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Treatment effects on brain activity during a working memory task in obstructive sleep apnea

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SUMMARY Positive airway pressure (PAP) is the most common form of treatment for obstructive sleep apnea (OSA). Treatment adherence is notoriously low, and holidays from treatment are common. To date, there is no literature on the effects of acute withdrawal from PAP treatment on the brain activity of individuals with OSA. Nine participants with OSA performed a 2-Back verbal working memory paradigm during repeated functional magnetic resonance imaging (FMRI). Counterbalanced FMRI sessions were under conditions of PAP treatment (at least one consecutive week) or non-treatment (for two consecutive nights). Treatment effects on 2-Back-related brain activity were significant, with greater deactivation in the right posterior insula and overactivation in the right inferior parietal lobule. The observed responses to PAP treatment withdrawal were more extreme in all regions of interest, such that 2-Back-related activity increased and 2-Back-related deactivation decreased further relative to the 0-Back control task. The withdrawal of PAP treatment in effectively treated individuals with OSA might result in the need to reallocate resources in order to perform at the same cognitive level.

KEYWORDS functional magnetic resonance imaging, neuroimaging, obstructive sleep apnea, positive airway pressure, treatment, working memory

INTRODUCTION

Obstructive sleep apnea (OSA) is a serious medical condition characterized by repeated complete or partial collapses of the upper airways during sleep (Young *et al.*, 2002), leading to notable daytime sequelae (Aloia *et al.*, 2004; Ancoli-Israel *et al.*, 1991; Nieto *et al.*, 2000; Young *et al.*, 1993). Although cognitive complaints are common in OSA, the pattern of deficits is less understood [for reviews see Aloia *et al.* (2004), Beebe *et al.* (2003), and Fulda and Schulz (2001)]. Several theories have been developed that consider various mechanisms of cognitive dysfunction in OSA, including the effects of sleep fragmentation, chronic sleep deprivation, neuronal cell loss due to hypoxemia, and vascular compromise (Aloia *et al.*, 2004; Beebe, 2005; Beebe and Gozal, 2002; Lanfranchi and Somers, 2001; Tonon *et al.*, 2007; Verstraeten and Cluydts, 2004; Verstraeten *et al.*, 2004). Common to all of these theories is the potential for dysfunction of higher order cognitive skills.

Functional neuroimaging studies performed during cognitive challenges can provide insight into the function and dysfunction of neuroanatomical circuits of the brain. For instance, under-representation (e.g., decreased activity) of a particular region might be due either to neural loss or the need to redistribute resources. Conversely, over-representation of a region has been postulated to be a reflection of compensation for inefficiencies somewhere else in the circuit [e.g., Drummond and Brown (2001), Drummond *et al.* (1999), and Portas *et al.* (1998)].

Despite the breadth of literature on cognitive dysfunction in OSA, functional imaging paradigms during cognitive

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challenges have been used only recently in these patients. One reason is the limitations of the technology to accommodate participants with larger girths, therefore limiting the availability of participants, given the increased prevalence of obesity in this population. To date, only two studies have been published that examine the magnetic resonance (MR) signal in patients with OSA performing a cognitive challenge. Thomas *et al.* (2005) presented averaged group activation maps that illustrated a lack of task-related blood oxygen level-dependent (BOLD) signal activity in the dorsolateral prefrontal cortex in 16 untreated patients with OSA compared with matched normal controls during a working memory challenge. In addition, OSA participants performed significantly more poorly and slowly on the working memory task compared with controls. Six of these patients were also examined after a minimum of 8 weeks of positive airway pressure (PAP) treatment. Although patients demonstrated improvements in their self-reported daytime sleepiness, a persistent lack of working memory-related signal activation was evident in the prefrontal cortex even after treatment. The authors note in their discussion that additional studies are needed and should be designed to address the question of cerebral recovery with treatment.

The second study by Ayalon *et al.* (2006), examined the functional magnetic resonance imaging (FMRI) response in apnea compared with matched normal controls on a verbal learning task. These investigators found increased activation in several brain regions within the apnea group. Performing at the same level as controls, the OSA patients recruited greater brain volume in task-related areas as well as the recruitment of additional regions, suggesting the need for compensatory resources.

Positive airway pressure is the most common treatment for OSA, yet adherence to PAP is notoriously low (1992) and holidays from treatment are common. There has been only one study examining the cognitive effects of acute withdrawal from continuous PAP (CPAP) (Yang *et al.*, 2006). This study examined cognitive functioning at baseline, after successful treatment, after withdrawal, and again after reintroduction of treatment. Cognitive deficits were noted off-treatment and were corrected only partially with treatment reintroduction. Notably, the primary cognitive improvement was seen in information processing speed and attention. To date, no study has examined treatment differences (i.e., on- and off-treatment) using FMRI methodology, and none have addressed the common condition of PAP holidays. We employed the same working memory task as Thomas *et al.* (2005) in a within-subjects design to examine the effects of PAP treatment on BOLD activity in OSA. Patients were studied in a counterbalanced manner under conditions of treatment (for at least two consecutive nights) and non-treatment (for at least two consecutive nights). The current study assessed the reversibility of the treatment effects reported by Thomas *et al.* In addition, our methodology extends the previous work to examine the effects of acute withdrawal of treatment, rather than examining treatment effects several weeks later in an untreated OSA group. We hypothesized that patients would show a decreased BOLD signal and worse performance under conditions of no treatment compared with the treatment condition, with the most prominent differences occurring in the posterior regions [as reported by Thomas *et al.* (2005)] as well as the potential for compensatory activation in other areas of the working memory network.

METHODS

Participants

Nine participants (four women; 75% Caucasian) were recruited from a larger study on the effect of PAP treatment on cognitive functioning conducted at the Sleep Disorders Center of Lifespan Hospitals of Rhode Island (Felver-Gant *et al.*, 2007). All participants met criteria for OSA by a full night of polysomnography. The common measure used to diagnose OSA and describe respiratory disturbances during sleep is the Apnea–Hypopnea Index (AHI); this index reflects the ratio of episodes of apneas (i.e., complete cessation of breathing for > 10 s) and hypopneas (i.e., $\geq 50\%$ reduction in breath flow with subsequent desaturation of O_2 levels for 10 s) during sleep divided by hours of sleep time. OSA was diagnosed if this AHI ratio was greater than 5 per hour. Verbal intelligence quotient was estimated using the American version of the National Adult Reading Test (Ryan and Paolo, 1992). Additional eligibility requirements included the following: (i) age between 25 and 65 years; (ii) native English-speaking; (iii) no comorbid medical or psychiatric disorder; (iv) normal sleep–wake schedules as reported on daily diaries; (v) adherence to PAP treatment (averaging > 5 h per night for at least 3 months) measured by objective monitoring of nightly use; (vi) did not currently take medication (e.g., stimulants) to treat the symptoms of OSA; and (vii) free of MRI contraindications (e.g., capable of fitting into the MRI scanner, no claustrophobia). Written informed consent was obtained for all participants. This study was approved by the Institutional Review Boards at Brown University and at the Memorial Hospital of Rhode Island where scanning was performed.

Procedures

All participants received training on the 2-Back working memory test. The 2-Back is used widely in FMRI research, and therefore has the advantage of a well-described brain response among patients and healthy volunteers [e.g., Braver *et al.* (1997), Sweet *et al.* (2008), and Thomas *et al.* (2005)]. Training was conducted first on a dedicated training day prior to any scanning session and was repeated prior to each scanning session. All participants were required to perform the 2-Back task to the criterion of 80% accuracy before entering the scanner. Scanning was conducted under two conditions: (i) after at least one consecutive week on treatment and (ii) after having refrained from PAP for two consecutive nights. The treatment withdrawal period was restricted to two nights to

mimic a treatment holiday and for the safety of the participants. Measures of objective adherence to PAP were obtained throughout the course of the study using a microprocessor housed within the PAP treatment device of each participant. Adherence was monitored as a validity check for the on-treatment phase of the study. Treatment condition was counterbalanced. All participants were asked to refrain from taking any medications, smoking cigarettes or drinking caffeinated beverages at least 3 h prior to each scanning session and adherence was verified by interview. All participants who enrolled in the study reported not having a current history of smoking.

Measures of subjective sleepiness were also administered before and after each scanning session using the Stanford Sleepiness Scale (SSS). The SSS was designed to measure state sleepiness and was utilized because we were interested in the potential change in sleepiness associated with the scanning session itself. Scores on the SSS range from 1 to 7, with higher scores reflecting greater subjective sleepiness. Sleep diaries were also obtained on the night prior to scanning to assure similar total sleep time across sessions.

FMRI paradigm

The 2-Back is a verbal working memory task in which a series of consonants are presented visually, one every 3000 ms. Participants were asked to determine whether the letter they saw was the same as or different from the consonant presented two earlier (e.g., f, N, b, ***N***, ***B***, K, ***b***, ***k***, N, G…) and to make a yes/no response using a two-button response box following each consonant (Fig. 1). Capitalization was randomized and each consonant block contained 33% targets. Executive coordination, phonemic buffering, and subvocal phonemic rehearsal are required to perform this task successfully. In addition to the 2-Back, the 0-Back control task required participants to respond 'yes' when they saw a predetermined target consonant ('X' or 'x') and 'no' for any other consonants. This condition included consonants presented at the same rate and with the same target frequency as the 2-Back. In total, there were four 6-min imaging runs of four 0-Back/2-Back cycles each. The dependent variable generated for this study was the number of correct responses under 500 ms. This cutoff was reflective of conscious and attentive behavior and assured that participants were not asleep during scanning.

FMRI acquisition

Whole-brain FMRI was conducted using a Siemen's Symphony 1.5 Tesla scanner (Erlangen, Germany). BOLD echoplanar images were acquired in the axial plane using sufficient contiguous 3-mm slices for whole brain coverage. Other parameters were repetition time = 3840 ms, echo time = 38 ms, filed of view = 192^2 mm, and matrix size = 64^2. This procedure yielded 94 whole-brain volumes for each 6-min imaging run, with a spatial resolution of 3 mm^3 per voxel. Whole-brain high-resolution 1 mm^3 T1 images were also acquired in the sagittal plane for anatomical reference.

FMRI data processing

Functional magnetic resonance imaging dataset processing and statistical analyses were performed with Analysis of Functional NeuroImages (AFNI) software (Cox, 1996; National Institutes of Health, Bethesda, MD, USA). Concatonated 3D + time echoplanar datasets were spatially registered and temporally smoothed to minimize movement artifact and improve reliability. A voxelwise, multiple regression procedure was conducted to quantify the relationship between

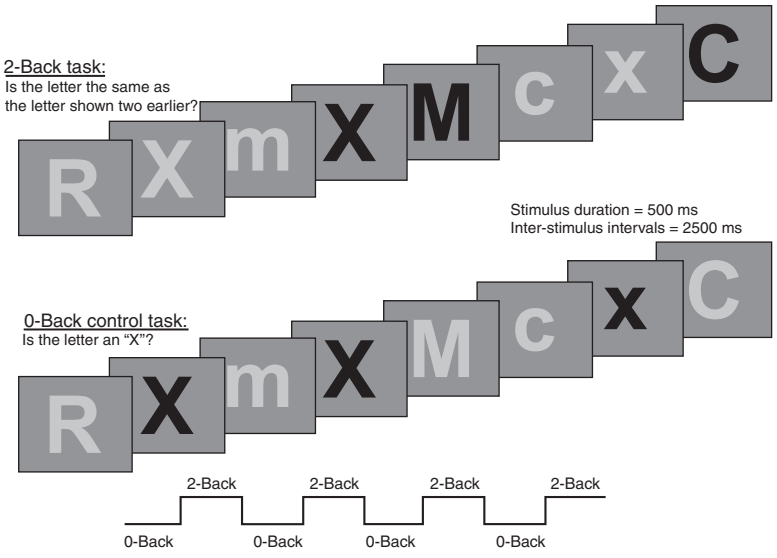

Figure 1. An example of the 2-Back task.

brain activity and the 2-Back paradigm. For each voxel of each individual, a regression of the temporal pattern of 2-Back presentation (including hemodynamic transitions modeled as a gamma function) and 0-Back control task and covariates (observed movement, linear drift) were performed using the BOLD signal over time as the dependent variable. Resulting individual activation maps of task-related effects expressed as *t*-scores were resampled to a resolution of 1 mm^3 and transformed into standard stereotaxic space for use in region of interest (ROI). A set of nine bilateral *a priori* ROIs were selected from the results of our previously published FMRI studies involving 34 healthy individuals performing the 2-Back task (Sweet *et al*., 2008). Mean task-related activity across the voxels in each ROI of each participant were used as dependent measures in contrasts of PAP condition to test our hypotheses. Group summary activation maps were also created by thresholding (two-tailed $P < 0.001$) one-sample voxelwise *t*-tests of individual activation maps for each condition against a hypothetical mean of zero (i.e., no differences between 0-Back and 2-Back conditions). Clusters of significant activity smaller than 200 mm^3 were excluded from group summary activation maps. In addition to qualitative contrasts of conditions, these maps allowed comparisons to previous 2-Back functional neuroimaging literature and provided evidence of the validity of the *a priori* ROIs used to test our hypotheses.

RESULTS

Demographic characteristics of the participants are presented in Table 1. Participants were generally middle-aged, highly educated, and exhibited moderate (AHI: 15–30) to severe OSA (AHI >30). On average, participants used PAP for 6.64 h per night during the week prior to scanning for the on-treatment condition. Objective adherence monitoring was used to verify no use on the two nights prior to scanning in the off-treatment condition. Total sleep time (taken from the sleep diaries on the night previous to the scan), subjective sleepiness, and number correct (under 500 ms) on the 2-Back task across treatment conditions (on versus off PAP) are presented in Table 2. The Wilcoxon-matched pair signed-ranks test was used to contrast treatment conditions due to the small sample size and this test's efficiency in determining effect size under non-normal distributions. There was no difference for condition in self-reported total sleep time (on = 7.57 versus off = 7.49, $Z = -0.65$, $P > 0.05$). Participants endorsed greater subjective sleepiness off-treatment prior to (on = 1.9 versus off = 3.4, $Z = -2.56$, $P < 0.05$) and after (on = 2.4 versus off = 4.0, $Z = -2.39$, $P < 0.05$) scanning. Differences in sleepiness attributed to time in the scanner were not significant for either condition.

Table 1 Demographic characteristics of the sample

Variable	*Means (SD)*	*Range*
Age (years)	51.1 (9.3)	32–61
Education (years)	15.6 (3.2)	13–22
Body mass index (kg m^{-2})	30.6 (2.0)	28–34
AHI (# per h)	42.4 (28.2)	17–80
Estimated verbal IQ	113.1 (9.1)	95–127

AHI, Apnea–Hypopnea Index; IQ, intelligence quotient.

Table 2 Behavioral characteristics across conditions

Variable	*On-treatment*	*Off-treatment*	*Z*-value	*P-value*
SSS (total score out of 7)				
Prescan	1.9 (0.33)	3.4 (1.1)	−2.59	<0.05
Postscan	2.3 (0.87)	4.0 (1.3)	−2.39	<0.05
TST (h per night)	7.94 (0.95)	7.47 (1.16)	−0.83	0.41
Number accurate under 500 ms				
2-Back	35.0 (31.4)	35.8 (41.5)	−0.30	0.77

SSS, Stanford Sleepiness Scale; TST, total sleep time.

2-Back performance

Participants' performance on the 2-Back task was greater than chance, with sampled average accuracy means above 80% for all trials. These performance levels did not differ by condition ($Z = -0.30$, $P > 0.05$), suggesting that any differences in brain activity across the PAP condition were not attributable to differences in performance. High performance levels and a lack of differences between PAP conditions were due probably to the level of training that participants received prior to each scanning session.

Brain activation

A priori ROIs are listed in detail in Table 3. Of the nine bilateral regions, treatment effects were significant in the right posterior insula and right inferior parietal lobule. There was a trend for treatment effects in the right posterior cingulate and left supplementary motor cortex (SMA). Note that activation patterns for all regions became more extreme in the off-treatment condition compared with the on-treatment condition, with the insula and posterior cingulate demonstrating significantly greater *deactivation* and the pariental lobe and SMA demonstrating significantly greater *activation*.

Significant brain activity associated with the 2-Back task on- and off-PAP treatment is presented together with *a priori* ROIs in Fig. 2. Ten clusters of at least 200 μL of significant activity were identified using a voxel threshold of $P < 0.001$. Although every ROI exhibited more extreme task-related activity or deactivation off-treatment compared with on-treatment, only the difference in the right medial frontal gyrus was significant ($r = 0.69$, $P < 0.05$).

Relationships between performance and brain activity were examined during the treatment withdrawal condition using Spearman's rho. Better 2-Back performance (correct responses under 500 ms) was associated significantly with less deactivation in the left posterior insula (rho = 0.745, $P = 0.021$) and the right posterior cingulate (rho = 0.753, $P = 0.019$), with a trend for the same effect in the left posterior cingulate

Table 3 Treatment and laterality effects in regions of interest

	Center coordinates				*Mean ROI activity (Z)*		*Effect of activity (Z)*	
Bilateral a priori ROIs	*x*	*y*	*z*	*Hemisphere*	*On*	*Off*	*Z*	*P*
Parahippocampal gyrus	±26	−36	−3	Right	−0.19	−0.17	−0.18	0.86
				Left	−0.33	−0.42	−0.77	0.44
Paracentral lobule	±3	−24	47	Right	0.07	−0.27	−1.01	0.31
				Left	−0.42	−0.65	−0.65	0.51
Posterior insula	±37	−22	21	Right	−0.20	−0.72	2.55	0.01
				Left	−0.27	−0.36	−0.30	0.77
Anterior insula	±30	22	5	Right	1.36	1.43	−0.41	0.69
				Left	1.53	1.52	0.06	0.96
Middle frontal gyrus	±40	16	31	Right	0.82	0.84	−0.06	0.95
				Left	0.78	0.86	−0.55	0.60
Inferior parietal lobule	±35	−47	44	Right	1.26	2.09	−2.83	0.05
				Left	1.59	1.82	−0.83	0.43
Medial frontal gyrus	±5	56	7	Right	−0.80	−0.76	−0.16	0.88
				Left	−1.87	−1.70	−0.93	0.38
Posterior cingulate	±5	−49	19	Right	−0.71	−1.14	2.36	0.09
				Left	−1.99	−1.76	−0.71	0.49
Supplementary motor area	±5	18	47	Right	1.31	1.63	−0.86	0.41
				Left	1.45	2.06	−2.21	0.09

ROI: region of interest.
Region labels refer to location of centroid coordinate; *P*-values are two-tailed.

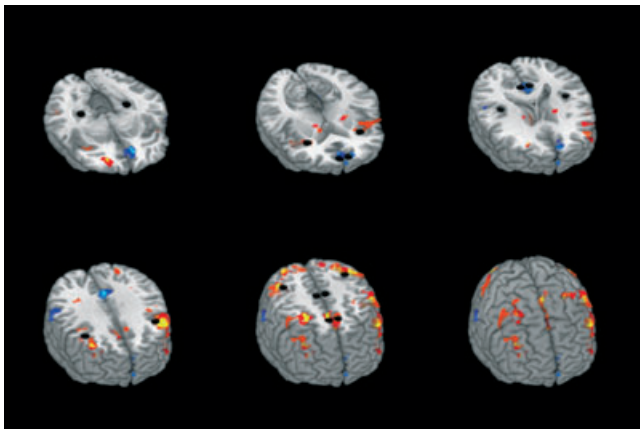

Figure 2. Working memory-related brain activity and *a priori* regions of interest. Black spheres indicate the location of bilateral *a priori* regions of interest (ROIs) listed in Table 3 from Sweet *et al.* (2008). Warm colors indicate recruited activity. Red: off-positive airway pressure (PAP); orange: on-PAP; yellow: both conditions. Cool colors indicate deactivation relative to the 0-Back baseline control task. Dark blue: off-PAP; blue: on-PAP; light blue: both conditions.

(rho = 0.644, $P = 0.061$). Relationships to performance were not significant for any of the regions that exhibited task-related activation ($P > 0.05$).

We also examined the association between change in activation of the *a priori* ROIs and sleepiness on the SSS prior to scanning to determine whether or not activation was influenced by clinical symptoms. Increased left posterior insula deactivation was associated with greater sleepiness after the removal of PAP ($r = -0.89$, $P < 0.01$).

DISCUSSION

The aim of this study was to determine the effects of acute withdrawal from PAP on brain function in patients with OSA. The study was unique, in that it was designed to mimic the common occurrence of a treatment holiday by withdrawing treatment in adherent participants. Results are therefore applicable to common clinical situations. Previous studies have suggested that OSA might compromise working memory ability and the recruitment of task-related brain regions compared with controls. Both overactivation as well as underactivation have been reported in the literature (Ayalon *et al.*, 2006; Thomas *et al.*, 2005) but only one of these studies has also attempted to address the effects of treatment on brain function. Thomas *et al.* (2005) demonstrated some increased activation in posterior brain regions with the initiation of treatment but no improvement was demonstrated in the dorsolateral prefrontal cortex, which was implicated in baseline assessments. Our study employed a within-subjects design to contrast directly counterbalanced treatment conditions. Thomas *et al.* (2005) findings were roughly consistent with our noted increase in activation in the right inferior parietal lobule but we also noted a decrease in activation with treatment in the right posterior insula.

Overall brain response patterns to the 2-Back task in our study were consistent with previous studies using this task in non-apneic samples (Braver *et al.*, 1997; Haley *et al.*, 2007; Sweet *et al.*, 2004; Thomas *et al.*, 2005). Areas of overlap included large bilateral frontal and parietal clusters of activity and large medial prefrontal and posterior cingulate clusters of deactivation relative to the 0-Back control task.

Treatment-specific differences were found in the right inferior parietal lobule which exhibited relatively greater task-related activity off-treatment compared with on-treatment. In addition, the right posterior cingulate deactivation associated with this task decreased further after treatment withdrawal.

One of the regions identified in our study, the inferior parietal lobule, has been implicated in attentional processing in previous FMRI studies [see Cohen *et al.* (2008)]. This suggests that patients withdrawn from treatment for only two nights may require abnormally high levels of attentional processing to perform this demanding cognitive task. Compensatory recruitment of the inferior parietal lobe during verbal working memory tasks has also been reported among multiple sclerosis patients (Staffen *et al.*, 2002; Sweet *et al.*, 2006). It is unclear if this over-recruitment will be evident after longer periods of treatment withdrawal or whether this is a more acute response. It is tempting to interpret the group activation maps presented in Fig. 2 by qualitative examination of color differences. This would lead us to see an overall pattern of overactivation off-treatment, supporting more global compensation. It is important, however, to rely more on the statistical analyses, especially in cases of small samples.

Deactivation in the posterior cingulate during the 2-Back task, even more so without treatment, and a significant relationship between successful performance and activity off-treatment also provide evidence for a possible compensatory mechanism. A study of the effects of total sleep deprivation on a complex navigational task reported similar brain behavior responses to a complex navigational task (Strangman *et al.*, 2005). In their within-subjects cross-over design, Strangman *et al.* found similar task performance, greater compensatory activity in the right inferior parietal lobe, and greater deactivation of the right posterior cingulate among the sleep-deprived group. Several studies have reported that the posterior cingulate activation is related to the anticipatory directing of visual attention (Small *et al.*, 2003) and attention to self-awareness (see Vogt and Laureys, 2005). Suspension of these processes, observed as deactivation, would lead logically to less distractibility and better concentration. Investigators employing different types of cognitive challenges have also described similar patterns of deactivation related to increased attentional focus. For instance, using parametric variations of short-term memory and auditory discrimination load, McKiernan *et al.* (2003, 2006) found that increases in difficulty level led to decreases in task-unrelated thoughts and further deactivation in the posterior cingulate. Sweet *et al.* (2008) found the greater posterior cingulate, posterior insula, and temporal deactivation during a distracting phonological similarity manipulation of the 2-Back task. Other support for this notion is suggested by experimental manipulation of attention by nicotine administration. Hahn *et al.* (2007) observed improved performance on a test of visuospatial attention associated with greater deactivation in the posterior cingulate following nicotine administration to smokers who had been minimally deprived of nicotine.

Analyses of the relationship between 2-Back performance and brain response during withdrawal of treatment also suggests that the additional deactivation in the posterior cingulate is compensatory. Despite overall greater deactivation relative to the treatment condition, those who exhibited the least deactivation (relative to the 0-Back baseline control task) in the posterior cingulate performed the most effectively. All participants performed well above chance; therefore, those who found it most difficult, but succeeded at the 2-Back task, also exhibited the greatest deactivation (relative to baseline).

Two other findings emerged from our study. First, the self-reported increase in sleepiness across conditions supports the notion that, at least subjectively, these patients noticed functional impairment when treatment was withdrawn. Secondly, the results suggest that adherence to treatment must be considered in further MRI studies of OSA considering the potential confounds of treatment withdrawal on the MR signal.

We note limitations to our conclusions. First, the sample size is relatively small. However, the commensurate SDs within regions across treatment conditions suggests that differences are not due to large variability between scans, which is one concern in making a Type I error. There were several pragmatic issues related to sample size that arose when conducting this study. Many patients failed to reach the adherence criterion set by the study, limiting the pool of potential participants. We also found that obese patients with apnea were less likely to be able to fit into the MRI scanner. Along with stringent inclusion/exclusion criteria and a within-subjects design, we have limited variability. Larger sample studies must be conducted to replicate the findings reported here, but such small sample studies provide at least initial proof of the concept needed to support these larger studies. A second limitation of the study is the lack of a 'sham' control condition for participants. It is possible that participants performed differently across conditions because of a subjective feeling that they *should* perform differently without treatment. Although this remains a definite possibility, one would expect decreased behavioral performance in the off-treatment condition if this were the dominant reason for these findings, which was not the case in our study. Also, a withdrawal study is inherently within subjects. Sham studies tend to be group comparison studies as withdrawal from effective CPAP to sham might break the blind in a within-subjects design. Finally, hypercapnia during the withdrawal condition could lead to global elevations in the BOLD signal. We know of no reason that such elevations would result in regional rather than global findings, but this remains possible. The possibility of an interaction is also plausible, such that hypercapnia alters the range between baseline and experimental condition.

Despite these limitations, we believe that these findings represent a unique contribution to the study of cognitive functioning in OSA. FMRI is a useful technique for examining brain function and is being utilized increasingly in sleep research. This is the first study to address treatment withdrawal effects on brain activation in OSA. We believe that the inclusion of this technique will add to the understanding on the effects of sleep apnea on brain function and to the extent that treatment influences such functioning.

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