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Hypocapnia related changes in pain-induced brain activation as measured by functional MRI

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Abstract

Stress, acute pain and chronic pain may often result in hyperventilation (HV) which produces hypocapnia. The aim of this fMRI-study was to investigate the influence of hypocapnia on cortical activation during noxious stimulation in 14 healthy volunteers. The intensity of voluntary HV was controlled by capnometry Three tasks were performed in the fMRI sessions: (I) three 3-min HV periods with 7-min periods of recovery in between; (II) mechanically induced phasic pain stimulation—pain task (PT); (III) tapping—motor task (MT). The last two of these protocols were performed under normocapnic and hypocapnic conditions. HV decreased the fMRI signal by 3–7% in all regions of the cortex and subcortical nuclei. This decrease was most prominent in the opercular, frontal and temporal areas. When the PT was performed during hypocapnia a strong reduction in cluster sizes and lower *t*-values in S1 and insular cortex were found. In contrast MT was accompanied by an increase in cluster sizes and higher *t*-values. From this we conclude that hypocapnia significantly influences the BOLD signal in nociceptive and motor systems, indicating that either the coupling between the BOLD effect and neuronal processing changed or that the activity in the cortical network which represents the pain processing is decreased. These effects should be considered for functional brain imaging studies on the nociceptive system.

Keywords: BOLD signal; Nociception; Pain; Hyperventilation; Carbon dioxide; Capnometry; Hypocapnia; Cerebral blood flow

Acute pain, stress or the combination of both may induce hyperventilation (HV) which in turn produces hypocapnia [20,21]. Hypocapnia can also often be observed in anxiety and panic disorders (e.g. hyperventilation syndrome) and chronic pain disorders (for review see [1,26]). The arterial partial pressure of carbon dioxide ($PaCO_2$) is an important regulator of the cerebral circulation, alterations in which affects CBF, and may interact with several physiologic or pathophysiologic processes in the brain. In the pathophysiology of cerebral ischemia, cluster headache and migraine the altered cerebrovascular reactivity also plays an important role [7,10]. fMRI is a tool that is widely used to detect the changes of local blood flow due to neural activation and to assess regional cerebrovascular reactivity with high spatial resolution [8,10,15,19]. The stress of the subjects in the MR scanner, especially for persons prone to anxiety, accompanied by subtle disturbances in breathing (hidden hyperventilation) leads to hypocapnia and a decrease in cerebral blood flow. This may also affect the sensitivity of functional MR imaging and thereby the ability to detect brain activation using the blood oxygenation level dependent (BOLD) effect which is sensitive to the amount of deoxyhemoglobin. Hypocapnia and respiratory alkalosis lead to a constriction of small arterial vessels (mainly at the arteriole level) and a decrease in cerebral blood flow. Oxygen consumption, however, remains at the same level. This will result in an increase in the level of paramagnetic deoxyhemoglobin and therefore a decrease in the intensity of the T_2-weighted MRI BOLD signal [16,18,25].

The aims of this study were to investigate the influence of hypocapnia on changes in regional blood flow in the brain and on possible changes in the BOLD effect during both noxious stimulation and a motor task in healthy volunteers.

Fourteen right-handed healthy subjects, eight male, mean age 29.1 ± 0.34 (S.D.) took part in this study. Before the MRI measurement subjects were familiarized with the experimental protocol, the task to perform and the types of stimuli. The study was approved by the Ethics Committee of the University. All subjects gave their informed consent to participate in the study. A state of hypocapnia was induced by voluntary hyperventilation

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feedback controlled by capnometry. HV periods were indicated to the subjects visually by a green light. Subjects were asked to increase the rate and depth of their breathing such that an end-tidal CO_2 (Pet CO_2) level of 23–28 mmHg was reached. Feedback was provided by the experimenter if the Pet CO_2 was outside this range. $PetCO_2$ was measured by infrared analysis, with the sample drawn off from a facial mask covering the mouth and nose (capnometer Invivo Research Inc., Magnitude 3150, USA). Head movements were minimized by stabilizing the subjects head with foam rubber pads.

MR imaging was performed with a 1.5 Tesla Sonata MRI scanner (Siemens, Erlangen, Germany). The first MRI session started with the MPRAGE sequence consisting of 160 saggital slices covering the brain with an in-plane resolution of 0.98 mm × 0.98 mm (field of view: 250 mm × 250 mm, data matrix: 256 × 256). Functional T2* weighted images were obtained using a multi slice echo planar imaging technique (EPI) (TR = 10000 ms during the HV experiment, TR = 3000 ms during PT and MT experiments, TE = 60 ms, flip angle −90°, matrix 64 × 64, 16 slices, slice thickness −4 mm, interslice gap-1 mm). For compensation of head movements the online motion correction option (MoCo) was used which is included in the acquisition software [24].

The first experiment was designed to examine the effect of hypocapnia on cerebral blood flow. For this three HV periods were induced, each lasting 3 min followed by a recovery period of 7 min.

Painful impact stimuli (pain task-PT) were delivered using a pneumatically driven device consisting of a guiding barrel in which a cylindrical plastic bullet, with a diameter of 5 mm and a mass of 0.5 g, was accelerated towards the back of the index finger of the right hand. This was done with a repetition rate of 1 Hz [19]. The velocity of the bullet determined the intensity of the stimulus which was adjusted to achieve a pain rating of 6 on a 10 point scale.

Tapping (motor task—MT) was performed by moving the right thumb sequentially to the opposing fingers. The subjects were instructed to do this with a frequency of about two taps per second. However, no external pace was set. Only start and end of the tapping task were indicated by a second visual command (red light).

An experimental sequence consisted of four periods of stimulation (PT) or a task (MT), respectively, each period lasted 20 s and was followed by a rest period of 20 s. This sequence was performed first during normal breathing (normocapnia) and subsequently during hyperventilation (hypocapnia). Each functional experiment started after the subject had reached a steady state baseline level Pet CO_2 (normocapnia or hypocapnia).

Data analysis was done using BrainVoyager^{TM} 2000 v.4.9.6 software. Statistical analyses were performed after applying an algorithm for spatial and temporal data correction included in the BrainVoyager software. The analysis was done with a general linear model (GLM). The factors used for the GLM were HV for the 1st protocol and stimulation or tapping, respectively, for the 2nd and 3rd protocol. The minimum cluster size for mapping of activated brain areas was set to 150 mm^3 to reject noisy isolated spots with correlation coefficients just above threshold. All individual data sets were spatially normalized according to the stereotaxic space given by Talairach and Tournoux [22] and group analysis was then performed.

For the pain study the brain regions of interest were S1, S2, insular and anterior cingulate cortex (ACC); while for MT only contralateral primary motor M_1, supplementary motor (SMA) and S1, S2, areas were analyzed. For anatomical localization of these areas Talairach Daemon was used (http://ric.uthscsa.edu/td_applet Research Imaging Center, University of Texas). A significance threshold of $p < 0.00001$ (corrected) for the mapping of activated clusters was chosen for HV data. Following previous experiences with a smaller activation during pain compared to motor tasks the statistical thresholds for mapping data were chosen as $p < 0.01$ for PT and $p < 0.0001$ for MT. The same thresholds were used during normocapnic and hypocapnic conditions. The data from subjects with head movement artifacts that could not be resolved by the motion correction were excluded from the analysis. Thus, for statistical analysis we used data from 11 subjects performing the HV task, 10 subjects in PT and 12 subjects in MT. Results are given as mean ± S.D.

Hyperventilation, PT and MT were generally well tolerated. Only one subject reported a state of discomfort and anxiety close to panic during MPRAGE. In this case the experiment was ended. During HV the $PetCO_2$ was reduced from 40.1 ± 3.5 mmHg to 24.1 ± 1.92 mmHg. After the end of the hyperventilation period $PetCO_2$ recovered to baseline within 1–3 min. During the hypocapnic periods of the 2nd and 3rd experiments the average $PetCO_2$ fell from a baseline level of 39.9 ± 3.6 mmHg to 23.7 ± 2.05 mmHg in the 2nd experiment (PT) and from 38.2 ± 3.9 to 22.3 ± 2.8 mmHg in the 3rd experiment (MT).

Hypocapnia due to voluntary HV strongly influenced regional blood flow in various areas of the brain. The grey matter BOLD signal decreased by 3–7% during the first 2 min of HV and recovered after the end of the HV as did the $PetCO_2$. The changes in BOLD signal during HV are presented in Fig. 1. The amount of BOLD signal decrease during HV was depended upon brain area. It was smallest in the thalamus (mean 1.24%; max 2%) and claustrum (mean 1.44%; max 2.45%) and showed the highest changes in frontal and opercular areas (BA 43, 44 mean 3.5%, max-7%), ACC (BA24 mean 2.5%, max 3.1%) temporal cortex (BA 42 mean 2.07%; max 3%) and insular cortex BA13 (mean 1.9%; max 2.9%). In general, white matter perfusion was influenced less than gray matter by CO_2 levels.

PT stimulation-related BOLD contrast activations during normocapnia were obtained in all regions of interest except ACC. During hypocapnia the total volume of pain-related activated clusters was only 2% of that which was obtained under normocapnia. During hypocapnia significant pain-related activations were detected only in contralateral S1 (BA 2) and insular cortex (BA 13). The localization of PT activated clusters under normocapnia and hypocapnia are presented in Fig. 2. Hypocapnia reduced the *t*-values in the PT activated clusters in S1 and the insular cortex. See Table 1.

Hypocapnia also changed cluster sizes in comparison with normocapnia during MT. In contrast to the results obtained