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Functional subdivision of the human periaqueductal grey in respiratory control using 7 tesla fMRI

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ABSTRACT

The periaqueductal grey (PAG) is a nucleus within the midbrain, and evidence from animal models has identified its role in many homeostatic systems including respiration. Animal models have also demonstrated a columnar structure that subdivides the PAG into four columns on each side, and these subdivisions have different functions with regard to respiration. In this study we used ultra-high field functional MRI (7 T) to image the brainstem and superior cortical areas at high resolution (1 mm^3 voxels), aiming to identify activation within the columns of the PAG associated with respiratory control. Our results showed deactivation in the lateral and dorsomedial columns of the PAG corresponding with short (~10 s) breath holds, along with cortical activations consistent with previous respiratory imaging studies. These results demonstrate the involvement of the lateral and dorsomedial PAG in the network of conscious respiratory control for the first time in humans. This study also reveals the opportunities of 7 T functional MRI for non-invasively investigating human brainstem nuclei at high-resolutions.

Introduction

The study of respiratory control is largely focused on the nuclei of the respiratory rhythm generators in the medulla, whilst suprapontine control of respiration is less well understood. The midbrain periaqueductal grey (PAG) is located at the junction of descending efferent commands and ascending sensory information, and has been suggested by animal models to participate within the localised pathway of respiratory response (Kabat et al., 1935; Subramanian, 2012; Subramanian et al., 2008). The human PAG is approximately 14 mm long and 4–5 mm wide (either side of the aqueduct), and almost completely encircles the aqueduct. The PAG has been proposed to be subdivided into four columns on each side; ventrolateral (vlPAG), lateral (lPAG), dorsolateral (dlPAG) and dorsomedial (dmPAG) (Bandler and Shipley, 1994; Dampney et al., 2013; Subramanian, 2012; Subramanian et al., 2008). Direct excitation of these columns in animals has revealed distinct respiratory functions, such as irregular breathing with the vlPAG, prolonged inspirations, expirations and vocalisations from the lPAG, active breathing and tachypnea from the dlPAG, and slow, deep breathing from the dmPAG (Subramanian, 2012; Subramanian et al., 2008).

Whilst animal models allow detailed investigation of functional neuroanatomy, subsequent studies in humans are essential to understand the role of these PAG subdivisions. Human respiratory control networks cannot be assumed to match those derived from animals. Additionally, humans allow the study of *conscious* control of breathing with the addition of subjective feedback, which is not possible in animals. Understanding these respiratory networks is imperative for effective treatment of breathing disorders, such as breathlessness from chronic obstructive pulmonary disease and heart failure (Hayen et al., 2013a; Herigstad et al., 2011), sleep disordered breathing (Morrell et al., 2000), and the dangerous respiratory depression associated with opioid painkillers (Pattinson, 2008).

Functional magnetic resonance imaging (fMRI) is a non-invasive technique that allows high-resolution functional imaging in humans (2–3 mm^3 voxels at 3 T). The recent introduction of ultra-high-field fMRI at 7 T vastly improves the signal-to-noise ratio of previous imaging, potentiating even higher resolution functional imaging (<2 mm^3) and the ability to specifically investigate small nuclei such as the subdivisions of the PAG, previously not possible at 3 T. However, 7 T imaging requires added methodological considerations during both scanning and analysis. Greater B_0 inhomogeneities at 7 T cause increased distortion and drop-out during echo-planar imaging (EPI), and increases in resolution require longer acquisition times (TR) and cause decreases in temporal signal-to-noise. Additionally, high resolution functional scanning may reveal greater structural and functional differences between individuals, amplifying the importance of image registration

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for successful group statistical analysis. Therefore, this study aimed to investigate and establish methods to image brainstem centres at 7 T.

Using MRI to investigate respiratory control presents further methodological challenges and requires additional considerations. Arterial pressure of carbon dioxide ($PaCO_2$) is a potent vasodilator of cerebral vessels, and thus changes in $PaCO_2$ often induced by respiratory challenges confound the blood oxygen level dependent (BOLD) signal (Pattinson et al., 2009a; Pattinson et al., 2009b). Additionally, bulk susceptibility variations in the lungs during the respiratory cycle cause changes in the B_0 magnetic field, producing physiological noise related to respiratory changes (Glover et al., 2000; Harvey et al., 2008; Raj et al., 2001). Finally, the location of the brainstem close to arteries and pulsating fluid-filled spaces (due to cardiac and respiratory cycles) (Brooks et al., 2013; Cohen et al., 2002) results in a particular susceptibility to physiological noise artefacts, yet it is of great importance as it houses many respiratory control centres.

In this study we used 7 T scanning to investigate the role of the subdivisions of the PAG in short respiratory tasks, taking careful consideration of respiratory imaging confounds. Based on previous work in animals, we hypothesised that BOLD signal changes within the lPAG and dmPAG (associated with prolonged expirations and depressed breathing) would be associated with the inhibitory respiratory tasks of breath holds and vocalisations, but not associated with a simple sensory and motor task.

Materials and methods

Subjects

The Oxfordshire Clinical Research Ethics Committee approved the study and volunteers gave written, informed consent. Sixteen healthy, right-handed volunteers (10 males, 6 females; mean age ± SD, 28 ± 7 years) undertook one training session, followed immediately by one MRI scanning session. One subject was excluded from the analysis due to an inability to comply with experimental protocol. Prior to scanning, all subjects were screened for any contraindications to magnetic resonance imaging at 7 T.

Breathing system

A breathing system was used to allow the administration of small CO_2 challenges mixed with room air, via a venturi entrainment system (Fig. 1a). The CO_2 challenges were administered to dissociate the changes in global BOLD signal due to changes in arterial PCO_2 from local BOLD signal changes correlating to activity associated with breath holds and vocalisations (Pattinson et al., 2009a). During scanning, medical air was administered through a loose fitting venturi mask (Ventimask, Intersurgical Ltd, Berkshire, UK) with a 1:1 entrainment ratio of compressed gas:room air. Gas was delivered to the mask at a rate of 20 L/min, and the mask was designed to entrain an equivalent amount of room air. The resulting high gas flow rate delivered by this system (40 L/min) minimises rebreathing of expired gases. The ventimask is loose fitting and therefore considerably more comfortable than a tight fitting mask, but its gas delivery characteristics allows control of end-tidal gases in the volunteer. For the CO_2 challenges during the functional scan, the medical air was substituted for a CO_2 mixture (10% CO_2, 21% O_2, balance nitrogen) at 20 L/min for periods of 10 s, the entrainment system meant that approximately 5% CO_2 was delivered to the face mask. The CO_2 challenges aimed to elevate end-tidal partial pressure of CO2 ($P_{ET}CO_2$) by approximately 0.8%, to match elevations caused by breath holds and vocalisations.

Physiological measurements

Physiological measures were recorded continuously during the training session and MRI scan. Chest movements were measured using respiratory bellows surrounding the chest at the approximate level of the 10th rib, and heart rate was measured using a pulse oximeter (9500 Multigas Monitor, MR Equipment Corp., NY, USA). The end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) was sampled via nasal cannula (Salter Labs, California, USA) and determined using a rapidly-responding gas

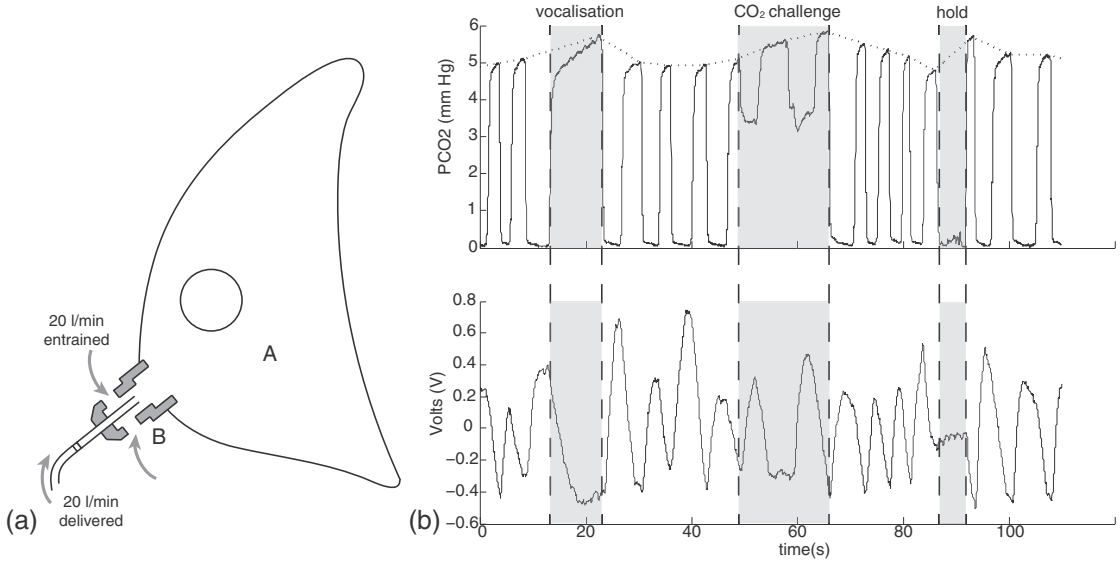

Fig. 1. a) Schematic diagram of the venturi mask used in the breathing system. A: Loose plastic venturi mask B: Venturi entrainment device (1:1). b) A section of a respiratory trace from one subject demonstrating the tidal CO_2 trace (top) and the tidal volume trace from the bellows (bottom). The end-tidal CO_2 ($P_{ET}CO_2$) trace was formed by interpolating between the end expiration peaks (dotted line, top trace). The breath hold duration was calculated from the time between the end of expiration CO_2 trace and the beginning of the subsequent expiration trace, to minimise inclusion of head movement. The vocalisation duration was calculated from the duration between the beginning and end of a vocalisation expiration trace.