Increased brain activation during verbal learning in obstructive sleep apnea

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Functional magnetic resonance imaging (fMRI)

- Measuring the haemodynamic response related to neural activity in the brain.
- Noninvasive technique.
- Using a powerful magnetic field, radio waves and a computer to produce detailed pictures of organs, soft tissues, bone and virtually all other internal body structures.

Functional magnetic resonance imaging (fMRI)

- Hemoglobin
  - diamagnetic when oxygenated
  - paramagnetic when deoxygenated
- The magnetic resonance (MR) signal of blood is therefore slightly different depending on the level of oxygenation.
- Detected by blood-oxygen-level dependent (BOLD) contrast.
- fMRI contrast is thus determined by the ratio of oxygenated to deoxygenated haemoglobin in blood

Obstructive sleep apnea (OSA) syndrome

- Repeated episodes of upper airway obstruction during sleep that result in intermittent hypoxemia with periodic arousals (Malhotra and White, 2002).
- Patients with OSA commonly report excessive daytime sleepiness and lack of concentration.
- OSA is recognized as a significant public health problem that imposes substantial cardiovascular and neurocognitive morbidities. (Kroehl et al., 1998; Engleman et al., 2000)
Beebe et al., 2003

- A comprehensive meta-analysis in OSA concluded that
  - vigilance and executive functioning are impaired
  - general intelligence, verbal ability and short-term verbal memory are intacted
- 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.

Thomas et al., 2005

- Untreated OSA patients
  - 2-back working memory task

  ![Diagram of brain regions](image)

  - 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 (adult) have been shown to lead to cognitive deficits.

Cerebral responses

- Decreased activation
  - both older adults and sleep deprived young adults during arithmetic working memory tasks. (Smith et al., 2001; Drummond et al., 1999; Thomas et al., 2000)
- Increased activation
  - both healthy aging and sleep deprivation during verbal learning tasks. (Cabeza et al., 1997; Marcom et al., 2003; Drummond et al., 2000, 2005)

- Increased activation during learning (and other tasks) is associated with better cognitive performance, leading many authors to interpret this increase 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 may also be secondary to a compensatory mechanism resulting in increased activation. (Beebe et al., 2003)
• 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.

Hypothesis
• OSA patients, relative to controls, would show intact verbal learning performance.
• 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
• Right-handed and free of current and past psychiatric and medical disorders as determined by history and physical exam.
• All participants obtained an average of 7.7 ± 0.9 h of sleep per night for the 3 nights preceding the study.
Sleep questionnaires

• The Epworth Sleepiness Scale (ESS) (Johns, 1991) – is a questionnaire intended to measure daytime sleepiness. This can be helpful in diagnosing sleep disorders.

- 0 = no chance of dozing
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

0 – 9 = average score, normal population
10 – 24 = sleepiness

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance Of Dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting inactive in a public place (e.g., theater or a meeting)</td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td></td>
</tr>
</tbody>
</table>

Polysomnography

- EEG
- EOG
- ECG
- Airflow
- Oxymeter
- Thoracic and abdominal excursions
- EMG
• 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.
• Apnea–hypopnea index (AHI) was calculated representing the number of apnea and hypopnea events per hour of sleep.

<table>
<thead>
<tr>
<th>AHI</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Normal</td>
</tr>
<tr>
<td>5-15</td>
<td>Mild</td>
</tr>
<tr>
<td>15-30</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Severe</td>
</tr>
</tbody>
</table>

• Records were scored for sleep stages according to the criteria of Rechtshaffen 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.

The verbal learning task
• During the fMRI session, participants performed a VL task.
• Stimuli, nouns, were presented visually via a video projector

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.
8 cycles of 15 s. on and 15 s. off

**Data analysis**

- **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

**For the VL performance analysis**

- bilateral inferior frontal gyrus
- bilateral inferior and superior parietal lobes
- bilateral thalamus and hippocampal formation

**The analysis for the sensorimotor task**

- precentral & postcentral areas (somatosensory, motor cortical)
- inferior, middle, and superior occipital gyri (visual cortical)

**Data analysis**

- **Memory** (immediate free recall, delayed recall and recognition memory scores) and **questionnaire data** were analyzed with Student’s **t** tests comparing the OSA & Control groups.
- Spearman correlations between free recall performance & questionnaires were calculated.
- FMRI data were processed and analyzed with AFNI, data sets were transformed to standard atlas coordinates (Talairach & Tournoux, 1988)
Results

Sleep and sleepiness

• Polysomnography
  – No significant differences between the groups were found in total sleep time or percentage of any sleep stage.
  – OSA group had significantly higher AHI, higher arousal index and higher oxygen desaturation index than the control group.
• Questionnaires
  – OSA group reported significantly higher daytime sleepiness than the control group as measured by the ESS

Behavioral data

Table 2
Verbal learning performance, concentration, task difficulty, motivation, and effort

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

d' = discriminability index.
P value is for independent samples t test.

Correlations between performance and subjective measures

• Subjective ratings of trait and state sleepiness were not significantly correlated with free recall performance
• 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

The verbal learning task

In the control group

• Activated mainly a left hemisphere
  – the inferior(BA47), middle(BA4,6,9), and superior(BA6,8) frontal gyri, middle temporal gyrus(BA21), and bilateral parahippocampal gyrus(BA28/35).
• Decreased activation
  – bilateral of the thalamus, right decline, right precuneus(BA7T), and right inferior parietal lobe(BA40).
**The verbal learning task**

In OSA patients

- Showed increased activation compared to controls
Correlations between BOLD response and VL performance in the OSA group

left inferior frontal gyrus (BA 47) left supramarginal area

Correlations between BOLD response and VL performance in the OSA group

left inferior parietal lobe (BA 40)

The sensorimotor task

Table 4

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>Volume (mm³)</th>
<th>Center (x, y, z)</th>
<th>Max. Eta-Sq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcentral</td>
<td>832</td>
<td>-36, -32, 51</td>
<td>0.33</td>
</tr>
<tr>
<td>Precentral</td>
<td>576</td>
<td>-55, -8, 32</td>
<td>0.30</td>
</tr>
</tbody>
</table>

- Comparison of the BOLD response in the control & OSA groups during the sensorimotor task revealed only decreased activation in the left postcentral and precentral gyri in the OSA group.
- 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.

OSA patients would show intact performance on the task along with increased activation as measured with the BOLD signal.

Increased activation in OSA patients manifests in regions both typically and some not typically associated with verbal encoding. (Stern, 2002)

Increased activation in regions related to verbal encoding may reflect task-related recruitment associated with the concept of cognitive reserve.
• OSA patients showed increased activation relative to controls (Cabeza and Nyberg, 2000)
  – left PFC: associated with a variety of verbal tasks
  – left superior temporal/inferior parietal lobes: involved in short-term memory store
  – cerebellum: related to articulatory control and phonological storage

• Increased 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.
  – right dorsolateral PFC
  – right middle temporal gyrus
  – right 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 or as disinhibition interfering with cognitive performance. (Cabeza, 2002, Drummond et al., 2000, 2004, Logan et al., 2002)

• With respect to potential compensation
  – OSA patients showed intact performance suggests that the increased activation may represent effective recruitment of resources beyond those utilized by controls.

The relationship between performance and cerebral responses in OSA also supports a compensation interpretation
• activation in areas related to semantic processing was significantly associated with better memory performance.

• activation of a left inferior parietal lobe area associated with phonological processing was associated with worse recall. (Ravizza et al., 2004)
• With respect to potential **disinhibition**
  – OSA patients showed positive activations in some areas showing negative activations in controls:
    • bilateral regions in the **thalamus**
    • right hemisphere declive, precuneus and inferior parietal lobe.

We suggest that recruitment of additional brain regions to participate in VL performance in OSA patients likely represents an adaptive compensatory recruitment response.

**Comparison with total sleep deprivation**

• Our findings are consistent with studies showing **compensatory recruitment in normal adults following TSD** (Drummond et al., 2000, 2005)
  – increased activation after TSD during verbal encoding was found bilaterally in PFC, parietal lobes, and thalamus.

**Comparison with aging**

• Increased activation in OSA patients seemed to be more widespread relative to TSD.
• 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.

• Increased activation in older adults has been reported during various tasks including verbal tasks. (Cabeza et al., 1997; Morcom et al., 2003)
• When encoding of verbal stimuli leads to successful memory (Morcom et al., 2003)
  – younger adults show left PFC cortex activation
  – older adults show activity in the homologous left and right PFC regions.
• Consistent with our finding of more bilateral activation in OSA patients.
• 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.

• We believe the increased activation found here in OSA relates to compensatory recruitment.
• Thomas et al. (2005) recently reported significantly reduced activation in OSA patients relative to controls
  – study used an 2-back working memory task
  – the OSA group performed with reduced accuracy and speed than controls

• Thomas et al. used a task of executive functioning known to be 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)
• 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
• 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.

• We have done our best to minimize these possible confounds by excluding participants with conditions that perturb basal CBF and/or cerebral neurovascular coupling
  – hypertension, stroke, diabetes, and coronary or cerebral vascular diseases
  – matching the groups on BMI and blood pressure.

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, who have not 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.
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.

Summary

• Increased cerebral responses and intact performance during VL in OSA patients relative to well-matched controls.
• Interpreted 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.

• 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.
• 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.
Thank you