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Functional magnetic resonance imaging suggests automatization of the cortical response to inspiratory threshold loading in humans

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ABSTRACT

Inspiratory threshold loading (ITL) induces cortical activation. It is sustained over time and is resistant to distraction, suggesting automaticity. We hypothesized that ITL-induced changes in cerebral activation may differ between single-breath ITL and continuous ITL, with differences resembling those observed after cortical automatization of motor tasks. We analyzed the brain blood oxygen level dependent (BOLD) signal of 11 naive healthy volunteers during 5 min of random, single-breath ITL and 5 min of continuous ITL. Single-breath ITL increased BOLD in many areas (premotor cortices, bilateral insula, cerebellum, reticular formation of the lateral mesencephalon) and decreased BOLD in regions colocalizing with the default mode network. Continuous ITL induced signal changes in a limited number of areas (supplementary motor area). These differences are comparable to those observed before and after overlearning of motor tasks. We conclude that the respiratory-related cortical activation observed in response to ITL is likely due to automated, attention-independent mechanisms. Also, ITL activates cortical circuits right from the first breath.

1. Introduction

Breathing is the only autonomic function to depend on motor control extrinsic to the concerned organ. Indeed, ventilation of the lungs is ensured by respiratory muscles innervated by spinal motoneurones relaying a motor drive to breathe that originates in the central nervous system. This organization allows for a permanent interplay between autonomic regulation of breathing (brainstem central pattern generators) and suprapontine respiratory programs producing voluntary respiratory maneuvers and speech-breathing interactions. Volitional breathing is subserved by cortical representations of respiratory muscles (Foerster, 1936; Gandevia and Rothwell, 1987; Maskill et al., 1991; Murphy et al., 1990; Similowski et al., 1996a,b) and various cortical networks (Colebatch et al., 1991; Evans et al., 1999; Fink et al., 1996; Koritnik et al., 2009; Macefield and Gandevia, 1991; McKay et al., 2003; Ramsay et al., 1993; Raux et al., 2007a; Simonyan et al., 2007; see also meta-analysis in Takai et al., 2010).

In awake humans, experimentally applied inspiratory constraints are "compensated" or "overcompensated", with maintenance or acceleration of alveolar ventilation (Pengelly et al., 1974; Yanos et al., 1990). During sleep, identical constraints produce hypoventilation (Morrell et al., 2000; Read et al., 1974; Wiegand et al., 1988). This difference between waking and sleeping suggests cortical mechanisms. Respiratory-related cortical activities are indeed observed in response to inspiratory constraints in awake humans (Gozal et al., 1995, 1996; Isaev et al., 2002; Raux et al., 2007a,b). This phenomenon is sustained over time (Tremoureux et al., 2010) and some of the observed respiratory-related

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cortical activities are resistant to distraction (Tremoureux et al., 2010). These observations are consistent with cortical automatization, the process that allows a task to be performed without requiring the subject to focus attention on the details of the corresponding motor sequence. Cortical automatization occurs in response to overlearning and is associated with pre-post differences in cortical and subcortical activations (Jansma et al., 2001; Jueptner et al., 1997a,b; Lehericy et al., 2005; Poldrack et al., 2005; Wu et al., 2004, 2008). A motor task corresponds to less intense activities after learning, than before learning in the cerebellum, presupplementary motor area, cingulate, premotor, parietal, and prefrontal cortices (Wu et al., 2004). In the basal ganglia, post-learning tasks are associated with less intense activation in the left caudate nucleus than their pre-learning counterpart and with more intense activation in the posterior putamen (Hikosaka et al., 2002; Lehericy et al., 2005). The importance of the selective attention network decreases concomitantly (Wu et al., 2008).

In the present functional magnetic imaging (fMRI) study, we hypothesized that if the respiratory-related cortical activity induced by inspiratory constraints can become automatic, then differences compatible with the learning process described above should be observed between the response to inspiratory load applied to a single breath (single-breath loading) and the response to the same load applied continuously (continuous loading). We tested this hypothesis by comparing the brain blood oxygen level dependent (BOLD) signal obtained during single-breath inspiratory loading and continuous inspiratory loading in normal volunteers. This approach is based on the pioneering work by Gozal et al. (1995) that suggested that the second presentation of a continuous inspiratory load is associated with less intense brain activity than the first presentation.

2. Materials and methods

2.1. Ethics board approval

The study complied with the standards defined in the latest revision of the Declaration of Helsinki for human research, and was fully approved by the McGill University Health Center Research Ethics Board. The subjects received detailed information about the methods used and gave their written consent to participate. However, they were initially not informed about the actual purpose of the study, but were told that they would be asked to answer questions about a movie that would be screened during MRI acquisition. They were also told that "some changes in their breathing" would be induced during the movie, but were not informed about the be two inspiratory loading paradigms (see below, Section 2.4.2) and were told that they would be asked about their respiratory sensations after the experiments (see below, Section 2.4.2). This "deception" was designed to distract the subject's attention from their breathing, according to a process commonly used in psychophysiology studies. Full explanations were provided at the end of the study, and the subjects were then given the possibility to withdraw their consent. Subjects were familiarized with the breathing apparatus outside the MRI tunnel, before starting the experiments. They were also familiarized with inspiratory threshold loading that was adjusted to induce a "mildly bothersome level of respiratory discomfort" (between 6 and 12 cm H_2O, see below, Sections 2.4.1 and 2.4.2).

2.2. Subjects

Participants were eleven healthy subjects (3 men) with a mean age of 23 years [interquartile range: 21–26], and a mean body mass index of 22 [21–23] kg m^{-2}. A screening questionnaire was used to exclude subjects with neurological, psychiatric or any other serious medical history, or presenting the usual contraindications to MRI (cardiac pacemaker, aneurysm clips, heart/vascular clips, prosthetic valves, any type of metal prosthesis, claustrophobia).

2.3. Experimental conditions

The experiments were performed in the MRI scanner, with the subject supine and their head immobilized using cushions fitted in the head coil of the scanner. Participants continuously watched a peaceful movie projected onto a screen placed at the end of the MRI tunnel using an appropriately oriented mirror. They wore headphones to ensure MRI scanning sound attenuation. An investigator checked each minute that their eyes remained open and that they had not fallen asleep. Heart rate and percutaneous oxygen saturation (SpO_2) were monitored and end-tidal carbon dioxide (CO_2) partial pressure ($PETCO_2$) was recorded.

2.4. Respiratory protocol

2.4.1. Measurements

The subjects wore a nose clip and breathed through a flanged mouthpiece and a low deadspace pneumotachograph (ref 279331, Hamilton Medical AG, Rhäzüns, Switzerland) connected to a ±2.5 cm H_2O linear differential pressure transducer (TSD 160A, Biopac System, Inc., Goleta, CA, USA) to measure ventilatory flow. The pneumotachograph was assembled in series to a medium two-way non-rebreathing valve (2600 series, Hans Rudolf, Kansas City, MO, USA). The inspiratory port of the two-way non-rebreathing valve was connected to a Y-piece. The first port of the Y-piece was connected to a threshold-loading device (Spring-to-Stretch®, Threshold Inspiratory Muscle Trainer No. 730, Health Scan, New Jersey, USA). The second port of the Y-piece was connected to a shutoff valve (9340 series, Hans Rudolf, Kansas City, MO, USA). Inflation of the shutoff valve balloon occluded the unloaded port of the Y-piece, thereby forcing the subject to breathe through the threshold-loading device during the next inspiration. The load was adjusted to induce a mildly bothersome level of respiratory discomfort (median: 10 cm H_2O, minimum: 6, maximum: 12). Expiration always remained free.

Tidal volume (V_T), respiratory frequency and ventilation (V'_E) were calculated from the integrated airflow signal. Mouth pressure (P_M) was measured from a side port of the mouthpiece, using a ±75 cm H_2O differential pressure transducer (TSD 160D, Biopac System, Inc., Goleta, CA, USA). $PETCO_2$ was measured from another side port of the mouthpiece, using an infrared CO_2 gas analyzer (Capnomac Ultima, Datex Corp., Helsinki, Finland).

The signals were digitized at 100 Hz (Biopac MP150, Biopac System, Inc., Goleta, CA, USA) and stored on a computer for subsequent analysis.

2.4.2. Experimental sequences (Fig. 1)

The study was divided into ten 5-min echo-planar image (EPI) runs, each comprising 120 scans (relaxation time = 2.5 s), segregated according to the duration of an inspiratory threshold load application, as follows.

Single-breath loading: During a first set of six 5-min "runs", threshold loading was randomly and unexpectedly applied to 25% of inspirations. The inspiratory load was applied during previous expiration so that subjects were not aware of load application and it was then maintained throughout a single breath and then removed.

Continuous loading: During a second set of four 5-min "runs", inspiration was unloaded for 1 min and inspiratory threshold loading was then applied continuously for 3 min. The load was then removed and inspiration was unloaded for one last minute.