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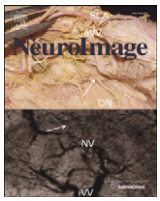

The effect of hypercapnia on resting and stimulus induced MEG signals

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ABSTRACT

The effect of hypercapnia (an increase in CO_2 concentration in the blood) on the functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) haemodynamic response has been well characterised and is commonly used for BOLD calibration. However, relatively little is known of the effect of hypercapnia on the electrical brain processes that underlie the BOLD response. Here, we investigate the effect of hypercapnia on resting and stimulus induced changes in neural oscillations using a feed-forward low gas flow system to deliver a reliable and repeatable level of hypercapnia. Magnetoencephalography (MEG) is used in conjunction with beamformer source localisation algorithms to non-invasively image changes in oscillatory amplitude. At rest, we find robust oscillatory power loss in the alpha (8 Hz–13 Hz), beta (13 Hz–30 Hz) and low gamma (30 Hz–50 Hz) frequency bands in response to hypercapnia. Further, we show that the spatial signature of this power loss differs across frequency bands, with the largest effect being observed for the beta band in sensorimotor cortices. We also measure changes in oscillatory activity induced by visual and motor events, and the effect of hypercapnia on these changes; whilst the percentage change in oscillatory activity on activation was largely unaffected by hypercapnia, the absolute change in oscillatory amplitude differed between normocapnia and hypercapnia. This work supports invasive recordings made in animals, and the results have potential implications for calibrated BOLD studies.

Introduction

Hypercapnia, an increase in CO_2 concentration in the blood, is a well characterised stimulus commonly used to investigate the nature of blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) signals. Hypercapnia is a potent vasodilator (e.g. Ito et al., 2003) which has been shown to increase the BOLD baseline signal and reduce stimulus-evoked BOLD signal changes (e.g. Cohen et al., 2002; Gauthier et al., 2010; Sicard and Duong, 2005). Posse et al. (2001) showed that the functional response to a visual stimulus decreased with both hypo and hypercapnia (20–70 mm Hg partial pressure of end tidal CO_2 ($PETCO_2$)) and that functional contrast was almost completely eliminated at 70 mm Hg $PETCO_2$. This effect has been confirmed in the motor cortex in humans (Stefanovic et al., 2006) and animals (Sicard and Duong, 2005). Cohen et al. (2002) showed that increased $PETCO_2$ lengthened the onset and the time to peak of the BOLD response. Recently Gauthier et al. (2010) showed that the BOLD response to a visual stimulus in humans can be eradicated by combined hypercapnia and hyperoxia (10% CO_2, 90% O_2 inhaled concentration). The effect of hypercapnia on CBF has been used to provide a method of normalising the BOLD signal for variations in baseline CBF (Cohen et al., 2004) and is widely used for calibrating the BOLD signal in terms of $CMRO_2$ (cerebral metabolic rate of oxygen consumption) (Ances et al., 2011; Davis et al., 1998). However, it is generally assumed that these changes in the BOLD response to hypercapnia are modulated by underlying changes in CBF, rather than being a direct result of changes in underlying neuronal activity.

In order to investigate changes in the brain's neural activity caused by hypercapnia it is necessary to directly assess the neuroelectrical response. Despite the importance of such measurements, electrical effects have not been studied widely. Zappe et al. (2008b) used direct invasive electrophysiological recordings in the visual cortex of monkeys to show that strong hypercapnia reduces local field potentials (LFP's) in the beta (13 Hz–30 Hz) and gamma (30 Hz–200 Hz) frequency range as well as multi-unit activity (MUA); oscillations in the theta and alpha frequency bands were unaffected. This study was extended to include measures of the BOLD response to visual stimulation as well as electrophysiology (Zappe et al., 2008a). A reduction in the BOLD response to visual stimulation with increasing CO_2 was found, with the BOLD response being forced negative at 6% CO_2; however the electrophysiological response to visual stimulation was unchanged. Jones et al. (2005) showed a reduction in resting state global electrical power in the barrel cortex of anesthetised rats, with no change in the response to whisker stimulation with mild hypercapnia (5% CO_2, inspired concentration) and a reduction in stimulus induced power with moderate hypercapnia (10% CO_2).

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Electroencephalography (EEG) and magnetoencephalography (MEG) are non-invasive methods to measure electrophysiological brain activity via the assessment of electrical (EEG) and magnetic (MEG) fields induced at or above the scalp surface by synchronised current flow in the brain. In recent years these non-invasive tools have been used to study neural oscillatory activity (rhythmic electrical activity in large cell assemblies) in humans, with some MEG results showing good agreement with invasive recordings of LFP's in animals (Hall et al., 2005; Zumer et al., 2010). MEG has advantages over EEG since, unlike electric fields, magnetic fields are not spatially distorted by the inhomogeneous conductivity profile in the head. This, coupled with a high number of magnetic field sensors (~300) and complex source localisation algorithms (Gross et al., 2001; Robinson and Vrba, 1998; Wipf et al., 2010; Zumer et al., 2007), provides high spatial resolution. Further, MEG has advantages over invasive measurements since, despite lower SNR and less precise localisation, it is non-invasive and provides whole brain coverage allowing spatial mapping of neuroelectrical effects. Despite these advantages, MEG has rarely been used to study the neural response to hypercapnia. Schellart and Reits (1999) investigated MEG and EEG responses to long breath holds to induce hypercapnia and hypoxia, and showed a frequency shift in the alpha band and an increase in the peak amplitude. However, changes were not statistically significant, likely to be a result of breath holding being an unreliable way of inducing repeatable and stable periods of hypercapnia. DC-MEG measurements have shown changes under respiratory challenges. Carbon et al. (2000) used hyperventilation to induce hypocapnia and showed a 1.1–6.2 pT increase in the global DC-MEG signal, however P_aCO_2 (arterial concentration of CO_2) was not recorded and P_aO_2 was not controlled, making it difficult to separate these effects. There was also large variability in the response, possibly due to the difficulty in inducing repeatable hypocapnia by hyperventilation. Blockley et al. (2008) also demonstrated a change in the MEG sustained field between controlled hypo and hypercapnia at rest. A recent study of the effect of hypercapnia on the EEG signal (Xu et al., 2011) found a global reduction in oscillatory power in the alpha band during hypercapnia compared to normocapnia. In the same study, BOLD mediated functional connectivity in the default mode network (DMN) was shown to be reduced (an effect also shown in the motor network by Biswal et al., 1997). Similarly Halpern et al. (2003) showed a reduction in alpha power, and also an increase in delta power, measured by EEG due to hypercapnia. Bloch-Salisbury et al. showed in humans that the EEG evoked response to an auditory stimulus was unaffected by $PETCO_2$ (Bloch-Salisbury et al., 2000). To date, no studies have attempted to localise changes in spontaneous neural oscillations induced by hypercapnia to specific brain regions in either EEG or MEG.

In this study we investigate the neuronal oscillatory response to controlled hypercapnia. We use a RespirAct™ system, which employs a feed-forward technique to deliver a reliable and repeatable level of $PETCO_2$ to the subject whilst maintaining oxygen levels approximately constant. We exploit the spatial accuracy of MEG by using a well characterised and robust adaptive spatial filtering beamformer approach to image the spatial signature of changes in neural oscillatory processes. This methodology is used to detect and characterise changes in neural oscillations induced by hypercapnia across a wide range of frequencies of interest. In addition, we assess the effect of hypercapnia on previously measured stimulus driven changes in neural oscillatory processes in the visual system and the motor system.

Methods

Data acquisition

Six healthy subjects (2 female, age range 24–33 years) took part in the study which was approved by the University of Nottingham Medical School Ethics Committee. All subjects gave informed, written consent.

Respiratory challenge

A RespirAct™ (*Thornhill Research Inc, Toronto, Canada*) system was used for end-tidal targeting (Slessarev et al., 2007). This is a feed-forward, low gas flow system combined with a sequential gas delivery (SGD) breathing circuit, which blends four gases (100% O_2, medical air, and two gas blends (10% O_2, 90% N_2 and 10% O_2, 20% CO_2, 70% N_2)) to achieve the targeted $PETCO_2$ and $PETO_2$. The breathing circuit includes inspiratory and exhaled gas reservoirs. Subjects were instructed to empty the inspiratory reservoir with every breath with the total gas flow being adjusted prior to the experiment to ensure subject comfort. The RespirAct™ is unaffected by changes in breathing frequency since extra gas is drawn from the exhaled reservoir when the inspiratory reservoir is empty, and the exhaled reservoir contains gas that has already equilibrated with the blood and thus has no impact on gas exchange. $PETCO_2$ has been shown to be a good measure of CO_2 concentration in arterial blood (Ito et al., 2008). The RespirAct™ measures the exhaled concentration of CO_2 and O_2, and the pressure to identify periods of inhalation and exhalation. The breathing circuit is placed over the subject's mouth and nose and fixed with Tegaderm™ (3M™, *St. Paul, MN*) to prevent leaks, and to stop subjects drawing in room air.

MEG acquisition

MEG data were acquired using the synthetic third order gradiometer configuration of a 275-channel CTF MEG system (*MISL, Port Coquitlam, BC, Canada*), at a sample rate of 600 Hz and with a 150 Hz anti-aliasing hardware filter. The scanner is housed inside a magnetically shielded room to reduce environmental magnetic interference, and gases were supplied to the subjects via a waveguide. During data acquisition the location of the subject's head within the MEG system was measured by energising electromagnetic coils placed at 3 fiducial points on the head (nasion, left preauricular and right preauricular). Prior to data acquisition, the position of these coils on the subject's head was measured using a 3D digitiser (*Polhemus isotrack*). For each subject, an MPRAGE structural image was acquired on a Philips Achieva 3 T MRI scanner (1 mm^3 isotropic resolution, $256 \times 256 \times 160$ matrix size, TE = 3.9 ms, TR = 8.3 ms, FA = 8°, TI = 960 ms, shot interval = 3 s, and SENSE factor = 3). The locations of the fiducial markers and MEG sensors with respect to the brain anatomy was determined by matching the digitised head surface to the head surface extracted from the structural MRI.

Subjects were instructed to lie supine in the MEG scanner. For each subject three experiments were performed during which $PETO_2$ was targeted to remain constant:

Experiment 1: Subjects were instructed to fixate their eyes on a dot presented on a screen located 40 cm in front of them. The gas challenge comprised an initial 2 min period of baseline (defined as each subject's resting $PETCO_2$), followed by 3 cycles of 2 min of hypercapnia ($PETCO_2$ level raised to baseline + 10 mm Hg) and 2 min of baseline. The total duration of this experiment was 14 min.

Experiment 2: Subjects fixated on the dot during a second gas challenge which comprised an initial 1 min of baseline followed by 2 cycles, each comprising 2 min of hypercapnia (baseline + 10 mm Hg) and 5 min of baseline. The total experimental duration was 15 min.

Experiment 3: Here, the gas challenge was identical to Experiment 1, but during the experiment the subject was presented with a visual stimulus and performed a motor task. The visual stimulus was a drifting sinusoidal grating (3 cycles/degree; 8 Hz drift rate; Michelson contrast of 1) presented in a circular window which