Brain Responses Associated With the Valsalva Maneuver Revealed by Functional Magnetic Resonance Imaging

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Received 11 February 2002; accepted in final form 2 August 2002

HENDERSON, Luke A., Paul M. Macey, Katherine E. Macey, Robert C. Fryssinger, Mary A. Woo, Rebecca K. Harper, Jeffry R. Alger, Frisca L. Yan-Go, and Ronald M. Harper. Brain responses associated with the Valsalva maneuver revealed by functional magnetic resonance imaging. J Neurophysiol 88: 3477–3486, 2002; 10.1152/jn.00107.2002. The Valsalva maneuver, a test frequently used to evaluate autonomic function, recruits discrete neural sites. The time courses of neural recruitment relative to accompanying cardiovascular and breathing patterns are unknown. We examined functional magnetic resonance imaging signal changes within the brain to repeated Valsalva maneuvers and correlated these changes with physiological trends. In 12 healthy subjects (age, 30–58 yr), a series of 25 volumes (20 gradient echo echo-planar image slices per volume) was collected using a 1.5-Tesla scanner during a 60-s baseline and 90-s challenge period consisting of three Valsalva maneuvers. Regions of interest were examined for signal intensity changes over baseline and challenge conditions in cardiorespiratory-related regions. In addition, whole brain correlations between signal intensity and heart rate and airway load pressure were performed on a voxel-by-voxel basis. Significant signal changes, correlated with the time course of load pressure and heart rate, emerged within multiple areas, including the amygdala and hippocampus, insular and lateral frontal cortices, dorsal pons, dorsal medulla, lentiform nucleus, and fastigial and dentate nuclei of the cerebellum. Signal intensities peaked early in the Valsalva maneuver within the hippocampus and amygdala, later within the dorsal medulla,pons and midbrain, and deep cerebellar nuclei, and last within the lentiform nuclei and the lateral prefrontal cortex. The ventral pontine signals increased during the challenge, but not in a fashion correlated to load pressure or heart rate. Sites showing little or no correlation included the vermis and medial prefrontal cortex. These data suggest an initiating component arising in rostral brain areas, a later contribution from cerebellar nuclei, basal ganglia, and lateral prefrontal cortex, and a role for the ventral pons in mediating longer term processes.

INTRODUCTION

The Valsalva maneuver consists of a prolonged expiratory effort resulting in increased intrathoracic pressure, with concomitant decreased venous return and alterations in arterial pressure (AP) and heart rate (HR). To maintain homeostasis, changes in sympathetic and parasympathetic outflow emerge, and the contributions of each component have been defined in the accompanying physiological patterns (Levin 1966; Sandroni et al. 2000). The maneuver has been valuable for assessment of autonomic disturbance in a number of clinical syndromes, including diseases of the CNS (e.g., Parkinsons disease), neuropsychies (diabetes) (Low 1996), and sleep disorders (obstructive sleep apnea) (Hanly et al. 1989; Naliboff et al. 1993; Netten et al. 1995).

Because the maneuver elicits a range of autonomic responses that may exhibit deficiencies in a number of conditions, it is important to determine the neural sites mediating these physiologic reactions. Examination of the time course of signal changes in these participating brain regions would assist understanding of the mechanisms integrating the responses to the challenge and aid in evaluation of the sympathetic or parasympathetic components of autonomic output. Determination of the multiple neural regions that take part in afferent, integrative, or efferent responses to the Valsalva maneuver requires procedures that are able to simultaneously examine diverse areas of the brain. We have previously (Harper et al. 2000) used functional magnetic resonance imaging (fMRI) procedures to examine the participation of certain brain areas that respond to the Valsalva effort and have shown that multiple sites, including cerebellar, cortical, and limbic regions, mediate aspects of the response to this challenge. Technical restrictions at that time precluded examination of signal changes in brain stem sites or temporal characteristics of signal intensity changes in relation to physiological variables. The advent of improved imaging procedures has provided a means to visualize signal changes over the entire brain, including medullary areas. Together with magnetic resonance (MR)–compatible electrophysiological recording equipment, the procedural developments allow examination of the time course of the signal intensity changes within defined regions of interest, and also allow evaluation of correlations of these signal changes with cardiovascular and respiratory patterns.

We examined the distribution and time course of extent of signal intensity changes in normal control subjects to Valsalva maneuvers and correlated signal change patterns to cardiovascular and respiratory patterns.

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www.jn.org  0022-3077/02 $5.00 Copyright © 2002 The American Physiological Society 3477
Subjects

Twelve healthy subjects (11 male and 1 female; mean age, 47 ± 3 yr; range, 30–58 yr) participated in the study. No subjects exhibited a history of autonomic dysfunction and none were currently taking beta-blockers, alpha-agonists, vasodilators, angiotensin-converting enzyme inhibitors, or cholinergic-stimulating drugs. All procedures were carried out with the adequate understanding and written consent of the subjects, and the study was approved by the Institutional Review Board at University of California, Los Angeles (UCLA).

Physiological recording

Subjects practiced the Valsalva maneuver three times outside the scanner for procedure familiarization. Each participant wore nose clips and breathed via a mouthpiece through a two-way nonrebreather respiratory valve (Hans Rudolph, Kansas City, MO). Two small airtight tubes were attached to the distal end of the mouthpiece. One tube was used to monitor end-tidal CO2 and the other was led outside the scanner room to a pressure transducer for monitoring of airway load pressure. An electrocardiogram (ECG) was obtained using standard MR-compatible surface electrodes and oxygen saturation was measured using a Nonin oximeter. The ECG and oximetry signals were fed to low noise amplifiers (Parker et al. 1999) and transferred outside the MR room via infrared devices (Harper et al. 2001). Thoracic wall movement was monitored using an air-filled bag placed against the thoracic wall and held in place using a cloth belt. A nondistensible tube attached to this bag was passed outside the scanner room to a pressure transducer. Arterial pressure readings were obtained immediately prior to and immediately following each scanning period. All physiological signals were digitized at 1 kHz. Respiratory and heart rates were calculated using a peak-detection algorithm.

MR imaging

Images were collected with a 1.5-Tesla MR scanner (General Electric Signa, Milwaukee, WI), and a standard head coil at the UCLA Center for the Health Sciences. Foam pads were placed on either side of the head and masking tape applied to the forehead to minimize head movement. Gradient echo echo-planar imaging of the head and masking tape applied to the forehead to minimize head movement. Gradient echo echo-planar imaging

Data analysis

Image analysis was performed with MedX (Sensor Systems, Sterling, VA) and SPM99 software (Friston et al. 1995). Following removal of the first volume to account for scanner saturation, image volumes were corrected for slice timing and motion-corrected. Images were then spatially normalized so that image volumes of all subjects were in the same three-dimensional (3D) space. This spatial normalization was carefully done to ensure that, in particular, brain stem sites were located in the same 3D space in all subjects. Spatially normalized images were Gaussian smoothed (full-width at half maximum = 8 mm). To evaluate whether global signal changes produced by the Valsalva maneuver varied across different regions of the brain, overall raw signal intensities for individual slices, averaged across all subjects, were calculated at each time point (Fig. 1A). The percent of total brain signal intensity at each time point for individual slices was

![Image](http://jn.physiology.org/noticeella.png)
calculated and plotted over time (Fig. 1B). Since the small decrease in global signal intensity was spread uniformly across the brain, images were intensity normalized so that the signal intensity of each slice remained constant.

Using the nonsmoothed, functional images, regions of interest (ROI) were selected using anatomical landmarks (Fig. 2). The medulla, dorsal pons, deep cerebellar nuclei, cerebellar vermis, dorsal midbrain, amygdala, hippocampus, and insular cortex were chosen on the basis of closely defined relationships. The striatum was selected for its role in motor control, and the frontal cortex for its participation in motor expression. The ventral pons and midbrain were chosen as control sites. These ROIs were then overlaid on the intensity normalized and smoothed images, and a single mean signal intensity value for each region of interest was calculated. The mean ± SE values at each time point were then subjected to a repeated measures ANOVA analysis, which accounts for multiple comparisons within subjects, and a probability value of $P < 0.01$ was used to establish statistical significance. Since we calculated mean signal intensity for each ROI and did not correlate individual voxel signal patterns with an a priori sequence of physiological changes, small volume correction was not performed. Cross-correlations were calculated between signal intensity change and both LP and HR. Maximum temporal resolution was limited by the TR of 6 s, giving three data points for each Valsalva maneuver per subject.

Using points of maximal correlation of signal intensity change with LP, a conjunction analysis, using a fixed effects model, was performed on a voxel-by-voxel basis between mean LP and signal intensity across all subjects. Significant voxels, corrected for multiple comparisons, (Resel corrected $P < 0.01$) were color-coded for significance and overlaid onto spatially normalized mean T1-weighted anatomical brain slices and rendered onto the surface of the brain. These significant voxels were initially overlaid onto a mean functional image to ensure that any nonlinear distortions did not affect the location of these significant regions when overlaid onto the anatomical image sets. The conjunction analysis identifies regions significantly activated in every subject of the study and

![Regions of interest (ROI) used for detailed time-trend analysis are outlined.](image_url)
with 99% confidence that at least one-half the population would show this effect (Friston et al. 1999).

Valsalva ratios (VR) for each subject were calculated (maximum R-R interval divided by the minimum R-R interval) for each of the three maneuvers. This ratio was used to establish that those physiologic values were within normal limits. Correlations of VR with age and LP with age were calculated to evaluate age as a confounding factor.

RESULTS

Physiology

Subjects showed a mean blood pressure of 93 ± 3 mmHg (systolic = 128 ± 4 mmHg; diastolic = 79 ± 2 mmHg) prior to onset of the maneuver. Prior to the challenge period, mean resting respiratory rate was 10 ± 1 bpm. During each Valsalva maneuver, subjects exerted a mean airway LP of 39 ± 3 mmHg (Fig. 3A). Approximately 7 s after the beginning of each effort, HR began to increase from a baseline value of 62 ± 3 bpm. Heart rate continued to increase during the effort, reaching a peak 3.4 ± 0.3 s after the completion of each Valsalva maneuver (mean max = 88 ± 5 bpm). This peak was followed by a rapid decrease below baseline (nadir = 53 ± 3 bpm), and a slow return toward baseline during the remainder of the 18-s recovery period. VR values ranged from 1.3 to 3.6 (mean = 2.1 ± 0.2); values for the three trials for all 12 subjects as a function of age are plotted in Fig. 3B. The decline in VR as a function of increasing age was revealed by a significant correlation between age and VR (Pearson’s r = 0.75, df = 34, P < 0.01). This significant correlation did not result from changes in LP with increasing age (Pearson’s r = 0.22, df = 34, P > 0.2; Fig. 3C).

fMRI signal changes

During each Valsalva maneuver, minor global signal intensity changes were distributed evenly throughout the entire brain and were removed by intensity normalization (Fig. 1).

Brain stem

Brain regions in which fMRI signal intensity was significantly correlated to LP with a lag-time of 5 s are shown in Figs. 4 and 5. Significant increases in signal intensity emerged within the dorsal medulla, the midline medulla, the dorsal pons, and the dorsal and ventral midbrain, reaching mean maxima of 2.0 ± 0.8%, 3.1 ± 1.5%, 3.3 ± 0.9%, 2.0 ± 0.8%, and 1.6 ± 0.5%, respectively (Fig. 6). The signal intensity increases of all these areas began shortly after the onset of the Valsalva maneuver, reached maxima approximately 14 s after the start of each Valsalva period, and declined in the intervening rest periods (Fig. 7A). In contrast, the signal intensity within the ventral pons increased gradually over the entire three-trial challenge period and was not correlated to either LP or HR.

Cerebellum

The Valsalva maneuvers evoked significant increases in signal intensity within the cerebellum, which were correlated to HR and LP. These signal intensity increases, which were limited to the fastigial (mean max = 2.1 ± 0.7%) and dentate nuclei (mean max = 1.7 ± 0.5%), peaked on average 15 s after the start of each Valsalva maneuver, and returned to baseline during the rest periods. No significant change in signal occurred in other cerebellar structures.

Rostral sites

Within limbic structures, significant increases in signal intensity developed immediately following the onset of each Valsalva maneuver in the amygdala (mean max = 1.2 ± 0.7%) and hippocampus (mean max: 1.2 ± 0.5%; Fig. 6). These regions reached maxima shortly after the onset of each Valsalva maneuver (amygdala: 5.4 ± 1.6 s; hippocampus: 5.5 ± 1.8 s); afterward, they rapidly returned to baseline levels. In basal ganglia and cortex, significant increases in signal intensity occurred in the lentiform nucleus (mean max: 0.9 ± 0.4%) and the insular cortex (mean max: 1.3 ± 0.4%; Figs. 4–6). As was the case with brain stem structures, the signal in the insular cortex began to increase early and peaked 14 ± 1 s after onset of each Valsalva effort. The rendered view of the cerebral cortex in Fig. 5 shows significant activation of a discrete region in the lateral prefrontal cortex (mean max: 0.7%).
2.4 ± 0.6%). Although signal intensity within the lentiform and lateral prefrontal cortex began to increase at approximately the same time as brain stem structures, they were last of all structures to peak, reaching maxima approximately 21 s after onset of the Valsalva effort (Figs. 7 and 8).

**Time onset**

Cross-correlations of neural signal changes with the LP and HR values, during the first Valsalva maneuver, were calculated and plotted (Fig. 7B). The morphology of cross-correlation plots for each ROI relative to LP and HR were similar, but the maximum cross-correlations of most structures showed an approximate 6-s delay in the HR peak with respect to LP. Signal maxima in the hippocampus and amygdala occurred earliest, followed by signal intensity peaks in the brain stem, cerebellum, and insular cortex. Later peaks occurred within the lentiform nucleus and the lateral prefrontal cortex (Fig. 7A). A summary of the mean HR, LP, O₂ saturation, and global and regional signal intensity traces is shown in Fig. 8. The regional changes in signal intensity are divided into three broad groups: short, medium, and long latency to peak.
DISCUSSION

Physiology

The HR response to the Valsalva maneuver was consistent with previous reports for subjects with no autonomic dysfunction (Ravits 1997). At onset of strain, the increased intrathoracic pressure compresses the great vessels, resulting in a transient increase in arterial pressure (AP). As increased thoracic pressures continues, venous return decreases, reducing AP to or below baseline levels. In an attempt to offset this fall in AP, the autonomic nervous system is recruited, evoking an initial withdrawal of vagal tone and a later increase in sympathetic drive resulting in increasing HR. Finally, as the strain is

FIG. 5. Areas significantly correlated \((P < 0.01; t > 0.72)\) with mean load pressure showing a lag-time of 5 s rendered onto the left and right surfaces of the brain. Significant voxels are color-coded.

FIG. 6. Averaged (±SE) time trends of functional magnetic resonance imaging (fMRI) signal changes during the course of 3 Valsalva maneuvers (gray shaded areas) for 17 brain areas outlined in Fig. 2. *Significant points \((P < 0.01)\) of the white square graphs. †Significant points of the black circle graphs. ‡Significant points of the white triangle graphs.

FIG. 7. A: mean time to maximum in signal intensity for the 1st Valsalva maneuvers in all 12 subjects for 12 ROIs. Time is relative to the onset of the 1st Valsalva maneuver. B: cross-correlation coefficients between fMRI signal and load pressure and heart rate for defined regions (in color) during the 1st Valsalva maneuver. Peak at 0 indicates a simultaneous change in inferred neural activity and the physiology measures. Peak to the right of 0 indicates the neural response lags the physiology.
released, a transient fall in AP below baseline occurs, followed by an overshoot of AP above baseline and HR below baseline.

The Valsalva maneuver has been standardized at a load pressure of 40 mmHg for a minimum of 15 s. We set a protocol that required subjects to initiate and maintain load pressures of 30–50 mmHg for ≥15 s. All subjects were able to meet this criterion and exhibited normal HR response to the Valsalva maneuver. All subjects produced mean VRs within normal limits (Baldwa and Ewing 1977; Levin 1966).

**Limitations**

**AUTOREGULATION.** The Valsalva maneuver has been used as a test of cerebral autoregulatory capacity. In healthy individuals, middle cerebral artery flow declines during the middle stages of the Valsalva maneuver but is quickly restored to baseline levels prior to the restoration of AP, indicative of appropriate autoregulatory functioning. These changes in flow are significantly smaller in the supine position than during standing (Pott et al. 2000; Tiecks et al. 1996). We observed a small overall decrease in global signal intensity during each Valsalva maneuver, likely resulting from changes in perfusion pressure as well as from alterations in arterial CO2. However, photic stimulation evokes regional signal intensity changes in the primary visual cortex even during extremely large changes in overall cerebral perfusion induced by changes in inspired CO2; the responses to photic stimulation are superimposed on the large increase in overall global signal intensity (Cortfield et al. 2001; Kemna and Posse 2001; Li et al. 2000). Further, follow-

ing intensity normalization, which removes global signal intensity changes, the signal intensity changes in the visual cortex were similar to those found during photic stimulation in the absence of increased CO2. Although the magnitude and timing of these changes differ slightly from those found without CO2, the overall pattern and direction remain unchanged. The normalization procedure, together with the findings that areas immediately adjacent to recruited sites showed different patterns of signal intensity response, including no signal intensity change, suggests that the signal changes reported in this study result from differential recruitment of brain sites and not from global changes in cerebral blood flow.

**MOTION ARTIFACTS.** Motion artifact is an issue of concern for all studies employing fMRI. To avoid motion artifact, we placed foam pads on either side of the head and secured the forehead of each subject to the scanner using tape. In addition, before scanning, each subject was trained to perform the maneuver while concentrating on keeping his/her head stationary. The success of these procedures was evident by the finding that at no time did any subject’s head move more than 1 mm in any direction. Despite the absence of gross movement, motion-correction was performed on the image sets of all subjects. These corrections, combined with the highly localized and varying nature of the signal intensity changes, provide confidence that the signal changes observed during the Valsalva maneuver resulted from recruitment of neural structures, and not as a result of movement artifact.

**HEMODYNAMIC DELAY.** The hemodynamic response varies in timing, amplitude, and pattern across brain regions. The central tendency of the response, however, is reproducible to within a second within any single brain site (Aguirre et al. 1998; Henson et al. 2002; Huettel and McCarthy 2001; Miezin et al. 2000), and some studies show no systematic difference in hemodynamic differences between the cortex and brain stem (Backes and van Dijk 2002). Sequential trial presentations can modify the hemodynamic response of subsequent trials (Huettel and McCarthy 2001; Miezin et al. 2000). To avoid this interaction, we measured the time to peak only to the first Valsalva maneuver. The 6-s scan interval in this study limits the resolution of this time to peak measurement. We therefore restricted our description to three broad groups—short, medium, and long latency to peak. The short latency group peaks at approximately 6 s, the medium latency at approximately 14 s, and the long latency group at approximately 21 s. The Valsalva maneuver results in a defined sequence of physiologic events including onset of a respiratory effort, a parasympathetic withdrawal and a subsequent sympathetic outflow increase. This physiologic sequence occurs over a period of ≥30 s, a period sufficiently long that recruitment of structures can be assessed despite a coarse sampling resolution. The timing of signal change over this prolonged period may give insights into contributions of particular areas to physiologic patterns. These large differences in timing suggest that some small hemodynamic timing differences that may occur between different brain regions would not significantly affect the relative order of the short, medium, and late latency to peak groups.

**Short latency to peak**

Regions in which signal intensity peaked at the onset of the Valsalva maneuver are likely to be involved in mediating the

![FIG. 8. Summary of the mean HR, LP, O2 sat, and global and regional SI changes plotted over time. Regional SI changes are divided into 3 groups: short, medium, and long latency to maximum peak in signal intensity as in Fig. 7A.](Image)
initiation of the respiratory effort or a preparatory component of the challenge. Taking into account a general hemodynamic delay of 5 s, the signal intensity in the amygdala peaked at approximately the onset of the Valsalva effort and slightly later in the hippocampus, both returning to baseline shortly thereafter (Figs. 6–8). Immediately prior to each Valsalva maneuver, subjects inspired deeply to ensure adequate air supply for the 18-s effort. The early onset of the hippocampal response suggests a role in mediating this initial inspiratory effort, an expected finding considering the demonstration of close interactions of breathing patterns and hippocampal single cell discharge (Frysinger and Harper 1989), electroencephalographic activity (Whishaw and Schallert 1977), electrical stimulation (Ruit and Neafsey 1988), and optical imaging findings (Poe et al. 1996). Collectively, this evidence suggests that the hippocampus participates in aspects of breathing control and is associated with initiation of the sequence of respiratory events accompanying the Valsalva maneuver.

The central nucleus of the amygdala projects heavily to the parabrachial pons, nucleus of the solitary tract, and the periaqueductal region (Hopkins and Holstege 1978), sites which contribute significantly to respiratory phase-switching or other aspects of autonomic control. Single pulse electrical stimulation of the amygdala central nucleus results in a switch to inspiration (Harper et al. 1984); thus the amygdala may also be participating, with the hippocampus, in the initial inspiratory effort required for the Valsalva maneuver. Structures within the amygdala mediate aspects of affect, and in particular, anxiety (Buchel and Dolan 2000; Lang et al. 2000). The confined space of the MR scanner, combined with the extreme effort required to perform the Valsalva maneuver, often lead to a mild feeling of anxiety, particularly during the first trial. The initial increase and subsequent decrease in signal intensity may reflect this feeling. We do not, however, have an independent measure showing such a decline in anxiety level.

**Medium latency to peak**

Regions exhibiting a delayed onset and gradual increase in signal intensity, a pattern similar to the HR response, are likely to represent those areas mediating the decrease in cardiac parasympathetic and increase in cardiac sympathetic drive. The medial medulla, dorsal medulla, dorsal pons, midbrain, and insular cortex all exhibited this response pattern, with the greatest magnitude in signal intensity change occurring in the dorsal pons (Figs. 6 and 8). The parabrachial complex, which lies within the dorsolateral aspect of the pons, sends direct projections to medullary sites that contain both respiratory and cardiovascular motor neurons [the nucleus of the solitary tract (NTS) and the rostral ventrolateral medulla (RVLM)] (Herbert et al. 1990). On activation, the parabrachial complex can evoke increases in sympathetic activity and HR (Chamberlin and Saper 1992) and alter the functioning of the baroreceptor reflex (Saleh and Connell 1997).

The NTS, which lies within the dorsal medulla, exhibited substantial signal increases with the challenge. The NTS is the primary termination site of afferents arising from almost all cardiovascular receptors, and on activation, can elicit profound changes in AP and HR. The NTS alters sympathetic cardiac outflow via projections to the RVLM, either directly or via the caudal ventrolateral medulla, and can modify parasympathetic cardiac outflow via direct projections to the vagal cardiac preganglinons near the nucleus ambiguus (Dampney 1994). Despite the close interconnectivity, increased NTS signal intensity did not alter ventrolateral medullary activity, a surprising outcome. The lack of significant signal intensity change may have been the product of the multiplicity of neuronal types in the ventrolateral medulla, which contains cells that both increase sympathetic and decrease parasympathetic outflow to the heart. The relatively poor spatial resolution of the fMRI technique may not allow sufficient resolution to differentiate discrete subsets of neurons. Localization within a region must await higher-resolution mapping.

The midline medulla (medullary raphe nuclei) plays a significant role in cardiac and respiratory control. Chemical activation of this region results in marked AP and HR changes, alters respiratory patterning and enhances phrenic nerve discharge (Bernard 1998; Haxhiu et al. 1998; Henderson et al. 1998). The increased signal intensity in the midline raphe during the Valsalva maneuver may represent compensatory responses to alter AP or may reflect action to increase phrenic nerve discharge and thus maintain the greatly enhanced respiratory effort.

The late onset, gradual rise in signal intensity in the insular cortex is consistent with previous work of King et al. (1999). Both animal and human studies show that the insular cortex plays a role in autonomic function, as indicated by electrical stimulation, stroke, lesion, and fMRI data (Corfield et al. 1995; Oppenheimer 1994). Strokes localized to insular cortex result in a great number of cardiovascular complications and increased mortality due to autonomic imbalance compared with strokes located in other cortical regions (Oppenheimer et al. 1996; Tokgozoglu et al. 1999). Previous PET studies reveal significant activation in insular cortex during air hunger (Banet et al. 2000; Liotti et al. 2001; Peiffer et al. 2001), a feeling subjects in this study experienced, by self-report, toward the end of each Valsalva maneuver. In addition to a role in the autonomic component of the Valsalva maneuver, the insular cortex may also be involved in dyspnea. Unlike the dorsal pons, the ventral pons did not show a correlation with the HR or LP; instead, signal intensity increased over time and remained elevated in the inter-trial gap (Fig. 6). This action may represent an overall arousal to the challenge.

As was the case in brain stem regions, deep cerebellar nuclei began to increase signal intensity early in the Valsalva maneuver; intensity remained significantly increased until after completion of each Valsalva effort. A cough bears many resem- blances to the respiratory pattern of the Valsalva maneuver, with an initial deep inspiration followed by expiration against a closed glottis. Studies in the cat have revealed that lesions encompassing the rostral interpositus nucleus, a deep cerebellar nucleus, attenuate coughing (Xu and Frazier 1997). During active expiration, PET studies also show significant increases in activation in the cerebellum (Ramsay et al. 1993). The cerebellar nuclei may act in a compensatory or “error correction” mode, mediating both somatomotor and AP components of the Valsalva response. Cerebellar structures play a significant role in somatomotor control of respiration: cerebellar damage can result in impaired breathing when coordination with other body movements is necessary, even if breathing at rest is normal (Ebert and Hefter 2001). The active somatomotor efforts required for the Valsalva challenge may require...
participation of cerebellar structures, particularly the dentate nuclei. Arterial pressure manipulations, such as cold pressor challenges or mental stressor tasks that have an absence of motoric action, show recruitment of cerebellar sites, especially the deep cerebellar nuclei (Critchley et al. 2000; Harper et al. 2000). The fastigial nucleus appears to play a significant role in compensating for extremes in AP; fastigial nuclei lesions result in a failure to restore AP during hypovolemia or endotoxic shock in animals, resulting in death (Lutherer et al. 1983). Patients presenting with multiple system atrophy, of which cerebellar pathology is a feature, or olivopontocerebellar degeneration, show central autonomic dysfunction (Chokroverty 1984; Smith et al. 1996). We speculate that the dentate and fastigial nuclei participate in regulatory roles for breathing and AP control, respectively, and that deficits in capability to develop LP or appropriate HR responses to the Valsalva maneuver may involve these cerebellar nuclei.

Long latency to peak

A discrete region of the lateral prefrontal cortex, corresponding to the supplementary motor area of the upper airway, and the lentiform nucleus, another motor region, showed significant increases in signal intensity during each Valsalva maneuver, with long latency to peak (Fig. 8). The supplementary motor area of the upper airway, on the left side, is known as Broca’s area. This region is involved in motor aspects of speech, involving complex interactions of upper airway muscle action. This region is also consistently activated during swallowing (Mosier et al. 1999), a task also integrating upper airway muscle activity. Given that this region is activated during the entire maneuver and has a signal intensity peak at the completion of each maneuver, we suggest that it is involved in mediating muscle control of the upper airway during the challenge.

The Valsalva maneuver recruits neural structures throughout the rostrocaudal extent of the brain. Early recruitment occurs within limbic structures, which may help initiate the maneuver. Slightly delayed, gradual increases were found in the dorsal brain stem, insular cortex, and cerebellum, and likely represent regions involved in increasing sympathetic and decreasing parasympathetic cardiac drive. Structures showing maximal increases in signal even later include regions of the basal ganglia and supplementary motor cortex. The findings emphasize the distributed nature of a relatively simple challenge, and suggest that participation of discrete brain sites can be partitioned by consideration of timing of signal changes.

We thank C. Valderama for technical assistance.

This research was supported by National Heart, Lung, and Blood Institute Grant HL-60296.

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