Cerebrovascular Response to Intermittent Hypoxia During Sleep in OSA

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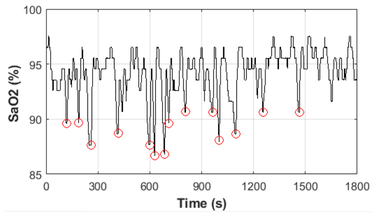
Introduction

- Obstructive sleep apnea (OSA) is associated with increased risks of cerebrovascular accidents, but the pathogenic mechanisms remain unclear. Intermittent hypoxia during sleep is a hallmark feature of OSA, but its impacts on the cerebral vasculature during sleep remain not studied.
- Functional magnetic resonance imaging (fMRI) that measures the blood oxygen level dependent (BOLD) signal has shown small differences in the cerebrovascular reactivity between awake humans with and without OSA. **[1,2]**
- Here we use BOLD fMRI to map the cerebrovascular response to endogenous intermittent hypoxia in OSA. This is also the first fMRI study of OSA patients during sleep.

Methods

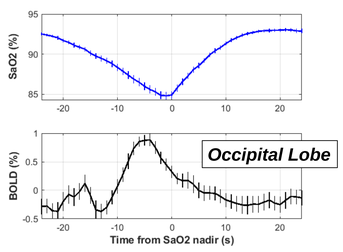
- Sixteen patients were enrolled based on their clinical sleep studies (home-based or in-laboratory), with: age 18-70, BMI < 40, weight < 120 kg, sleep efficiency > 70%, apnea-hypopnea index (AHI) > 15, and body position was primarily supine. All but one patients either never received or could not tolerate therapies for OSA.
- Each subject first attempted to sleep while lying supine in the MRI scanner and listening to sound recordings of fMRI. Oxygen saturation (SaO_2), chest movement, end-tidal carbon dioxide were recorded and monitored continuously. If obstructive respiratory events began to occur repeatedly, the subject was considered able to sleep amid fMRI, and actual fMRI scans were started. Subjects who could not sleep usually described discomforts and elected to quit this study within 1-2 hours. Thus, it was unnecessary to use a separate acclimatization night that was utilized by other groups. **[3]**
- The actual fMRI study comprised 2-D T2*-weighed gradient-echo BOLD fMRI scans of the whole brain, conducted for 0.5 hour per scan, 1.5-3 hours in total per subject (TE: 35 ms, TR: 2.0 s, 35-38 sagittal slices, 3.5 x 3.5 mm in-plane and 3.5-4.0 mm slice thickness).
- FMRI data were corrected for rigid-body head motion across time and slow intensity variations (< 0.01 Hz) were removed in each subject. Obstructive respiratory events (apneas and hypopneas) were identified. For those events with significant oxygen desaturation (SaO_2 drop ≥ 4 % and nadir < 92 %), the timepoints of SaO_2 nadirs were demarcated (see the red circles in figure), and fMRI signals from 24 s before to 24 s after these timepoints were extracted for further analysis.

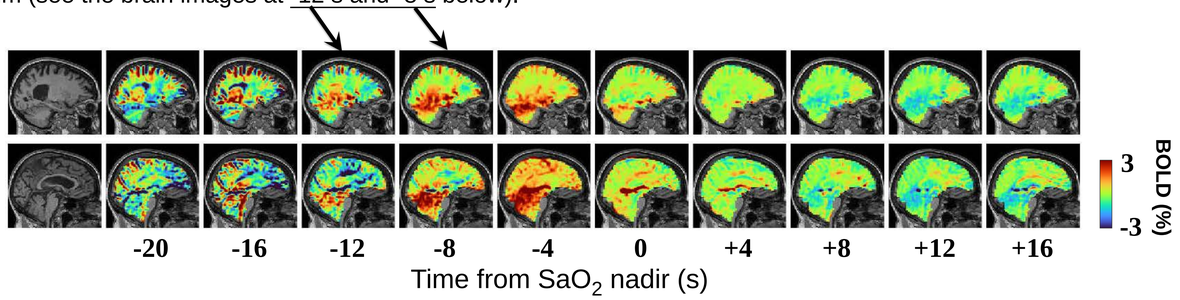


Results

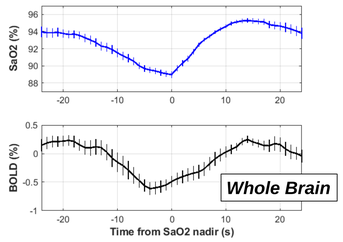
- Nine out of 16 (57%) enrolled OSA patients completed the overnight MRI study. The ability to sleep during fMRI could not be predicted from the demographics (see table).
- In the majority of subjects (6/9 = 67%), BOLD signals showed robust increases during hypoxia (started from ~10 s before SaO_2 nadir). The BOLD increases were much stronger and started slightly (2-4 s) earlier in the posterior brain, especially in the Occipital Lobe and the Cerebellum (see the brain images at -12 s and -8 s below).

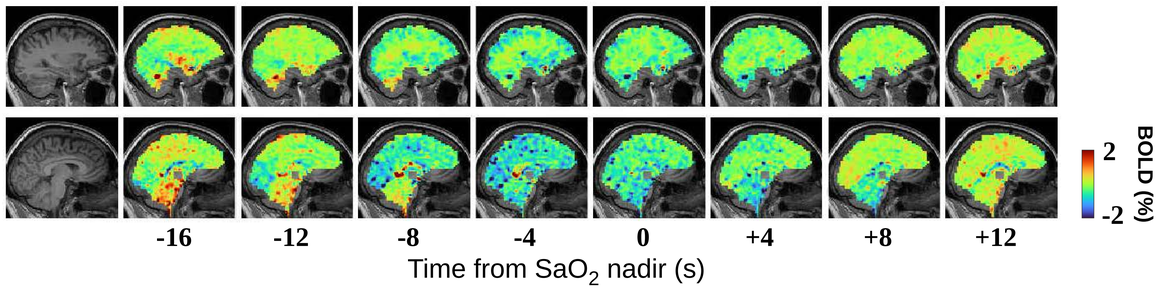
Subj. ID	Age (year)	Gender	BMI (kg/m²)	Supine AHI (3%)	Supine AHI (4%)	SaO_2 ≤ 88% (minute)	SaO_2 nadir (%)	Mean SaO_2 nadir (%)	Anti-HTN meds	Epworth score
1	61	M	33	68	66	127.0	58	83	3	1
2	29	M	37	86	83	8.0	82	92	2	20
3	55	M	31	41	25	31.8	84	88	1	8
4	70	F	29	35	26	19.1	80	88	1	18
5	46	M	28	38	28	12.1	79	89	0	8
6	26	M	37	24	14	0.0	89	93	0	8
7	47	M	33	92	75	3.5	87	90	1	11
8	57	M	27	75	59	2.6	85	90	0	9
9	61	F	24	29	18	1.0	87	91	0	N/A





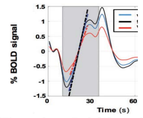
- In some subjects (ID# 3, 6, 9), BOLD signals showed only decreases during hypoxia (also started from ~10 s before SaO_2 nadir), generally limited to the gray matter across the whole brain. These subjects might fare better clinically (no excessive daytime sleepiness).





Discussion

- This study is, to our knowledge, the first study of the brain in OSA patients during sleep. BOLD fMRI of the brain during natural sleep was feasible for the majority of OSA patients.
- In awake subjects undergoing breath-holding that induces brief hypoxia and hypercapnia, BOLD signal shows an initial decrease followed by a larger increase. **[1]** The increase of BOLD signal represents vasodilation reaction, does not show spatial heterogeneity, and may be slightly stronger in OSA.



(Figure from Ref. [1], copied here for comparison)

- In contrast, here we show that during sleep, in the majority of OSA patients, BOLD increase to endogenous brief hypoxia (and hypercapnia) is much stronger and starts earlier in the posterior brain regions. This novel finding of spatiotemporal heterogeneity suggests higher cerebrovascular reactivity of posterior circulation than anterior during sleep in OSA.
- In some OSA patients, BOLD signal only shows decreases during the endogenous brief hypoxia, suggesting weaker cerebrovascular reactivity compared to other OSA patients. This might be a clinically protective feature, as the cerebrovascular reactivity can be four-fold stronger when hypoxia is accompanied with high sympathetic activity. **[4]**

Acknowledgement

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References

1. **Wu** PH, *et al.* and Wehrli FW. "MRI evaluation of cerebrovascular reactivity in obstructive sleep apnea", *J. Cereb. Blood Flow Metab.* 40(6):1328-37 (**2020**).
2. **Ponsaing** LB, *et al.* and Jennum P. "Impaired cerebrovascular reactivity in obstructive sleep apnea: a case-control study", *Sleep Med.* 43:7-13 (**2018**).
3. **Moehlman** TM, *et al.* and Picchioni D. "All-night functional magnetic resonance imaging sleep studies", *J. Neurosci. Methods* 316:83-98 (**2019**).
4. **Marullo** AL, *et al.* and Day TA. "Cerebrovascular and blood pressure responses during voluntary apneas are larger than rebreathing", *Eur. J. Appl. Physiol.* 122(3):735-43 (**2022**).