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Functional Magnetic Resonance Imaging study of Working Memory in Obstructive Sleep Apnea Patients before and after Treatment with Continuous Positive Airway Pressure

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1. Obstructive Sleep Apnea (OSA)

1.1 Introduction

Obstructive sleep apnea syndrome (OSAS) refers to a breathing disorder during sleep characterized by repeated episodes of upper airway obstruction resulting in cessation (apnea) or reduction (hypopnea) in airflow during sleep. OSAS results in recurrent hypoxic episodes during sleep, fragmented sleep, cardiovascular comorbidities, neurocognitive impairment during the day, and excessive daytime sleepiness.[1-6] It is a frequent but insufficiently recognized disorder that involves at least 2% to 4% of subjects between 30 to 60 years old and up to 15% of the elderly population, with a 2:1 men/women ratio in Caucasians.[7]

The scope of this work focuses on the role of OSA in associated cognitive impairment, the investigation of neural correlates of cognitive deficits and their evolution in response to treatment.

1.2 OSA and cognitive function

It is now well recognized that OSAS is associated with cognitive impairment. Whereas there is no impact on general intelligence and verbal ability and there are inconsistent findings in respect to impact on memory, visual and motor skills[8], a consistent negative impact of OSA is found in the literature in the realm of executive function and the ability to sustain attention for extended periods of time (vigilance) [8-10].

"Executive function" is generally defined as a high-level cognitive function that allows us to organize our thoughts in a goal-directed way, plan and perform the sequence of necessary

actions while inhibiting irrelevant information and inappropriate behaviors. Executive abilities are believed to be supported essentially by the frontal lobes[11].

The domains of executive function that were most often impaired across studies of OSA patients are working memory, phonological fluency, cognitive flexibility and planning[12, 13].

In an attempt to link the physiological consequences of OSA to its behavioral and cognitive effects Beebe and Gozal have proposed a theoretical model, that attributes executive dysfunction to disruption of normal functioning of the prefrontal cortex (PFC), secondary to adverse cellular and biochemical events triggered by sleep disruption, intermittent hypoxia and hypercarbia in the context of OSA[14].

PFC has been established as the neurological correlate of executive function with different regions of PFC linked to different aspects of executive function, such as behavioral inhibition (orbital cortex) and working memory (DLPFC) and it is also the region primarily affected in aging subjects, schizophrenic patients and in healthy subjects after total sleep deprivation, all of whom manifest a certain degree of executive function impairment [15-22]. The high sensitivity of this brain region to the effects of sleep deprivation was well demonstrated by several studies done on healthy volunteers [20, 23]. However, even if the PFC is recognized as the primary brain region supporting executive function, neuroimaging studies have revealed that an efficient interplay of activation and deactivation of a network of regions is necessary for optimal behavioral performance (see below). Therefore, executive dysfunction can arise not only from lesions to the PFC, but also other regions of this network, or even from a less efficient functional connectivity within it.

1.2.1 Working memory and n-back task

Working memory (WM) represents an aspect of "executive function" and is defined as an online information processing system that enables the maintenance and manipulation of information in the service of higher-order tasks, such as reasoning, planning and problem-solving[24].

WM is commonly the most studied aspect of executive function in neuroimaging and behavioral literature, often using the n-back task that requires subjects to compare the current stimulus with the one presented n-stimuli back.

The *n*-back paradigm requires a continuous monitoring of sequentially presented stimuli, and subjects must answer whether the current stimulus matches the stimulus occurring *n* positions back in the sequence. The task combines maintenance as well as active manipulation, i.e., executive processes, because of the necessity to continuously encode, update, and discard the information held in WM with the presentation of each new stimulus. The value of *n* is regarded as proportional to memory load[25].

Load manipulation yields information in respect to the cognitive capacity and limit thereof in the studied population. This is particularly important in situations where cognitive deficit is mild and could be masked by a ceiling effect of an easy cognitive task. It is worth mentioning that most studies in OSA patients that used an n-back task, have used 2-back as their maximal task load, which possibly did not allow to examine the limit-of-capacity domain of WM in these patients.

1.3 Continuous Positive Airway Pressure (CPAP)

Historically, the first treatments of OSA were surgical, consisting in the beginning of tracheostomy, uvulopalatopharyngoplasty (UPPP), followed in later years by maxillo-mandibular advancement. In 1981 Collin Sullivan proposed a new non-surgical treatment of OSA, which quickly became the gold standard treatment option for the majority of OSA patients.

Positive air-pressure of nasal CPAP, acting as a pneumatic splint for the nasopharangeal airway allows normalization of sleep by preventing airway collapse secondary to sleep-induced decrease of muscle tonus of pharyngeal walls and base of the tongue.

It is well established that CPAP treatment significantly improves daytime sleepiness, quality of life and several aspects of cognitive function in OSA patients. However, it now appears

that even the most optimally treated and compliant patients with OSA may not experience a complete reversal of daytime symptoms and functional abnormalities[26]. Moreover, some aspects of cognitive impairment, such as executive function, seem to be less reversible than others. This observation led to the hypothesis that OSA patients sustain permanent cellular damage, possibly due to repetitive hypoxic injury, which is supported by recent results of volumetric studies.

Most studies assessing the efficacy of CPAP on cognition have been conducted using behavioral measures as their outcome. However, little could be inferred about the neurological substrate of the observed deficits until behavioral performance was coupled with neuroimagery.

2. Neuroimagery

A number of neuroimaging studies have been conducted in OSA patients in order to uncover the particularities of brain metabolism (Positron Emission Tomography studies) and brain structure (spectroscopy, Voxel Based Morphometry studies)[27].

In the current work we are going to focus on Functional Magnetic Resonance Imaging (fMRI) studies that allow the investigation of neural correlates of the behavioral performance during a given cognitive task with a high spatial and temporal resolution.

2.2 Functional Magnetic Resonance Imaging (fMRI)

BOLD (Blood Oxygenation Level Dependent) fMRI is a relatively new imaging technique that enables non-invasive investigation of brain function by detecting changes in the magnetic susceptibility of blood[28].

Neural processes related to a given cognitive task require an increase in neuronal metabolism with increased demand for energy consumption. Vascular response to this demand in the

brain has the particularity of a disproportional increase of local cerebral blood flow in respect to the metabolic demand, leading to a local shift in the relationship of oxygenated to deoxygenated hemoglobin towards an increase of oxygenated hemoglobin. BOLD fMRI is based on the detection of changes in magnetic signal related to changes in deoxyhemoglobin concentration in the small vessels supplying the brain region involved in a given cognitive task. Therefore, whereas BOLD fMRI represents a non-invasive and safe technique for investigation of neuronal processes, it is important to account for the fact that it does so indirectly, by looking at vascular changes related to neuronal changes, and is thus susceptible to conditions that can introduce vascular confounds.

fMRI studies of WM in healthy volunteers have established a network of brain regions activated during WM tasks, consistent mostly of fronto-parietal regions and referred to as Task Positive Network (TPN). More recently, research has started to focus on a network of regions that exhibits a progressive deactivation during performance of cognitive tasks, the Task-Induced Deactivation Network. The Task-Induced Deactivation Network has been shown to consist of the same brain regions as the functionally connected resting state Default Mode Network (DMN), which is anti-correlated with the TPN and plays a crucial role for optimal behavioral performance. Since Task-Induced Deactivation Network and the DMN consist of the same brain regions and represent the same functional entity, in this work we shall refer to task-induced deactivation regions as the DMN.

To date, 3 neuroimaging studies have examined aspects of executive function in OSA patients, with varying results. Patterns of reduced or increased brain activation have been reported in association with decreased or comparable behavioral performance relative to that of healthy controls.[29-32] However, most of the interest has been directed at the network of brain regions known to be consistently activated during sustained attention and performance of cognitive tasks and referred to as the task positive network (TPN), which comprise a set of frontal and parietal cortical regions.[33, 34]

In particular, the dorsolateral prefrontal cortex (DLPFC) is known to be a key region for performance of executive function tasks but is also the region primarily affected in aging subjects, schizophrenic patients, and in healthy subjects after total sleep deprivation, all of whom manifest a certain degree of executive function impairment.[15-22] The high sensitivity of

this brain region to the effects of sleep deprivation was well demonstrated by several studies done on healthy volunteers,[20, 23] making the DLPFC a region of special interest in cognition-related research in OSA patients.

However, there is increasing evidence that examination of activation in TPN alone does not yield a comprehensive view of cerebral response to cognitive demand. Contrary to TPN, it has been demonstrated that a set of brain regions referred to as the default mode network (DMN), comprising medial prefrontal, posterior cingulate, anterior temporal and lateral parietal cortices, exhibits tonic activation at rest and responds with progressive deactivation as the brain engages into a goal-directed activity.[35, 36] There is growing evidence that DMN plays a key role in enabling optimal cognitive functioning and that DMN dysfunction, as well as DMN versus TPN anti-correlation imbalance, are associated with cognitive performance impairment.[37] Several studies demonstrate that both networks and their reciprocal relationship contribute to the behavioral deficits observed in several pathological conditions as well as normal aging.

In OSAS patients, repetitive hypoxia and repetitive disruption of sleep associated with sleep disordered breathing have been considered as potential factors in induction of cognitive deficit; however, given their simultaneous occurrence, teasing apart the degree to which each of those factors influences cognition as well as what aspects of cognition are preferentially influenced by which OSAS factor is a challenge. Obesity is known to be associated with OSA, and the complex syndrome involving both abdominal obesity and OSA may lead to the metabolic syndrome (MetS), which comprises insulin resistance, central obesity, HTN, glucose intolerance, and dyslipidemia.[38, 39] Several components of MetS are also associated with cognitive dysfunction. In particular, there is increasing evidence that obesity as expressed by the body mass index (BMI) is associated with cognitive impairment and is a risk factor for developing dementia.[40-42] Since sleep fragmentation, intermittent hypoxia, and obesity are all factors commonly associated with OSA, it is likely that each of those factors has an impact on cognitive function of OSA patients and that their association may have a synergistic effect.

Therefore in an attempt to provide a more comprehensive view of neuronal activation changes in OSA patients in our study we are investigating changes in both WM-activation

related (TPN) and deactivation related (DMN) networks and examine the independent contributions of sleep fragmentation (SF), intermittent hypoxia (IH), and BMI on brain activation of untreated patients with OSAS during the performance of a parametric working memory (WM) task in respect to both TPN and DMN.

Part 1

Task Positive and Default Mode Networks during a Parametric Working Memory Task in Obstructive Sleep Apnea Patients and Healthy Controls

Part 1

Task Positive and Default Mode Networks during a Parametric Working Memory Task in Obstructive Sleep Apnea Patients and Healthy Controls

The aims of the first part of this study were: (a) to examine the behavioral performance and the underlying brain activation and deactivation patterns in TPN- and DMN-related regions of a sample of untreated OSA patients on a parametric WM n-back task including a limit-of-capacity 3-back level with functional magnetic resonance imaging (fMRI); (b) to compare these patterns to findings in a matched group of healthy controls (HC); and (c) to examine the possible correlations between SF, IH, and BMI and brain activation in TPN and DMN.

Based on results of previous literature, we hypothesized that:

a) OSA patients will have larger areas of activation in the TPN than HC (spatial recruitment) in order to compensate for a possibly impaired function of the TPN, which would be manifested by higher BOLD signal in HC than in OSA patients in the TPN regions.

b) OSA patients will have larger areas of deactivation in the DMN (compensatory spatial recruitment) as compared to HC in order to compensate for possibly ineffective deactivation of DMN, which would be manifested by higher BOLD signal in OSA patients than in HC in the DMN regions.

Methods

Subjects

Seventeen men diagnosed with moderate to severe OSAS were recruited from the Stanford Sleep Clinic and surrounding area via advertisement. All participants were right-handed nonsmokers and were screened for current or previous neurological and psychiatric disorder as determined by history, clinical evaluation, and Hamilton Depression Scale score. All participants reported regular sleep schedules with ≥6 h of sleep per night as determined by sleep habits questionnaires. Seven age-matched subjects without history of sleep disorders were recruited from the community as HC; and absence of sleep pathology, including sleep disordered breathing (SDB), was confirmed by an overnight polysomnography (PSG: AHI <5) (Table 1).

The study was approved by the Stanford Institutional Review Board, and all subjects signed informed consent.

Polysomnography (PSG)

Overnight PSGs were performed in all subjects. The following variables were systematically monitored: EEG, electro-oculogram, electrocardiogram, chin and leg myogram, nasal air flow with nasal cannula, abdominal and thoracic respiratory movements with piezo-electrical belts, and pulse oximetry. Studies were scored by independent technicians and reviewed by a qualified sleep medicine physician according to the AASM scoring criteria.

Experimental Procedure and n-Back Task

All subjects were instructed to abstain from ingestion of any caffeinated beverages ≥9 h prior to scanning.

During the fMRI session, participants performed 2 sessions of visuospatial n-back task that was generated with E-Prime 1.0 software and visually projected on a mirror in front of the

subject's eyes. They performed two 9 min 40 sec sessions of a block-designed parametric n-back task with 4 levels of difficulty (0-back, 1-back, 2-back, and 3-back). Each session comprised 2 blocks of each WM condition (1-, 2-, and 3-back) of 63 sec duration, separated by 5 blocks of the baseline condition (0-back) of 25.2 sec duration each (0-1-0-2-0-3-0-1-0-2-0-3). During the task, a white dot flashed for 200 ms in 6 pseudo-random locations on a black screen. Fifty percent of stimuli were matches.

Subjects were instructed to respond with their right hand (index finger for matches and middle finger for mismatch) whether the dot appeared on the left or on the right side of the screen in the 0-back condition, or whether each given dot appeared in the same or different location as the dot n-dots before for the 1-, 2-, and 3-back conditions, respectively. Subjects' responses during the n-back sessions and their response times (RT) in the scan were recorded via a custom-made response box in E-Prime Data Aid software.

fMRI Data Acquisition

Functional MRI data was acquired on a 3.0T GE (Milwaukee, WI) whole-body scanner with a custom quadrature bird-cage head coil. Head movement was minimized with foam padding. Thirty oblique axial slices were taken parallel to the anterior/ posterior commissure plane (AC-PC) with 4-mm slice thickness, 1-mm interslice gap. High resolution T2 weighted fast spin echo structural images were acquired for anatomical reference. A T2*-sensitive gradient echo spiral in/out pulse sequence[43] was used for functional imaging (TR = 2000 ms, TE = 30 msec, flip angle = 70, FOV = 24 cm, matrix = 64 x 64). An automated high-order shimming procedure based on spiral acquisitions was used to reduce B0 heterogeneity.[44] A high resolution T1 volume scan (124 slices, 1.2-mm thickness) was collected for every subject using an IR-prep FSPGR sequence for T1 contrast.

fMRI Data Analysis

Functional MRI data were preprocessed and analyzed using Statistical Parametric Mapping software (Welcome Department of Cognitive Neurology, London) and custom MATLAB

routines (MathWorks Natick, MA). The preprocessing steps consisted of realignment of all images to the first image, normalization to MNI template, and spatial smoothing with a Gaussian filter of 6 mm full-width-half-maximum.

To test for the effect of each task load, we used a standard general linear approach with 4 regressors for the 3 task load and baseline conditions, modeled as a boxcar function convolved with the canonical HRF. The 6 motion parameters from the realignment were added as 6 regressors of no interest. Statistical analysis at the single-subject level treated each voxel according to a general linear model.[45] Individual contrast images were created by computing each WM task load versus the 0-back load baseline (1 > 0, 2 > 0, 3 > 0). OSA and HC groups were then compared for each WM task load by entering individual contrast images in a 2-sample *t*-test. For each of the 3 main contrasts, we also used an ANOVA and performed an exclusive masking procedure to reveal any voxel significantly activated in one group but not in the other group (Fig. 1).

In order to minimize the type I error, a cluster threshold method was used,[46] requiring that any given voxel be significantly activated at P level of 0.001 and be a part of a cluster of ≥10 contiguous significantly activated voxels.

To test for correlation of a general task load effect with clinical measures, we performed a second analysis on the patient dataset using a multiple regression approach. We first designed a parametric model where all task blocks were modelled as one single regressor, with 2 additional regressors modeling a linear modulation of the task-related activity by load level (1-, 2-, and 3-back), a quadratic modulation of the task-related activity by load level, and 7 regressors of no interest (behavioral performance per task block and 6 motion correction parameters). Contrast images generated by the linear load regressor from each subject entered the multiple regression group analysis with AHI, time spent under 90% SpO_2 (minutes), and BMI as covariates. These analyses were performed on the data from the OSA patients only.

Results

Clinical Measure and Behavioral Performance

For 17 OSA patients, the mean AHI was 39.7 (±22.8), the mean Epworth score was 7.3 (±4), and the mean BMI was 27.8 (±4) kg/m^2. Mean minimal nocturnal oxygen saturation was 87.8% (±8.9%). Details of sleep quality and sleep stages are reported in Table 1.

During scanning subjects' accuracy decreased and response time increased with increasing n-back load. There was no difference in RT between OSA patients and HC on any level of the task load. OSA patients performed significantly worse than HC on the 3-back (79% versus 89% correct, P = 0.005), but there was no significant difference in performance for the other levels of task load (Table 2). Significant negative correlation between BMI and behavioral performance was found at the 3-back level (r = −0.7).

In order to exclude an influence of sleepiness on brain activation and performance, we examined a possible relationship between RT during the 0-back epochs throughout both sessions of the n-back task with task duration. There was no correlation between RT and task duration for either session.

fMRI

Working Memory Load

Comparing activity during each WM load versus baseline revealed 2 distinct networks. Significant activations were found in several brain regions previously described to be involved in WM processing in other fMRI studies using n-back tasks. Those included bilateral SMA, bilateral DLPFC, anterior cingulate cortex (ACC), and parietal cortex bilaterally.

On the other hand, significant deactivations with increasing load were found in the medial PFC, posterior cingulate cortex, bilateral insular and hippocampal cortex (DMN).

Both activation and deactivation networks showed a progressively marked pattern with increasing task load (Fig. 3).

Comparison between OSA Patients and Healthy Controls

For the 1-back versus baseline comparison, significantly higher activation was found in HC than in OSA patients in bilateral parahippocampal regions, right insula, bilateral claustrum, left precentral gyrus (BA 4), and right precuneus (BA 7) (Fig. 2A, Table 3). Significantly higher activation was found in the left temporo-occipital area (BA19) in OSA patients than in HC.

For the 2-back versus baseline comparison, HC had higher activation than OSA patients in right precentral (BA 44) and left middle frontal gyrus (BA 10), whereas OSA patients had higher activation in bilateral temporal (BA 37) and left occipital (BA 17) regions (Fig. 2B, Table 2).

In the 3-back versus baseline comparison, HC had higher activation than OSA patients in right precentral gyrus (BA 44), whereas OSA patients had higher activations in the left middle frontal (BA 8) region (Fig. 2C, Table 2).

Using exclusive masking of WM activated regions in OSA patients by activation in HC, we found a higher number of activated regions in OSA group at both 2- and 3- versus 0-back loads, with maximal effect at the highest difficulty level (3- vs 0-back) in TPN-related regions (Fig. 3A). DMN pattern showed a different pattern with higher number of deactivated regions in OSA patients as compared to HC in the 1 and 2- vs 0-back comparison and a recruitment of a different set of deactivated regions in HC at the 3- vs 0-back comparison, consisting of bilateral occipital (cuneus) and temporal regions (BA 21) (Fig. 3B) At the 3-back level, OSA patients still showed more widespread DMN recruitment in the bilateral insulas, anterior and posterior midline and posterior parahippocampal regions as compared to HC.

Multiple Regression Analysis

Multiple regression analysis yielded significant positive correlation between AHI and brain activation across WM task loads in the left and right frontal regions (L BA 6, 10, R BA 10) (Fig. 2A, Table 4).

We found a positive correlation between brain activation across WM task loads and sleep time spent under 90% SpO_2 in bilateral inferior frontal lobe regions (BA 47), right medial frontal gyrus (BA 11), right anterior and bilateral posterior cingulate (R BA 24, L BA 23, 29), left subcallosal gyrus (BA 25), left precentral region (BA 6), bilateral temporal poles (BA 38), right parahippocampal gyrus (BA 34), bilateral occipital regions (L BA 18, R BA 31), and left cerebellar regions (culmen). Negative correlation was found in the bilateral frontal (L BA 6, R BA 8) and left parietal lobes (BA 2, 7) (Fig. 2B, Table 4).

Significant negative correlations have been found for BMI in left frontal cortex (BA 10), right temporal (BA 42), left claustrum, bilateral occipital (BA 18, 19), and cerebellar regions. There was no positive correlation between BMI and brain activation across the WM task loads.

Discussion

Recent research on task positive and default mode networks in the human brain indicates that dysfunction of both those networks, as well as the imbalance of the antagonistic relationship between them, can lead to behavioral impairment and are in fact observed in several conditions associated with cognitive deficit, such as normal aging, Alzheimer disease, schizophrenia, ADHD, and depression.[47] In particular, it has been shown that the extent of task-related deactivations in the DMN could differentiate between subjects with mild cognitive impairment, Alzheimer disease, and healthy controls, with lesser deactivation in MCI than healthy controls and in Alzheimer patients than in MCI.[48] Furthermore, Lawrence et al have demonstrated that good behavioral performance on a sustained attention/WM task can arise from stronger activation in the TPN, stronger deactivation in the DMN, or a mixture of strong levels of activation and deactivation.[49]

In our study, both groups demonstrated a progressive increase of spatial recruitment of regions within and adjacent to the TPN from 1- to 3-back level of task, probably reflecting a continuous compensatory effort, with a larger recruitment in OSA subjects as compared to HC. However, the groups differed in the task-related deactivation of the DMN with more widespread deactivation (DMN spatial recruitment) in OSA than in HC at the 1 and 2-back level and a different pattern of compensatory recruitment in the two groups at the 3-back level, in spite of a continuous spatial recruitment of DMN regions in both groups with increasing load (Fig. 3).

Therefore, significantly worse behavioral performance of OSA patients at the 3-back level appears to be related more to a different pattern of recruitment and deactivation of DMN-related regions than a defective TPN.

Our finding of positive correlation between cerebral activation during the n-back task and the measure of nocturnal desaturation in a number of regions of and adjacent to the DMN (particularly in bilateral temporal poles and mesial temporal regions) suggests intermittent hypoxia to be a major factor for the DMN dysfunction in OSA patients. IH was also found to have a negative impact on TPN regions, with a negative correlation between IH and cerebral activation in bilateral frontal and left parietal regions.

Defective deactivation of a network of brain regions commonly more active during rest than during a cognitive task (DMN) has been demonstrated to be related to worse behavioral performance in a number of conditions associated with cognitive impairment and sleep disturbances (normal aging, Parkinson disease, schizophrenia, ADHD), suggesting that inability to reallocate neuronal resources and suppress activity in neighboring regions plays a role in cognitive impairment.[50-53] Disruption of task-related deactivation within the midline regions of DMN has been reported after acute sleep deprivation,[54] and slower reaction times on a psychomotor vigilance task have also been associated with increased activation in midline DMN regions after total sleep deprivation,[55] suggesting that sleep deprivation has a direct impact on DMN. Similarly, reduced deactivation in the posterior regions of DMN has been shown to be related to attentional lapses in healthy subjects.[56] In regard to those findings, the observed recrutement in midlineregions of DMN in OSA patients in our study

together withthe absence of changes in reaction times suggests that sleep deprivation is not the mechanism that dysregulates DMN in OSA patients.

We found significantly increased brain activation in HC as compared to OSA patients in several regions of the limbic system at the 1- versus 0-back comparison. The analysis of parameter estimates trend revealed a peak of BOLD signal at 1-back in HC that is absent in OSA patients. Several of those brain regions are known to be implicated in emotional and autonomic nervous system control.[57-60] It is well established that OSAS is associated with autonomic nervous system dysfunction.[61, 62] Therefore, we believe that the observed difference in activation reflects a blunted autonomic response in OSA patients. Indeed, the design of our task means that each session began with the 1-back task as the first load block (see Methods), clearly enhancing the risk of task-related stress due to the new situation during this test. This proposition is further supported by a re-analysis of data that considered only the second part of each session, in which there was no difference between patients and HC in those regions. Further studies including autonomic nervous system measures are needed in order to evaluate more in depth this specific aspect of the testing situation.

Finally, more and more attention is being directed to the effect of obesity per se on cognitive function, as it has been shown that excess body weight is associated with brain structural and functional alterations[63] and a higher risk of developing dementia in later life.[40] Higher BMI was found to be associated with hypometabolism as well as reduced NAA/Cho ratio of the prefrontal and cingulated regions.[64, 65] Behaviorally, several studies find a significant relationship between high BMI and cognitive dysfunction in otherwise healthy adults or after controlling for BP, age, and diabetes.[40, 41, 66] Since obesity is strongly associated with OSA due to patient recruitment, it is important to examine the independent effect of BMI on cognitive function of OSA patients and to systematically account for its effect in cognition studies in these subjects. Our results are in line with previous literature, as we found only negative correlations between BMI and brain activation during the WM task in a number of brain regions of the TPN, in particular in bilateral DLPFC and occipital and cerebellar regions. Not surprisingly, BMI and desaturation time were significantly correlated in our sample, hence using a multiple regression model allowed us to tease apart their independent influence on cerebral activation during the WM task. However, despite the significant

correlation between BMI and desaturation time, only BMI was significantly negatively correlated with behavioral performance at the limit-of-capacity level of task (3-back), suggesting that BMI has a more deleterious role on WM function in OSA than sleep fragmentation and nocturnal desaturation. This finding and the fact that only negative correlations were found between BMI and cerebral activation suggests that BMI has a structural impact on the grey matter of the TPN. Thus, further studies are needed to investigate the independent impact of BMI and the effect of obesity treatment on cognitive function in OSA.

Several neuroimaging studies have previously investigated executive function aspects in OSA patients. Thomas et al reported a decreased brain activation in anterior cingulate, bilateral DLPFC, and posterior parietal regions in OSA patients during the performance of a 2-back verbal task, which paralleled a significantly worse behavioral performance as compared to healthy controls.[29] Ayalon et al, using a Go-no-Go task, reported a decreased cerebral activation in several regions typically involved in attentional tasks in patients compared to controls, whereas there was no significant difference in behavioral performance and response time between the two groups for the Go versus rest (although there was a trend towards worse performance in patients for the No-go versus rest comparison).[30, 31] Castronovo et al have reported an increased activation in OSA patients versus HC in left frontal regions, precuneus, putamen, hippocampus, and cerebellum, as well as decreased activation in brainstem, left occipital, and right orbital regions at similar behavioral performance at a 2-back task.[32]

Our study differs from previous studies on several points: (a) it considers a visuospatial (and not a verbal) n-back task, (b) it involves 4 levels of difficulty, and (c) it examines BOLD signal changes in not only the TPN but also the DMN regions. It is therefore more difficult to draw direct comparisons between our results and results of previous studies. However, similar to previous studies we found an increase in spatial recruitment of TPN, in particular of the left hemisphere, in OSA patients as compared to HC, as well as a decrease in activation in frontal regions involved in WM function, particularly at more difficult task levels. Moreover, Castronovo et al have reported an increased activation in the precuneus in

their OSA group, which partly corroborates our results of decreased deactivation in posterior regions of DMN.

Our study has limitations: we have examined only male subjects, as controversy exists about gender effects on brain activation during cognitive performance; therefore our results cannot be extended to female OSA patients. Our patient and HC groups also significantly differed in the average of years of schooling, introducing the question of contribution of intelligence level (when based on years of schooling) to the observed behavioral and neuronal differences. We believe however that this bias is not as important as it seems: although statistically significant, the schooling difference between the groups was small, and both groups had a high educational level (mean of 16.5 and 18.9 years). Having a more reliable measure of fluid intelligence than the education level would be certainly more relevant.

Whereas the design of our task demanded an alternation between four task levels—the 1-, 2-, and 3-back blocks having a duration of 1 min for a total of 4 min on each task level per patient not allowing observation of potential effects due to a long time-on-task—it enabled us to include a limit-of-capacity 3-back level in our parametric design, requesting more effort from patients and HC. As our primary interest was the difference in WM function, shorter block duration gave us the advantage of not having the confounding effect of fatigue, typically seen in sleep deprived subject in designs with long time-on-task blocks. But the fixed order of increasing load difficulty in our task design, while likely enabling us to uncover a different trend of response to stress between the two groups, may have masked more WM-related effects at the low-load level. We believe that differences in task designs between various studies, although making the result comparison more difficult, yield complementary information on brain function in OSAS.

Table 1: Sample characteristics

Age	43.2 (±8.4)
BMI	27.8 (±4)
AHI	39.7 (±22.8)
Ethnicity	4 Asian, 12 Caucasian, 1 Hispanic
TST	376.8 (±71.1)
Sleep efficiency	83.1 (±13.1)
REM	17.9 (±4.9)
Stage 1	12 (±7.3)
Stage 3+4	7.9 (±8.9)
Min SpO_2	87.8 (±8.9)

BMI = body mass index, AHI = apnea hypopnea index, TST = total sleep time

Table 2: Behavioral performance in OSA patients and HC

	OSA patients	HC	P value
Accuracy 0-back	99 (±2.5)	99.5 (±0.8)	0.5
RT 0-back	466.9 (±125.6)	446.2 (±117.5)	0.7
Accuracy 1-back	96.7 (±4.7)	96.3 (±4.3)	0.9
RT 1-back	762.7 (±167)	671.3 (±182.8)	0.3
Accuracy 2-back	91.4 (±6.8)	93.6 (±5.3)	0.4
RT 2-back	984.6 (±318.2)	806.8 (±274.2)	0.19
Accuracy 3-back	78.9 (±10.6)	89 (±5.2)	0.005
RT 3-back	1197.1 (±322)	992.1 (±239.6)	0.1

HC = healthy controls; RT = reaction time

Table 3: Talairach coordinates of brain regions showing significant differences in cerebral activation between OSA patients and healthy controls (*t*-test analysis)

X	Y	Z	Brodman region
OSA >HC 1- vs 0-back			
-42	-59	18	L BA 19
HC >OSA 1- vs 0-back			
-30	-6	-11	L BA 34,38
-40	2	-11	
-32	1	-9	
49	-19	-18	R BA 20
20	-9	-18	R BA 34
27	-20	-22	R BA 36
18	-14	-24	R BA 28
36	-8	8	R claustrum
45	-7	1	R insula
-45	-18	-22	L BA 20
-17	-16	-23	L BA 28
-51	-11	26	L BA 4
-12	-88	-13	L BA 18
38	4	-4	R claustrum
2	-44	47	R BA 7
OSA >HC 2- vs 0-back			
6	-33	17	R pulvinar

51	-50	-9	R BA 37
-44	-49	-8	L BA 37
-12	-95	-3	L BA 17
HC >OSA 2- vs 0-back			
-38	39	9	L BA 10
51	3	13	R BA 44
OSA >HC 3- vs 0-back			
-27	-76	-5	L BA 19
-35	18	38	L BA 8
HC >OSA 3- vs 0-back			
56	7	11	R BA 44

(P = 0.001, voxel extent threshold = 10)

Table 4: Talairach coordinates of brain regions showing significant correlation with AHI, desaturation time, BMI, and cerebral activation during the WM task

X	Y	Z	Brodman region
Positive correlations with AHI			
-32	37	9	L BA 10
-57	-2	27	L BA 6
38	43	7	R BA 10
Negative correlations with AHI			
-16	-30	-19	culmen
Positive correlations with Desaturation Time			
-49	29	-3	L BA 47
24	34	29	R BA 47
5	28	-15	R BA 11
-1	17	-12	L BA 25
5	31	-5	R BA 24
-9	-13	24	L BA 23
6	-69	21	R BA 31
-16	-48	14	L BA 29
-43	17	-16	L BA 38
38	19	-13	R BA 38
-9	-73	21	L BA 18
29	2	-17	R BA 34
-14	-31	-21	culmen
Negative correlations with Desaturation Time			
45	11	42	R BA 8
-57	-2	30	L BA 6

-29	-50	39	L BA 7
-48	-16	48	L BA 2

Negative correlations with BMI

-29	50	12	L BA 10
60	-13	14	R BA 42
-11	-73	21	L BA 18
-23	-50	-3	L BA 19
19	-52	0	R BA 19
-34	-12	-5	L claustrum
29	2	-18	R BA 34
-23	-34	-28	L cerebellum
-19	-39	-23	L cerebellum
20	-33	-26	R cerebellum
23	-38	-30	R cerebellum

(P = 0.001, voxel extent threshold = 10)

Figure 1: Spatial recruitment of A: TPN in OSA patients after exclusive masking by brain activation of the HC group (left) and spatial recruitment of TPN in HC after exclusive masking by brain activation of OSA group (right); B: DMN in OSA patients after exclusive masking by brain deactivation of the HC group (left) and spatial recruitment of DMN in HC after exclusive masking by brain deactivation of OSA group (right). Exclusive masking (p=0.05), FDR correction for multiple comparisons (p=0.05).

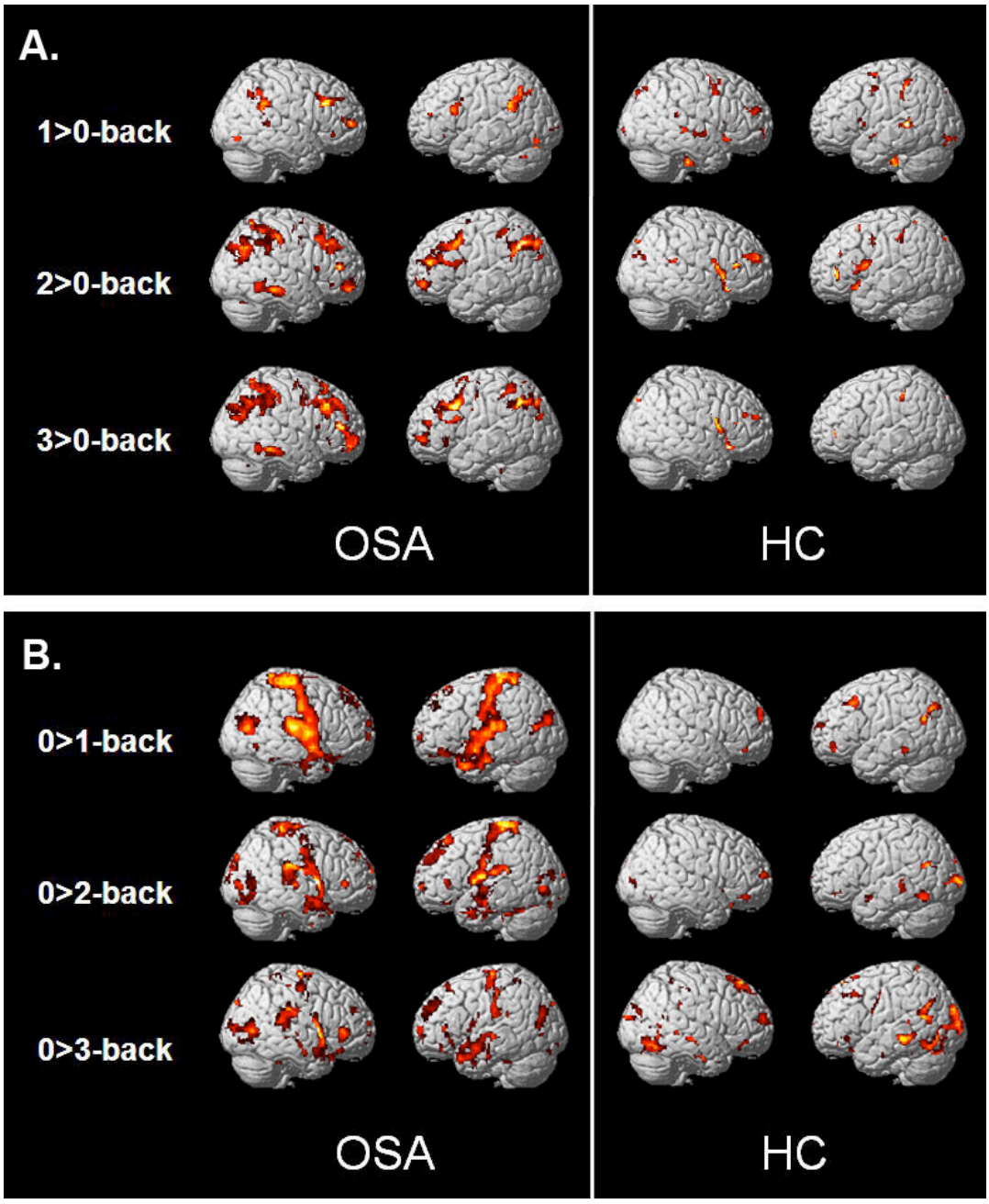


Fig. 2: Brain regions significantly higher activated in HC compared to OSA patients in cold scheme; brain regions significantly higher activated in OSA patients as compared to HC in warm color scheme. A: 1- versus 0-back comparison, B: 2- versus 0-back comparison, C: 3- versus 0-back comparison. Correlations between cerebral activation during WM task in OSA patients and D: AHI, E: nocturnal desaturation time (min), F: BMI. Images presented in radiologic convention.

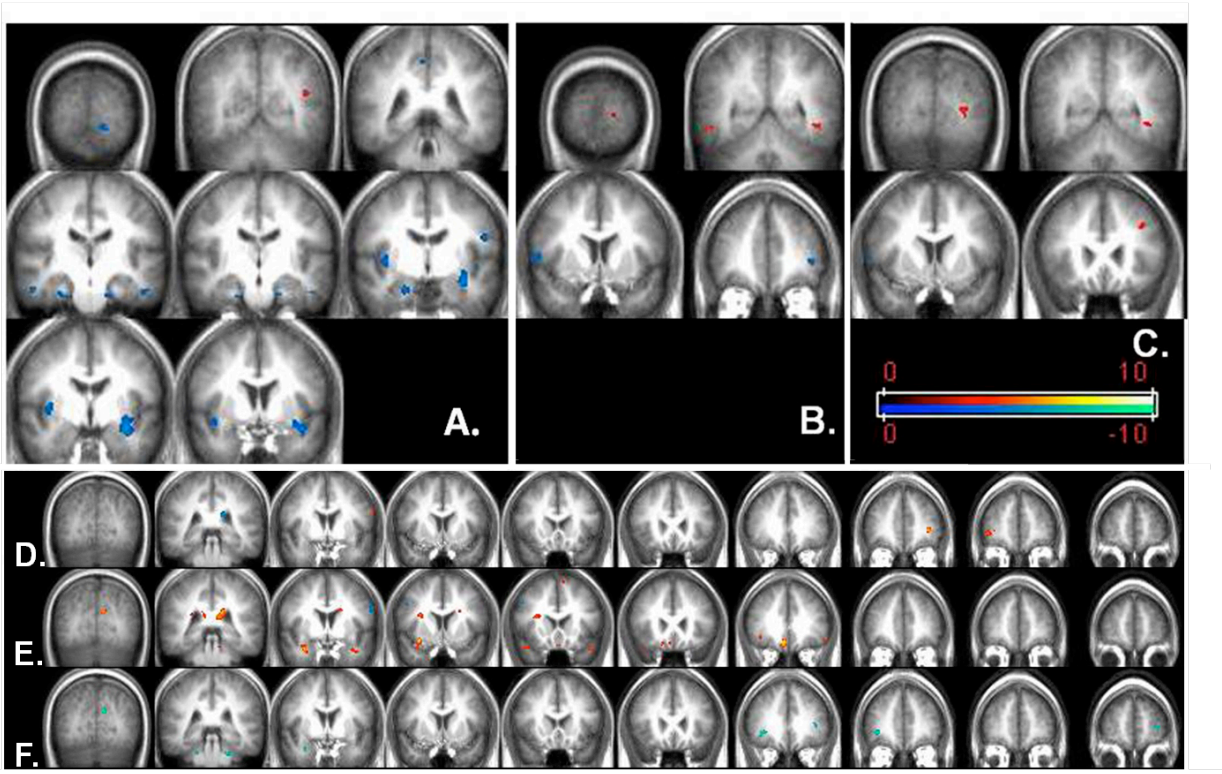
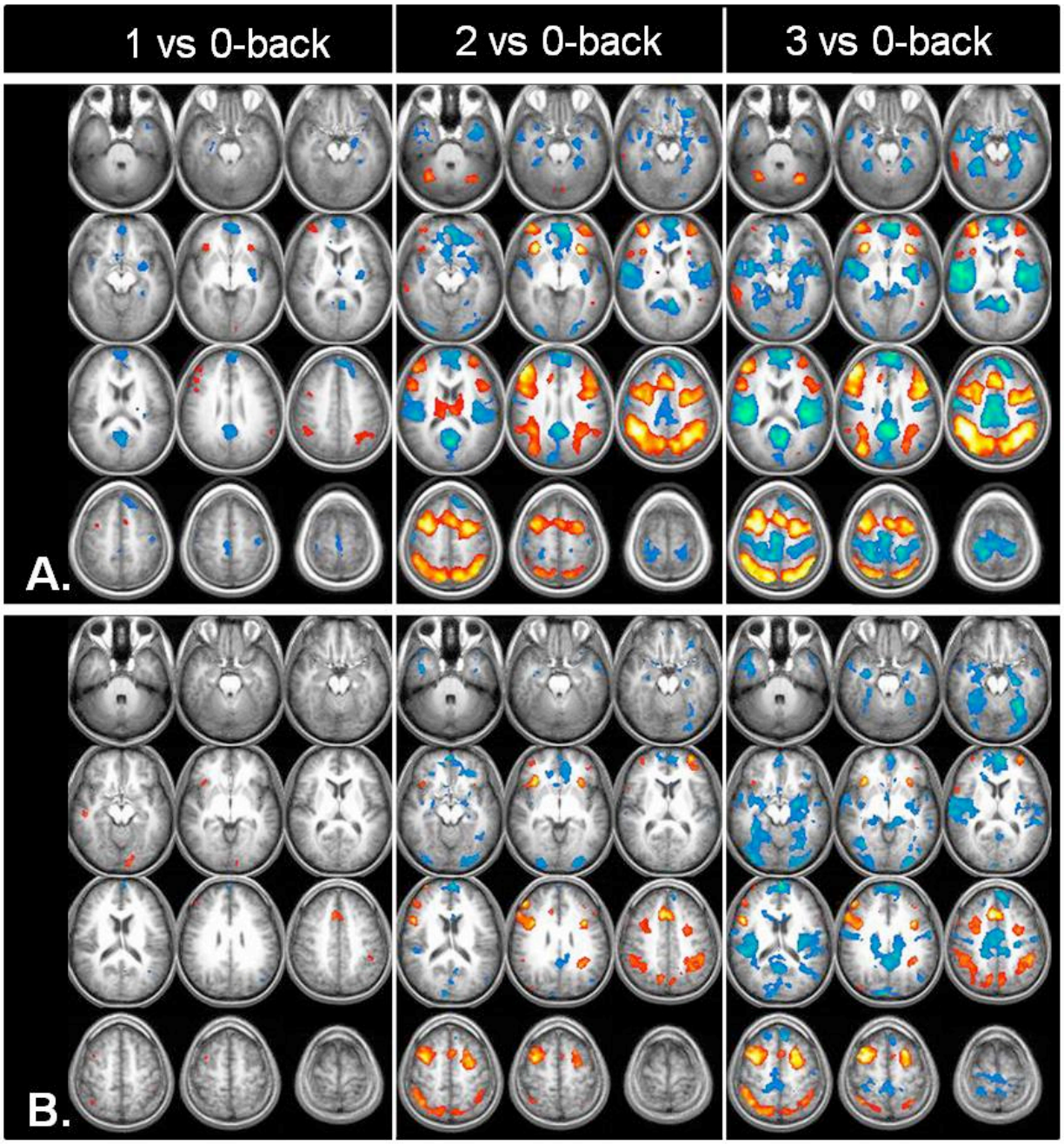


Fig. 3: Cerebral activation (warm color scheme) and deactivation (cold color scheme) in A: OSA patients and B: healthy controls for 1-, 2-, and 3 versus 0-back contrasts.



Part 2

The Effects of CPAP treatment on Task Positive and Default Mode Networks in Obstructive Sleep Apnea Patients

Part 2

The Effects of CPAP treatment on Task Positive and Default Mode Networks in Obstructive Sleep Apnea Patients: an fMRI Study

The aim of the second part of this study was to investigate both cerebral activation and deactivation patterns in response to a visuo-spatial parametric working memory (WM) task (executive function) in patients with moderate to severe OSA before and after CPAP treatment in a randomized, sub-therapeutic CPAP (sham)-group controlled fashion, and to compare it to the response of healthy controls.

Methods

Subjects

Seventeen men diagnosed with moderate to severe OSAS were recruited from the Stanford Sleep Clinic and surrounding area via advertisement. All participants were right-handed nonsmokers and were screened for current or previous neurological and psychiatric disorder as determined by history, clinical evaluation, and Hamilton Depression Scale score. All participants reported regular sleep schedules with ≥6 h of sleep per night as determined by sleep habits questionnaires. Seven age-matched subjects without history of sleep disorders were recruited from the community as HC; and absence of sleep pathology, including sleep disordered breathing (SDB), was confirmed by an overnight polysomnography (PSG: AHI <5).

Patients who were confirmed to have OSA on diagnostic PSG were randomly assigned to either the active (therapeutic) or sham (sub-therapeutic) nasal CPAP group. A CPAP titration study was conducted for patients in both groups, during which active group subjects were effectively titrated and sham group subjects slept with the sub-therapeutic nasal CPAP. The sham-CPAP device closely simulated the airflow through the exhalation port and the operating noise of the active-CPAP device. Prior study using a functionally similar sham-CPAP device revealed that oxygen saturation, end-tidal CO2, and mean temperature and humidity measured at the CPAP mask were the same
with active versus sham-CPAP[67]. No significant difference was found in sleep parameters or the number of abnormal respiratory events between the sham-CPAP group and a no-treatment group in 10 men with OSA. Subjects in both groups were treated for 2 months and treatment compliance was monitored using Encore® Pro Smart Card® system. At the end of the treatment period, sham-CPAP group subjects underwent a second CPAP titration night and left the study with therapeutic CPAP treatment.

The study was approved by the Stanford Institutional Review Board, and all subjects signed informed consent.

Polysomnography (PSG)

See Methods Part 1

Experimental Proedure and n-Back Task

See Methods Part 1

.

fMRI Data Acquisition

See Methods Part 1

fMRI Data Analysis

Functional MRI data were preprocessed and analyzed using Statistical Parametric Mapping software (Welcome Department of Cognitive Neurology, London) and custom MATLAB routines (MathWorks Natick, MA). The preprocessing steps consisted of realignment of all images to the first image, normalization to MNI template, and spatial smoothing with a Gaussian filter of 6 mm full-width-half-maximum.

To test for the effect of each task load, we used a standard general linear approach with 4 regressors for the 3 task load and baseline conditions, modeled as a boxcar function convolved with the canonical HRF. The 6 motion parameters from the realignment were added as 6 regressors of no interest. Statistical analysis at the single-subject level treated each voxel according to a general linear model.[45] Individual contrast images were created by computing each WM task load versus the 0-back load baseline ($1 > 0$, $2 > 0$, $3 > 0$). For group analysis, for each of the 3 main contrasts a one-sample T-test was used for each group and an exclusive masking procedure was performed on baseline and post-treatment sessions to reveal any voxel significantly activated in one but not in the other session.

We also designed a parametric model where all task blocks were modeled as one single regressor, with 2 additional regressors modeling a linear modulation of the task-related activity by load level (1-, 2-, and 3-back), a quadratic modulation of the task-related activity by load level, and 6 regressors of no interest (behavioral performance per task block and 6 motion correction parameters).

Individual contrast images obtained from linear modulation of the parametric analysis were used in a paired t-test to compare baseline and post-treatment scans for sham and active CPAP groups. Full factorial analysis was used to examine the group x scan interaction.

OSA and HC groups were compared for the 3 main contrasts (1 vs 0-back, 2 vs 0-back and 3 vs 0-back) using an exclusive masking procedure to reveal voxels significantly activated in one but not in the other group.

In order to minimize the type I error, a cluster threshold method was used,[46] requiring that any given voxel be significantly activated at P level of 0.001 and be a part of a cluster of ≥10 contiguous significantly activated voxels.

Results

Clinical Measure and Behavioral Performance

Baseline patient data

For 17 OSA patients, the mean AHI was 39.7 (±22.8), the mean Epworth score was 7.3 (±4), and the mean BMI was 27.8 (±4) kg/m^2. Mean minimal nocturnal oxygen saturation was 87.8% (±8.9%). Details of sleep quality and sleep stages are reported in Table 5. There was no significant difference between sham and active-treatment groups in AHI, duration of nocturnal desaturation or performance. There was a significant difference in BMI (p=0.01) between the 2 patients' groups (29.9+/-4.2 for active and 25.4+/-2.1 for sham).

Behavioral performance at baseline and post-treatment

During scanning subjects' accuracy decreased and response time increased with increasing n-back load. There was a significant group x session interaction between active and sham CPAP groups for RT on 3-back load (p=0.023). Active CPAP OSA patients' group performed significantly worse than HC on the 3-back, both before (75.2% vs 89% correct, p=0.002) and after CPAP treatment, even if a trend for improvement after treatment was observed (78.7% versus 89% correct, P = 0.04). However, the significantly worse performance at 2-back before treatment got significantly better after CPAP treatment. There was no significant difference in performance for the other levels of task load (Table 6).

In order to exclude an influence of sleepiness on brain activation and performance, we examined a possible relationship between RT during the 0-back epochs throughout both sessions of the n-back task with task duration. There was no correlation between RT and task duration for either session.

fMRI

Categorical analysis

The activation/deactivation patterns in our HC group mobilized cerebral regions previously described to be involved during performance of WM tasks. In line with previous studies both activation and deactivation increased with increasing task difficulty in all groups. Activation was maximal at the 2-back level and deactivation at the 3-back level in the HC group, suggesting that TPN is more capacity constrained than DMN. In patient groups TPN activation was relatively comparable for 2 and 3-back, but inferior to that of HC at 2-back in a number of frontal and parietal regions, particularly DLPFC. We used the activation/deactivation pattern of our HC as our reference frame of comparison for TPN and DMN activity in our OSA patients.

Sham-treatment group baseline scan exclusively masked with post-treatment scan

Exclusive masking of activation of baseline scan by the post-treatment scan in sham-CPAP group revealed activation in left cuneus (BA 18), right inferior temporal gyrus (BA 37) and right inferior frontal gyrus (BA 47) for the 1>0 contrast; left hippocamal/parahippocampal region, left fusiform gyrus (BA 37), and right middle temporal gyrus (BA 21) for the 2>0 contrast; right frontal (BA 8,9,10), left frontal (BA 6,46), right inferior parietal lobule (BA 40), right superior temporal gyrus (BA 39) and left insula (BA 13) for the 3>0 contrast (Table 7).

Deactivation was found in the right amygdale/uncus (BA 36) for the 1>0 contrast; bilateral superior temporal gyri (BA 38), left anterior and posterior cingulate gyrus (BA 25, 30), left inferior frontal gyrus (BA 47), left inferior temporal gyrus (BA 20) for the 2>0 contrast;

bilateral parietal (BA 5,7), bilateral amygdalas, right uncus (BA 34), right parahippocampal gyrus (BA 27, 30), medial frontal (BA 6,9), left medial frontal (BA 6), left precentral (BA 4), bilateral cerebellar regions, bilateral lingual gyri (BA 17, 18), right cuneus (BA 18), right fusiform gyrus (BA 19), right cingulate (BA 25, 31), bilateral posterior cingulate (BA 29, 30), right superior temporal (BA 38) for the 3>0 contrast (Fig. 4a).

Sham-treatment group post -treatment scan exclusively masked with baseline scan

Activation was found in bilateral superior frontal gyri (BA 6), right middle frontal gyrus (BA 8), left superior frontal gyrus (BA 9,10), left precuneus (BA 7), bilateral cerebellar regions, periaqueductal grey and tectum in 1>0 contrast; left precentral, superior, and middle frontal gyri (BA 6,8,9), right precentral gyrus (BA 4), left middle temporal gyrus (BA 20), bilateral precuneus (R BA 31, L BA 7), left postcentral gyrus (BA 3) for 2>0 contrast; right medial frontal gyrus (BA 10) and right precuneus (BA 7) for 3>0 contrast.

Deactivation was found in the left middle temporal gyrus (BA 19) for the 1>0 contrast; right medial frontal gyrus (BA 9) for 2>0 contrast; left inferior frontal gyrus (BA 45), bilateral insula (BA 13), right putamen, bilateral superior (BA 22) and right middle temporal gyri (BA 21), right superior and middle temporal gyri (BA 39, 41), left postcentral and fusiform gyri (BA 20), right lingual gyrus (BA 17/19) and left superior occipital gyrus (BA 19) for 3>0 contrast (Fig.4b).

Active-treatment group baseline scan exclusively masked with post-treatment scan

Activation was found in right inferior frontal gyrus (BA 45/46) for the 1>0 contrast; right cerebellum (tuber) for the 2>0 contrast; left precentral gyrus (BA 6) for the 3>0 contrast (Table 8).

Deactivation was found in left middle temporal (BA 39), left medial frontal (BA 10), right inferior temporal gyrus (BA 20), right subcallosal (BA 34) and right parahippocampal gyri (BA 36) for the 1>0 contrast; right superior and medial frontal gyri (BA 8, 10), right insula

(BA 13), right putamen, right head of the caudate nucleus, right superior temporal gyrus (BA 38), bilateral postcentral gyri (BA 3), left precentral gyrus (BA 6) for the 2>0 contrast; left superior parietal lobule and left cuneus (BA 7, 17), left paracentral lobule (BA 6), bilateral insula (BA 13), left medial frontal gyrus (BA 10),right medial frontal gyrus (BA 6), right precentral gyrus (BA 4), bilateral superior temporal gyri (BA 22), right precuneus (BA 31), right parahippocampal gyrus (BA 19), left fusiform gyrus (BA 19) and left culmen for 3>0 contrast (Fig.5a).

Active-treatment group post -treatment scan exclusively masked with baseline scan

Activation was found in bilateral parietal lobules (BA 40), left middle frontal gyrus (BA 10), right superior frontal gyrus (BA 6), left precentral gyrus (BA 6) for the 1>0 contrast; bilateral medial and superior frontal gyri (BA 6), bilateral precuneus (BA 7), right superior temporal gyrus (BA 22), bilateral insula (BA 13), bilateral frontal regions (BA 6, L BA 4), right lingual gyrus (BA 18), right cuneus (BA 19), right cingulated gyrus (BA 24, 31), right precentral gyrus (BA 44), left superior, middle and inferior frontal gyri (BA 9), right middle occipital gyrus (BA 37), right inferior parietal gyrus (BA 40) for the 2>0 contast; left middle frontal gyrus (BA 9), right middle frontal gyrus (BA 6, 10), left middle frontal gyrus (BA 46), bilateral cerebellum for 3>0 contrast.

Deactivation was found in the right anterior cingulate gyrus (BA 24) and left inferior parietal lobule (BA 40) for the 1>0 contrast; bilateral insula (BA 13), right anterior cingulated gyrus (BA 24), right superior temporal gyrus (BA 41), left cuneus (BA 30), left postcentral gyrus (BA 43), left caudate nucleus, left superior frontal gyrus (BA 8) for the 2>0 contrast; bilateral superior temporal gyri (BA 22), right anterior cingulated (BA 25), right cingulate (BA 24, 31), left medial globus pallidus, left putamen, right medial frontal gyrus (BA 11), right postcentral gyrus (BA 3, 5), right medial frontal gyrus (BA 10), left inferior frontal gyrus (BA 47), left middle temporal gyrus (BA 21), left cerebellum for 3>0 contrast (Fig.5b).

Parametrical analysis

Paired T-test of baseline and post-treatment scan for the sham-treatment group revealed significantly higher activation in the right superior and middle frontal gyrus (BA 6, 8, 9), left superior and middle temporal gyri (BA 21, 22, 38), left inferior frontal gyrus (BA 47), bilateral putamen, head of the right caudate nucleus, left caudate nucleus body, left lateral globus pallidus, left middle occipital gyrus (BA 18, 19), right precentral gyrus (BA 4, 6). No areas of significantly higher activation were found in the post-treatment as compared to the baseline scan (Fig.6a, Table 9).

Paired T-test of baseline and post-treatment scan for the active-treatment group revealed significantly higher activation in the left superior temporal gyrus (BA 22), left middle occipital gyrus (BA 18) and right cuneus (BA 17). No areas of significantly higher activation were found in the post-treatment as compared to the baseline scan (Fig.6b).

Discussion

This is the first study, to our knowledge, to specifically examine the effects of CPAP on TPN and DMN networks of untreated OSA patients as compared to sham CPAP treatment and HC.

Our results show that active- and sham-CPAP groups follow opposite trends of cerebral activation after 2 months of treatment. Whereas sham-CPAP group exhibited a decrease in TPN activation associated to an increase of DMN deactivation at the limit of capacity task (3-back), the active CPAP group presented an increase of TPN activation et all task levels, associated with an increase of DMN deactivation in the anterior midline at 3-back. In association with a significant improvement of response times (at 2 and 3-back) and accuracy (2-back) in the active group, these findings suggest a positive effect of CPAP on the active-treatment group when the sham-CPAP group seems to sustain additional effects of untreated OSA.

An alternative interpretation of our results for the sham group is that sham-CPAP per se had a negative impact as it may lead to more mouth-breathing and sleep disruption. Significant worsening of RTs and decreased TPN activation at the 3-back after 2 months of sub-therapeutic treatment in the sham group reflect a rather faster evolution than what would be expected of untreated OSA-related effects. Increased deactivation of the DMN has been previously reported by Sweet at al after two nights of CPAP withdrawal and correlated with better behavioral performance and higher sleepiness[68]. Thus our finding of increased spatial recruitment of DMN in the sham CPAP group for the 3-back task is consistent with these previous results and with our hypothesis of increased sleep disruption secondary to sham CPAP use.

Basal ganglia (BG) have been previously reported to show specifically load-dependent activation[69] and be activated during complex WM tasks (2-back)[70, 71]. Drummond et al have described higher activation in bilateral putamen and caudate for fast as compared to slow RTs after a normal sleep night using a Psychomotor Vigilance Task[55]. After acute sleep deprivation (SD) there was an increase in activation in those regions for slow, but not fast RTs. Similarly, Habeck et al found increased activation in BG after acute SD, which may reflect an increased effort in order to maintain adequate level of attention and arousal[72]. Our sham group patients exhibited significantly higher BG activation on pre-treatment as compared to post-treatment session, which, in association with slower RTs at 3-back may reflect lower capacity for WM performance.

Defective deactivation of DMN regions has been reported to be related to worse behavioral performance in a number of conditions associated with cognitive impairment and sleep disturbances (normal aging, Parkinson disease, schizophrenia, ADHD), suggesting that inability to reallocate neuronal resources and suppress activity in neighboring regions plays a role in cognitive impairment.[50-53] Disruption of task-related deactivation within the midline regions of DMN has been reported after acute sleep deprivation,[54] and slower reaction times on a psychomotor vigilance task have also been associated with increased activation in midline DMN regions after total sleep deprivation,[55] suggesting that sleep deprivation has a direct impact on DMN. Similarly, reduced deactivation in the posterior regions of DMN has been shown to be related to attentional lapses in healthy subjects[56]. Furthermore, Mitzenberg

et al have demonstrated that task-induced deactivation in the ventro-medial PFC significantly predicted speeding of RTs on a sensori-motor task after administration of Modafinil[73]. Modafinil inhibits norepinephrine and dopamine transporters, leading to increased synaptic NE and DA concentration and has been shown to enhance cognitive performance in both OSA patients and healthy individuals[74].Therefore the observed increase of deactivation in vmPFC together with speeding of RTs in our active-treatment group could indicate an improvement in catecholamine systems modulation of the DMN, reflecting an improved arousal level.

Despite randomization, our patient groups differed in BMI, with active-CPAP group being more overweight. This was associated with a significant negative correlation between BMI and the behavioral performance at the 3-back level in OSA patients, as well as OSA group differences in the behavioral performance at the intermediate (2-back) and maximal WM loads (3-back), with active-treatment group performing significantly worse than HC, although there was no significant difference between the active and sham-CPAP groups. In a previous report we showed that BMI had a major negative impact on the cerebral activation in the TPN, particularly in the prefrontal regions[75]. Although there was a trend towards better performance on the 3-back task load after CPAP treatment in the active group, it still remained significantly worse than that of HC. The incomplete reversal of deficits by CPAP treatment has been attributed in prior literature to irreversible structural hypoxic damage, however, since we found an independent negative effect of BMI on TPN activation in the PFC, we postulate that the incomplete response to CPAP treatment may also be related to the presence of overweight, unchanged by CPAP treatment alone. This is supported by the fact that nasal CPAP does not act on the restrictive aspect of thoracic breathing presented by obese OSA patients, who thus will persist having breathing problems during sleep even if they translate only by airflow limitation and lower oxygen saturation than expected for their age group. Furthermore, other mechanisms than impaired breathing, such as metabolic and hormonal changes associated with obesity, likely contribute to the observed cerebral activation deficit.

It is increasingly recognized that excess body weight is associated with brain structural and functional alterations[63], a higher risk of developing dementia in later life[40], as well as

cognitive dysfunction in otherwise healthy adults or after controlling for BP, age, and diabetes[40, 41, 66]. Therefore, it would be of great interest to examine whether reduction in BMI in conjunction with CPAP treatment could improve executive function deficits in OSA patients.

OSA patients in our study were all high-performing individuals which suggests that neuronal damage secondary to OSA was rather minimal. The role of CPAP treatment in those individuals might therefore reside not so much in improving performance, but in protection from further damage. In that sense, longitudinal studies of CPAP effects on initially well performing patients would be needed in order to assess the degree of protection that CPAP treatment might offer and tease apart the contribution of CPAP versus placebo effect in the long term.

Two other studies have investigated the effect of CPAP on cerebral activation of OSA patients. Thomas et al have found no improvement in DLPFC activation on a verbal 2-back WM task in 6 OSA patients after CPAP treatment, although there was some increase in the parietal activation[29]. Since their patient group had performed significantly worse than HC at baseline and did not improve after treatment, the lack of cerebral activation changes in the DLPFC was interpreted as an indication of a more permanent cerebral damage. No information was reported on the deactivation pattern.

More recently Castronovo et al examined the effect of CPAP on cerebral activation on a verbal 1- and 2-back WM task in 17 OSA patients[32]. Greater spatial activation was reported in a number of prefrontal regions, bilateral precuneus, left putamen, left hippocampus and was interpreted as a compensatory over-recruitment. Whereas more extensive activation in the PFC of never treated OSA patients in the presence of the same level of performance is indeed suggestive of over-recruitment of the TPN, more important activation in the hippocampus and precuneus were more difficult to explain. However, these latter observations are consistent with our hypothesis and findings of defective DMN functioning in OSA, as both hippocampus and precuneus are constituents of DMN. Furthermore, the authors have found an increased activation in bilateral hippocampus, fusiform gyrus and ACC (BA 24) in the preatreatment as compared to posttreatment scans in OSA patients,

which is consistent with less effective DMN at baseline with subsequent improvement after treatment.

Those findings as well as results of our study are in line with our previous observation that DMN is more severely affected by OSA than TPN[75].

In light of the results of functional and structural neuroimaging studies it appears that CPAP treatment could be most useful in high-functioning OSA patients, by preventing or at least slowing OSA-related neuronal damage. Further long-term longitudinal studies are needed in order to investigate this hypothesis. Finally, high-functioning OSA patients should be tested with limit-of-capacity tasks in order to avoid ceiling effects.

In conclusion, both TPN and DMN can show spatial over-recruitment in OSA patients in order to maintain an adequate behavioral response. When the compensation capacity is overwhelmed, decrease in behavioral performance is observed. In our study we found that OSA patients' performance accuracy significantly differed from that of HC only at the limit-of-capacity 3-back WM level. However, RT of accurate responses was a more sensitive measure of impairment, showing a significant patient group versus treatment interaction. CPAP treatment appears to have a generally positive effect on both cerebral activation and deactivation patterns, however, in accord with previous studies, it does not allow complete reversal of already established deficits, at least within two months of CPAP treatment. Increased BMI has an independent negative effect on TPN activation in the PFC and may thus account for part of the remaining deficits.

Further research is needed in order to establish whether a conjunct treatment of obesity and CPAP could yield better improvement in behavioral performance and frontal TPN activation than CPAP treatment alone.

Table 5: Sample characteristics

Age	43.2 (±8.4)
BMI	27.8 (±4)
AHI	39.7 (±22.8)
Ethnicity	4 Asian, 12 Caucasian, 1 Hispanic
TST	376.8 (±71.1)
Sleep efficiency	83.1 (±13.1)
REM	17.9 (±4.9)
Stage 1	12 (±7.3)
Stage 3+4	7.9 (±8.9)
Min SpO_2	87.8 (±8.9)

BMI = body mass index, AHI = apnea hypopnea index, TST = total sleep time

Table 6: Behavioral performance

	Sham-CPAP group		Actif-CPAP group	HC		Sham vs HC	Actif vs HC
	pre-treatment	post-treatment	pre-treatment	post-treatment		p value	p value
Accuracy 0-back	98.8 (+/-3.5)	98.8 (+/-2.3)	99.3 (+/-1.2)	99 (+/-2.4)	99.5 (+/-0.8)	0.6; 0.5	0.6; 0.6
RT 0-back	436.9 (+/-52.7)	440.4 (+/-79.4)	493.6 (+/-165.6)	501.5 (+/-159.8)	446.2 (+/-117.5)	0.9; 0.9	0.5; 0.4
Accuracy 1-back	98 (+/-2.4)	98.3 (+/-3.1)	95.5 (+/-6)	97.3 (+/-2.2)	96.3 (+/-4.3)	0.4; 0.4	0.8; 0.6
RT 1-back	719.4 (+/-168.5)	867 (+/-249.8)	801.2 (+/-165.5)	703.3 (+/-323)	671.3 (+/-182.8)	0.6; 0.1	0.2; 0.8
Accuracy 2-back	93.2 (+/-0.3)	91.1 (+/-7.3)	89.7 (+/-7.9)	89.3 (+/-7.2)	93.6 (+/-5.3)	0.9; 0.5	0.3; 0.2
RT 2-back	838.5 (+/-361.3)	1184.9 (+/-443.2)	1114.4 (+/-219)	909.7 (+/-278.7)	806.8 (+/-274.2)	0.9; 0.7	**0.03**; 0.5
Accuracy 3-back	83.1 (+/-11)	86.2 (+/-6.6)	75.2 (+/-9.2)	78.7 (+/-11.6)	89 (+/-5.2)	0.2; 0.4	**0.002; 0.04**
RT 3-back	1014.5 (+/-337.5)	1349.9 (+/-220.3)	1359.5 (+/-211.5)	1083.2 (+/-357.7)	992.1 (+/-239.6)	0.9; **0.01**	**0.008**; 0.6

Table 7: Cerebral regions showing significant activation and deactivation after exclusive masking in sham CPAP group (MNI coordinates).

Region	X Y Z	Brodman	Region	X Y Z	Brodman
Exclusive masking baseline by post-treatment scan					
	1>0			0>1	
	none			none	
	2>0			0>2	
R middle/inf frontal	34 56 -14	10	L middle frontal/ant cingulate	-26 38 -16	11/10/32
R inf/middle frontal	58 20 22	9	R medial frontal	6 -12 62	6
L inf frontal	-34 32 -4	47	L sup frontal	-22 40 48	8
R inf/middle frontal	40 36 -8	47/10	L cuneus	-4 -92 32	19
R precentral	42 -2 30	6	L sup/middle temporal	-42 16 -34	38/21
R middle frontal	30 40 22	9	L insula/sup temporal	-40 -24 20	13/41
R sup frontal	36 30 48	8	R ant cingulate	4 22 -10	25/24
L middle frontal	-32 26 22	9	R insula	52 -24 16	41/13
L inf parietal lobule	54 -28 40	40	L insula	-36 4 12	13
L precuneus	30 -72 22	31	L cingulate	-8 -34 38	31
L lingual	-18 -82 -2	18/19	L post cingulate	-6 -68 18	31/30
R lingual	26 -74 -4	19	R ant cingulate	16 32 -16	32
L fusiform	-44 -48 -10	37			
R fusiform	52 -36 -14	37			
R middle temporal	64 -40 4	22/21	R ant cingulate	10 40 -12	24
R middle temporal	64 -54 -8	37	Culmen	-12 -36 -10	
L uvula	-10 -74 -30			0>3	
R hippocampus	40 -32 -8		R medial frontal	10 -6 66	6
L thalamus	-6 -20 18		L sup/medial frontal	-10 66 8	10
R thalamus	8 -14 20		L sup/medial frontal	-24 30 48	8
L lentiform nucleus	-12 0 2		L middle frontal	-22 28 56	6
	3>0		R precentral	66 -8 38	6
R middle frontal	40 18 52	6	L middle frontal	-46 36 8	46
R precentral	44 26 38	9	L precentral	-28 -20 70	4/6
R sup/middle frontal	42 44 26	9	L sup frontal	-12 56 -12	10
R sup/middle frontal	36 58 6	10	R middle frontal	56 38 6	46
L middle frontal	-44 32 38	8	R precentral	44 -10 60	4
R middle frontal	52 18 38	8/9	L sup/middle frontal	-20 42 28	9/8
L middle frontal	-52 18 36	8	R postcentral	26 -20 64	3
R insula	32 30 0	13	R postcentral	28 -38 74	5
R cingulate	10 28 38	32	L postcentral	-22 -26 64	3
R sup parietal lobule	28 -60 60	7	R precuneus/cuneus	10 -74 34	31/19
R inf temporal	64 -38 -16	20	L inf parietal lobule	-32 -46 64	40
L claustrum	-30 26 -4		L paracentral lobule	-22 -38 50	5
			L precuneus	-4 -60 34	31
			R inf parietal lobule	66 -32 32	40
			L sup occipital	-42 -78 36	19
			R parahippocampal/amygdala	24 -6 -22	
			R sup temporal	52 8 -20	38
			L hippocampus/parahippocampal	-24 -36 -2	
			R fusiform/parahippocampal	38 -48 -10	37/19/36
			L sup temporal	-44 -46 18	13

			R cingulate	24 -26 36	31
			R ant cingulate	6 20 -16	25
			R ant cingulate	0 22 18	24
			L cingulate	-20 -26 46	31
			L insula	-38 4 18	13
			L thalamus	-4 -2 4	
			R thalamus	6 0 10	
			R med globus pallidus	20 -6 -4	
			L putamen	-16 18 -14	

Region	X Y Z	Brodman	Region	X Y Z	Brodman
Exclusive masking post-treatment scan by baseline					
	1>0			0>1	
R cuneus	6 -80 44	19		none	
	2>0			0>2	
L sup/medial frontal	-10 -8 70	6		none	
L middle frontal	-38 36 34	9/8		0>3	
L precentral	-58 6 36	6	L middle frontal	-34 22 48	6
L middle frontal/precentral	-30 6 40	6	R sup frontal	14 68 20	9/10
L precentral	-38 -10 62	4	L inf frontal	-58 20 12	44
R sup frontal	28 54 -14	10	L sup frontal	-20 54 18	10
R inf frontal	30 34 -8	47	L paracentral lobule	-4 -30 62	5
R medial frontal	24 56 0	10	R paracentral lobule	0 -36 66	5
R middle frontal	38 42 36	8	L postcentral	-34 -16 50	3/2
R inf frontal	-34 38 12	46	L sup parietal lobule/precuneus	-14 -54 74	7
L precentral	-44 24 34	9	R precuneus	28 -40 50	7
R medial frontal	26 46 10	9	R cuneus	16 -86 40	19
L sup frontal	-6 26 48	8	L cuneus	-16 -78 14	17
L precuneus/cingulate	-4 -68 58	7/31	L sup temporal	-48 -20 -8	22/21
R precuneus/cuneus	14 -62 34	31/7	R sup temporal	52 -16 -14	22
L inf parietal lobule	-40 -50 64	40	L fusiform/middle tmporal	-38 -10 -28	20/21
R inf parietal lobule	56 -42 26	40	R ant cingulate	12 14 20	33
L angular	-54 -62 42	39	R cingulate	12 4 34	24
R angular	60 -58 38	39	R ant cingulate	6 44 0	32
L precuneus	-30 -78 46	19	L cingulate	-2 26 32	32
R lingual	14 -88 0	18	R post cingulate	4 -24 22	23
L lingual	-8 -82 -6	18/17	L insula	-54 -34 26	13
R inf temporal/parahippocampal	58 -28 -20	20/36	R insula	46 -24 -4	13
L sup temporal	-50 10 -22	38	L caudate head	-8 16 -14	
L sup temporal	-54 -50 10	22	L caudate body	-2 12 4	
L middle temporal	-30 -62 28	39	R caudate body	8 24 8	
L sup temporal	-50 -48 10	39	R caudate head	16 24 -16	
R middle temporal	44 -82 28	19	L caudate tail	-12 -30 24	
L inf temporal	-5 -34 -12	20	R thalamus	0 -20 2	
L fusiform	-46 -60 -8	37	L pyramis	-20 -88 -26	
R cingulate	22 -42 38	31	R culmen	10 -38 -10	
R cingulate	14 28 30	32	L declive	-12 -70 -14	
L post cingulate	-8 -34 24	23	L culmen	-2 -72 -8	
L ant cingulate	-22 54 0	32			
L insula/putamen	-38 16 8	13			
R insula	36 18 10	13			
L insula	-34 32 6	13			
R lentiform nucleus	12 -2 -2				
L lentiform nucleus	-16 -2 -2				
	3>0				
L inf frontal	-46 2 24	9			

Table 8: Cerebral regions showing significant activation and deactivation after exclusive masking in the active CPAP group (MNI coordinates).

Region	X Y Z	Brodman	Region	X Y Z	Brodman
Exclusive masking baseline by post-treatment scan					
	1>0			0>1	
	none		R sup frontal	2 52 44	8
	2>0		L sup frontal	-16 42 50	8/6
L middle frontal	-44 18 38	9	R/L medial frontal	0 -12 68	6
L middle frontal	-32 10 40	6	L precentral	-44 -14 36	4/6
	3>0		R middle frontal	28 42 -18	11
L middle frontal	-38 24 22	9	R middle/inf frontal	40 40 -16	47
L sup frontal	-36 58 6	10	R precentral	38 -16 58	4
R middle frontal	34 8 46	6	R medial frontal	8 54 -8	10
R middle frontal	38 24 28	9	L medial frontal	-18 52 -6	10
L inf parietal lobule	-52 -38 56	40	L superior/medial frontal	-8 68 16	10
R inf temporal	56 -50 -12	37	R medial frontal	4 62 0	10
			L medial frontal	-2 66 6	10
			R medial frontal	10 30 -22	11
			L inf parietal lobule	-48 -26 30	40
			L postcentral	-56 -14 50	1
			L postcentral	-46 -14 60	3
			L postcentral	-42 -30 60	40
			L postcentral	-52 -24 58	2
			L postcentral	-38 -42 64	5
			Postcentral Gyrus	30 -26 64	3
			R sup parietal lobule/precuneus	28 -50 72	7
			R postcentral	44 -30 62	40
			R postcentral	52 -24 56	2
			R postcentral	40 -40 64	5
			L precuneus	-24 -80 50	19
			L inf occipital	-42 -78 0	19
			L lingual	-22 -84 -2	18
			R lingual	34 -64 8	19
			L cuneus	-6 -80 18	17
			L middle occipital	-40 -88 16	19
			L middle temporal	-64 -42 0	21
			L inf temporal	-52 -76 4	19
			R fusiform/parahippocampal	44 -10 -32	20/36
			R sup temporal	58 2 -16	38

L middle temporal	-46 -68 30	39
L cingulate	-8 0 44	24
R post cingulate	32 -74 12	30
R ant cingulate	22 44 2	32
L ant cingulate	-22 48 -12	10
R cingulate	20 -30 42	31
R cingulate	16 -12 42	24
R post cingulate	18 -58 20	30
R ant cingulate	4 26 -18	32
L caudate	-8 -14 26	
L putamen	-20 16 6	
	0>2	
L inf/middle frontal	-32 28 -16	47/11
L middle frontal	-34 40 -18	47
R precentral	64 -12 38	4/6
L sup frontal	-20 42 52	6
R middle/sup frontal	22 44 36	8
L medial frontal	-12 62 2	10
R medial frontal	6 54 -14	10
L medial frontal	-4 -12 56	6
R sup frontal	16 56 28	8/9
R inf frontal	44 34 2	13
L postcentral	-14 -44 76	7
L inf parietal lobule	-58 -32 26	40
R sup parietal lobule/postcental	30 -38 66	5
R inf parietal lobule	54 -26 28	40
R postcentral	64 -14 22	3
R postcentral	52 -18 56	3/2
L postcentral	-44 -14 54	3
R cuneus	8 -72 20	18
R cuneus	14 -94 34	18
R middle occipital	40 -78 8	19
L lingual	-36 -72 0	18
R lingual	16 -52 4	19
R sup temporal	54 2 -6	22
R parahippocampal	28 -46 -12	36
R fusiform	46 -16 -32	20
L middle temporal	-58 -2 -6	21
L sup temporal	-58 8 -12	38
R inf temporal	50 -66 -4	37
R sup temporal	66 -28 6	22
L sup temporal	-50 10 -32	28
R parahippocampal	22 -14 -26	

R middle temporal	54 0 -34	21
L sup/middle temporal	-54 12 -20	38/21
L cingulate	-4 2 34	24
R cingulate	6 6 42	24
R ant cingulate	4 24 10	33
R post cingulate	4 -64 12	30/23
L cingulate	-6 0 44	6
L cingulate	-12 -22 40	31
L insula	-44 -26 24	13
L claustrum	-30 4 10	
R claustrum	42 8 -6	
	0>3	
R inf frontal	40 32 -16	47/13
L paracentral lobule/postcentral	-18 -30 60	3,7
L inf/middle frontal	-38 28 -16	47
L medial frontal	-10 60 -6	10
R precentral	24 -16 70	4
R medial/sup frontal	0 50 32	Brodmann area 6/9
L sup frontal	-16 48 44	8
R medial frontal	0 -18 74	6
L medial frontal	-6 -12 58	6
L inf frontal	-32 16 -30	47
L paracentral lobule	-4 -42 68	Brodmann area 5/6
R medial/sup frontal	12 66 -4	10
R precentral	40 -8 38	6
R inf parietal lobule	52 -28 30	40
L precuneus	-14 -60 34	31
L inf parietal lobule	-54 -28 26	40
L cuneus	-14 -74 28	18/19
R middle occipital/temporal	54 -74 6	37/39
R lingual	0 -92 10	17/18
R middle occipital	-32 -90 4	18
R fusiform/hippocampus	38 -46 -16	37
R sup temporal/insula	52 0 -6	22/13/38
Uncus	32 -8 -30	
L parahippocampal	-30 -34 -22	36
L sup temporal	-50 4 -30	38
L middle temporal	-48 -64 12	37
L claustrum, insula/putamen	-38 -16 -4	
L post cingulate	-16 -66 14	30
R cingulate	16 4 42	24
R ant cingulate	0 10 -16	25

L cingulate	-6 -12 36	23/24/31
R ant cingulate	4 50 -14	32
R post cingulate	8 -40 12	29
R putamen	32 -4 4	
R putamen/claustrum	40 -22 2	
R pulvinar	18 -22 8	

Exclusive masking post-treatment scan by baseline

	1>0			0>1	
L precentral	-32 -2 62	6	L precentral	-62 -6 12	43
R middle frontal	34 0 58	6	R inf frontal	50 40 4	46
R middle/sup frontal	50 30 26	9/10	R medial frontal	10 54 12	9
R sup frontal	4 28 48	8	L inf parietal lobule	-64 -26 34	40
R medial frontal	16 8 60	6	L middle occipital	-38 -66 2	37
R middle frontal	46 8 52	6	R cuneus	6 -76 24	18
L middle frontal	-42 54 12	46	L middle temporal	-48 -68 10	37
R inf frontal	52 10 30	9	L middle/sup temporal	-56 -38 6	22
R inf frontal	54 16 16	44	R middle temporal/occipital	50 -66 12	37/19
R middle frontal	36 0 46	6	L ant cingulate	-2 30 14	24
R precentral	38 0 36	6	R insula	48 2 2	13
R inf parietal lobule	48 -48 44	40	L subcallosal	-10 0 -16	34
L inf parietal lobule/supramarginal	-50 -48 42	40	L medial globus pallidus	-14 -6 -8	
L middle temporal	-58 -30 -14	21		0>2	
R insula	42 24 2	13	L sup/medial frontal	-20 26 48	8
	2>0		R sup frontal	10 42 44	8
L precentral	-28 -4 66	6	L sup frontal	-18 60 16	10
R precentral	38 -2 62	6	L sup frontal	-26 30 48	8
L inf/middle frontal	-58 12 32	9/8	R precuneus/lingual	6 -64 32	31/18
L precentral	-44 2 32	6	L postcentral	-50 -18 52	2
R middle/sup frontal	36 44 32	9/10	R cuneus	16 -80 26	18
L sup/middle frontal	-40 48 28	9	R inf/middle occipital	22 -96 -8	17/18
L sup parietal lobule	-18 -64 62	7	R parahippocampal	28 -22 -12	28
R inf parietal lobule	46 -32 34	40	L middle/sup temporal	-54 -36 10	22/41
R sup parietal lobule	12 -60 66	7	L sup temporal	-58 -16 2	22
R precuneus	26 -70 62	7	L middle temporal	-52 -68 26	39
L precuneus	-20 -70 32	31/7	R sup temporal	64 -4 -2	22
R precuneus	26 -70 38	19	R sup temporal	54 -24 4	41
L inf parietal lobule	-52 -30 36	40	L parahippocampal	-20 -20 -12	35
L supramarginal/sup parietal lobule	-52 -42 38	40	R ant cingulate	10 44 6	32
R supramarginal	56 -46 36	40	R subcallosal	14 0 -18	34
R lingual/cuneus	22 -74 0	18/17	L post cingulate	-12 -68 20	31
L middle occipital	-28 -82 26	19	L cingulate/precuneus	-6 -54 36	31
L lingual	-30 -64 -2	19	R ant cingulate	6 32 2	24

R cuneus	30 -78 24	18
R parahippocampal/lingual	40 -54 2	19
L fusiform	-48 -54 -8	37
R insula	38 22 6	13
L insula	-34 18 8	13
R cingulate	6 24 40	32
	3>0	
L precentral	-28 -4 68	6/4
R precentral	36 -4 64	6
R middle frontal	32 34 40	8
L sup frontal	-10 2 70	6
R sup/middle frontal	32 52 14	10
L sup frontal	-32 44 28	9
L middle frontal	-36 46 10	10
L supramarginal/inf parietal lobule	-54 -40 38	40
R inf parietal lobule	58 -38 42	40
L precuneus	-18 -62 38	7
R cuneus	24 -72 38	7
L middle occipital	-28 -84 28	19
culmen	6 -44 -26	
R insula/claustrum	42 -14 14	13
L ant cingulate	-16 44 6	32
L insula	-42 -10 8	12
	0>3	
R precentral	52 -10 24	6
L postcentral/precentral	-22 -22 70	3,4
R precentral/postcentral	44 -18 58	4,2
L medial frontal/cingulate	-10 -18 50	6,24
L sup frontal	-18 60 14	10
L sup frontal	-12 32 48	6,8
R precentral	68 -6 26	4
L inf frontal	-30 28 -18	47
L postcentral	-8 -38 74	5,7
L precuneus	-12 -36 54	7
L inf parietal lobule	-44 -26 52	40
R postcentral	28 -26 48	3
L inf parietal lobule	-32 -34 64	40
R lingual	22 -92 0	17
R middle occipital/cuneus	14 -92 20	18/17
R middle occipital	54 -72 -6	37
L lingual	-14 -54 0	19
L inf occipital/cuneus	-20 -98 -4	17
L fusiform	-42 -76 -8	19
L transverse temporal/insula	-34 -38 14	41/13
L sup temporal	-56 -40 12	22
R parahippocampal/amygdala	28 -22 -12	28
R sup temporal	56 -18 -4	22
L middle temporal	-36 -60 20	19
R parahippocampal/post cingulate	18 -42 -6	30/29
R fusiform	32 -82 -10	19
L parahippocampal	-26 -26 -14	28/27
R sup temporal	46 8 -36	38
L sup temporal	-44 8 -36	38
R inf temporal	46 -10 -34	20
L sup temporal	-54 -14 -14	22
R ant cingulate/caudate	14 34 0	24
R cingulate	20 -24 48	31
L cingulate	-18 32 22	32
R post cingulate	0 -58 8	30
L cingulate/caudate tail	-16 -42 32	31
R insula	32 -30 20	13
L insula	-46 -6 20	13
L subcallosal	-8 0 -16	34

R putamen/lat globus pallidus	24	8 -14
R caudate	24	2 28
	2	2 -2
L caudate	-4	8 4
Thalamus	0	-6 0

Table 9: Cerebral regions showing significant activation/deactivation differences on a paired t-test between pre- and post-treatment sessions for active and sham groups.

region	X	Y	Z	Brodman area
	Sham-CPAP group			
R middle frontal	56	24	34	9/8
R sup frontal g	22	54	24	9
L inf frontal	-34	22	-22	47/putamen
R precentral g	52	10	36	4-Jun
L sup/middle temporal	-50	-32	-2	21/22
L middle occipital	-22	-84	24	18/19
L sup temporal	-42	4	-18	38
R putamen/caudate head	24	22	-6	
	24	6	-10	
L globus pallidus	-12	6	-12	
L caudate body	-16	14	12	
	Active-CPAP group			
L sup temporal	-66	-36	22	22
L middle occipital	-12	-94	18	18
	-26	-98	20	18
R cuneus	20	-86	14	7

Figure 4: Cerebral activation (warm scheme) and deactivation (cold scheme) exclusive masking of pre-treatment session by post-treatment session (A); and of post-treatment session by pre-treatment session (B) in the sham-CPAP group for 2 vs 0-back and 3 vs 0-back contrasts (FDR multiple comparisons correction, p=0.05, 10voxels).

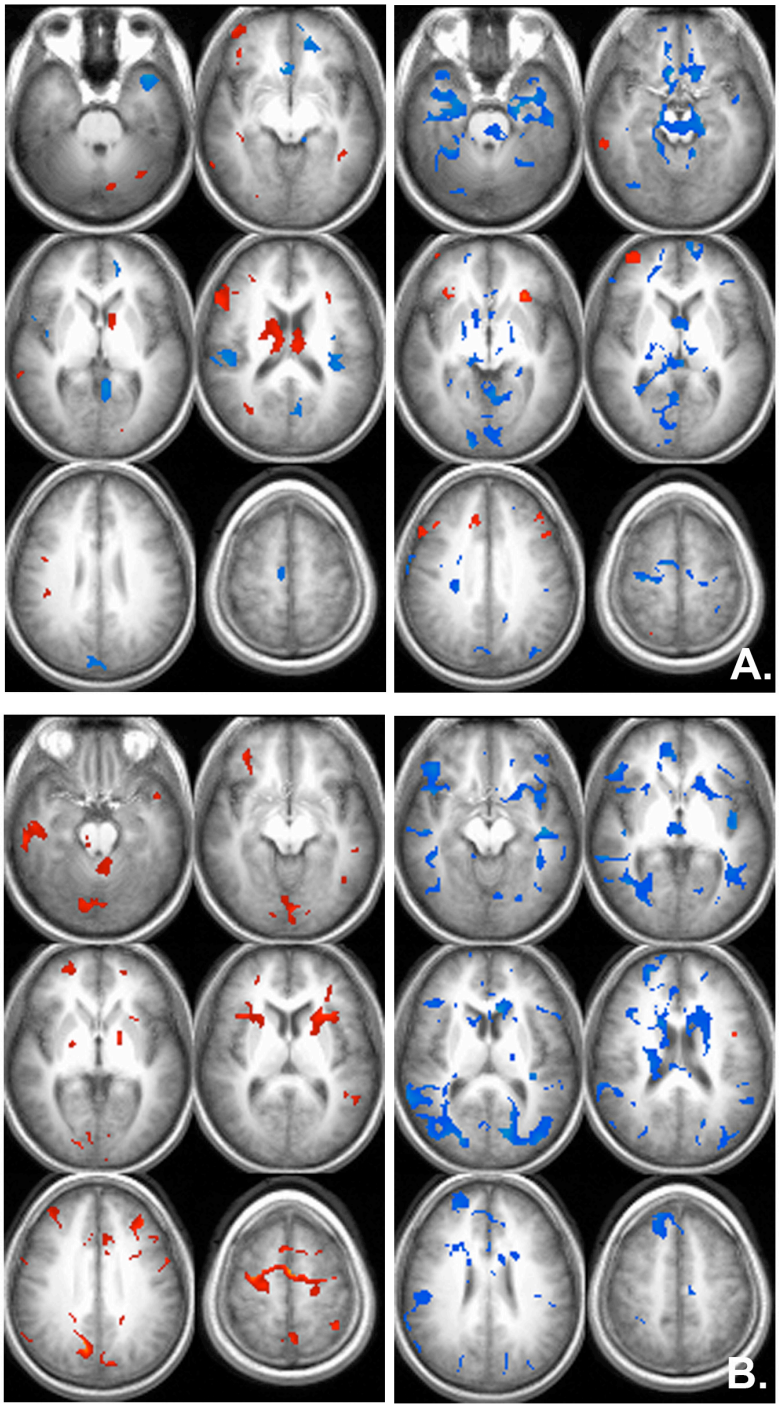


Fig.5: Cerebral activation (warm scheme) and deactivation (cold scheme) exclusive masking of pre-treatment session by post-treatment session (A); and of post-treatment session by pre-treatment session (B) in the actif-CPAP group for 1 vs 0-back, 2 vs 0-back and 3 vs 0-back contrasts (FDR multiple comparisons correction, p=0.05, 10voxels).

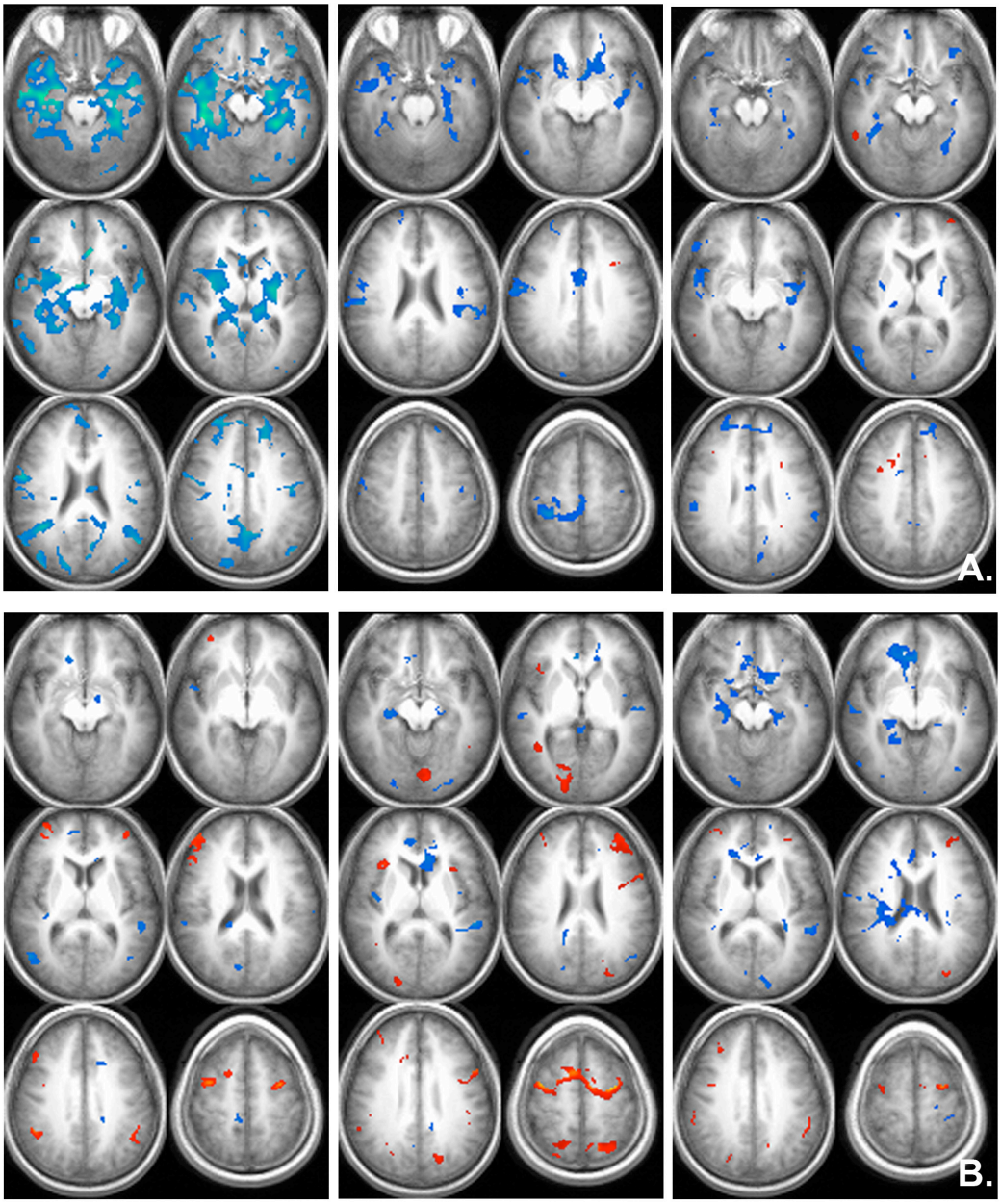
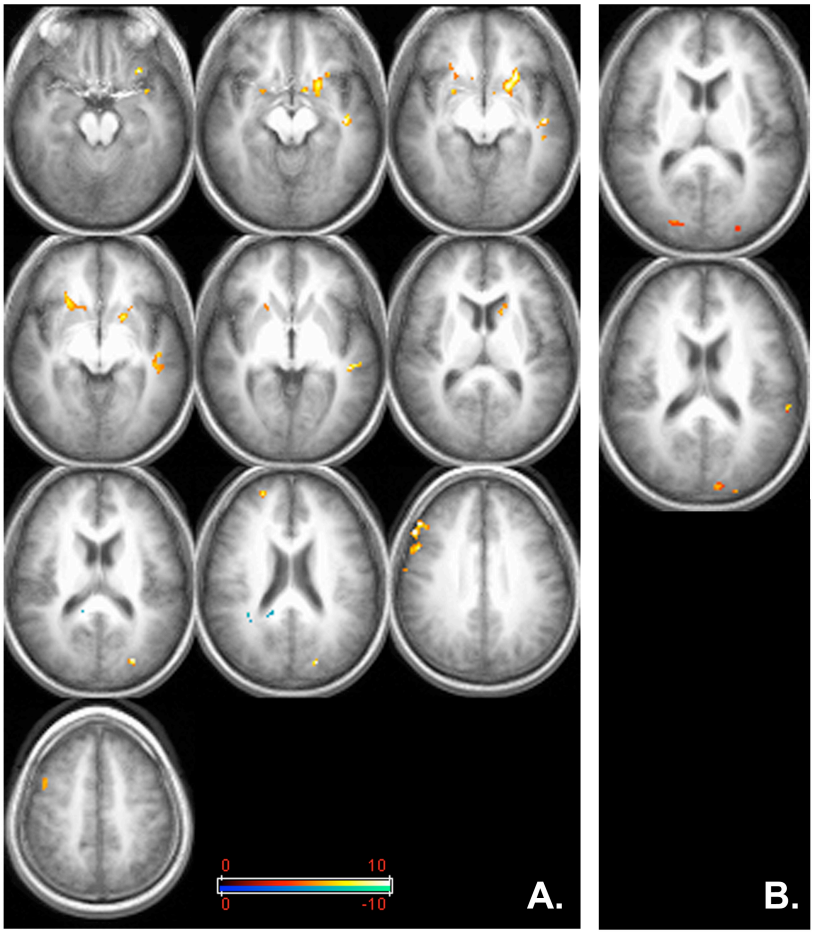


Figure 6: brain regions showing significantly higher brain activation in pre-treatment as compared to post-treatment session in sham-CPAP (A) and actif-CPAP (B) groups on a paired t-test.



Conclusions

The goal of our work was to investigate the patterns of cerebral activation and deactivation in the TPN and DMN during the performance of a parametric WM task and to compare them to those of HC, as well as to assess the effect of CPAP treatment as compared to sham-CPAP.

In our study we found that OSA patients' performance accuracy significantly differed from that of HC only at the limit-of-capacity 3-back WM level. However, RT of accurate responses was a more sensitive measure of impairment, showing a significant patient group vs treatment interaction.

Our results revealed impairment of both TPN and DMN in our OSA patients, although to a different extent and by different factors. Whereas nocturnal desaturation has a negative impact on both TPN and DMN by decreasing cerebral activation in the former and increasing it in the latter, its major impact appears to be on the DMN dysfunction. BMI per se has a negative effect, predominantly on prefrontal regions, decreasing cerebral activation in the TPN and showing a significant negative correlation with behavioral performance at the maximal level of WM load. Cerebral activation in the TPN network is thus negatively affected by both nocturnal desaturation and the BMI, whereas DMN deactivation is mostly impaired by nocturnal desaturation.

Thus, it appears that both TPN and DMN can show spatial over-recruitment in OSA patients in order to maintain an adequate behavioral response. When the compensation capacity is overwhelmed, decrease in behavioral performance is observed. CPAP treatment appears to have a generally positive effect on cerebral activation and deactivation pattern in OSA patients, however, it appears that its main effect is that of preventing or at least slowing the development of OSA-related damage, more than reversing the already established deficits. Increased BMI has an independent negative effect on TPN activation in the PFC which is not sufficiently improved by CPAP treatment alone.

Further research is needed in order to establish whether a conjunct treatment of obesity and CPAP could yield better improvement in behavioral performance and frontal TPN activation than CPAP treatment alone.

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