

ONLINE SUPPLEMENT

The Effect of Pain Conditioning on Experimentally Evoked Cough: Evidence of Impaired Endogenous Inhibitory Control Mechanisms in Refractory Chronic Cough

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METHODS:

Study Questionnaires:

At the screening visit, a series of psychological questionnaires were completed by participants under guided supervision. These included:

(i) State-Trait Anxiety Index (STAI)

(ii) Hospital Anxiety and Depression Scale (HADS)

(iii) Perceived Stress Scale (PSS): validated to measure the degree to which situations are appraised as stressful and assesses recent (<1 month) stress levels.

(iv) Pain Catastrophising Scale (PCS): a validated self-report scale assessing the individual's tendency towards pain catastrophizing. Pain catastrophising has been characterized as "the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain, and by a relative inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter"[1]. Negative correlations between DNIC effect and pain catastrophising score have been shown in healthy subjects[2].

(v) Anxiety Sensitivity Index (ASI): measures the individual's fear of bodily sensations that are interpreted as having potentially harmful physical or psychological consequences.

(vi) Body Vigilance Scale (BVS): measures the tendency to attend to or focus on internal body sensations.

(vii) IBS sub-section of the ROME III questionnaire). Healthy subjects were excluded if they met the criteria for a diagnosis of IBS because DNIC are known to be impaired in IBS patients[3, 4].

(viii) Sino-nasal Outcome Test

(ix) Reflux Symptom questionnaire to determine whether they were symptomatic of reflux disease or post-nasal drip syndrome.

(x) Chronic cough patients completed a Cough-Specific Quality of Life questionnaire to indicate the degree to which the cough was impacting on quality of life, as a marker of cough severity.

RESULTS:

Psychological Questionnaires:

Compared to HC, CC patients had significantly higher hospital anxiety and depression (HAD) scores for depression ($p=0.001$) and anxiety ($p=0.002$), state anxiety ($p=0.022$), trait anxiety ($p=0.003$) and anxiety sensitivity index ($p=0.007$). However, there were no significant group differences for perceived stress ($p=0.086$), body vigilance ($p=0.057$) or pain catastrophising ($p=0.138$) despite a trend towards higher scores in CC patients (Table E1).

TABLE E1: Comparison of questionnaire scores between healthy controls and patients with chronic cough. HADS-a = Hospital Anxiety and Depression scale for anxiety, HADS-d for depression. Mean (SD)* or median (IQR)** shown.

Questionnaire	Healthy Controls (HC)	Chronic Cough (CC)	p-value
HADS-d*	1.90 (1.65)	4.9 (3.58)	0.001
HADS-a*	3.25 (3.19)	7.40 (4.42)	0.002
State anxiety**	23.00 (5.75)	28.50 (14.0)	0.022
Trait anxiety**	28.00 (6.75)	44.50 (20.75)	0.003
Perceived stress*	10.9 (6.08)	15.15 (8.86)	0.086
Body vigilance*	11.85 (6.86)	15.95 (6.31)	0.057
Pain catastrophising*	13.8 (11.26)	18.80 (9.55)	0.138
Anxiety sensitivity index**	9.50 (7.25)	18.50 (14.75)	0.007

Table E2: Changes in blood pressure and pulse rate before and after each intervention block.
Mean (SD) shown.

Intervention	Healthy Controls (HC)	Chronic cough (CC)	p-value
Change in systolic blood pressure (mmHg)			
No intervention	-3.35 (5.41)	-1.65 (5.62)	0.336
Warm water	-0.85 (3.88)	1.40 (9.27)	0.326
Cold water	2.30 (9.95)	1.20 (6.41)	0.680
Suppression	-0.85 (9.37)	-2.10 (11.37)	0.706
Change in pulse rate (beats per minute, bpm)			
No intervention	0.40 (4.12)	3.20 (8.02)	0.176
Warm water	0.40 (5.80)	1.10 (5.89)	0.707
Cold water	-0.60 (6.63)	-0.15 (6.00)	0.823
Suppression	-0.25 (5.50)	0.70 (9.34)	0.697

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