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Inspiratory loading elicits aberrant fMRI signal changes in obstructive sleep apnea

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Abstract

We hypothesized that neural processes mediating deficient sensory and autonomic regulatory mechanisms in obstructive sleep apnea (OSA) would be revealed by responses to inspiratory loading in brain regions regulating sensory and motor control. Functional magnetic resonance imaging (fMRI) signals and physiologic changes were assessed during baseline and inspiratory loading in 7 OSA patients and 11 controls, all male and medication-free. Heart rate increases to inspiratory loading began earlier and load pressures were achieved later in OSA patients. Comparable fMRI changes emerged in multiple brain regions in both groups, including limbic, cerebellar, midbrain, and primary motor cortex. However, in OSA subjects, altered signals appeared in primary sensory thalamus and sensory cortex, supplementary motor cortex, cerebellar cortex and deep nuclei, cingulate, medial temporal, and insular cortices, right hippocampus, and midbrain. Signal delays occurred in basal ganglia. We conclude that areas mediating sensory and autonomic processes, and motor timing, are affected in OSA; many of these areas overlap regions of previously demonstrated gray matter loss.

Keywords: Cerebellum; Broca's area; Limbic; Dyspnea; Autonomic

1. Introduction

Although a number of anatomic features, such as a small upper airway, hypertrophied tonsillar or tongue structures, and obesity, characterize

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obstructive sleep apnea (OSA) patients (Bassiri and Guilleminault, 2000), several features of the syndrome suggest pathologic neural mechanisms that could maintain or worsen the condition. These features include altered responses to mechanical stimulation of the airway during waking (Kimoff et al., 2001), enhanced sympathetic tone (Somers et al., 1995), and deficient cardiovascular responses to autonomic challenges, including the Valsalva maneuver (Hanly et al., 1989; Henderson et al., 2003). These differing physiologic patterns, which appear during waking, could reflect neural dysfunctions that mediate the markedly diminished upper airway tone which occurs in OSA patients during sleep. It is unclear whether the responses to ventilatory and autonomic challenges in OSA result principally from affected peripheral structures or faulty central nervous system integration. However, the demonstration of significant gray matter loss in cerebellar, motor cortex, and autonomic control areas in OSA patients (Macey et al., 2002) suggests underlying aberrant central mechanisms, especially since some of these areas, in particular, cerebellar structures, participate in the normal mediation of loaded breathing (Xu et al., 1993a,b; Henderson et al., 2002).

Obstructive events during sleep induce large negative airway pressures; the inadequate mechanical sensory components described in patients with OSA during wakefulness may contribute to the diminished airway muscle tone found during sleep through errant sensorimotor integration to negative pressure accompanying obstructive breathing. Inspiratory loading provides a means to examine neural responses to increased negative pressure in the upper airway, and to the sequence of blood pressure changes resulting from the breathing efforts. Although the patterning of neural responses to inspiratory loading during the waking state may not directly parallel the negative pressure and cardiovascular changes associated with obstruction during sleep, anomalous responses in neural structures mediating afferent and motor components of negative pressure may provide insights into affected mechanisms in OSA.

We hypothesized that negative airway pressure stimulation of inspiratory loading and accompanying autonomic and motor patterns would reveal disparate functional magnetic resonance imaging (fMRI) signals in sensory areas mediating such stimulation, and show differing responses in motor and autonomic areas.

2. Methods

2.1. Subjects

Seven male subjects diagnosed with OSA were recruited after undergoing an overnight polysomnographic sleep study at an accredited sleep center. Twelve male control subjects were recruited from the general population and did not undergo a polysomnographic study, but, while in an MR scanner, underwent respiratory and electroencephalogram (EEG) monitoring until quiet sleep was established and absence of sleep-disordered breathing was verified. One control subject showed a mild degree of periodic breathing and was excluded, leaving 11 subjects for the study. Since cardiovascular-related medications (e.g., beta-blockers, alpha-agonists, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, cholinergic stimulating drugs), or mood-altering medications (e.g., serotonin reuptake inhibitors) could modify physiologic and neural responses, any subjects taking such medications were excluded. Subjects afflicted with syndromes that included autonomic effects (e.g., diabetes mellitus) were also disqualified. Attributes of the OSA and control groups (e.g., age, body mass index (BMI), disease severity, treatment) are shown in Table 1. The ages and BMI of OSA and control subjects were similar ($p < 0.83$ and 0.56, respectively (two-tail t-test, assuming unequal variances)). The apnea–hypopnea index (AHI) and respiratory disturbance index (RDI) (Chervin, 2005) were established during the overnight sleep study for OSA subjects. The procedures were conducted with the approval of the Institutional Review Board at the University of California, Los Angeles, and with the written informed consent of the subjects.

2.2. Data collection

Physiologic and fMRI data were collected concurrently during the challenge protocol. Subjects were monitored while lying supine and breathing through a mouthpiece for a trial. Each trial consisted of 60 s of unrestricted breathing, followed by 90 s of inspiratory loading (−6 to −15 mmHg). A 90 s duration was chosen as sufficiently long to allow respiratory and autonomic responses to develop, and sufficiently short