortness of breath when hurrying on the level *or* walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness *or* has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 m *or* after a few minutes on the level
4	Too breathless to leave the house *or* breathless when dressing or undressing

fMRI feasibility study

Exclusion criteria:
- contra-indication to MRI
  - claustrophobia
  - metal, e.g. pacemaker/artificial heart valve/shrapnel
  - transdermal patches/tattoos
- brain metastases
- history of significant head injury, neurosurgery or neurological disease affecting brain morphology/function, e.g. Alzheimer's disease
- psychiatric disorder requiring care of a psychiatrist or limiting ability to take part in the study

1.	Do you have any implants in your body e.g. replacement joints, drug pumps?	YES / NO
2.	Do you have a pacemaker or artificial heart valve? *(These stop working near MR Scanners)*	YES / NO
3.	Do you have aneurysm clips (clips put around blood vessels during surgery)?	YES / NO
4.	Have you ever had any surgery? Please give brief details over. (We do not need to know about uncomplicated caesarian delivery, vasectomy or termination of pregnancy)	YES / NO
5.	Do you have any foreign bodies in your body (e.g. shrapnel)?	YES / NO
6.	Have you ever worked in a machine tool shop without eye protection?	YES / NO
7.	Do you wear a hearing aid or cochlear implant?	YES / NO
8.	Have you ever suffered from tinnitus?	YES / NO
9.	Are you susceptible to claustrophobia?	YES / NO
10.	Do you suffer from blackouts, epilepsy or fits?	YES / NO
11.	Do you wear dentures, a dental plate or a brace?	YES / NO
12.	Do you have any tattoos? (If yes, you may be asked to sign another form)	YES / NO
13.	Do you have any body piercing jewellery that cannot be removed?	YES / NO

14.	Do you have any skin patches (trans-dermal patches)?	YES / NO
15.	Could you be pregnant?	YES / NO
16.	Do you have a coil in place (IUD) for contraception? Do you know what type?	YES / NO
17.	Do you have any condition that may affect your ability to control your temperature (e.g. Do you have a fever, cardiovascular disease, hypertension, diabetes or cerebrovascular disease?)	YES / NO
18.	Will you remove all metal including coins, body-piercing jewellery, false-teeth, hearing aids locker key etc before entering the magnet hall? (lockers available in changing rooms)	YES / NO
19.	Is there anything else you think we should know? If yes, give details	YES / NO

fMRI feasibility study

Exclusion criteria:
- requirement for continuous oxygen
- pain interfering with ability to lie flat
- regular use of benzodiazepines
- chest infection requiring antimicrobials in last 2 weeks.

fMRI feasibility study

- following consent and confirmation of eligibly
- completed MRI Safety Screening Questionnaire
- basic demographics, including drugs etc.
- rated breathlessness (and any pain, if present)
  - after siting resting for 5min
  - after lying flat for 20min
- used Multidimensional Dyspnea Profile (MDP)
- if able to tolerate lying flat, arrangements were made for a separate visit to the scanning department.

MULTIDIMENSIONAL DYSPNEA PROFILE
©2011 R.B.Banzett

Script for first time use:

The purpose of this questionnaire is to help us understand how your breathing feels.
There are no right or wrong answers. We want to know what you tell us about your own breathing.

On this page we ask you to tell us how unpleasant your breathing feels. On a later page we will ask you about the intensity or strength of your breathing sensations. The distinction between these two aspects of breathing sensation might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. For example, music that you hate can be unpleasant even when the volume is low, and will become more unpleasant as the volume increases; music that you like will not be unpleasant, even when the volume increases.

A1 Scale

Use this scale to rate the **unpleasantness or discomfort** of your breathing sensations, how **bad** your breathing feels **right now**

←	←	0	1	2	3	4	5	6	7	8	9	10
PLEASANT		NEUTRAL										UNBEARABLE

SQ choice

Below are phrases or terms arranged in groups of similar meaning.
Step 1: Check each group that describes how your breathing feels **right now**.
Step 2: Please also **mark *one* group** that most accurately describes how your breathing feels.

	Step 1		Step 2
If *ANY* term in the group applies, choose that group.	DOES NOT APPLY	DOES APPLY	MOST ACCURATELY DESCRIBES
My breathing requires muscle work ***or*** effort			
I am not getting enough air ***or*** I am smothering ***or*** I feel hunger for air			
My chest and lungs feel tight ***or*** constricted			
My breathing requires mental effort ***or*** concentration			
I am breathing a lot			

SQ Scales

Use these scales to rate the intensity of the breathing sensations you feel **right now** (like the loudness of sound, regardless of whether the sensation is pleasant or unpleasant; for example a sensation could be intense without being unpleasant.)

If ANY term in the group applies, rate that group.	NONE										AS INTENSE AS I CAN IMAGINE
My breathing requires muscle work ***or*** effort	0	1	2	3	4	5	6	7	8	9	10
I am not getting enough air ***or*** I am smothering ***or*** I feel hunger for air	0	1	2	3	4	5	6	7	8	9	10
My chest and lungs feel tight ***or*** constricted	0	1	2	3	4	5	6	7	8	9	10
My breathing requires mental effort ***or*** concentration	0	1	2	3	4	5	6	7	8	9	10
I am breathing a lot	0	1	2	3	4	5	6	7	8	9	10
Other*	0	1	2	3	4	5	6	7	8	9	10

*If you need to, you can add additional descriptions of your breathing sensations.

fMRI feasibility study

At scanning department:

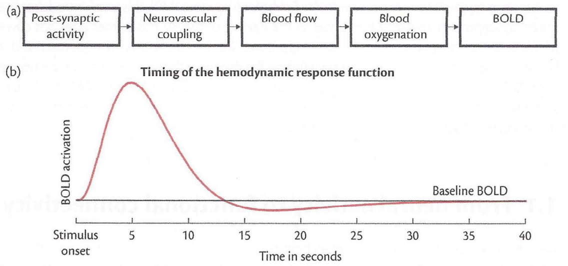
- confirmed MRI Safety Screening Questionnaire
- completed Abbreviated Mental Test Score (AMTS)
- completed Patient Health Questionnaire - somatic, anxiety, depressive symptoms (PHQ-SADS):
  - PHQ-15
  - GAD-7 (+ anxiety attacks)
  - PHQ-9
  - How difficult have these problems been?

fMRI feasibility study

Placed within scanner:

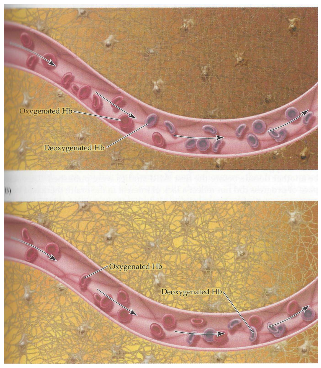
- 3T scanner + 32-channel head coil
- completed baseline MDP
- underwent single MRI scan of the brain comprising:
  - resting state functional imaging, eyes closed (BOLD)

Blood-oxygenation-level dependent (BOLD) contrast



- reflects summed inputs to a population of neurones
- an indirect, delayed and temporally imprecise measure

Blood-oxygenation-level dependent contrast



fMRI feasibility study

Placed within scanner:

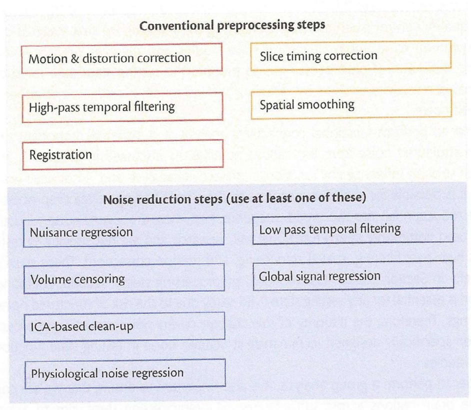
- 3T scanner + 32-channel head coil
- completed baseline MDP
- underwent single 20min MRI scan of the brain comprising:
  - resting state functional imaging, eyes closed (BOLD)
  - cerebral blood flow assessment (arterial spin labelling)
  - a high resolution anatomical scan
- repeated MDP at end of functional imaging
- asked – prepared to have a scan again?

fMRI feasibility study

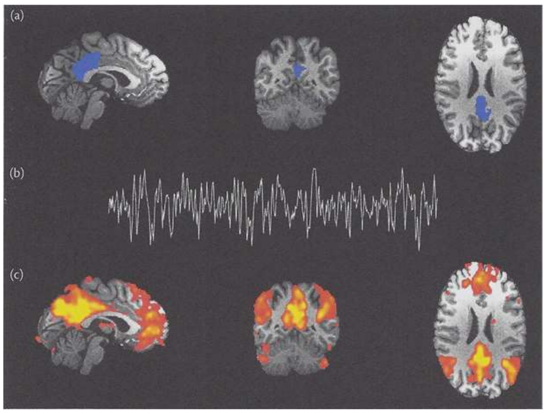
The MRI protocol consisted of resting-state fMRI (eyes-closed, TR/TE: 2000/30ms, FOV: 192mm, 37 slices of 3mm thickness, 160 volumes, matrix: 64 × 64), the pulsed-continuous ASL (pCASL) labelling with a 3D spiral read-out (Flip angle: 111°, TR/TE: 4632/10.5ms, labelling duration: 1450 ms, post-labelling duration: 1525 ms, FOV: 240 mm, 36 slices of 4mm thickness, slice gap: 4 mm, matrix: 128 × 128) and a high-resolution T1-weighted, 3D-FSPGR scan of the whole brain (Flip angle: 12°, TR/TE/TI: 9.12/3.64/450ms, FOV: 204mm, slice thickness: 1mm, matrix: 256 × 204).

Exploratory analyses

- rigorous data quality assessment
- region-of-interest analysis
  - more focused approach
- bilateral anterior insula and ACC
  - identified in previous work as important in breathlessness processing
  - 'involved in detection of personally salient internal and external stimuli to direct behaviour with the goal of maintaining homeostasis'
- compared with historical HC dataset.



Region-of-interest analysis



Region-of-interest analysis

- measure of similarity of BOLD signals between region-of-interest and other brain regions
- correlation between BOLD signals suggest a coupling of inputs to the regions
- describes relationship between regions but not directionality or anatomical connectivity.

Exploratory analysis

- CBF values of anterior insula and ACC obtained from registered CBF maps, and compared between patients and HCs, controlled for age and whole brain grey matter CBF
- bilateral anterior insula and ACC fc was examined by seed-based analysis using FEAT in FSL on pre-processed resting-state fMRI data
- voxel-based group comparison (patients vs. HCs) and correlation analysis (with A1 scores) was undertaken for bilateral anterior insula fc maps
- comparisons controlled for age and mean relative displacement
- statistical threshold set at family-wise error rate (FWE) corrected P<0.05 (Z>2.3).

Results

Aspects of feasibility
Patient demographics

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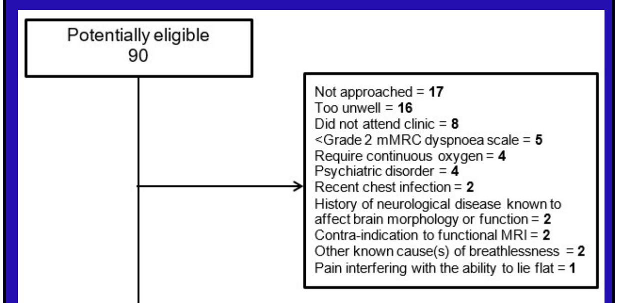
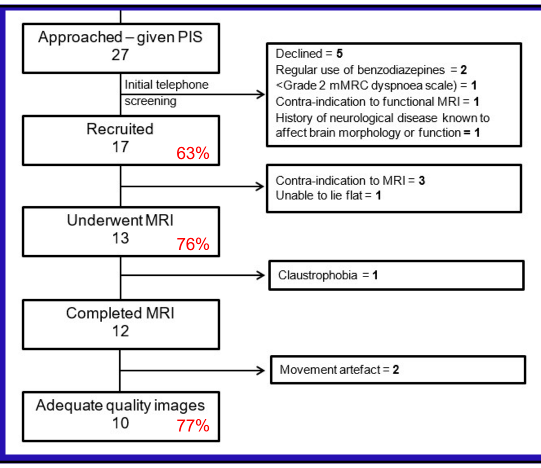
fMRI feasibility study: recruitment

Over 12 months





fMRI feasibility study

- no patients with cancer were approached or recruited:
  - generally too unwell/too unstable
- of the 13 recruited and underwent a scan:
  - 10 IPF; 3 COPD
  - 12/13 were prepared to undergo another scan

Patients providing usable data (n=10)	
Age, mean (SD)	71 (10)
Sex, male (%)	7 (70%)
IPF	7
TLco %predicted	38 (31–59)
COPD	3
GOLD Stage	3 (2); 4 (1)
mMRC score	2 (3); 3 (7)
Charlson co-morbidity score	5 (2–8)
Score <5	4
Score ≥5	6
Abbreviated Mini-mental test score	
10 (maximum)	5
9	5

Patient	*Centrally acting drugs*
1	Citalopram 20mg o.d, morphine sulfate 5mg b.d.
2	Gabapentin 600mg b.d.
6	
8	
10	Fluoxetine 10mg b.d.
11	
12	
13	
14	
15	

Patient Health Questionnaire	Number
PHQ-15 (somatic symptom severity)	
0–4 (minimal)	3
5–9 (low)	4
10–14 (medium)	3
15–30 (high)	0
PHQ-9 (depression)	
Score <8	8
Score ≥8	2
Generalized anxiety disorder-7	
Score <10	9
Score ≥10	1
PHQ - anxiety attacks in last 4 weeks	
Yes	1

PHQ: Difficulty of any problems?

In relation to work, home or getting along with others:

Not difficult at all	5
Somewhat difficult	2
Very difficult	2
Extremely difficult	1

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Results
Assessment of breathlessness

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Group A1 scores

0–10 rating of unpleasantness or discomfort of breathing sensations, how bad breathing feels right now

	Mean (SD) score
Baseline (sitting)	1.4 (1.6)
Prescan (lying)	3.1 (2.7)
Postscan (lying)	3.1 (3.0)

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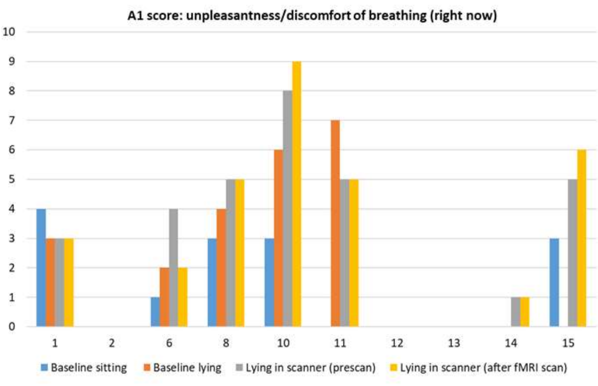

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MDP: How breathing feels

- some patients struggled to complete this, especially within scan
- variable responses even when lying within scanner over short time
- unclear what this adds over the simpler (more relevant?) unpleasantness or discomfort of how bad breathing feels?

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How breathing feels

Patient ID		Unpleasant/discomfort	Work/effort	Not enough air	Chest tight	Mental Effort	Breathing a lot
001	BL Sitting	4	3	0	6*	0	5
COPD Stage 3	BL Lying	3	6	6	5	4	6*
MRC Dyspnoea	BL in scanner	3	3	0	4	3	3
grade 3	After Fmri in scanner	3	0	4	4	0	3
002	BL Sitting	0	0	0	0	0	0
IPF	BL Lying	0	0	0	0	0	0
MRC Dyspnoea	BL in scanner	0	0	0	0	0	0
grade 3	After Fmri	0	0	0	0	0	0
006	BL Sitting	1	0	0	1	0	0
IPF	BL Lying	2	0	0	0	0	0
MRC Dyspnoea	BL in scanner	4	0	0	0	0	0
grade 2	After Fmri	2	0	0	0	0	0
008	BL Sitting	3	3	0	5	0	0
IPF	BL Lying	4	4	2	4	3	3
MRC Dyspnoea	BL in scanner	5	0	0	5*	4	0
grade 3	After Fmri	5	0	0	4	4*	0
010	BL Sitting	3	6	3*	5	3	3
COPD Stage 3	BL Lying	6	6	7	8*	6	7
MRC Dyspnoea	BL in scanner	8	7	7	8*	7	7
grade 2	After Fmri	9	9	9	8	9	8*

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How breathing feels (cond.)

Patient ID		Unpleasant/discomfort	Work/effort	Not enough air	Chest tight	Mental Effort	Breathing a lot
11	BL Sitting	0	0	0	0	0	0
IPF	BL Lying	7	6*	0	6	6	6
MRC Dyspnoea	BL in scanner	5	6*	0	0	0	0
grade 3	After Fmri	5	0	0	0	0	0
12	BL Sitting	0	0	0	0	0	0
COPD Stage 4	BL Lying	0	5*	0	0	0	0
MRC Dyspnoea	BL in scanner	0	3*	0	0	0	0
grade 3	After Fmri	0	0	0	0	0	0
13	BL Sitting	0	0	0	0	0	0
IPF	BL Lying	0	0	0	0	1*	0
MRC Dyspnoea	BL in scanner	0	0	0	0	0	0
grade 2	After Fmri	0	0	0	0	0	0
14	BL Sitting	0	0	0	0	0	0
IPF	BL Lying	0	0	0	1*	0	0
MRC Dyspnoea	BL in scanner	1	0	0	0	0	0
grade 3	After Fmri	1	0	0	0	0	0
15	BL Sitting	3	2	0	2	2*	0
IPF	BL Lying	0	0	0	0	0	0
MRC Dyspnoea	BL in scanner	5	0	0	0	6*	0
grade 3	After Fmri	6	5	0	4	5*	0

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Results

MRI findings

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Exploratory analyses

- patients cf. healthy controls:
  - historical dataset, n = 20, 11 F
  - mean (SD) age 67 (6) years
  - similar protocol on same scanner/head coil.

Exploratory analyses

Between patients and HC:

- no differences found in ACC in relation to CBF or fc
- remaining results relate to anterior insula.

Exploratory analyses

Compared to HC, patients have:

- significantly reduced cerebral blood flow of both left and right anterior insula, relative differences (Z-score):
  - -5.14 [95%CI -9.98 to -0.30]; P = 0.04
  - -5.29 [95%CI -9.77 to -0.80]; P = 0.02
- significantly reduced functional connectivity (fc) of the left and right anterior insula with multiple regions including the precuneus

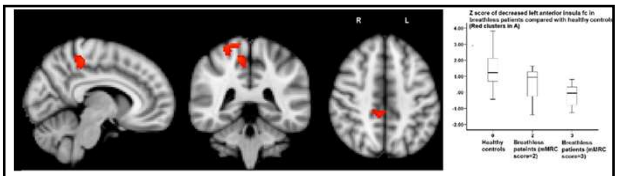


Fig 1 Decreased left anterior insula functional connectivity in breathless patients compared to healthy controls. Significant level was at FWE-corrected P<0.05

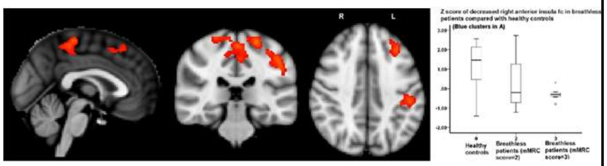
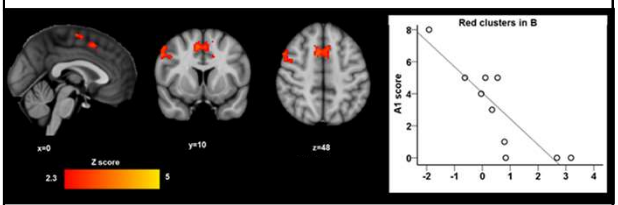


Fig 2 Decreased right anterior insula functional connectivity in breathless patients compared to healthy controls. Significant level was at FWE-corrected P<0.05.

fMRI work

In patients with chronic breathlessness:

- fc between the left anterior insula and anterior cingulate cortex was correlated with the unpleasantness/discomfort of breathing
- such that the lower the fc, the more unpleasant/uncomfortable the breathlessness.



Functional connectivity (fc) between the left anterior insula and anterior cingulate cortex (+ right pre-frontal cortex & parietal lobe) was correlated with unpleasantness/discomfort of breathlessness (A1) score, such that as fc decreased, unpleasantness increased (r=-0.813, P=0.014).

Conclusions

Conclusions: feasibility

- it can be done in IPF/COPD: reasonable rates of uptake and quality data acquisition
- lying within the scanner alone can be sufficient to produce mild-moderate levels of unpleasant breathing - scope for enriched enrollment?
- repeated use of A1 scale feasible, but not rest of MDP
- important to include psychological evaluations to aid interpretation and comparison of findings.

Conclusions: exploratory analyses

- findings preliminary, in small sample
- suggests that even at rest, in patients with chronic breathlessness:
  - anterior insula are down regulated (↓ blood flow) and disconnected (↓ fc)
  - the lower the fc between the left anterior insula and dorsal ACC, the higher the unpleasantness/discomfort of breathing
  - ? impaired top-down modulation of threat signals (e.g. through cognitive evaluation) may underlie the perceived unpleasantness/discomfort of breathing.

Next steps

- awarded Nottingham Respiratory BRC innovation funding to explore potential for development as an *imaging biomarker* of breathlessness for use in future trials
- initially to look at feasibility of inducing breathlessness through stepping exercise
- optimise protocol, and ensure the stability of findings (within day)
- initially with HC.

Ergospect Cardio Step Module

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