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Abstracts

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1. Effects of feedback and stimulus duration in a load discrimination task

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Resistive and elastic loads of subjectively equal magnitude presented briefly (for around 200 ms) at the onset of inspiration are discriminated from one another at chance levels (Bloch-Salisbury and Harver, 1994). In three related studies, young adults, with or without asthma, improved in their ability to discriminate between the presence or absence of added resistive loads, or between levels of added resistance, in training tasks involving feedback or fading-plus-feedback (Harver, 1994; Stout et al., 1993, 1997). In this study, the ability of subjects to distinguish between added resistive and elastic loads was evaluated prior to, and following, feedback training in a load discrimination task. Eighteen undergraduates (mean = 25.1 years) with normal lung function, seven males and 11 females, participated in a single session comprised of three experimental periods. Each period was comprised of 32 trials (16 resistive and 16 elastic in random order). In each trial, subjects judged the presence of a load added to inspiration and then decided on the type of load presented (resistive or elastic) by pressing buttons on a keyboard. Loads were presented briefly at the onset of inspiration without warning, one every

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2–5 breaths, for around either 200 or 300 ms in duration. In the first and third experimental periods subjects were not informed about the correctness of their load-type decision; in the second experimental period, feedback about correct and incorrect load-type responses was provided on a video monitor. Participants detected equivalent numbers of both resistive (61, 65, and 65% [$F(2,32) = 0.46$, $P = 0.63$]) and elastic loads (59, 62, and 58% [$F(2,32) = 0.30$, $P = 0.74$]) in the first, second, and third experimental periods. The ability of subjects to correctly distinguish the presence of a resistive load did not vary as a function of either stimulus duration [$F(1,16) = 0.99$, $P = 0.34$] or feedback [$F(2,32) = 0.84$, $P = 0.44$]. On the other hand, the ability of individuals to correctly distinguish the presence of an elastic load was reliably greater in the 300 ms condition compared to the 200 ms condition [$F(1,16) = 4.61$, $P < 0.05$]. Feedback resulted in greater improvements in the proportion of correct elastic load discriminations in the 200 ms condition compared to the 300 ms condition; the Feedback × Stimulus Duration interaction was nearly significant [$F(2,32) = 2.73$, $P = 0.08$]. We conclude that the ability of young adults to distinguish elastic loads improves when feedback for correct responses is provided in a discrimination task involving stimuli of short duration.

2. Higher centre control of breathing with particular reference to the hypothesis of Krogh and Lindhard (1913)

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The objective of this study is to review recent experimental evidence on mechanisms underlying behavioural control of breathing. The basic anatomical facts underlying such breathing control are outlined by reference to animal and human studies (both normal and pathological). The ventilatory response to exercise constitutes the main theme. Review of the famous paper by Krogh and Lindhard (The regulation of respiration and circulation during the initial stages of muscular work, J. Physiol., 47, 112–136, 1913) which produced evidence in man of the cortical activation in exercise somehow 'irradiating' other cortical or medullary centres of respiratory control, is followed by supportive evidence gained from recent imaging studies in man using positron emission tomography (PET) (Fink et al., Hyperpnoea during and immediately after exercise in man: evidence of motor cortical involvement, J. Physiol. 489, 663–675, 1995). Psycho-physiological studies on imagining exercise (while standing still and relaxed on non-moving parts of a moving treadmill) have not produced much support for the hypothesis in normal non-athletic man, but have supported the hypothesis in athletes (Decety et al., Vegetative responses during imagined movement is proportional to mental effort, Behav. Brain Res., 42, 1–5, 1991; Wuyam et al., Imagination of dynamic exercise produced ventilatory responses which were more apparent in competitive sportsmen, J. Physiol., 482, 713–723, 1995). There is evidence that imagination of the relevant exercise in athletes is used by trainers as a means of improving performance. Hypnosis has been used by some authors in the last 25 years to ascertain

whether cardio-respiratory responses occur when leg exercise is 'suggested' to a subject in a deep hypnotic state. There has been no agreement on results. Work by a group in Oxford (Paterson et al.) together with myself, has shown that consistent ventilatory increases do occur when (1) the hypnotised subject is at rest and suggestion of leg exercise is given-but there is no real increase, or (2) the hypnotised subject is doing leg exercise on a bicycle and is told that the exercise has become harder—but there is no real increase in exercise load. Suggestion that the level of exercise has been reduced—when this is has not happened—gives minimal changes in ventilation only at the onset and offset of the suggestion (Thornton et al., Ventilatory response to the imagination of exercise and altered perception of exercise load under hypnosis, Proc. Meeting of the Phys. Soc. UMDS, 6–8 November 1997). We, with the Charing Cross group are currently imaging the brain using PET to ascertain which central command areas are active. Evidence in favour of Krogh and Lindhard's hypothesis is slowly increasing. 'Central command' mechanisms are likely to be active not only at the onset of exercise but also during the exercise.

3. Resistive-load detection in children with asthma

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The present study seeks to quantify perceptual accuracy for airway changes in children with asthma through resistive-load detection. Perceptual thresholds for children with asthma are compared to data previously obtained with healthy children, and the relation of perceptual threshold to asthma morbidity is also examined. **Methods**: 103 children and adolescents with asthma (mean age = 10.8 years, range 9–15 years) participated in the study while attending summer camp. Data were previously collected from 38 healthy controls (mean age = 9.8 years). Resistive loads were presented as a percentage of the child's initial R_o, measured by forced oscillations. In the tracking procedure, an initial load approximately equal to the subject's initial R_o was presented. Subsequent loads were decreased by approximately 10% following a detection, and increased by approximately 10% following a non-detection. In the random procedure, subjects were presented with 25 resistive loads in a preset, randomly generated order. Children indicated whether or not they detected a load by pressing a button. The racking threshold was the value around which the child achieved two consecutive detections and non-detections. The random threshold was defined by regression techniques determining what load value was detected 50% of the time. **Results**: 68% of asthmatics and 69% of controls achieved a measurable threshold on the tracking procedure; 48% of the asthmatics and 62% of the controls achieved a measurable threshold on the random procedure. The average threshold, by group and protocol, is presented below:

	Asthma	Control
Tracking	63.4% of R_o	100.4% of R_o
Random	90.4% of R_o	105.7% of R_o

Intrinsic resistance was less strongly related to height for asthmatics ($r = 0.39$, $P < 0.01$) than for controls ($r = 0.82$, $P < 0.001$). Intrinsic resistance was associated with the tracking threshold for asthmatics ($r = 0.49$, $P > 0.001$), and tended to be associated for controls ($r = 0.35$, $P < 0.10$). The random threshold was strongly related to intrinsic resistance for asthmatics ($r = 0.66$, $P < 0.001$) and controls ($r = 0.81$, $P < 0.001$). Thresholds were not related to measured indices of morbidity (all rs < 0.22, ns).

Measurable thresholds for resistive-load detection were achieved in approximately two-thirds of children studied. Methodological improvements to enhance attention might increase this proportion. Thresholds for detection were related to intrinsic resistance for children with asthma and controls, suggesting larger absolute changes in airway function are needed for children with higher levels of intrinsic resistance. Further research is necessary to determine links between thresholds for detection and long-term outcomes.

4. Distinct brain regions are involved in the genesis and the modulation of perception of induced dyspnea

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Dyspnea, like pain is a complex sensory experience and frequently a distressing clinical symptom. Numerous studies have investigated putative underlying mechanisms of dyspnea, but little is known about the brain regions involved in its central processing. This study assesses brain activation associated with an important aspect of dyspnea: respiratory discomfort during loaded breathing. Respiratory discomfort was induced in eight healthy volunteers by a moderate or a high external load. Brain activation (increase in regional cerebral bloodflow, rCBF) was assessed by positron emission tomography (PET). During loaded breathing, respiratory discomfort is predominantly related to increased peak mouth pressure, an index of the respiratory motor response to the load, reflecting increased central motor command which is commonly considered as the main stimulus of respiratory discomfort. In order to distinguish brain activation related to discomfort from that of increased peak mouth pressure, we increased perceived intensities of discomfort at similar high pressure levels by concomitant menthol inhalation. We used a categorical design (subtraction of rCBF between loaded and unloaded conditions) and a parametric design (correlation between rCBF and discomfort and peak mouth pressure, respectively). The comparison high loaded vs unloaded breathing showed

a significant increase in rCBF in three discrete brain regions: the right anterior claustrum-insula, the cerebellar vermis and the left medial pons. No significant activation was detected between moderate loaded and unloaded breathing. Parametric analysis showed a significant correlation between rCBF and perceived intensity of discomfort as well as between rCBF and peak mouth pressure, in brain regions that were similar to those activated by high loaded breathing. Separate analysis of brain activation specifically associated with the part of respiratory discomfort that is unrelated to achieved peak mouth pressure, revealed an activation area in the right posterior cingulate gyrus. This study revealed two distinct patterns of brain activation. The first includes brain structures activated by both discomfort and peak mouth pressure suggesting that these areas are involved in the concomitant processing of the respiratory motor response to the load and the genesis of discomfort. The second is an integration area that may process the effect of factors e.g. emotion, that can modulate perception of discomfort at similar levels of achieved mouth pressure.

5. Recovery from prolonged voluntary overbreathing in conscious humans

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It has been suggested that prolonged hyperventilation can induce a positive feedback and a state of self-perpetuating hyperventilation after removal of the voluntary drive. To investigate this, we induced hypocapnia during an hour of voluntary overbreathing (VHV) to an end-tidal P_{CO_2} ($P_{ET}CO_2$) of about 20 mmHg in six normal subjects breathing oxygen enriched air via a mouthpiece and open circuit. We measured respiratory patterning at the beginning and end of this time, and we compared these recovery responses with the response to inhaled CO_2 studied in the same subjects. During the first 25 min of recovery, $P_{ET}CO_2$ increased to about 37 mmHg while ventilation increased from about 4.5 l/min immediately after VHV to a plateau of 7.5 l/min due to shortening ($P < 0.05$) of expiratory time and reduction of end-expiratory pauses. Mean inspiratory flow, a measure of respiratory 'drive', remained constant (NS) over this range. After 15-min break, steady state CO_2 inhalation of 0, 3, 4, and 5% of inspired CO_2 caused ventilation to increase rapidly from a resting value which was close to the final value after VHV. In summary, we were unable to confirm the clinical finding that prolonged overbreathing can induce a sustained and self-perpetuating increase in breathing. During recovery from VHV, there was no change in respiratory drive but a shortening of expiratory time. The resting set point lay at the beginning of the steep slope of the CO_2 response curve, and the $P_{ET}CO_2$ during recovery from VHV increased until it reached this point, suggesting that the central chemoreceptors provide the upper limit of the resting set point. By contrast, apart from change of expiratory time they are few reflex mechanisms to prevent $P_{ET}CO_2$ from falling below resting.

6. Transcutaneous measurement of P_{CO_2}; dynamic aspects

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Measurements of transcutaneous P_{CO_2} ($P_{tc}CO_2$) have been used in ambulatory monitoring of subjects with possible hyperventilation syndrome. This means taking measurements of $P_{tc}CO_2$ in situations that are essentially non-steady state. To our knowledge, there are no data on the dynamic properties of the $P_{tc}CO_2$ measurement system. The purpose of this study was to measure the response of the $P_{tc}CO_2$ measurement system to step changes in end-tidal P_{CO_2} ($P_{et}CO_2$) in 12 healthy subjects (six male, six female, mean age 34 years, range 21–54 years). Step-changes in $P_{et}CO_2$ of -0.5, -1, -2, and -2.5 kPa were made by instructing the subjects to hyperventilate, and giving them simultaneous visual feedback about the level of $P_{et}CO_2$. Each step was repeated, keeping the $P_{et}CO_2$ at that level for 0.5, 1, 2, and 5 min. The lagtime, between the start of change in $P_{et}CO_2$ and the beginning of the response in $P_{tc}CO_2$, ranged from 27.5 ± 8.25 to 51.6 ± 82.2 s. The response time was the time from the start of the change in $P_{tc}CO_2$ to the maximum change that was achieved, and ranged from 74.6 ± 26.1 to 274.8 ± 83.4 s. The amplitude of the change in $P_{tc}CO_2$ ranged from 0.17 ± 0.10 to 1.26 ± 0.67 kPa. Skin thickness was measured with the caliper method. No relation was found between skin thickness and any response parameter in $P_{tc}CO_2$. Nor were there any correlations between age, gender, and responses of $P_{tc}CO_2$. Movements of the arm caused substantial artifacts and changes in readings of $P_{tc}CO_2$. We conclude that measurements of $P_{tc}CO_2$ very slowly and only partially reflect changes in $P_{et}CO_2$, and thus are very difficult to use and to interpret in ambulatory measurements for investigating the hyperventilation syndrome.

7. Behavioral correlates of ventilatory conditioning to hypoxia in rats

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Breathing can be conditioned in rats by pairing hypoxia and an odor (Nsegbe et al., Behav. Neurosci., 1998, in press). The conditioned ventilatory response may be associated with defense-arousal responses to the conditioned stimulus. Because these behaviors may increase metabolism and stimulate breathing, it is important to determine whether the conditioned ventilatory response is the consequence of these changes. In this study, we performed a differential conditioning experiment in 24 rats using two odors as the conditioned stimuli (CS+ and CS−) and hypoxia (7.5% O_2) as the unconditioned stimulus. Vanillin was the CS+ and rose the CS− in half the rats, and vice versa in the other half. Twenty-six paired CS+/hypoxia trials and 26 CS− only trials were alternately performed, followed by two CS+ only and two CS− only trials to test for conditioning. Breath durations (T_{tot}) were

about 20% lower in response to CS+ compared to CS− following the odor stimulus as assessed by time by CS type interaction, $P < 0.006$). The V_t response to the CS+ was initially lower and then higher than the response to CS− (time by CS type interaction, $P < 0.013$). Mean ventilation did not display significant differences between CS+ and CS−. Sniffing, rearing, turns, and immobility in wakefulness, which characterized the orienting response were significantly more frequent in response to CS+ than to CS− ($P < 0.028$, 0.010, 0.016, 0.041 respectively). Furthermore, lying during wakefulness was less frequent in response to CS+ than to CS− at the beginning of the stimulation (P interaction < 0.003). Grooming, and behavioral sleep were not significantly different. However, the different time courses of the ventilatory variables and the observed behaviors suggested that the conditioned process elicited an immediate integrated response including a ventilatory component, but also that the conditioned ventilatory response was not uniquely determined by changes in behavior.

8. The arterial-end-tidal P_{CO_2} as a measure of P_aCO_2 in mild asthmatics

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End-tidal P_{CO_2} ($P_{ET}CO_2$) is accepted as an accurate and non-invasive measure of arterial P_{CO_2} (P_aCO_2) in normal subjects. The difference between arterial and end-tidal P_{CO_2} (a–et gradient) increases in lung disease in parallel with change in ventilation/perfusion ratio. We studied 14 subjects with mild-asthma as diagnosed by a clinical questionnaire. All subjects took no medication other than inhaled salbutamol as required, reported no history of exacerbation of their asthma requiring steroid therapy for at least 3 months prior to the study, and had lung function within the normal range (mean FEV_1 97.5, S.D. 12.4). During normal resting breathing through a mouthpiece $P_{ET}CO_2$ was measured by a computerised data acquisition programme while a blood sample was taken under local anesthetic from a radial artery over at least 30 s. There was no significant difference between mean arterial and end-tidal P_{CO_2} during the sample time. The mean a–et gradient was 0.13 mmHg (S.D. 1.74).

9. Mild asthma and hyperventilation

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It has long been known that asthma induces hyperventilation, and we have previously suggested that very mild asthma may be particularly associated with severe and clinically significant hyperventilation. To investigate this, we have studied eight normal control (group C) and 15 mild asthmatic (group A) subjects diagnosed by a clinical questionnaire. In all of group A, lung function was within

the normal predicted range (mean FEV_1 95.6% S.D. 12.9) but 11 (group AP) had a positive Pc20 to methacholine (GM 0.606 mg/ml, range 0.128–4.51 mg/ml) suggesting that they had active bronchial hyperreactivity. A radial arterial sample of blood for measurement of arterial blood gases was taken under local anaesthetic while the subject breathed quietly via a mouthpiece through a Fleisch pneumotachograph, and arterial P_{CO_2} (P_aCO_2) and respiratory pattern were compared between the two groups. In group A, P_aCO_2 (mean 36.53 mmHg, S.D. 3.59) was significantly lower than in the control group (mean 39.81 mmHg, S.D. 3.19, $P < 0.05$). There was no correlation of P_aCO_2 with any aspect of lung function (FEV_1, FEV_1/VC, PEF, T_{co}), respiratory pattern (V_t, T_i, T_e, T_t, MIF), or cell count from induced sputum (a measure of airway mucosal inflammation). However, the depression score, derived from the Beck Depression Inventory was significantly negatively correlated with P_aCO_2 in the AP group ($P = 0.027$) and a high score was associated with an increase in expiratory time ($P < 0.05$) and cycle duration T_t ($P < 0.05$). These results suggest that even in the presence of normal lung function, mild asthma is associated with hyperventilation but that this reduction in P_aCO_2 may be associated with depression rather than any aspect of lung function. We were not able to confirm that mild asthma alone is associated with hypocapnia sufficiently severe to cause clinically significant hypocapnic symptoms.

10. Respiratory correlates of treatment outcome in panic disorder

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One of the most consistently reported respiratory abnormalities in patients with panic disorder (PD) is the tendency to hyperventilate. If hyperventilation induced low end-tidal CO_2 level (ET_{CO_2}) is a state-specific phenomenon, clinical remission, regardless of the treatment modality, should normalize ET_{CO_2}. In the context of a multi-site, placebo-controlled treatment study that was designed to compare the efficacy of anti-panic medication (IMI), cognitive behavioral treatment (CBT) and the combination of the two, ET_{CO_2} was monitored with capnograph at baseline and at the end of the 12-week acute treatment period in 130 patients with panic disorder. Response to treatment (regardless of modality) was associated with significant increase in ET_{CO_2}. Only IMI treatment was significantly related to the change in ET_{CO_2}. Low ET_{CO_2} appeared to be a predictor of treatment response to IMI. All active treatments were accompanied by increased ET_{CO_2} but only the response to the combination of IMI and CBT reached significance. **Conclusion**: ET_{CO_2} is a convenient respiratory parameter that can be easily utilized to predict and monitor treatment response in at least a subgroup of patients with panic disorder.

11. Types of panic attacks: an internet survey of severity of symptoms

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The present study reports the findings of an internet survey of panic disorder sufferers (World Wide Web site devoted to self-help treatment of panic) conducted for the purposes of determining (1) which four of the 13 symptoms listed in the DSM-IV classification of panic disorder are reported to be most severe and (2) the rank order of severity (1–4) of the four symptoms reported most frequently to be most severe. Based on an analysis of reports from 126 respondents, the four symptoms most frequently reported to be most severe were (1) Cardiac complaints (palpitations, racing/pounding heart): 82/126 = 65%, (2) Dizziness (lightheaded, faint): 77/126 = 61%, (3) Dyspneic complaints: 66/126 = 52%, and (4) Fear of losing control 56/126 = 44%. Of these four symptoms, the rank order in terms of symptoms reported most frequently as most severe (i.e. the single most severe of the four symptoms reported by the 126 respondents) was (1) Dyspnea: 32/126 = 25%, (2) Cardiac: 28/126 = 22%, (3) Dizziness: 18/126 = 14%, and (4) Fear of losing control: 13/126 = 10%. Based on Ley's (1992) tripartite classification of panic attacks (Type I/Classic PA—marked by dyspnea, dyspnea suffocation fear, and sense of loss of voluntary control of breathing; Type II/Anticipatory panic attack—marked by conditioned dyspnea/suffocation fear; and Type III/Cognitive PA—marked by apprehensive anxiety and little or no physical changes), additional sorting of the 504 responses suggested two major categories of panic attacks: Dyspneic (52%) and non Dyspneic (48%). Based on symptom data alone, six subcategories of panic attacks are suggested. The data of this study are in general agreement with those of Moynihan (1996), whose findings also lend support to Ley's tripartite classification of PAs.

12. Loss of voluntary control of respiration during a dyspnea/suffocation panic attack precipitated by relaxation

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A severe adventitious dyspnea/suffocation panic attack occurred while a patient was being monitored for respiratory volume (abdominal expansion), respiratory frequency (breaths per min), respiratory effort (left trapezius and right scalene EMG), and finger temperature (middle finger of dominant hand). Comparison of measurements during the panic episode with measurements immediately prior and subsequent to the attack demonstrated clearly that the patient was essentially unable to breathe for several minutes (i.e. breathing was severely retarded to the point where the patient could not exercise voluntary control of the respiratory muscles). The panic episode, which lasted 3.5 min, included one overarching extremely slow respiratory cycle with a duration of 2 min (70 s for inspiration and 50 s for expiration). Loss of voluntary control of breathing prevented the patient

from talking during the attack; she was rendered speechless. Physiological measurements were in accord with the experimenter's observations and the patient's report subsequent to the attack. In addition to loss of control of breathing, the patient reported extreme dyspnea and dyspnea/suffocation fear that led her to believe she might die. The data of this study support Ley's dyspnea/suffocation fear theory of panic, a theory which maintains that the extreme fear which marks the classic (type I) panic attack is a consequence of uncontrollable dyspnea, as contrasted with the conditioned dyspnea/suffocation fear that marks the anticipatory (type II) panic attack, and the apprehensive anxiety that marks the cognitive (type III) panic attack. Discussion of findings suggests that the type I panic attack may be a biologically adaptive response in which breathing is temporarily retarded, thus allowing for restoration of arterial CO_2 from the severe hypocapneic level that results from prolonged excessive hyperventilation.

13. Carbon dioxide inhalation challenges in multiple chemical sensitivity

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Multiple chemical sensitivity (MCS), a condition of unknown cause, is associated with a variety of unexplained physical symptoms. The symptoms of MCS overlap considerably with those of panic disorder (PD). Individuals with MCS and PD report similar symptoms (e.g. breathing difficulties, dizziness) and tend to be intolerant of these and other uncomfortable physical sensations. Providing preliminary evidence to support a link between MCS and PD, Binkley and Kutcher (J. Allergy Clin. Immunol., 1997, 99:570) reported on five patients with MCS who experienced a panic response following intravenous sodium lactate infusion, a challenge that has been shown to trigger panic attacks in patients with PD. The present study expands on these findings with a larger sample and a less invasive panic induction challenge. Single breath 35% CO_2 inhalation has previously been demonstrated to trigger a panic attack in roughly 70% of patients with PD compared to 5% in healthy controls. We hypothesize that some individuals with symptoms to suggest MCS may exhibit features of PD in response to non-noxious environmental stimuli. The extent to which PD and MCS are related may be predictive of whether established treatments for panic are also effective for MCS. This study compared patients with symptoms to suggest MCS with healthy controls in their response to a single breath inhalation of 35% CO_2 in O_2. Subjects underwent one vital capacity inhalation of air followed by 35% CO_2 in O_2 through a one-way demand valve, separated by a 10-min resting phase. The primary outcome measure was the Diagnostic Symptom Questionnaire (DSQ) which lists the 15 DSM-IV panic attack symptoms. A panic attack was classified as (1) at least

four DSM-IV panic attack symptoms, one of which must be a cognitive symptom and (2) a sensation of panic or fear. Seventeen patients with symptoms to suggest MCS (mean age, 36.1 years) were matched by sex with 20 healthy controls (mean, 31.9 years) without evidence of MCS. No subjects had any previous psychiatric diagnoses. Fourteen of 17 (82.4%) patients with MCS fulfilled DSM-IV panic attack criteria after CO_2 compared to five of 20 (25%) of controls ($P < 0.001$, Fisher's Exact Test). This study shows that the responses of patients with symptoms to suggest MCS are comparable to those of patients with PD. This suggests that panic disorder likely accounts for at least some of the symptomatology in these patients.

14. Symptom profiles of panic attacks

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Aim: To evaluate the symptom profiles of 'naturally' occurring panic attacks compared to laboratory provoked panic attacks. Data of 101 panic disorder patients were retrospectively analysed: Sixty-seven subjects were asked to fill in auto evaluation cards, containing the 13 DSM IV symptoms of a panic attack (PA) plus a visual analog anxiety scale (VAAS) after each spontaneous PA. Each subject was given 10 cards. Sixty-one subjects underwent a laboratory 35% CO_2 challenge, resulting in a PA. The symptoms were similarly evaluated, using a panic symptom list and a VAAS. Both groups overlapped partly: 27 subjects both filled in the cards and underwent the CO_2 challenge. The percentage of subjects that reported a particular symptom in each group was compared, using a χ^2 test for each symptom. For the patients who reported more than one spontaneous PA, the first attack was used for analysis. A total of 347 spontaneous PAs were reported by 67 patients. Symptoms with highest frequency were palpitations (73%) and dizziness (71%). Shortness of breath was reported with the second lowest frequency (29%). Comparison of frequency of symptoms between spontaneous PAs ($n = 67$) and laboratory PAs ($n = 61$) showed significant differences for: shortness of breath (25% spont–85% chall, $P < 0.001$), dizziness (72–95%, $P < 0.001$), choking (39–82%, $P < 0.001$), nausea (27–47%, $P < 0.02$) and depersonalisation/derealisation (37–69%, $P < 0.001$). In the overlapping subgroup significant differences were found for the same symptoms: shortness of breath (30–89%, $P < 0.001$), dizziness (48–100%, $P < 0.025$), choking (41–85%, $P < 0.01$), nausea (18–52%, $P < 0.025$) and depersonalisation/derealisation (48–78%, $P < 0.025$). In the spontaneous PAs, the low frequency of breathlessness is striking, given the importance that is given to the respiratory aspects of panic by some. The majority of symptoms of a 'naturally' occurring PA are reliably reproduced by a laboratory PA, supporting the reliability of the 35% CO_2 method as experimental model for panic. However, respiratory symptoms are significantly more frequent in the provoked PAs, compared to the spontaneous ones. This indicates that the use of a respiratory challenge might result in overemphasis on respiratory symptoms of panic.

15. Effects of low dose cholecystokinin on respiratory function in healthy volunteers

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A high dose of cholecystokinin (CCK) causes anxiety and panic symptoms in healthy volunteers, as well as changes in respiration. The latter is probably due to stimulation of brain stem regions. Anxiety and arousal in general are also accompanied by changes in respiration. The aim of the present study was to investigate whether a low dose of CCK, sufficient to cause anxiety, would still cause changes in respiration. Sixteen healthy volunteers participated in the study. Each subject received an injection with 10 μg CCK or placebo in a double blind, random order, cross over design. Behavioral response to the challenge was assessed with a Panic Symptom List (PSL) consisting of the DSM panic symptoms, rated on a 0 to 4 scale and with a Visual Analog Anxiety Scale (VAAS). Heart rate was measured every 20 s following each injection, during 2 min. Respiratory parameters were measured throughout the experiment, via a pneumatograph. Respiratory data were analyzed by MANOVA using the average values of Tidal volume (V_t), breathing frequency (f), minute ventilation (V_E), oxygen volume (V_{O_2}) and carbon dioxide volume (V_{CO_2}), obtained during the 2-min period following the challenge; t-tests were used to evaluate heart rate and behavioral responses to the challenge, using the difference with baseline. A two-tailed significance level of $P < 0.05$ was used for all analyses. Significantly higher scores were found in both anxiety and panic symptoms after CCK, compared to placebo: for the VAAS $t = 2.155$, $P < 0.05$ and for the PSL $t = 5.775$, $P < 0.001$. Also, a significantly higher heart rate was found after CCK: $t = 5.308$, $P < 0.001$. There were no order effects. No significant effect was found for any of the respiratory parameters; f ($F = 0.05$), V_t ($F = 0.52$), V_{CO_2} ($F = 0.977$), V_{O_2} ($F = 0.000$), V_E ($F = 0.763$). At a dose sufficient to cause a rise in anxiety and autonomic symptoms as well as in heart rate, CCK has no effect on any of the respiratory parameters. It seems therefore unlikely that the panicogenic effect of CCK depends on stimulation of respiration only. Stimulation of the brain stem nuclei that control respiration may play a causal role in panic. The results from this study and the fact that panic attacks can be provoked during placebo infusions indicate however that respiratory stimulation may not be the only way panic can be provoked.

16. Is there a stronger attentional focus to internal sensations in subjects with negative affect?

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The association between negative affectivity (NA) and health complaints is thought to reflect a stronger attentional focus to bodily sensations in high NA

subjects. Using an on-line registration of attentional deployment, we tested whether high NA subjects were spending more attentional resources to internal sensations compared to external stimuli.

High and low NA subjects ($N = 64$) performed a Stroop-like primary task during a number of trials in which (1) only an internal, (2) only an external or (3) both an internal and an external stimulus could occur. Internal sensations were induced by 5.5% CO_2 (experiment 1) and 7.5% CO_2 (experiment 2) administrations, causing increases in ventilation. A decrease in the rate of presented tones served as the external stimulus. Subjects were asked to press a button when they noticed one of both events. High NA subjects tended (1) to detect internal responses to 5.5% CO_2 administrations more often, (2) to react faster to internal responses induced by 7.5% CO_2 administrations, (3) to perform poorer on the external tone task, when a respiratory challenge was expected to occur, (4) to perform slower on the Stroop task during 7.5% CO_2 inhalations. Because physiological data showed no difference between high and low NA participants as regards their reactivity to the CO_2 challenges, these findings indicate that high NA subjects have a stronger attentional bias to internal sensations.

17. Hypocapnia, hypoxia and attentional performance following voluntary hyperventilation

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In a previous study (Van Diest et al., submitted) we observed an attentional deficit during 3 min of recovery after hypocapnic, but not after normocapnic overventilation. This deficit was not due to attention disruption caused by the subjective symptoms, nor to motor decrement when performing the reaction time task. The deficit appeared specific for participants characterized by apneas (> 4 s) and a depressed ventilation, suggesting a causal role for cerebral hypoxia. In addition, the deficit increased across the 3-min recovery time. The present study investigated the role of cerebral hypoxia to explain these results. Participants ($N = 41$) performed the same attentional Stroop-like task twice following hypocapnic overventilation: once in regular room air and once in hyperoxic air. In order to trace the course of the deficit across a longer time window than in the previous study, the attentional task was performed during 6 min of recovery. An attentional deficit was expected in participants showing apneas following hypocapnic overbreathing, but only in room air and not in the hyperoxic mixture. Participants showing apneas also had decreased S_aO_2-values following hypocapnic overventilation in room air, but not in hyperoxic air. However, we failed to replicate the attentional deficit effect in participants showing apneas after room air overventilation and no difference with hyperoxic air overventilation was observed. Results relating S_aO_2-measures to performance on a within-subject basis are currently being

processed and will be presented. The role of methodological differences (e.g. longer duration of the attentional performance) between the studies will be discussed as potential causes for the failure to replicate.

18. Selective associative learning of bodily sensations in a respiratory learning paradigm: the role of affective valence

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With odors as conditioned stimuli (CSs) and 7.5% CO_2-inhalation as unconditioned stimulus (US), we previously observed a selective conditioning effect in a respiratory learning paradigm: conditioned somatic complaints and respiratory behavior only occurred with foul smelling ammonia as CS+ and not with positively smelling niaouli (Van den Bergh et al., 1997, 1998). In this study ($N = 56$), we investigated the importance of affective valence matching between the CSs and the US effects of CO_2. Niaouli and ammonia were used as CSs; inhalation of 5.5% CO_2 was used as US. The induced sensations were either labeled positively ('positive arousal') or negatively ('negative arousal'). Three CS+ and three CS− acquisition trials were run, followed by one CS+ only and a CS− test trial. Respiratory behavior was measured throughout the experiment; subjective ratings after each trial were (1) the intensity and (2) the (un)pleasantness of the experienced sensations. A selective conditioning effect to ammonia was expected with negatively labeled US-sensations and to niaouli with positively labeled US-sensations. A manipulation check showed only minimal effects of the labeling manipulation. Across labelings, however, a conditioning effect to positively valenced niaouli was observed on (un)pleasantness ratings of the sensations. Physiological responses were unaffected by the conditioning manipulation. The results suggest that the typical negative wording of symptom checklists may have obscured conditioning effects to positive odors in previous studies. The results are discussed in relation to the problem of selective learning and to Multiple Chemical Sensitivity.

19. Conditioned hyperventilation in test-anxious adults: preliminary findings

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The first experimental evidence that hyperventilation in healthy adults can be acquired as a conditioned response (CR) using a Pavlovian conditioning paradigm was reported by Ley et al. in 1996 (End-tidal CO_2 as a conditioned response in a Pavlovian conditioning paradigm, Annual meeting of the International Society for the Advancement of Respiratory Psychophysiology, ISARP, Groesbeek, The

Netherlands). Subsequent studies by Ley et al. (Sensitization control in the acquisition of a conditioned decrement in end-tidal CO_2 and preliminary findings from a differential conditioning experiment, ISARP, North Falmouth, 1997), replicated the earlier findings and offered preliminary evidence of stimulus generalization and extinction. In related concurrent research, Ley and Yelich (1998, Biol. Psychol., in press) reported a decrease in $ETCO_2$ in test-anxious adolescents under conditions of stressful testing. The present study, which is an outgrowth of the research cited above, extends the earlier conditioning findings to test-anxious adult men and women. On the assumption that test-anxious adults are acutely sensitive to the stress of mental arithmetic (counting backward by 7s) as an unconditioned stimulus (UCS), it follows that the magnitude of their unconditioned response (UCR-drop in $ETCO_2$ from baseline) should be greater than that of non test-anxious adults. If this effect obtains, then the conditioning process for high test-anxious adults should be enhanced, and the magnitude of their conditioned response (CR-drop in $ETCO_2$ from baseline) should be greater than that for non test-anxious adults. Other deductions derived from the tenability of this hypothesis regarding high test-anxious adults would include: (1) faster rate of conditioning, (2) greater resistance to extinction, (3) faster rate of re-establishment of CR, (4) broader range of stimulus generalization. In addition to $ETCO_2$, the present study monitors heart rate, electrodermal conductivity, and EMG of forearm extensor and upper trapezius muscles. Preliminary findings and their implications for generation of musculoskeletal disorders will be discussed.

20. Does parallel changes in patients' apex temperature (AT) and reported stress support the hypothesis of interactions between cerebral blood flow (CBF) behavior and appraisal of stress?

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Aim: To discuss the observed interplay between reported mental stress and AT during stress profile analysis and biofeedback sessions.

Material: Laboratory data and subject reports.

Results: Case data show that a change from positive to negative mental events in some patients results in a pronounced change in AT, e.g. in one patient a clear decrease in AT paralleled a report of a panic attack during verbal stress condition in stress profile test. In some patients there is a clear relation between parameters but in others there is not.

Discussion: When a decrease in $P_{et}CO_2$ paralleled patients' (with chronic dysfunctional breathing behavior (CDB)) report of appraised stress we observe changes in AT, mostly a decrease but not in others. Why? First, there might be more than one psychophysiological pathway—called different 'responders' by some clinicians. Second, it might be differences in threshold sensitivities. Third, it might be differences in buffering system functioning. Lastly, it might be a secondary effect,

sometimes visible. Although behavioral treatment results in increased functionality, confounding cannot be excluded. More precise knowledge is needed. Until then the hypothesis above is clinically useful as a treatment and pedagogical tool for patients fitting reported observations.