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Increased brain activation during verbal learning in obstructive sleep apnea[☆]

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This study examined the cerebral response to a verbal learning (VL) task in obstructive sleep apnea (OSA) patients. Twelve OSA patients and 12 controls were studied with functional magnetic resonance imaging (fMRI). As hypothesized, VL performance was similar for both groups, but OSA patients showed increased brain activation in several brain regions. These regions included bilateral inferior frontal and middle frontal gyri, cingulate gyrus, areas at the junction of the inferior parietal and superior temporal lobes, thalamus, and cerebellum. Better free recall performance in the OSA group was related to increased cerebral responses within the left inferior frontal gyrus and left supramarginal area. Recall was negatively related to activation within the left inferior parietal lobe. The findings support the predictions that intact performance in OSA patients is associated with increased cerebral response. Recruitment of additional brain regions to participate in VL performance in OSA patients likely represents an adaptive compensatory recruitment response, similar to that observed in young adults following total sleep deprivation and in healthy older adults. These data, and those of the only other fMRI study in OSA, suggest that individuals with OSA show characteristic differences in the BOLD signal response to cognitive challenges. Including subjects with untreated OSA in neuroimaging studies may potentially influence the results by altering individual and group level activation patterns. Given this, future neuroimaging studies may want to be aware of this potential confound.

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Obstructive sleep apnea (OSA) syndrome is characterized by repeated episodes of upper airway obstruction during sleep that result in intermittent hypoxemia with periodic arousals (Malhotra and White, 2002). Prevalence estimates for OSA in adults range from 9 to 28% for at least mild severity, and 2 to 14% for at least moderate severity (Young et al., 2002). OSA is recognized as a significant public health problem that imposes substantial cardiovascular (Placidi et al., 1998) and neurocognitive (Engleman et al., 2000) morbidities. Patients with OSA commonly report excessive daytime sleepiness and lack of concentration.

Although it is well recognized that OSA is associated with neuropsychological morbidities, patients do not show deficits in all cognitive domains. A comprehensive meta-analysis concluded that while vigilance and executive functioning are markedly impaired, general intelligence and verbal ability are typically not affected by OSA. In addition, OSA does not seem to impact short-term verbal memory (Beebe et al., 2003).

Despite considerable data about the cognitive correlates of OSA, less is known about the associated cerebral substrate of these changes or why some cognitive domains are impacted and others are not. To our knowledge, only one study has been published using functional neuroimaging to examine cognitive function in OSA. Consistent with the behavioral literature, Thomas et al. reported that untreated OSA patients showed reduced performance on a 2-back working memory task, as well as reduced activation within anterior cingulate, dorsolateral prefrontal (PFC), and posterior parietal cortices. They also concluded that the sleep loss associated with fragmented sleep likely contributed to these deficits more than the nocturnal hypoxia (Thomas et al., 2005).

From a cognitive neuroscience perspective, OSA appears to share characteristics in common with both healthy aging and acute total sleep deprivation (TSD). Both aging and sleep deprivation have been shown to lead to cognitive deficits in many, although not

all domains, and functional neuroimaging studies often report altered BOLD signal response relative to appropriate controls. These changes in cerebral responses can be either decreases or increases in activation, depending on the task administered. For example, decreased activation has been reported in both older adults (Smith et al., 2001) and sleep deprived young adults (Drummond et al., 1999; Thomas et al., 2000) during arithmetic working memory tasks. A more commonly reported finding, though, is increased activation during verbal learning tasks in both healthy aging (Cabeza et al., 1997; Morcom et al., 2003) and sleep deprivation (Drummond et al., 2000, 2005). In both literatures, increased activation during learning (and other tasks) is associated with better cognitive performance, leading many authors to interpret this increased activation as compensatory in nature (Cabeza, 2002; Reuter-Lorenz and Lustig, 2005; Drummond et al., 2000, 2005). Given this, we postulate that the intact verbal learning typically seen in patients with OSA (Beebe et al., 2003) may also be secondary to a compensatory mechanism resulting in increased activation.

The current study examined the cerebral substrates of intact performance in OSA patients, using fMRI. We were interested in the mechanisms allowing OSA patients to maintain normal performance on some tasks, despite showing deficits in a number of other areas. A verbal learning (VL) task was employed, because the potential parallels between OSA and both sleep deprivation and aging outlined above allowed us to make a priori hypotheses. Specifically, we hypothesized that OSA patients, relative to controls, would show intact verbal learning performance and increased cerebral activation in bilateral inferior frontal and left inferior and superior parietal lobes, similar to healthy young adults following TSD (Drummond et al., 2000).

Materials and procedures

Participants

Twenty-four participants (12 non-treated OSA patients and 12 matched healthy controls) were studied (11 men, 1 woman in each group; for sample and matching characteristics see Table 1). There were no differences between the groups on any demographic variables, body-mass index (BMI), or blood pressure. All participants were right-handed, healthy, and free of current and past psychiatric and medical disorders as determined by history and physical exam, the Composite International Diagnostic Interview for mental disorders, routine lab work, and urine

Table 1
Sample characteristics

	OSA (<i>n</i> = 12), mean (SD)	Control (<i>n</i> = 12), mean (SD)	<i>P</i> value
Age	44.2 (11.9)	43 (9.1)	0.79
BMI	31.3 (5.9)	29.2 (3.5)	0.3
Blood pressure (systolic)	126.3 (13.2)	119.2 (9.9)	0.15
Blood pressure (diastolic)	76.5 (9.6)	74 (9.1)	0.52
Education	16.2 (2.7)	16 (3.4)	0.84
English fluency (WAIS)	113.9 (8)	114.8 (4.7)	0.72

BMI = body-mass index.

WAIS = Wechsler Adult Intelligence Scale.

toxicology screens. All participants reported regular sleep–wake schedules and based on daily sleep diaries, obtained an average of 7.7 ± 0.9 h of sleep per night for the 3 nights preceding the study with no significant differences between the groups. The OSA patients were treatment naïve. They were either initially diagnosed as part of our study or were referred from a sleep disorders center prior to initiating treatment.

The study was approved by the University of California San Diego Human Research Protection Program, and all participants provided written informed consent.

Experimental protocol

Patients with a known diagnosis of OSA were referred from the UCSD Medical Center or from their private physicians. Control subjects and potential OSA patients were recruited from the general San Diego community by the UCSD Database of Clinical Research and through advertisements in local media. Interested individuals were screened via telephone for major inclusion/exclusion criteria. Individuals who were deemed eligible were scheduled for an appointment. After signing informed consent, participants had medical and psychiatric screening and completed sleep questionnaires. Five to 14 days after screening, participants reported to the UCSD General Clinical Research Center's J. Christian Gillin Laboratory for Sleep and Chronobiology 2 h before their prearranged bedtimes. An overnight polysomnography (PSG) was used to confirm OSA diagnosis in the OSA patients, rule out OSA in the control group, and rule out sleep disorders other than OSA in both groups. Sleep schedules in the laboratory were based on self-reported habitual sleep schedules. Two to three hours after waking on the morning after the PSG, participants underwent a fMRI. During the fMRI session, participants performed a VL task and sensorimotor task.

Sleep questionnaires

The Epworth Sleepiness Scale (ESS) (Johns, 1991) was used to evaluate subjective levels of daytime sleepiness. The ESS is a self-administered questionnaire that rates the likelihood of falling asleep in different situations on a scale of 0 (no chance of falling asleep) to 3 (high likelihood of falling asleep). The ESS has been shown to reliably distinguish good sleepers from those with disorders characterized by excessive daytime sleepiness, including OSA. A score of 10 or above is considered pathological daytime sleepiness.

Polysomnography

A Grass Heritage Digital PSG system (Grass, West Warwick, RI) was used for recording sleep. Standard electroencephalograms, electrooculogram, chin electromyogram, electrocardiogram, airflow, thoracic and abdominal excursions, oximetry, and tibialis electromyogram to screen for periodic leg movements were recorded. Apnea was defined as any >10 s of >80% drops of respiratory amplitude. Hypopnea was defined as any >10 s of >30% drops of respiratory amplitude, plus >3% desaturation, or plus arousal. Apnea–hypopnea index (AHI) was calculated representing the number of apnea and hypopnea events per hour of sleep. Records were scored for sleep stages according to the

criteria of Rechtschaffen and Kales (1968). Number of arousals per hour of sleep (arousal index) and number of oxygen desaturation per hour of sleep (desaturation index) were calculated.

FMRI session

The verbal learning task

During the FMRI session, participants performed a VL task. Stimuli were presented visually via a video projector onto a screen placed at the foot of the MRI bed that participants viewed through a mirror fitted to the head coil. Two of the OSA subjects used a fiber optic goggle system (Avotec, Stuart, FL) mounted to the head coil due to the fact that their girth made viewing the screen at the foot of the bed impossible.

The VL task started and ended with baseline and contained 6 memorization blocks and 7 baseline blocks. During the entire task, nouns were presented one at a time, each for 4 s followed by 1 s of a fixation asterisk. The blocks were visually identical. Each block started with directional prompts for 2.5 s and lasted a total of 22.5 s. The task lasted 300 s (including 7.5 s at the start for FMRI data not analyzed due to partial saturation effects).

During the memorization blocks, subjects were instructed to learn the words for an immediate free recall test. For the baseline condition, participants were instructed to press a button on a hand held button box (Current Designs, Philadelphia) to indicate whether the word was printed in all capital or all lowercase letters. They were instructed to not memorize these words. In our previous studies, this condition proved an effective control for the lexical components of the memorization condition. In an attempt to prevent falling asleep, the experimenters interacted with subjects whenever active scan collection was not ongoing. In addition, subjects' responses on the button box were tracked during the task and there was no period of non-responding greater than 10 s.

At the conclusion of the task, while still in the scanner, participants were given an immediate free recall task. In addition, participants were administered the Stanford Sleepiness Scale (Hoddes et al., 1973) and Karolinska Sleepiness Scale (Akerstedt and Gillberg, 1990) and a 10-point Likert scale assessing the following subjective factors: task difficulty, ability to concentrate, effort put into the task, and motivation to perform the task well. After completion of the entire scanning session, i.e. about 30–40 min after the immediate recall, participants were given unexpected delayed free recall and recognition memory tests.

The sensorimotor task

The sensorimotor task measured basic primary sensory cortex function not dependent on cognitive processing, thus providing a measure of non-specific effects of OSA and serving as a control task. The scan employed a block trial with 8 cycles of 15 s on and 15 s off blocks, where the on condition was a flashing logarithmic radial checkerboard pattern contrast reversing at 3 Hz, and the off condition was a fixation cross. Subjects were instructed to fixate on the central cross and repeatedly tap their thumb to each finger in succession (index finger to little finger and then the reverse, little finger to index finger) bilaterally in time with the stimuli when present. The total task lasted 248 s.

FMRI data acquisition

The FMRI session took place on a General Electric 3T scanner (GE Medical Systems, Milwaukee, WI). Functional images consisted of 120 gradient echo Echo-planar images (repetition time: 2.5 s, echo time: 30 ms, field of view: 256 mm, 4 mm × 4 mm in-plane resolution) of 32 4 mm axial slices covering the whole brain and measuring the blood oxygenation level-dependent (BOLD) signal. Functional data were aligned with high-resolution anatomical images (fast spoiled gradient recalled echo: 1 mm³ resolution).

Data analysis

Memory and questionnaire data were analyzed with Student's *t* tests comparing the OSA and the Control groups. The main outcome variable was considered immediate free recall, but delayed recall, and recognition memory scores were also analyzed. Spearman correlations between free recall performance and questionnaires were calculated.

FMRI data were processed and analyzed with AFNI (Cox, 1996) in a two-step procedure: individual time course analysis followed by group statistical analysis. After motion coregistration, individual time-course BOLD signal data were fit to a design matrix using the general linear model (Ward, 2002). Parameters estimated from the design matrix represented the constant, linear drift, 6 motion correction parameters derived from the motion coregistration step (3 relational and 3 translational movement directions), and the reference function. The reference function was a representation of the task design (baseline vs. memorization or fixation vs. sensorimotor condition, respectively) convolved with an idealized hemodynamic response function (Cohen, 1997). The parameter used in group analyses was the regression coefficient associated with the reference function in the general linear model. Prior to group analyses, data sets were smoothed with a Gaussian filter of 4.0 mm full-width-half-maximum and transformed to standard atlas coordinates (Talairach and Tournoux, 1988).

For group analyses, *t* tests were used to examine group differences (OSA vs. Control) in cerebral responses for the VL and the sensorimotor tasks. To assess the correlation between brain activation and performance in the OSA group, BOLD response data were regressed onto performance data.

For the VL task *t* test, we utilized a whole brain voxel-wise analysis. To protect against Type I error, we used a cluster threshold method (Forman et al., 1995). This required any given voxel to be statistically significant at the $P < 0.05$ level and part of a cluster of at least 12 contiguous voxels (768 mm³), each individually significantly activated. Hence, the clusters we report are equal to or larger than the single largest cluster of activation expected by chance at $\alpha = 0.05$. We chose a whole-brain approach here because, although prior studies in controls allowed us to define specific hypotheses concerning regions of interest, we wanted to allow for the possibility that OSA patients may utilize different brain regions to perform the task than what is typically reported in healthy controls. Such a finding would be consistent with our compensatory recruitment hypothesis (Drummond et al., 2005).

For the VL performance analysis, a search region approach (Eyler Zorrilla et al., 2003) was taken to confine the analysis to areas previously found to be involved in compensatory recruitment on a VL task after TSD (Drummond et al., 2000) or VL in

Table 2

Verbal learning performance, concentration, task difficulty, motivation, and effort

	OSA ($n = 12$), mean (SD)	Control ($n = 12$), mean (SD)	P value
Immediate recall	6.6 (3.5)	8.0 (2.7)	0.28
Delayed recall	5.25 (3.2)	6.25 (2.7)	0.42
Recognition (d')	2.2 (0.9)	2.2 (0.7)	0.84
Concentration	7.4 (2.5)	8.3 (1.8)	0.31
Task difficulty	7.25 (1.7)	6.7 (3.1)	0.57
Motivation	8.7 (2.3)	8.6 (2.1)	0.93
Effort	8.5 (2.35)	9 (1.8)	0.56

d' = discriminability index.

P value is for independent samples t test.

general. The search region consisted of the following areas bilaterally: inferior frontal gyrus, inferior and superior parietal lobes, thalamus, and hippocampal formation. Within this search region, we identified clusters of activation as areas containing at least 7 contiguous voxels (448 mm³), each activated at the $P = 0.05$ level.

The analysis for the sensorimotor task was confined to the somatosensory, motor, and visual cortical areas bilaterally, including: precentral, postcentral, and paracentral areas; inferior, middle, and superior occipital gyri; lingual gyrus, fusiform gyrus, and cuneus. The coordinates of the Talairach and Tournoux (1988) atlas within AFNI defined these regions. Confining the analyses to these regions of interest allowed us to detect smaller activations (we

identified clusters containing at least 8 contiguous voxels (512 mm³), each activated at the $P = 0.05$ level), thereby serving as a stronger control for non-specific effects of OSA.

Results

Sleep and sleepiness

No significant differences between the groups were found in total sleep time or percentage of any sleep stage. However, as expected, the OSA group had significantly higher AHI (mean = 35.1, SD = 21.1) than the Control group (mean = 1.9, SD = 1.7) ($U = 0$, $P < 0.001$). In addition, the OSA group had significantly higher arousal index and higher oxygen desaturation index than the Control group (Arousal: OSA: mean = 37.32, SD = 24.2, Control: mean = 7.09, SD = 4.29, Mann–Whitney $U = 6$, $P < 0.001$; Desaturation: OSA: mean = 29.95, SD = 19.2, Control: mean = 5.39, SD = 5.26, Mann–Whitney $U = 11$, $P < 0.001$). Subjectively, the OSA group reported significantly higher daytime sleepiness (11.8 ± 4.8) than the Control group (7.4 ± 4.1) as measured by the ESS ($U = 33.5$, $P = 0.024$), implying a greater tendency to fall asleep while engaging in a variety of daytime activities.

Behavioral data

The performance analysis revealed that OSA patients recalled a similar number of words as the control group during both

Table 3

Brain regions showing group differences (OSA Vs. Control) during the verbal learning task

Anatomical location	BA	Volume (mm ³)	Center (x, y, z)	Max Eta-Sq
Inferior frontal	44/9	1408	53, 3, 23	0.41
	44/47	1024	51, 14, 5	0.35
	45/46	2112	−38, 34, 13	0.39
Middle frontal	10	14720	32, 32, 24	0.50
	6/8	3264	−35, 3, 41	0.43
Superior frontal	6	1152	13, 12, 59	0.50
	9	3072	−25, 44, 30	0.37
Cingulate gyrus	32/24	3584	−3, 2, 34	0.51
		832	−14, 8, 25	0.35
Medial frontal	11/32	1920	8, 34, −10	0.37
Inferior parietal	40	896	−48, −40, 47	0.35
Inferior parietal and superior	40/22	6208	36, −53, 36	0.43
Temporal	40/22	4224	−56, −43, 20	0.52
Precuneus	7	4224	2, −58, 43	0.39
Middle temporal	21	768	58, −23, −11	0.40
Superior and transverse temporal	22/41	3648	−44, −18, 6	0.51
Inferior/middle temporal,	19/37	10752	44, −61, −4	0.56
Inferior/middle occipital, fusiform	19/37	7232	−39, −64, 1	0.44
Thalamus and mammillary body	Lateral posterior,	1920	14, −20, 10	0.43
	medial dorsal, vental–lateral, ventral–posterior			
Cerebellum	Medial dorsal, pulvinar	1856	−11, −26, 7	0.49
	Declive	1216	15, −73, −14	0.32
	Culmen	768	−12, −58, −14	0.42
	Culmen	1024	−1, −48, −5	0.46

Clusters shown survived our cluster threshold alpha protection procedure (whole brain $P < 0.05$; see Materials and procedures for details).

Anatomical locations and Brodmann's Areas (BA) list every region covered by a given cluster. This does not imply that all portions of a listed region were covered. Eta-Sq = effect size measuring variance accounted for by Group. Talairach coordinates refers to center of mass of activation.

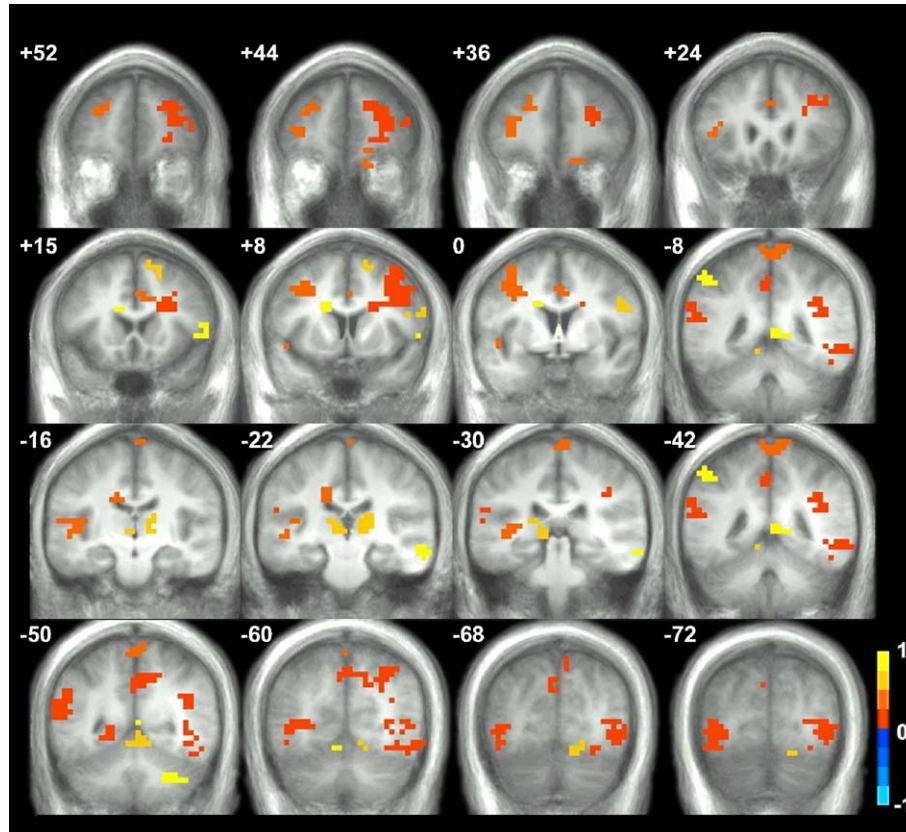


Fig. 1. Brain regions showing significant Group differences (OSA minus Control) in activation during the verbal learning task (see Table 3). In all clusters showing Group differences, OSA group exhibited greater responses (Red, smallest differences; yellow, largest). The panel shows coronal slices from anterior to posterior. Numbers correspond to Talairach and Tournoux coordinates of the coronal slices. For all images, clusters surviving our cluster threshold method are overlaid in color on top of the group average anatomical image. The color corresponds to the effect size η^2 , corresponding to the amount of variance accounted for by Group membership. Slices are presented in neurological orientation (left = left; right = right).

immediate and delayed recall. Both groups also scored similarly on the recognition memory test (determined with the discriminability index d'), in their ability to concentrate, perceived task difficulty, in the amount of effort put into the task, and motivation to perform well (Table 2).

Correlations between performance and subjective measures

Subjective ratings of trait and state sleepiness were not significantly correlated with free recall performance (ESS: $r = 0.01$, $P = 0.97$; Stanford Sleepiness Scale: $r = 0.33$, $P = 0.1$; Karolinska Sleepiness Scale: $r = 0.03$, $P = 0.89$). Similarly, none of the other subjective factors (task difficulty, ability to concentrate, effort put into the task, and motivation to perform the task well) were related to performance (all P s > 0.05).

FMRI data

The verbal learning task

In the control group, the VL task activated mainly a left hemisphere network typically activated during performance of verbal memory tasks (Frackowiak, 1994; Smith et al., 1998), including the inferior (Brodmann's area (BA) 47), middle (BA4, 6, 9), and superior (BA6, 8) frontal gyri, left middle temporal gyrus (BA21), and bilateral parahippocampal gyrus (BA28/35). Decreased activation during the VL task was observed in controls in bilateral

medial dorsal nucleus of the thalamus, right declive, right precuneus (BA31), and right inferior parietal lobe (BA40).

All significant clusters in the comparison between the control and the OSA groups showed increased activation in the OSA group. As can be seen in Table 3 and Figs. 1 and 2, OSA patients showed increased activation compared to controls in a number of cortical regions including right inferior frontal gyrus, bilateral middle frontal gyrus, bilateral cingulate gyrus, and bilaterally at the junction of the inferior parietal and superior temporal lobes. Other regions showing increased BOLD response in OSA patients included bilateral thalamic nuclei and bilateral cerebellar regions.

Correlations between BOLD response and VL performance in the OSA group

Better immediate recall was associated with increased BOLD response in the left inferior frontal gyrus (BA 47) and left supramarginal area. Increased BOLD response in the left inferior parietal lobe (BA 40) was associated with poor performance. Plots showing the correlations between recall and BOLD activation in these areas are presented in Fig. 3.

The sensorimotor task

Comparison of the BOLD response in the control and the OSA groups during the sensorimotor task revealed only

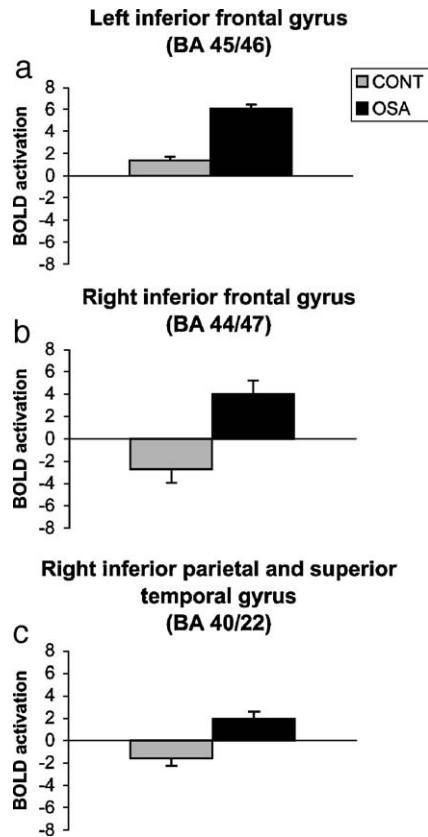


Fig. 2. Mean BOLD activation and standard error of 3 of the brain regions showing a significant increased activation in the OSA group. For each area showing a group effect (including those in Table 3 but not depicted here), there was a significant increase in the BOLD response in the OSA patients compared to the Control groups ($P < 0.05$). (a) Left inferior frontal gyrus was involved in VL in the Control group, with increased activation in the OSA group; (b) right inferior frontal gyrus showing right hemisphere activation in the OSA group but no such activation in Control group; (c) right inferior parietal and superior temporal gyri showing decreased activation in controls with potential disinhibition in the OSA group. BOLD activation units are dimensionless values that represent the mean parameter estimates.

Table 4

Brain regions showing group differences (OSA vs. Control) during the sensorimotor task

Anatomical location	Volume (mm ³)	Center (x, y, z)	Max Eta-Sq
Postcentral	832	-36, -32, 51	0.33
Precentral	576	-55, -8, 32	0.30

Clusters shown survived our cluster threshold alpha protection procedure (search region, $P < 0.05$; see Materials and procedures for details).

Anatomical locations and Brodmann's Areas (BA) list every region covered by a given cluster. This does not imply that all portions of a listed region were covered.

Eta-Sq = effect size measuring variance accounted for by Group. Talairach coordinates refers to center of mass of activation.

decreased activation in the left postcentral and precentral gyri in the OSA group (see Table 4). No differences were observed in visual areas.

Discussion

This study was one of the first to examine the cerebral correlates of learning and memory performance in a group of patients with OSA. The main findings were consistent with our hypotheses that OSA patients would show intact performance on the task along with increased activation as measured with the BOLD signal. The finding of intact immediate free recall in OSA patients in this study was consistent with other studies showing minimal or no impairment in short-term verbal memory in OSA patients (Beebe et al., 2003).

Increased activation in OSA patients manifests in regions both typically and some not typically associated with verbal encoding. Increased activation in regions related to verbal encoding may reflect task-related recruitment associated with the concept of cognitive reserve (Stern, 2002). OSA patients showed increased activation relative to controls in left PFC (associated with a variety of verbal tasks), the left superior temporal/inferior parietal lobes (involved in short-term memory store), and the cerebellum (related to articulatory control and phonological storage) (Cabeza and Nyberg, 2000). Increased

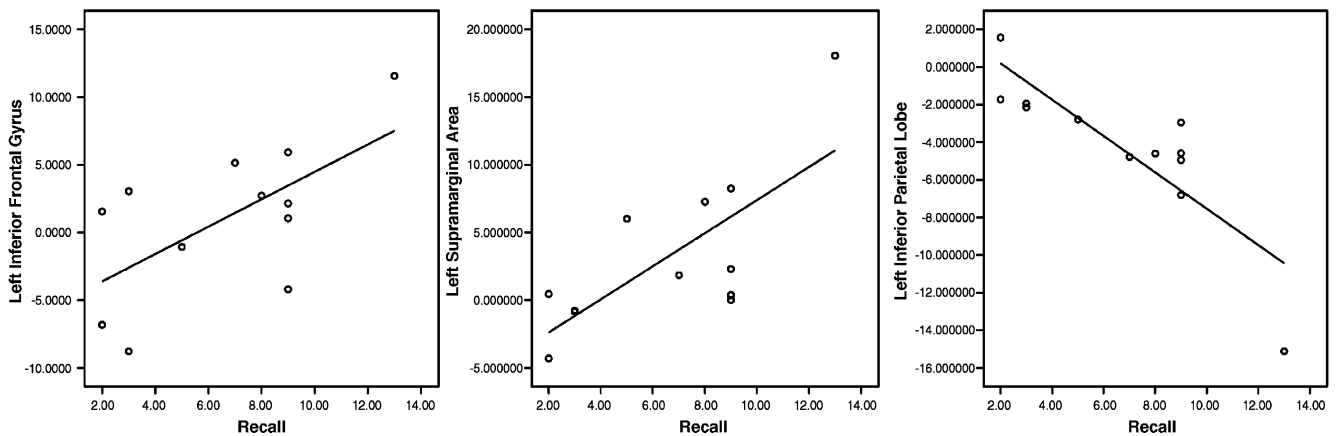


Fig. 3. Correlations between task performance (number of words recalled) and BOLD activation in the left inferior parietal lobe ($r = -0.84$, $P = 0.001$), left supramarginal area ($r = 0.73$, $P = 0.007$), and the left inferior frontal gyrus ($r = 0.63$, $P = 0.03$) in the OSA group. BOLD activation units are dimensionless values that represent the mean parameter estimates.

activation in OSA patients in areas not typically activated during verbal encoding involved right hemisphere homologues of left hemisphere regions typically related to verbal encoding. Examples include right dorsolateral PFC, middle temporal gyrus, and inferior parietal lobe, as well as the right hemisphere homologue of Broca's area (BA 44).

Compensatory recruitment in OSA

Increased brain responses in one group relative to another can be interpreted either as compensatory recruitment benefiting performance or as disinhibition interfering with cognitive performance (Cabeza, 2002; Drummond et al., 2000, 2004; Logan et al., 2002). With respect to potential compensation, the fact that our OSA patients showed intact performance relative to controls suggests that the increased activation may represent effective recruitment of resources beyond those utilized by controls. For example, activation within temporo-occipital and parieto-occipital regions associated with object and spatial processing, respectively, may have contributed to more effective encoding or maintenance in the OSA patients. The relationship between performance and cerebral responses in OSA also supports a compensation interpretation. Specifically, increased activation in areas related to deeper semantic processing and forming heteromodal associations was significantly associated with better memory performance. On the other hand, activation of a left inferior parietal lobe area associated with shallower phonological processing (Ravizza et al., 2004) was associated with worse recall. With respect to potential disinhibition in OSA, the patients showed positive activations in some areas showing negative activations in controls (Fig. 2c), including bilateral regions in the thalamus, and right hemisphere declive, precuneus, and inferior parietal lobe. Of course, in the absence of significant relationships with memory scores, it is unclear whether these regions are involved in an active compensatory mechanism or are more passively disinhibited and interfere with task performance. Consequently, we suggest that, overall, recruitment of additional brain regions to participate in VL performance in OSA patients likely represents an adaptive compensatory recruitment response. This argument is further supported by comparisons with the sleep deprivation and aging literatures.

Comparison with total sleep deprivation

Our findings are consistent with studies showing compensatory recruitment in normal adults following TSD. Similar to changes observed in this study with OSA patients, increased activation after TSD during verbal encoding was found bilaterally in PFC, parietal lobes, and thalamus (Drummond et al., 2000, 2005). Increased thalamic activation in OSA patients, including in the ventrolateral thalamus, is also consistent with similar findings during performance of attention tasks after TSD in controls (Portas et al., 1998) and may reflect the increased level of state sleepiness in the OSA patients. Similarities between the brain's response to OSA and experimentally induced TSD suggest similar cerebral compensatory responses in these two conditions. However, increased activation in OSA patients seemed to be more widespread relative to TSD, both in terms of the number of regions and the size of activated clusters. Furthermore, while TSD is an acute experimental condition, OSA is chronic and involves intermittent hypoxia. Thus, it is unlikely that all of the cerebral repercussions of OSA are related to the associated sleep loss.

Comparison with aging

While increased activation in experimentally induced TSD implies acute compensatory recruitment of brain resources, increased activation in OSA patients actually relate to more permanent OSA-related changes in brain anatomy and physiology, whose effects are likely exacerbated by nightly sleep fragmentation. This may be similar to the functional compensation suggested to be associated with healthy aging. Increased activation in older adults has been reported during various tasks including verbal tasks (Cabeza et al., 1997; Morcom et al., 2003). Consistent with our finding of more bilateral activation in OSA patients, older adults often show more bilateral activation than younger adults especially when performance level and effort are matched (Cabeza, 2002; Cabeza et al., 1997; Reuter-Lorenz and Lustig, 2005). For example, when encoding of verbal stimuli leads to successful memory, younger adults show left PFC cortex activation, whereas older adults show activity in the homologous left and right PFC regions (Morcom et al., 2003). These changes in older adults may reflect an attempt to counteract age-related neurocognitive decline (Cabeza, 2002; Reuter-Lorenz and Lustig, 2005). Since OSA, like aging, involves gradual anatomical and physiological changes as well as cognitive decline, recruitment of additional brain regions in order to cope with cognitive challenges in the face of neurocognitive decline may suggest a global functional reorganization processes. Future studies using functional connectivity analyses and/or longitudinal designs would be needed to address this issue.

While we believe the increased activation found here in OSA relates to compensatory recruitment, this explanation is not consistent with the findings from the only other published neuroimaging study in OSA patients. As described above, Thomas et al. (2005) recently reported significantly reduced activation in OSA patients relative to controls. A few important differences between the studies may explain the discrepancies. Thomas et al. study used an *n*-back task, assessing working memory, on which the OSA group performed with reduced accuracy and speed than controls. As recognized in the sleep deprivation literature (Drummond and Brown, 2001), cognitive task-related factors may have an effect on whether an increased or decreased response to cognitive challenges is observed. Thomas et al. used a task of executive functioning known to be both sensitive to sleepiness and impaired in OSA patients, while we used a task of verbal short-term memory, a function that is usually preserved in this population (Beebe et al., 2003). Thus, the brain's ability to demonstrate compensatory recruitment in the latter but not the former may account for differences typically seen in OSA patients performing such tasks. In addition, OSA severity in Thomas's study was higher than in our study, as they used a minimal AHI of 40. It is possible that compensatory recruitment is less likely in patients with more severe OSA.

Potential limitations and future directions

Since the BOLD contrast is a relative fMRI response, it is sensitive to baseline physiological parameters such as cerebral blood flow (CBF), cerebral blood volume, tissue oxygenation, and oxidative metabolism (Shen et al., 2005). As OSA is often associated with vascular changes, one may suspect that differences in relative stimulus-evoked BOLD changes do not necessarily indicate differences in stimulus-evoked neural activity,

but may rather be due to differences in baseline physiology. Though our data cannot conclusively demonstrate that differences in baseline physiology are not partially responsible for the observed increased activation in the OSA group, we have done our best to minimize these possible confounds by excluding participants with conditions that perturb basal CBF and/or cerebral neurovascular coupling such as hypertension (Fujishima et al., 1995), stroke (Krainik et al., 2005), diabetes (Rosengarten et al., 2004), and coronary or cerebral vascular diseases (Hamzei et al., 2003) and by matching the groups on BMI and blood pressure. Furthermore, the facts that OSA patients showed only very minimal differences to controls on the sensorimotor task and these differences were in the opposite direction as group differences on the VL suggest that the observed increased activation during VL does not reflect a global change in the baseline BOLD response. Future research could further address this issue by measuring CBF via arterial spin labeling to better scrutinize various physiological contributions to the fMRI signal in OSA patients relative to controls.

Another limitation is the representativeness and relatively small size of the sample. In an effort to minimize possible confounds, we studied a sample of relatively healthy OSA patients that is by no means a representative sample of the OSA population, who often have various comorbid conditions (e.g. hypertension, cardiovascular diseases, diabetes). However studying a “clean” sample is important in these early attempts to understand the cerebral changes associated with OSA. While our sample size was sufficient to detect effects in the fMRI data, it was likely underpowered to detect possible smaller effect sizes in the behavioral data. Future studies should employ larger samples as well as explore the role of various comorbidities in the behavioral and cerebral abnormalities seen in OSA patients.

Finally, assessing the reversibility of changes in brain activation in OSA following treatment will shed light on the nature of the compensatory processes described here and will help determine to what extent these changes resemble the anatomical/functional reorganization occurring in older adults. Given that at least some aspects of cognitive performance deficits are reversed with treatment, this may be reflected in neuroimaging measures of brain function. Such outcome studies may improve our understanding of OSA and its effects on the brain and assist in developing appropriate treatments for the neurocognitive aspects of this highly prevalent syndrome.

In summary, we found increased cerebral responses and intact performance during VL in OSA patients relative to well-matched Controls. We interpret these findings as being compensatory in nature. Differential patterns of compensatory vs. diminished responses may account for why OSA patients show intact performance on some tasks and deficits on others. Furthermore, since sleep apnea is a very common syndrome (up to 28% of the adult population), the findings of altered brain activation in this group suggest that this is a potential confound in functional neuroimaging studies, especially those that compare two groups at differential risk for OSA. For example, OSA could influence the findings from studies comparing younger adults with older adults, who show a higher prevalence of OSA. Potential ways to address this would include administering the ESS along with specific questions covering the main OSA symptoms as part of subject screening procedures. This would allow investigators to exclude anyone at high risk for OSA.

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