

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 results 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.

References: [1] Greicius, MD *et al.*, *PNAS* 101, 4637-4642 (2004); [2] Birn, RM *et al.*, *Neuroimage* 31, 1536-1548 (2006); [3] Wise, RG *et al.*, *Neuroimage* 21, 1652-1664 (2004); [4] Slessarev, M *et al.*, *J Physiol* 581(3), 1207-1219 (2007)

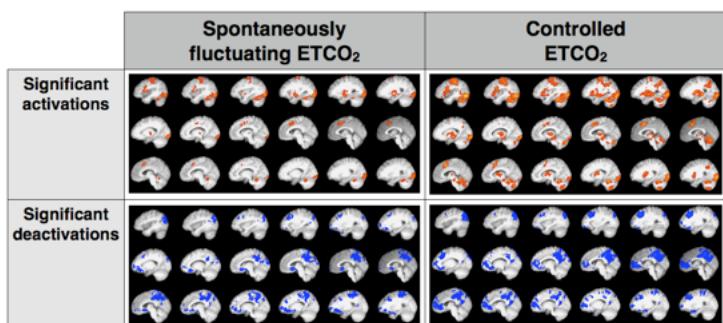


Figure 1: Significant lexical task-related group activations and deactivations for both breathing conditions. As expected, left motor and language areas were activated while subjects were performing the task and areas commonly associated with the DMN (such as ACC and PCC) were deactivated. Controlling tightly ETCO₂ values revealed larger patterns of activations and deactivations. (overlap and size ratios: 0.53 and 0.75 respectively)

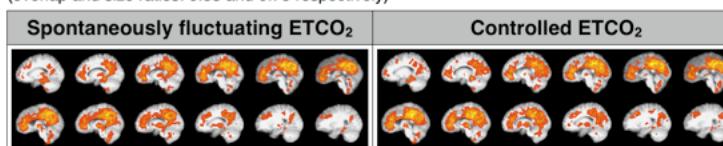


Figure 2: Regions correlating with PCC signal time-course for both breathing conditions at the group level. Regions commonly associated with the DMN such as ACC and PCC were identified using a seed based approach with the PCC as seed region for both breathing conditions. Controlling ETCO₂ did not affect DMN identification at the group level (overlap and size ratios: 0.74 and 0.96)

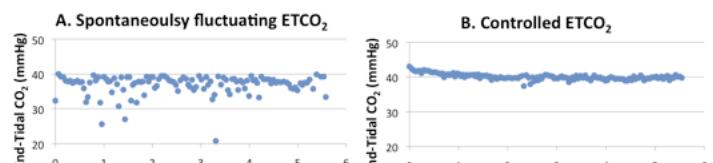


Figure 3: ETCO₂ measures recorded during both breathing conditions in a subject of the subgroup with high spontaneous variability in ETCO₂. There were more variations of ETCO₂ during acquisitions where ETCO₂ was allowed to vary spontaneously (A) than during scans where ETCO₂ was tightly controlled (B).

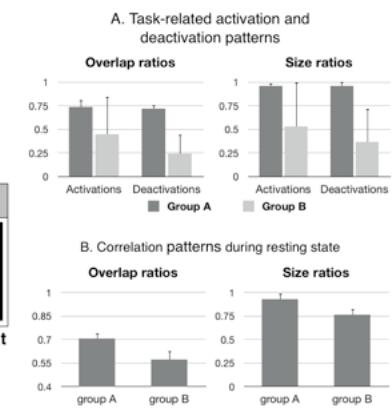


Figure 4: Overlap and size ratios between both breathing conditions at subject level.

A. Subjects with spontaneous ETCO₂ standard deviation lower than 1mmHg (group A) showed highly reproducible activation and deactivation patterns between both breathing conditions while subjects with higher spontaneous ETCO₂ fluctuations (group B) did not.

B. Same observation can be made while comparing correlation patterns with PCC signal time-course at rest.