Mapping BOLD sensitivity to CO2 in the human brainstem.

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INTRODUCTION: The aim of this study was to map BOLD reactivity to CO_2 in the human brainstem. Areas in the brainstem which are responsible for the control of breathing are known to be exquisitely sensitive to CO_2.[1] We hypothesised that these chemosensitive areas would exhibit a stronger BOLD response to CO_2 than non-chemosensitive areas, because there would be both passive vasodilatation caused by CO_2 effect on the vasculature, and a hemodynamic response to neural activation.
METHODS: 12 healthy volunteers (2 female) were examined in a Siemens Trio 3T scanner. T2* weighted gradient-echo EPI scanning was performed (TE=30 ms, TR=1000 ms, 1530 volumes, voxel size 2.5x2.5x3mm). A limited field of view comprised 16 coronal oblique slices of the brainstem. CO_2 challenges were delivered via a computer controlled gas mixing system (dynamic end tidal forcing [2]) which altered CO_2 levels dependent on the end-tidal partial pressure of CO_2 ($PETCO_2$) in the previous breath and a pre-determined model and maintained the $PETO_2$ at 200mmHg independent of changes in breathing. The CO_2 challenges aimed to raise the subject's $PETCO_2$ by either 2 or 4 mmHg from a baseline level maintained at 1mmHg above the subject's natural $PETCO_2$ level. Fig. 1 shows the recorded $PETCO_2$ in one subject. Analysis was carried out using FSL [3]. Correction for B_0 distortion was performed with FUGUE. RETROICOR [4] was used to correct for cardiac cycle and respiratory cycle related changes in BOLD signal. Voxel-wise statistical analysis was extended to a second (group) level in a mixed effects analysis using FLAME[3]. Registration to standard images was carried out with FLIRT [3], using a three stage registration procedure, making use of a single volume whole brain EPI, and a T1 structural with a brainstem weighting mask [5]. The responsiveness of BOLD signal to hypercapnia, defined as the percentage BOLD signal change per unit change in $PETCO_2$, was evaluated and compared between different areas. A region of interest analysis was performed, that compared the BOLD response to CO_2 in predefined areas (pons, medulla, thalamus, putamen, rostral ventral lateral medulla (RVLM)) and also areas identified by the voxel wise analysis to have the strongest response to CO_2 (areas in the pons and subthalamic nuclei). We estimated the time delay between the CO_2 challenge and the BOLD response, by calculating the time lag of maximal cross-correlation. To examine the magnitude (slope) of the BOLD response to CO_2, we performed a linear regression between CO_2 and BOLD at this optimal delay time. The slope of the BOLD response to CO_2 was compared between different regions of interest using repeated measures ANOVA and differences were located using Tukey's Least Significant Difference post-hoc test. *P* values of <0.05 were considered significant. Finally, the impulse response (IR) function between $PETCO_2$ and BOLD signal was calculated by expansion of the former in terms of the Laguerre basis and least-squares estimation of the expansion coefficient [6].

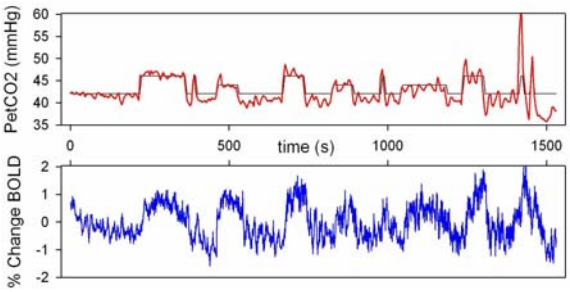

Figure 1. Changes in $PETCO_2$ in one subject (red), the model programmed into the gas control system (black) and the BOLD response to CO_2 (blue) in one region of interest (subthalamic nuclei).

RESULTS: We observed a generalised increase in BOLD signal in response to the CO_2 challenges. The voxel wise analysis (figure 2) showed most significant BOLD increase to CO_2 bilaterally in an area comprising caudal thalamus and subthalamic nuclei, in an extensive area in the pons extending from the ventral pontomedullary junction to the rostral dorsal pons, and in the rostral dorsal medulla. Region of interest analysis shows variation in BOLD signal change between the different areas (figure 3). The calculated time delays between CO_2 and BOLD, are shown in table 1. The RVLM had greater BOLD response to CO_2 than either the pons or the medulla (*P<0.01*). The IR analysis revealed similar differences between the regions of interest and is displayed in figure 4. Specifically, IR models, showed maximal values in the subthalamic and putamen (not in diagram for clarity), for which maximal IR magnitude values as well as minimal values for the time lag of its occurrence were also observed, with the latter suggesting faster dynamics for the CO_2 effects in these areas, On the other hand, the smallest mazimal IR magnitude values and slowest dynamics were observed in the medulla; however, the characteristics of the RLVM IR were different than those of the rest of the medulla.

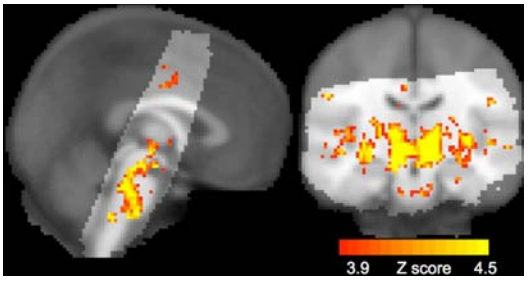

Figure 2. Group map of statistical significance of BOLD signal change per mmHg change in $PETCO_2$. Significant regions are displayed with a threshold of Z>3.9 and cluster probability threshold of P<0.05. The area scanned is shown in lighter gray scale, and superimposed on MNI standard brain (darker gray)

DISCUSION: We have mapped BOLD reactivity to CO_2 in the human brainstem. Although the pons and the medulla have lowest overall BOLD response to CO_2 we have found that the RVLM appears to have a greater response than the rest of the medulla. The RVLM is hypothesised to contain the Pre-Botzinger complex, which is considered to be the kernel of respiratory rhythm generation, and is highly chemosensitive, and therefore we would expect to see this greater response being a composite of CO_2 induced vasodilatation and the haemodynamic response to neural activation. The activation in the pons is also likely to be related to respiration. The activation in the area labelled 'subthalamic nuclei', is potentially involved with motor control of breathing, but caution must be attached to the fact that the red nuclei lie within this region of interest, these are a highly vascular and therefore the magnitude of BOLD response may also be related to the higher blood volume in these areas.

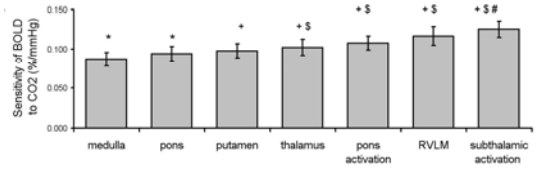

*Figure 3. Percentage BOLD signal change per mmHg change in $PETCO_2$ (±sem) obtained with cross correlation. RVLM = rostral ventral lateral medulla. * P<0.05 compared with RVLM, + medulla, $ pons, # thalamus.*

area	r^2	*delay*
medulla	0.21 (0.03)	12.5 (1.2)
pons	0.34 (0.03)	10.6 (1.1)
pons activation	0.41 (0.04)	9.9 (1.1)
RVLM	0.22 (0.05)	11.0 (0.9)
subthalamic activation	0.46 (0.04)	9.1 (1.1)
putamen	0.36 (0.04)	8.5 (1.1)
thalamus	0.48 (0.04)	9.9 (1.1)

Table 1. Regression coefficients and time delay between $PETCO_2$ change and maximum BOLD signal $PETCO_2$ (±standard error of the mean).

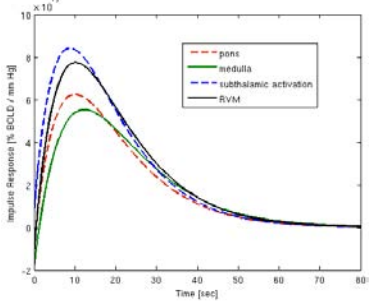

Figure 4. Averaged impulse responses between $PETCO_2$ and BOLD

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