Relationship between spontaneous fluctuations in end-tidal PCO2 and apparent resting state functional connectivity

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Introduction: There has been a growing interest in the default-mode network (DMN) of the brain, especially in patient populations where this network may be altered [1]. Concerns have been raised that some of the synchronous BOLD fluctuation attributed to the DMN may in fact be partly due to physiological processes such as respiration [2]. Variations in respiration cause fluctuations in partial pressure of end-tidal CO2 (PETCO2), which have in turn been shown to exert a significant effect on the BOLD fMRI signal [3]. Here we present data comparing resting-state correlations in the DMN, as well as task-related activations, between two conditions: 1) while controlling end-tidal PCO2 values within very narrow limits, and 2) while end-tidal PCO2 values were allowed to vary spontaneously.

Methods: Eight healthy English native speakers underwent a scanning session comprising an anatomical scan and eight BOLD acquisitions. Subjects’ PETCO2 was allowed to vary spontaneously in four BOLD acquisitions, and was tightly controlled at individual resting PETCO2 using a computer-controlled breathing system in the other four acquisitions [4]. For both breathing conditions, subjects were asked to either rest with eyes open or complete a lexical decision making task. This task required subjects to decide whether a series of letters presented on the screen formed an English word or not, during 5 blocks of 30 seconds alternated with cross fixation blocks. Physiological data including breathing depth, end-tidal PCO2 values and heart-rate were recorded during all BOLD scans. Analysis was performed using the FMRIB Software Library (FSL). Two subjects were removed from the analysis because of excessive movements or technical issues during acquisitions. Data were motion corrected and smoothed spatially with a 6mm Gaussian kernel. Motion correction parameters were regressed out from the general linear model (GLM) testing for responses to the lexical task. Mixed effect group analysis was then performed to obtain group maps of Z-score. Because of a missing task run, one subject was removed from this analysis. The conjunction of thresholded (p<0.05 corrected and Z>2.3) deactivations obtained during the lexical task in the posterior cingulate cortex (PCC) for both breathing conditions was then used to create a mask for seed based analysis of the resting runs. Regions correlating with the extracted mean signal in the PCC mask were identified after regressing out the global mean signal over the whole brain. Fixed effect analyses were also computed at subject level. Overlap and size ratios of group maps between both breathing conditions were calculated.

Results: Mean PETCO2 values were 35.3±1.6 during scans where PETCO2 were allowed to vary spontaneously and 37.8±0.9 during controlled PETCO2 scans. Task-related deactivations in regions associated with the DMN such as anterior and posterior cingulate cortex (ACC and PCC) were identified for both breathing conditions (fig. 1). The signal in regions commonly associated with the DMN correlated significantly with PCC signal time-course during resting state scans. Breathing condition did not affect DMN detection as patterns of correlated regions were found to be highly reproducible at the group level during rest (overlap and size ratios: 0.74 and 0.96) (fig. 2). Two subgroups of subjects were identified, a subgroup where PETCO2 values were very stable while breathing spontaneously (group A, three subjects, with a mean standard deviation of 0.8) and a subgroup showing a wide range of PETCO2 values (group B, three subjects, with a mean standard deviation of 2.5) (fig. 3). Task-related patterns of activation and deactivation were very reproducible in group A while group B showed more variability between both breathing conditions (fig. 4A). DMN detected for both breathing conditions during resting runs were less reproducible in group B than in group A (fig. 5B).

Conclusion: Controlling PETCO2 concentrations within very narrow limits did not affect the identification of the DMN at the group level suggesting that correlations within the DMN are not simply the result of variations in PETCO2. However, further analyses revealed that this effect may be driven by the presence of two subgroups of subjects with a different level of spontaneous PETCO2 variability. Subjects with low spontaneous PETCO2 variability showed highly reproducible patterns of activation irrespective of breathing condition, both for the task and resting runs. In the second subgroup, with more spontaneous PETCO2 variability, breathing condition affected the reproducibility of activation patterns for both task and resting runs. These tendencies reveal the importance of either controlling or accurately accounting for PETCO2 variations when quantifying the DMN in patient groups.