



Supportive care, Early Diagnosis and
Advanced disease research group

Neuro-imaging to understand refractory breathlessness

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Different perceptions

- Two people with the same patho-physiology
 - Different perceptions
 - Different restrictions
 - Different lives

Central perception – the final common pathway

- Perception of breathlessness correlates poorly to measures of lung function and respiratory physiology
- Perception modified by distraction and behavioural manipulation – eg mindfulness, music, cognitive techniques
- Response to opioids
 - Independent of cause of breathlessness

- Banzett R et al Eur Resp J 2015 *in press*
- Johnson MJ et al Eur Resp J 2013 42(3) 758-766

Model of breathlessness

- Perception intensity/quality
- Perception unpleasantness
- Emotional reaction
- Functional response
 - Immediate
 - Delayed
 - Adapt
 - Stop

Lansing RW et al. The multiple dimensions of dyspnea: Review and hypotheses. *Respiratory Physiology & Neurobiology* 167 (2009) 53–60

What do we know from neuro- imaging studies so far?

- few published full studies (only one with mild asthmatics)
- heterogeneous:
 - Imaging (fMRI, PET)
 - Stimuli (various models of induced acute breathlessness)
 - Number of participants (N, 6-14)
 - Approach to patient report data

Pattinson K, Johnson MJ Neuroimaging of central breathlessness mechanisms. Current Opinion in Supportive & Palliative Care 2104; 8: 225 - 233

What do we know?

- fMRI consistently supports model of primary sensory and a primary affective component followed by a secondary emotional response
- brain activity in the amygdala, anterior cingulate cortex and insula, associated with participant reported sensations
- “unpleasantness” (amygdala and anterior insula) can be manipulated using emotional picture viewing (Von Leupoldt et al 2008) and activity heightened in anxious individuals (Von Leupoldt et al 2011)

Herigstad et al 2011

What do we know?

- remifentanyl reduced brain responses to breath holding in the anterior cingulate, prefrontal and insular cortices
- reduction in subjective “urge to breathe” score
- opioid action on respiratory control extends beyond the brainstem (Pattinson KT, et al.. J Neurosci 2009)
- Pain studies: alfentanil has differential effects on ‘sensory’ and ‘affective’ brain regions (Oertel BG et al. Clin Pharmacol Ther 2008)

What do we know?

Emerging evidence

- 44 patients COPD, 40 matched controls
- During scanning,
 - breathlessness-related word cues
 - visual analogue scale breathlessness rating
- Controls: similar activation pattern to previous fMRI studies
- COPD: greater activation in the medial prefrontal cortex (emotion control and memory consolidation)
- Distorted processing of sensations: greater reliance on fear memories and expectations,
- Vicious cycle of avoidance and fear.

Herigstad et al Breathlessness in COPD is associated with altered cognitive processing in the medial prefrontal cortex. Abstract S116. Thorax 2013

Advantages of fMRI

- Brain activity
 - spatial location,
 - pattern
 - time-course
- does not require administration of:
 - contrast agents,
 - radiation or radioactive tracers.

How does it work?

- Localised increases in metabolic activity.
- Localised increased cerebral blood flow , cerebral blood volume and oxygen saturation
- Localised decrease in deoxyhaemoglobin concentration.
- Deoxyhaemoglobin more disruptive to the magnetic field than oxyhaemoglobin,
- Localised increase in the MR signal in the region of neural activation = blood oxygenation level dependent (BOLD) response.

How does it work?

- Experiments: blocks of 'on' periods of stimulation followed by 'off' periods of rest or a control condition,
- e.g. studies of breathing where 15-30 seconds of stimulation are followed by rest periods.

Cautions

- Due to signal drift, stimulus block duration of much longer than 1 minute can become ineffective.
- Correct for physiological noise (e.g. respiratory and cardiac motion) and head motion
- Control for changes in arterial blood gases (e.g. CO₂ and O₂) and intrathoracic pressure which may affect the BOLD response.
- Drugs and disease states may affect chemical signalling mechanisms, vascular reactivity, cerebral metabolism

Challenges

- Risk of mis/overinterpretation
- Signal drift
 - Full effect of a breathing challenge not instant (unlike a painful stimulus elicited by a laser),
 - recovery may take several minutes or longer, especially in patients
- Space
 - Claustrophobia
 - Restricted movement
 - Breathlessness induced “artificially” by manipulating blood gases or resistive load, breath-holding to produce “urge to breathe”.

Magnetoencephalography (MEG)

- method of functional brain imaging potentially tolerated more easily.
- sitting position within the scanner
- can exercise
- neuronal activity is measured directly rather than changes in blood flow in response to the activity.

What is MEG?

- Synaptic flow of neurotransmitter chemicals change the electrical current in the recipient neurone and generates small magnetic fields
- The magnetic fields pass through the skull and can be measured using electrical coils in a helmet shaped sensor holder.
- A structural MRI scan is required in order to delineate the source of the brain activity,
- a few minutes with a 3Tesla scanner

MEG appearances in breathless patients with and without air flow directed to the face.

- 4 MEG scans
 - 1) at rest (5 mins),
 - 2) during post exercise dyspnoea recovery immediately following maximally tolerated breathlessness (10 mins),and then repeat 1) and 2) after an hour
Recovery scans were conducted with or without facial cool airflow in random order.
- NRS breathlessness intensity T_b , T_{max} , T_{min}
- Structural MRI scan (2-10mins)
- Acceptability questionnaire (scans and exercise)

Johnson MJ et al BMJ Open 2015 in press

Analysis - rest

- Rest:
 - prefrontal cortex; amygdala; anterior cingulate cortex; anterior insula; post and precentral gyrus.
 - compare the activity in the patient and normal volunteers
- Recovery from exercise
 - first and last three minutes of post-exercise data were contrasted : alpha, beta, gamma frequency bands.
 - beamformer analysis was performed,
 - anatomical source limited to lobe

Results

- 7/8 patients (mean age=62;[47-83]; 4 males; median modified MRC dyspnoea scale=4) completed all scans.
- 4 - COPD, (1 also sarcoid);3 – asthma; 1 - bronchiectasis.
- 7/8 had dyspnoea for >5 years
- Maximum dyspnoea intensity was induced by 5 minutes.
- The same level was induced for repeat scans (median=8; IQR=7-8).
- All recovered to baseline by 10 minutes.
- All procedures well tolerated except 1 xMRI

results

- Differences in activity were seen: between patients/normal volunteers at rest ;
- post-exercise/on recovery for alpha, beta and gamma activity
- with/without airflow where the pattern of alpha activity in the parietal-temporal regions appeared to be reduced by the presence of airflow.

MEG is a feasible, potentially useful method to investigate chronic breathlessness, able to identify neural activity related to changes in breathlessness

Next steps

- confirm our findings
 - at rest with age-matched controls,
 - on exertion with a larger number of participants
- explore the mechanisms of interventions which may modify the perception of breathlessness
- identify those with a physiological rationale and which could be developed further as treatments

Neuroimaging in breathlessness

- Supports model of perception (intensity/unpleasantness), emotional and functional response
- Future understanding of:
 - opioidergic mechanisms
 - central processes involved with perception of and emotional response to breathlessness
 - how these may be manipulated
- Development of novel interventions

Neuroimaging in breathlessness

- For the clinical syndrome of chronic refractory breathlessness, identified central processes could be the:
 - final common pathway
 - pathophysiological marker
- Neuroimaging is an important tool to help us understand and delineate this possibility