

SUPPLEMENTARY MATERIAL

Title: Obstructive sleep apnea during REM sleep and daytime cerebral functioning: A regional cerebral blood flow study using high-resolution SPECT

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SUPPLEMENTARY MODELS AND RESULTS

Model S1: daytime regional cerebral blood flow (rCBF) changes between rapid-eye movement (REM) sleep obstructive sleep apnea (OSA) quartiles

We divided the complete sample into quartiles according to REM sleep OSA variables. These four groups were compared between them regarding their daytime rCBF as a dependent variable with non-REM (NREM) sleep OSA as a covariate. This analysis was performed in previous studies¹⁻³ and allowed investigating the effects of the severity of REM sleep OSA independently of NREM sleep OSA in a group design.

The quartiles were adjusted for total sleep time by computing the apneas and hypopneas during REM (REM-AH) by hours of total sleep in the complete sample (n=96). The first quartile included subjects between 0 and 1.2 REM-AH by hours of sleep; the second between 1.3 and 3.4; the third between 3.5 and 5.6; and the fourth with subjects with 5.7 and over (range: 5.7 – 14.2). The second REM-AH quartile was associated with reduced daytime rCBF in the right putamen extending to the right insula compared to the first quartile (see Table S1). The fourth REM-AH quartile had reduced daytime rCBF in the left superior medial frontal cortex compared to the first quartile. These group differences were not significant, however, when sex was entered as a covariate or when the apnea-hypopnea

index in REM sleep (REM-AHI) was used to separate quartiles instead in subjects with a REM sleep duration ≥ 30 minutes. No region of increased daytime rCBF was observed.

In ANCOVA group analyses, the fourth REM-AH quartile had a lower Montreal Cognitive Assessment (MoCA) score when compared to the first quartile ($p=0.03$) adjusted for total sleep duration, age and NREM-AH, which was still observed when sex was entered as a covariate ($p=0.04$). No other difference between REM sleep OSA severity quartiles was observed for the Epworth Sleepiness Scale (ESS), Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI) scores.

Model S2: Regression between REM sleep OSA and daytime rCBF in subjects with an NREM-AHI<15

Although regression models 1 and 2 are adjusted statistically for NREM sleep OSA, we performed an additional analysis specifically in subjects with an NREM-AHI<15, which correspond to either no or mild NREM sleep OSA. This model allowed investigating daytime rCBF as a dependent variable in relationship with REM sleep OSA in subjects that do not present NREM sleep OSA. Thus, this analysis highlights the impacts of REM sleep OSA when it is present exclusively. REM-AH was associated with reduced daytime rCBF in the right insula extending to the inferior frontal (see Table S1). The same cluster of

reduced daytime rCBF was observed in association when sex was entered as a covariate or when the REM-AHI was used instead in subjects with a REM sleep duration ≥ 30 minutes (see Table S1). No region of increased daytime rCBF was found.

Table S1. Significant clusters of reduced daytime rCBF with REM-AH and NREM-AH in specific subsamples

Cluster size (k)	T	MNI coordinates			Peak location with AAL atlas
		x	y	z	
<i>Model S1: Daytime rCBF in REM-AH quartile 1 > quartile 2</i>					
166	3.7	30	14	-2	R putamen
	3.5	22	6	0	R putamen
	3.3	22	0	10	R putamen
					(extending to the R insula)
<i>Model S1: Daytime rCBF in REM-AH quartile 1 > quartile 4</i>					
109	3.8	-12	64	4	L superior frontal medial
<i>Model S2: Reduced daytime rCBF with REM-AH in subjects with NREM-AHI < 15</i>					
192*	3.9	36	20	4	R insula
	3.8	46	16	10	R inferior frontal pars opercularis

Group analysis (model S1) in quartiles was adjusted for total sleep duration and NREM-AH. Regression model S2 included REM-AH as well as age and total sleep duration as covariates. The cluster marked with (*) was still significant when sex was added as a covariate (cluster size: 121 voxels) and when REM-AHI was

used instead of REM-AH in subjects with REM sleep duration ≥ 30 minutes (cluster size: 192 voxels). Significant regions of daytime rCBF were obtained with the following threshold: $p < 0.001$ uncorrected for peaks voxels found within a cluster of >100 continuous voxels. rCBF, regional cerebral blood flow; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; AH, apneas + hypopneas; AHI, apnea-hypopnea index; MNI, Montreal Neurological Institute; AAL, Automated Anatomical Labeling; OSA, obstructive sleep apnea; L, left; R, right.

REFERENCES

1. Chami HA, Gottlieb DJ, Redline S, et al. Association between Glucose Metabolism and Sleep-disordered Breathing during REM Sleep. *Am J Respir Crit Care Med* 2015; 192: 1118-1126. DOI: 10.1164/rccm.201501-0046OC.
2. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. *Am J Respir Crit Care Med* 2014; 190: 1158-1167. DOI: 10.1164/rccm.201406-1136OC.
3. Mokhlesi B, Hagen EW, Finn LA, et al. Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. *Thorax* 2015; 70: 1062-1069. DOI: 10.1136/thoraxjnl-2015-207231.