Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome

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Henderson, Luke A., Mary A. Woo, Paul M. Macey, Katherine E. Macey, Robert C. Fryssinger, Jeffry R. Alger, Frisca Yan-Go, and Ronald M. Harper. Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. J Appl Physiol 94: 1063–1074, 2003. First published November 1, 2002; 10.1152/japplphysiol.00702.2002.—The repetitive upper airway muscle atonic episodes and cardiovascular sequelae of obstructive sleep apnea (OSA) suggest dysfunction of specific neural sites that integrate afferent airway signals with autonomic and somatic output. We determined neural responses to the Valsalva maneuver by using functional magnetic resonance imaging. Images were collected during a baseline and three Valsalva maneuvers in 8 drug-free OSA patients and 15 controls. Multiple cortical, midbrain, pontine, and medullary regions in both groups showed intensity changes correlated to airway pressure. In OSA subjects, the left inferior parietal cortex, superior temporal gyrus, posterior insular cortex, cerebellar cortex, fastigial nucleus, and hippocampus showed attenuated signal changes compared with controls. Enhanced responses emerged in the left lateral precentral gyrus, left anterior cingulate, and superior frontal cortex of OSA patients. The anterior cingulate, cerebellar cortex, and posterior insula exhibited altered response timing patterns between control and OSA subjects. The response patterns in OSA subjects suggest deficits in particular neural pathways that normally mediate the Valsalva maneuver and compensatory actions in other structures.

functional magnetic resonance imaging; cerebellum; insula; anterior cingulate; hippocampus

PATIENTS WITH OBSTRUCTIVE SLEEP APNEA (OSA) exhibit atonia of the upper airway musculature in the presence of continued diaphragmatic efforts during sleep, resulting in cessation of airflow, enhanced venous return, and exaggerated transient rises in arterial pressure, together with a tachycardic-bradycardic sequence (44). The syndrome is associated with a cluster of anatomic features, including obesity, enhanced airway resistance, and micrognathia. However, certain characteristics of OSA suggest that central neural dysfunction, as well as body morphology, contribute to the syndrome. These neurogenic features include impaired autonomic responses to the Valsalva maneuver (48), the occasional emergence of central apnea before obstructive events (3), a propensity for the syndrome to worsen without significant weight gain or change in upper airway anatomy (36), and amelioration of the syndrome with atrial pacing, an effect presumably mediated by central integration of cardiac afferent information with respiratory control mechanisms (10).

The potential for dysfunctional brain areas in OSA patients to respond inappropriately to respiratory or cardiovascular challenges should be viewed in the context of findings of significant gray matter loss in affected patients (24). The affected brain areas included sites that serve upper airway muscle control, limbic sites involved in initiation of inspiratory effort or affective control of vocalization musculature, and cerebellar sites mediating coordination of motor and cardiovascular control. The gray matter loss may result in specific deficiencies in response to autonomic and breathing challenges, but the functional role in OSA is unknown.

The Valsalva maneuver consists of a prolonged expiratory effort against a high resistance, resulting in increased thoracic and upper airway pressure and a sequence of sympathetic and parasympathetic effects on blood pressure and heart rate that have been useful for autonomic evaluation of a range of clinical syndromes (5, 20, 28). The procedure offers a temporal assessment of participation of neural structures medi-
Neural changes in OSA during Valsalva maneuvers

Methods

Twenty-one healthy male control subjects and 21 male OSA subjects participated in the study. Subjects were subsequently excluded from the study if they were currently using cardiovascular-altering medications such as β-blockers, α-agonists, vasodilators, angiotensin-converting enzyme inhibitors, cholinergic stimulating drugs, or mood-altering medication such as serotonin reuptake inhibitors. Similarly, subjects with syndromes, other than OSA, characterized by autonomic effects (e.g., diabetes mellitus) were excluded. Any subject who did not maintain a load pressure of 30 mmHg for 15 s during the Valsalva challenges was also excluded. Of the initial 42 subjects, data from 15 control (mean age 45 ± 3 yr; range 30–58 yr) and 8 OSA subjects (mean age 44 ± 4 yr; range 31–63 yr) were used for further analysis. Data from 12 of the 15 control subjects have been reported previously (14).

The body mass index of both OSA subjects and controls was similar (controls, 31 vs. OSA, 27). Values for age, systolic, diastolic and mean blood pressure (BP), body mass index, respiratory disturbance index, disease severity [diagnosed according to standard techniques (40)], continuous positive airway pressure or mandibular prosthesis use, and time from initial diagnosis to image recording are shown in Table 1. The study was approved by the Institutional Review Board of the University of California at Los Angeles. The procedures were conducted with the understanding and written consent of the subjects.

Each subject wore nose clips and breathed through a mouthpiece during a two-way nonrebreather breathing valve (Hans Rudolph, Kansas City, MO). The ECG was measured by using standard magnetic resonance imaging-compatible surface electrodes and arterial oxygen saturation was acquired by use of a Nonin oximeter. These signals were amplified (32) and transferred externally via magnetic resonance-compatible equipment (13). End-tidal CO₂ was monitored through a cannula on the mouthpiece. Airway load pressure and thoracic wall movements were measured via tubing attached to the mouthpiece and to an air-filled bag held in place with a belt on the thoracic wall, respectively. The tubing was fed to pressure transducers external to the scanner room. Arterial pressure (AP) readings were obtained immediately before and after each scanning period. All physiological signals were acquired on digital media (Quatech, Akron, OH) with 12-bit analog-to-digital converters. Peak detection software was used to calculate heart rate (HR), respiratory rate, and mean O₂ saturation.

Three Valsalva maneuvers were performed during the challenge period. Subjects were instructed to exhale strongly into a mouthpiece for a period of 18 s, maintaining a mean

Table 1. Characteristics of control and OSA subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr</th>
<th>BP, mmHg</th>
<th>BMI</th>
<th>RDI</th>
<th>Severity</th>
<th>Treatment</th>
<th>Diagnosis to Image Recording, mo</th>
</tr>
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<tbody>
<tr>
<td>OSA 1</td>
<td>58</td>
<td>142</td>
<td>99</td>
<td>31</td>
<td>60</td>
<td>severe</td>
<td>CPAP 13</td>
</tr>
<tr>
<td>OSA 2</td>
<td>31</td>
<td>132</td>
<td>86</td>
<td>25</td>
<td>95</td>
<td>severe</td>
<td>CPAP 16</td>
</tr>
<tr>
<td>OSA 3</td>
<td>63</td>
<td>118</td>
<td>81</td>
<td>24</td>
<td>20</td>
<td>mild</td>
<td>CPAP 66</td>
</tr>
<tr>
<td>OSA 4</td>
<td>43</td>
<td>127</td>
<td>81</td>
<td>38</td>
<td>30</td>
<td>moderate-severe</td>
<td>CPAP 36</td>
</tr>
<tr>
<td>OSA 5</td>
<td>28</td>
<td>110</td>
<td>75</td>
<td>24</td>
<td>20</td>
<td>mild-moderate</td>
<td>CPAP 2</td>
</tr>
<tr>
<td>OSA 6</td>
<td>37</td>
<td>129</td>
<td>77</td>
<td>34</td>
<td>23</td>
<td>moderate-severe</td>
<td>none 1</td>
</tr>
<tr>
<td>OSA 7</td>
<td>47</td>
<td>125</td>
<td>86</td>
<td>41</td>
<td>45</td>
<td>severe</td>
<td>none 1</td>
</tr>
<tr>
<td>OSA 8</td>
<td>43</td>
<td>133</td>
<td>86</td>
<td>33</td>
<td>41</td>
<td>severe</td>
<td>none 12</td>
</tr>
<tr>
<td>Means ± SE</td>
<td>44±4</td>
<td>126±4</td>
<td>84±3</td>
<td>31±2</td>
<td>45±3</td>
<td>126±3</td>
<td>76±2</td>
</tr>
</tbody>
</table>

Age, mean systolic and diastolic blood pressures (BP), and body mass index (BMI) of control and obstructive sleep apnea (OSA) subjects and respiratory disturbance index (RDI), disease severity, treatment, and time from initial diagnosis to image recording for each OSA subject. Mean ± SE values for age, BP, BMI, and RDI are also shown. CPAP, continuous positive airway pressure.

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load pressure (LP) above 30 mmHg. Each effort was followed by an 18-s recovery period. Breathing was restricted by a flow resistor, that allowed a slow air leak, ensuring an open glottis and accurate intrathoracic pressure measures. Before the scanning period, each subject practiced this sequence a minimum of three times until the required load pressure was maintained for an 18-s period. Valsalva ratios (VR = maximum cardiac interbeat interval/minimum cardiac interbeat interval) were calculated for each maneuver for each subject and plotted against age and LP.

Images were collected with a 1.5-T magnetic resonance scanner (General Electric Signa, Milwaukee, WI). Foam pads placed on both sides of the head and masking tape, applied over the forehead to the scanner head holder, were used to minimize head movement. Gradient echo echo-planar imaging using blood oxygen level-dependent contrast was used. A time series of 25 echo-planar image volumes (repetition time = 6 s per volume, echo time = 60 ms, flip angle = 90 degrees, field of view = 30 × 30 cm, no interslice gap, voxel size = 2.3 × 2.3 × 5.0 mm thick), composed of 20 oblique sections, was acquired continuously during a 150-s period, with the first volume (10 volumes) followed by a 90-s challenge period (15 volumes). A series of T1-weighted anatomical images (repetition time = 500 ms, echo time = 9 ms, field of view = 30 × 30 cm, no interslice gap, voxel size = 1.2 × 1.6 × 5.0 mm thick) was collected at the same levels as the functional images.

In four control and five OSA subjects, replicate sessions were collected, resulting in a total of 25 individual scanning sessions for the control group and 17 for the OSA group. The first volume in each series was removed to account for signal saturation. Image volumes were then corrected for slice acquisition timing, and motion was spatially normalized to the Montreal Neurological Institute co-ordinate system, Gaussian smoothed (full-width-at-half-maximum = 8 mm) using SPM99 software (8). All image sets were then intensity normalized by use of in-house software. Multiple trials in a single subject were considered by averaging the image sets for that subject. Thus for each subject, one series of images was used for subsequent statistical analysis.

Cluster Analysis

With the use of SPM99, the intensity normalized images for each subject were analyzed with second level population effects procedures. Each subject’s time series was modeled with load pressure (convolved with the hemodynamic response function) as the independent variable. The resulting parameter values for each voxel were stored in a contrast image. A one-sample t-test was performed on the resulting contrast images to determine regions responding in a similar fashion across both groups. For presentation purposes, the resulting statistical maps were thresholded (corrected \( P < 0.01 \), color-coded for statistical significance, and overlaid onto spatially-normalized mean T1-weighted anatomical images. The statistical maps were initially overlaid onto a mean functional image set to verify the anatomical localization of the significant voxels. A two-sample t-test was performed to determine regions responding differently between the control and OSA groups. For comparisons between groups, the design comparing contrast images is less powerful, and we used less conservative uncorrected t-tests to identify the empirically derived clusters that represent areas of potential difference in the OSA population. These areas were also thresholded (uncorrected \( P < 0.05 \)) and overlaid onto a mean anatomical image set. For selected clusters, the average (±SE) signal intensities at each time point were extracted from the intensity normalized images and plotted over time by group; group differences in these time courses were confirmed using repeated measures ANOVA (RMANOVA), a method that accounts for the repeated measures across time.

Volumes of Interest Analysis

Volumes of interest (VOI), including those of known cardiorespiratory function, were selected from the functional images using anatomical landmarks, on a subject-by-subject basis. With the use of custom designed software, the average voxel intensity of the VOI in each volume was calculated from the intensity normalized images, resulting in a time trend for each subject. For both VOI and cluster time trends, signal intensity changes were calculated relative to baseline and compared between baseline and challenge periods and between groups at each time point using RMANOVA. Significance was set at \( P < 0.05 \). To examine differences in global signal intensity changes between the two groups, the mean signal intensity of each volume was calculated at each time point for each subject and then averaged for each group. Significant differences in global signal intensity between the control and OSA groups at each time point were determined using a standard t-test (\( P < 0.01 \)). VOI analysis highlighted patterns of response across entire, well-delineated structures, whereas cluster analysis distinguished responses in subregions of one or more structures.

RESULTS

Physiology

Resting BP was higher in OSA subjects compared with controls (mean BP: controls = 91 ± 3 mmHg, OSA = 102 ± 5 mmHg). During each Valsalva maneuver, control and OSA subjects exerted a similar mean LP (mean LP: control = 42 ± 1 mmHg; OSA = 41 ± 3 mmHg) (Fig. 1A). Although the initial mean HR in the OSA group was significantly higher than that of controls (mean HR: control = 64 ± 1 beats/min; OSA = 74 ± 1 beats/min; t-test, \( P < 0.01 \)), the patterns of HR responses during each Valsalva maneuver were similar. Heart rate began to increase ~7 s after onset of each effort, reaching a maximum ~3 s after completion of each Valsalva effort (mean HR max: control = 88 ± 5 beats/min; OSA = 92 ± 4 beats/min). Heart rate then declined rapidly below baseline, followed by a slow return toward baseline during the remainder of the 18 s rest period.

The VR decreased significantly with age in controls (\( r = 0.54, df = 44, P = 0.0001 \)) but not in the OSA group (\( r = 0.12, df = 23, P = 0.59 \)). Age and LP were not correlated in either control (\( r = 0.02, df = 44, P = 0.88 \)) or OSA subjects (\( r = 0.04, df = 23, P = 0.87 \)), suggesting that the decline in VR with age did not result from differences in LP (Fig. 1, B and C). The VR, however, did not show a significant group effect (mean VR: controls = 1.89 ± 0.1; OSA = 1.76 ± 0.2; t-test, \( P > 0.05 \)).

fMRI Signal Changes

The Valsalva maneuver showed very little stimulus-related head motion. In no subject was there any head movement greater than 1.5 mm in the x, y, or z direct-
tion, or rotation of >1°. Although in most subjects head movement was greater during the challenge, it did not appear to be directly correlated to the onset or completion of each Valsalva maneuver.

**Comparable Control and OSA Patterns**

The cluster analysis highlighted a number of brain sites that exhibited similar patterns of response in both control and OSA groups. Two regions within the cerebral cortex exhibited significant changes in signal intensity during the Valsalva maneuver: an area of the inferior frontal cortex encompassing Brodmann’s areas 45 and 47, corresponding functionally to the supplementary motor cortex supplying upper airway musculature, and a site within the anterior insular cortex (Fig. 2A). Signal intensities within these regions increased significantly during each Valsalva maneuver and returned to or below baseline during each rest period (Fig. 2B). Signal intensity within the ventral pons also changed significantly, gradually increasing during the entire challenge period. No significant signal intensity change emerged within the ventral and medial medullary regions.

**Group Differences**

There was no significant difference in global signal intensity between the control and OSA groups at any time point. However, cluster analysis revealed multiple brain sites in OSA subjects that showed significantly different patterns of regional signal intensity response to the Valsalva maneuver, compared with controls. Five major regions of difference emerged in the cerebral cortex: 1) an area of the left inferior parietal lobe showed significantly greater increases in signal intensity during each Valsalva maneuver in control, relative to OSA subjects. This region corresponds

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**Fig. 1.** A: Mean (black) ± SE (gray) heart rate, respiratory rate, and load pressure (LP) for control and obstructive sleep apnea (OSA) subjects during the Valsalva maneuvers indicated by vertical shaded areas. B: Valsalva ratios (VR; maximum cardiac interbeat interval/minimum cardiac interbeat interval) for each of the 3 Valsalva maneuvers in control (black squares) and OSA (gray circles) subjects, expressed as a function of age. C: LP, plotted as a function of age for control and OSA subjects.
functionally to Wernicke’s area (Brodmann’s area 40), which integrates reception of sensory information for expression of speech (Fig. 4, A and B; Ref. 37). 2) A region of the left precentral gyrus showed increased signal change in OSA and no change or a decline in controls during each Valsalva maneuver. This region, corresponding to Brodmann’s area 4, supplies musculature of the upper airway and diaphragm (37). 3) Bilateral regions of the anterior superior temporal gyrus (within Brodmann’s area 22), showed significantly greater increases in signal intensity in controls compared with OSA subjects. 4) A region of the left frontal cortex, confined to the superior frontal gyrus (Brodmann’s area 10), showed signal intensity increases during each Valsalva maneuver that were enhanced in OSA relative to control subjects, although this difference was reduced over subsequent trials. 5) A portion of the posterior insular cortex exhibited significant increases in signal intensity bilaterally in controls but little change in OSA subjects during each maneuver. This difference was greater on the left side than the right (Fig. 5; Table 2).

Regional differences also emerged in deeper brain structures. Within the cerebellum, the fastigial nucleus and a discrete region within the quadrangular lobule of the cerebellar cortex showed significant changes in signal intensity in controls and little change in signal in the OSA subjects during each Valsalva maneuver. Enhanced responses in OSA subjects also appeared in the left anterior cingulate gyrus (Fig. 5), and region-of-interest analysis revealed diminished responses bilaterally in the hippocampus (Fig. 3).

Time course patterns. In a number of regions, signal intensity changes in OSA subjects differed from controls in their time course pattern as well as in magnitude. The response in the cerebellar cortex of OSA
subjects was initially inverse to that of the controls and subsequently remained elevated while the controls responded in a cyclic fashion during each Valsalva maneuver (Fig. 5). During the initial Valsalva maneuver, there was no signal change in the posterior insula, after which it followed a pattern similar to controls but with diminished magnitude (Fig. 5). In the anterior cingulate, the OSA response initially led the control response, as did responses from the left precentral gyrus (Figs. 4B and 5).

DISCUSSION

Subjects with OSA showed altered neural responses to the Valsalva maneuver in several regions where gray matter loss had been previously demonstrated (24). The affected areas included sites involved in motor control of diaphragmatic and upper airway muscles; sensory integration from the oral airway, cerebellar cortical, and nuclear sites involved in blood pressure and breathing control; and limbic structures that can exert roles in inspiratory onset and blood pressure modulation. These findings suggest ineffective responses from selected structures normally mediating the challenge, combined with recruitment of alternative areas that, we speculate, are attempting to mount an effective physiological output. The functional reorganization of neural mechanisms found in OSA patients responding to the Valsalva maneuver may play a significant role in mediating the cardiovascular and respiratory patterns found during obstructed breathing within sleep.

Physiology

The Valsalva maneuver leads to a number of well-characterized autonomic changes (5, 19). At the beginning of the strain, AP increases transiently due to the increase in intrathoracic pressure (phase I). However, as the increase in intrathoracic pressure continues, atrial filling falls and AP declines, resulting in a baroreceptor mediated increase in HR (phase II); at
this time, a significant increase in sympathetic tone and circulating catecholamines moves net arterial pressure toward baseline. At the completion of the maneuver, the sudden decrease in intrathoracic pressure results in a transient fall in AP (phase III), followed by an overshoot in AP as sympathetic tone remains elevated after intrathoracic pressure has returned to normal (phase IV). The magnitude of the increase in HR during phase II compared with the fall in HR during phase III (Valsalva ratio) has been shown to give a measure of autonomic functioning (21). OSA patients exhibit a number of autonomic deficiencies, including significantly lower VR (11), decreased overall HR variability, and abnormal HR variability to an orthostatic maneuver (41). Furthermore, OSA subjects exhibit high sympathetic activity during wakefulness (45) and, possibly as a consequence, have a greater propensity for systemic arterial hypertension (27); the present group of OSA subjects also showed higher AP. The VR of the OSA subjects presented in this study did not decrease with age to a statistically significant degree. Our OSA subjects ranged in age from 28 to 63, a range that would not be expected to show a sufficiently large variation to be significant with only eight subjects (21).

fMRI Signal Similarities

The Valsalva maneuver evoked similar signal intensity changes in control and OSA subjects in a number of neural regions. These areas included the dentate nucleus of the cerebellum, dorsal brainstem, amygdala, anterior insular cortex, lateral prefrontal cortex, and lentiform nucleus. These regions all responded in a pattern that followed the LP, and signals increased gradually over the course of the Valsalva maneuver. The ventral pons showed a gradual increase in signal intensity over the entire challenge period without a return to baseline between separate maneuvers. Respiratory and cardiovascular functions of the neural regions responding to the Valsalva maneuver in healthy subjects, including those areas just described, have been discussed elsewhere (14).

Decreased Responsiveness in OSA Subjects

Six regions exhibited decreased responsiveness in OSA subjects, relative to controls. These areas were the left inferior parietal cortex, superior temporal gyrus, posterior insular cortex, cerebellar cortex, fastigial nucleus, and hippocampus.

The inferior parietal cortex, which partially corresponds to Wernicke’s area, integrates sensory input from the head and upper airway. A one-third reduction in two-point discrimination in the oropharynx and an 82% higher vibratory threshold occur in the upper airway of OSA patients compared with controls (17). The diminished recruitment of this upper airway sensory integration area during the Valsalva maneuver may reflect a dysfunction of this region in OSA patients. Impairment of afferent information of mechanical stimulation of the upper airway can lead to diminished airway muscle tone, because stimulation by airflow pressure or vibration has long been known to assist airway patency (38).

The superior temporal gyrus also exhibited decreased responsiveness compared with controls. This cortical area is a complex region involved in a number of functions, including language production and word recognition (15), and the left side has been previously implicated in voluntary expiratory efforts (7), findings comparable to those described here. Swallowing, a task requiring integration of sensory and motor aspects of
the upper airway, also activates the superior temporal gyrus (25); a high level of integration is also required by the Valsalva maneuver. A reduction in afferent input or integration within the superior temporal gyrus may contribute to the prolongation of apnea in OSA.

The posterior insular cortex showed diminished responsiveness bilaterally to the challenge in OSA subjects. The insular cortex plays a significant role in autonomic regulation (42). Lesions of the posterior insula interfere with baroreceptor functioning, a result not apparent from anterior insular lesions (54). Parasympathetic and sympathetic modulation appear to be lateralized in the insula, with parasympathetic related control principally sited in the left side and sympathetic in the right (29). Lesions of the left insular cortex of humans enhance basal sympathetic tone (30). The decreased reactivity found during the Valsalva maneuver was greater on the left side. Impaired insular function may underlie the higher sympathetic tone reported in OSA (45), and the higher heart rate found here. The near absence of posterior insular responses in OSA subjects during the first Valsalva maneuver may delay blood pressure changes during apneic periods. The close interaction of blood pressure and breathing patterns provides a potential mechanism to alter the time course of apneic events (47).

The Valsalva maneuver requires considerable respiratory effort; dyspnea can occur near completion of each exertion. Air hunger has been shown to recruit, among other structures, the insular cortex (1, 35). If the insula signal increase during the Valsalva challenge is associated with dyspnea, the signal changes in this region would be expected to increase principally near the completion of each maneuver. Because the signal intensity increases were gradual and occurred

Fig. 5. Areas of significant difference in signal intensity between control and OSA subjects during each Valsalva maneuver in deep brain structures (P < 0.05; corresponding to t > 2). Voxels are color coded for t-statistic and overlaid on an average anatomical image set of all control and OSA subjects. The MNI axial (z-level) and sagittal (x-level) levels are shown in the top left of each slice. Averaged ± SE time trends of fMRI signal changes during the course of 3 Valsalva maneuvers (vertical shaded areas) for significant voxel clusters are shown on the right of each overlay. *Significant differences (P < 0.05) between control and OSA groups.
the respiratory or autonomic aspects of OSA is substantial. Areas within the hippocampus that showed muted signals in OSA overlapped areas of gray matter loss (24). The hippocampus contains neurons that discharge in a respiratory cycle-dependent fashion (9) and show marked activity pattern changes to sigh-apnea sequences (39). The contribution from hippocampal sources likely relate to restoration of inspiratory onset after apnea.

**Increased Responsiveness in OSA Subjects**

The region of the cortical precentral gyrus showing altered responsiveness in OSA subjects serves the diaphragm and upper airway musculature. Not only did the response in this region differ in OSA subjects, but it was the only site in which the direction of signal change was opposed to that of controls. During expiration, the upper airway is fully dilated due to increased intraluminal pressure, and upper airway dilator muscles are largely inactive (51). Similarly, the upper airway is fully dilated during the Valsalva maneuver, and this dilation is enhanced in OSA (43). The decrease in signal intensity in the motor cortex of controls may underlie the decline in upper airway dilator activity during the Valsalva maneuver. The increased signal in the OSA subjects may reflect an overcompensation of the upper airway musculature, resulting in the enhanced upper airway dilation observed in these subjects. Alternatively, the increase in signal intensity may represent an overcompensation of drive to the diaphragm to overcome a motor system that is ineffective during difficult resistive challenges.

Substantial evidence demonstrates that the anterior cingulate plays a significant role in respiration and vocalization associated with affect and, in particular, upper airway musculature control (49). Vocalization requires exquisite integration of upper airway and diaphragmatic musculature to obtain a sequence of enhanced thoracic pressure through inspiratory effort followed by expiratory airflow. A critical aspect of OSA is initiation of inspiration after prolonged cessation of airflow. The region of delayed and opposite reactivity of the left anterior cingulate overlapped the area of previously demonstrated gray matter loss in OSA subjects (24); we speculate that the increased responses within this area represent a compensatory effort by neuronal inputs to overcome the anatomic loss in this region.

The anterior cingulate markedly reacts to several different blood pressure challenges, as demonstrated by fMRI evidence in both animals and humans (12, 18, 53); elicits large changes in blood pressure and HR on stimulation (2); and contains single neurons that fire in a discharge pattern related to the respiratory and cardiac cycle (9). The fMRI signal increases in the anterior cingulate of OSA subjects, with relatively little change in control subjects, may reflect an attempt in OSA subjects to overcome loss of normal neural function in other brain regions to mediate an almost-adequate HR response to changes in blood pressure.

**Table 2. Brain regions of significant difference**

<table>
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<tr>
<th>Region</th>
<th>MNI Coordinates</th>
<th>P Value (uncorrected)</th>
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<tbody>
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<td>Fastigial nucleus</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>left</td>
<td>-24 -14 -14</td>
<td>*</td>
</tr>
<tr>
<td>right</td>
<td>24 -14 -14</td>
<td>*</td>
</tr>
<tr>
<td>Posterior insula</td>
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<td></td>
</tr>
<tr>
<td>left</td>
<td>-46 -8 -4</td>
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</tr>
<tr>
<td>right</td>
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</tr>
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<td>Anterior cingulate, left</td>
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<td>Superior temporal gyrus</td>
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<td>Inferior parietal cortex, left</td>
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</table>

Brain regions exhibiting significant differences in signal intensity change in OSA subjects compared with controls. The center of each significant cluster is given in Montréal Neurological Institute (MNI) coordinates. *Regions in which volume-of-interest analysis resulted in significance.
The increased responses in the left superior frontal gyrus may be related to the enhanced signal changes found in the anterior cingulate. Transcranial stimulation near the superior frontal gyrus recruits the anterior cingulate (34). A cortical region bordering the superior frontal gyrus responsive site has also been implicated in aspects of working memory (31). It may be the case that the increased responses in the cortical areas reflect an “intention” aspect of recruitment of upper airway muscles, complementing a role that has been proposed for other motor actions from the anterior cingulate (33).

Limitations

Global signal changes. The issue of global signal changes with blood pressure manipulation is frequently overlooked in fMRI studies, especially in studies of neural signal responses to pain; pain of either deep or superficial origin evokes profound changes in AP, much larger than those observed in the Valsalva maneuver. During phases I and IV of the Valsalva maneuver, AP increases 5–10%, and in early phase II and during phase III AP declines ~5% (5). Studies investigating the effects of changes in AP show that changes of 20 to 60 mmHg have no significant effect on regional blood oxygen level-dependent signal changes in a number of selected brain regions (52). Large global changes in signal intensity induced by hypercapnia can be removed by intensity normalization to reveal regional changes related to a simultaneous stimulus (4, 16). It is assumed that these hypercapnia-induced increases result from the action of CO₂ on cerebral vasculature. However, AP and sympathetic activity increase substantially during brief periods of hypercapnia. Narkiewicz et al. (26) report that AP increased ~15% during a 3 min period breathing 7% CO₂, and Edwards et al. (6) show that this AP increase was up to 30% in women during certain times in the menstrual cycle. Although AP was not measured, given the high levels of CO₂ and the long duration exposure, subjects in both the Corfield et al. (4) and Kemna and Posse (16) studies likely experienced substantial increases in AP and sympathetic drive; thus the increases in global cerebral blood flow reported likely result from a combination of increased AP as well as the direct effects of CO₂ on cerebral vasculature. The effectiveness of intensity normalization used in those studies is likely shared by procedures in this study and can account for any changes in global intensity from increases in AP and direct effects of CO₂ on cerebral vasculature.

The Valsalva maneuver evokes a decline in overall cerebral blood flow (46) and therefore a decline in global signal intensity. If the autoregulatory system differed between the groups, the magnitude of the changes in global signal intensity should also differ. Although OSA is generally associated with cardiovascular dysfunction, in this study, both the control and OSA groups exhibited similar changes in global signal intensity during the Valsalva maneuvers. The effectiveness of intensity normalization is supported by the finding that most of the regional signal intensity changes during the Valsalva maneuver were located in previously well-defined cardiovascular or respiratory related regions, and some were unilaterally represented. Furthermore, because the overall changes in signal intensity did not differ between OSA and control subjects, differences between the two groups can be inferred to result from differences in the regional blood flow resulting from changes in synaptic activity.

Temporal resolution. The repetition time in this study precluded an examination of the rapid phases of the Valsalva maneuver, particularly phases I and III. Alterations in sympathetic tone and the circulating catecholamines endure for up to several minutes (21). Our findings almost certainly reflect a temporal summation of central mechanisms of withdrawal of vagal influences, activation of sympathetic drive to adrenals and peripheral vasculature, as well as increased cardiac rate and stroke volume.

We used an analytic model that tracks load pressure, the relevant stimulus for central mediation of the reflex. The load pressure stimulus is inevitably confounded with respiratory muscle activation but is coincident with activation of central nervous systems mediating autonomic responses, even though autonomic responses may take a period of time to develop. Although the humoral and vascular bed responses require a finite period of time to develop into the late phase II of the Valsalva maneuver, central initiation of these responses is likely quite rapid. Therefore, even though the peripheral effects may outlast the intrathoracic pressure and be out of phase with it, many central components of interest in this study could be imaged, despite the coarse temporal resolution and abbreviated phase IV of our protocol. Regions that show enhanced signal that closely follows the time course of the intrathoracic pressure signal are unlikely to be responding to either the initial transient neuronal responses or the more enduring autonomic features of the reflex.

This is the first attempt to measure regional brain changes in an OSA patient population during this common autonomic test; because the sites of participating regions were unknown, it was important to examine the entire brain. Subsequent studies using higher field strength imaging, with improved spatial and temporal resolution, will allow examination of more rapid and transient neural participation in the Valsalva maneuver.

In conclusion, although a number of neural sites responded in a similar fashion to the Valsalva maneuver in both OSA and control subjects, particular sites showed differing response patterns in OSA subjects not medicated with cardiovascular or mood-altering agents. In certain regions, signal responses to the Valsalva maneuver increased in OSA over controls; in other areas, responses in OSA subjects were substantially lower or phase-shifted. In several regions, areas of signal pattern differences overlapped sites of previously demonstrated gray matter loss in OSA subjects.
The increased signal change in particular structures suggests a compensatory response to the aberrant integrated neural organization in OSA. Areas of altered responsivity have the neuroanatomic and functional properties to mediate significant sensory or motor integration or coordination perspectives. Deficiencies in sensory reception from the airway, deficits in initiating inspiratory efforts of the upper airway, or phase alterations in initiating blood pressure responses may mediate the respiratory muscle patterns found in OSA.

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REFERENCES


