Cerebral responses to Valsalva manoeuvre consists of multiple components reflecting different aspects of autonomic function in patients suffering from chronic fatigue syndrome

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Introduction: Chronic fatigue syndrome (CFS) is associated with cognitive problems (>80%) and autonomic dysfunction (AD, >89%), where the patient shows abnormal responses to autonomic challenge such as the Valsalva manoeuvre (VM)[1]. The VM (exhaling forcefully into a closed or narrow space to a target pressure of 40 mmHg) causes transient changes in arterial blood pressure (Figure 1b) stimulating the sympathetic and parasympatheic nervous system and leads to associated changes in cerebral blood flow via autoregulation[2,3]. The root cause of CFS is unclear, whether neurological or physiological, but in other chronic diseases AD and cognitive impairment are mechanistically linked.   In this work, we conducted dual echo GE fMRI to monitor the tissue water density and cerebral oxygenation level during the VM in CFS patients, and found that the BOLD signal dynamics correlated to measures of autonomic activity.

Methods: The study was carried out on a 3T whole body system (Achieva, Philips Medical System, Netherlands). A GE dual echo EPI sequence (20 x 4mm thick slices,   TE=14/39.2 ms, TR= 2s, resolution 2.1x2.1mm^2, matrix size 112x112) was used to study 17 CFS patients. Subjects performed a 270s long fMRI paradigm (Figure 1a) consisting of 30s baseline and 4 cycles of VM (each for a 16s duration) interspersed with 44s long rest periods (fig 1a). To aid in VM performance pressure was monitored, digitised and fed-back to the subject in real time via a projection system.The fMRI data was analysed in SPM with standard preprocessing steps, and the pixel wise effective transverse relaxation rate R2* calculated. The time course of the first echo and R2* in grey and white matter were then extracted, interpolated to 0.1s resolution using SPLINE fitting and averaged across cycles in each subject. The magnitude and timing of peak first echo signal and R2* changes were extracted and compared with parameters collected from clinical autonomic testing including heart rate (HR), heart rate variability in different frequency bands, left ventricular ejection time (LVET), orthostatic grading score (OGS), baroreceptor effectiveness index (BEI) and test scores measuring cognitive failure (COGFAIL).

Results: The group averaged time course of the first echo (red) and R2* (blue) is shown in Figure 1c, with each characteristic peak marked out in sequential order. There was a significant positive correlation (Figure 2a, r = 0.85, p = 0.00062) between very low frequency heart rate variability and R2* peak 3 magnitude. Significant negative correlation (Figure 2b, r = -0.76, p = 0.0064) was also found between baroreceptor effectiveness index and R2* peak 2 time. There was a significant negative correlation (Figure 2c, r = -0.89, p = 0.00056) between cognitive failure score and first echo peak 1 time and a negative correlation (Figure 2d, r = -0.63, p = 0.0091) between orthostatic grading score and first echo peak 1 magnitude.

Discussion: It is clear that cerebral responses to autonomic challenges contains elements reflecting different aspects of the physiological challenge. The physiological responses (Figure 1b) to the VM have four phases: (I) onset of the initial strain increases intrathoracic pressure and pulmonary blood is forced into the left atrium to increase cardiac stroke volume and mean arterial blood pressure (MABP); (II) due to reduced venous return, the stroke volume decreases causing transient reduction in MABP until sympathetic activation induces vascular constriction causing MABP and heart rate to rise; (III) immediately after releasing the breathing pressure, the reduced pressure in the chest induces a reduction in stroke volume and further vascular constriction; (IV) with unimpeded venous return, cardiac output increases rapidly and rises above normal level, before returning to resting condition under sympathetic control. Since the vascular constriction and dilation are distinctively associated with each phase of the physiological responses, the vascular dilation time course allows the identification of the four phases. The vascular dilation characteristic peak is at the end of phase IV, where vascular dilation and sympathetic control reach their maximum. Since the first echo is mainly sensitive to the blood inflow and outflow, its time course represents the vascular dilation process. These results indicate that the COGFAIL and OGS score reflect the vascular dilation capability, where poorer scores are associated with reduced duration and magnitude of cerebral vascular dilation in phase I. It can also be deduced that a more effective baroreceptor is associated with a more rapid tissue oxygen intake after the VM. The precise role of very low frequency heart rate variability is still debated, although there are suggestions that it is related to hormone and body temperature regulation. Its relationship with the R2* before reaching the baseline may indicate a compensatory system in action. It is clear that different component of cerebral response to VM are associatd with different aspects of autonomic functions in CFS patients.

References: [1] Newton, J. L. et al. QJM (2007). [2] Dawson, S. L. et al. J Appl Physiol (1999). [3] Woo, M. A. et al. Congest Heart Fail (2007).

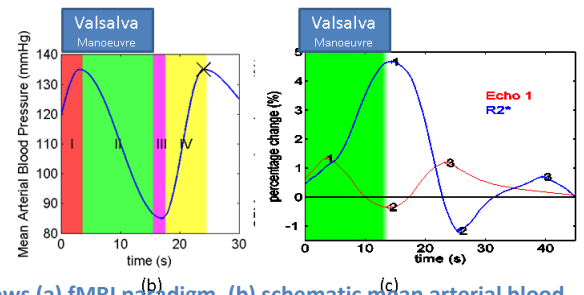fMRI paradigm: 30 s baseline and four 60 s cycles.
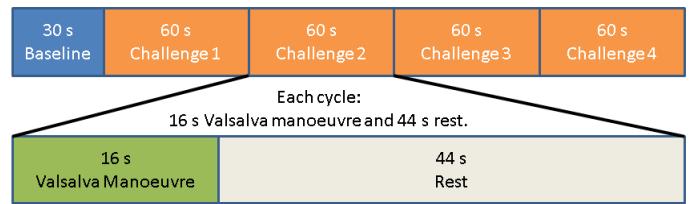
Figure 1 shows (a) fMRI paradigm, (b) schematic mean arterial blood pressure response and (c) the mean fMRI short echo and R2* time course.
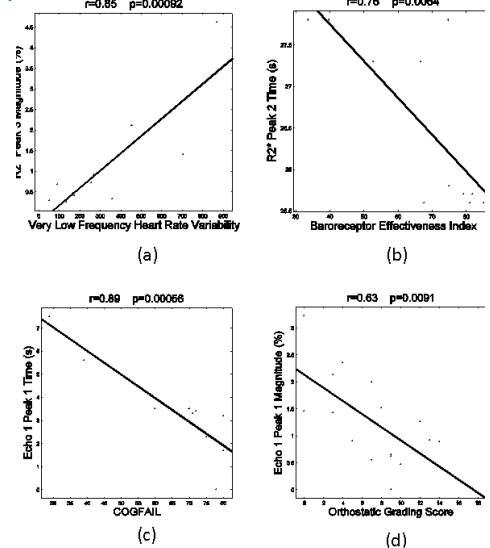

Figure 2 shows the correlations between (a) very low frequency heart rate variability and R2* peak 3 magnitude; (b) baroreceptor effective index and R2* peak 2 time: (c) cognitive failure score and first echo peak 1 time; and (d) orthostatic grading score and fi