SUPPLEMENTARY MATERIAL

How does obstructive sleep apnea alter cerebral hemodynamics?

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1 Clarification of data-set and comparison to the previous studies

The data that is presented in this work has been obtained during the same measurement campaign as reported in our previous, proof-of-concept publication 10.1117/1.NPh.5.4.045003. At the time of the publication of the original work, it was not yet reported that diffuse correlation spectroscopy (DCS) was a suitable method for sleep studies due to presumed sensitivity to confounding factors such as motion artifacts. As reported in the original manuscript, we had to introduce a new method for outlier detection to DCS data analysis in order to minimize the effects of various artifacts. The same was done to the PSG data. Furthermore, the results showed a clear dependence of the hemodynamics on the apnea duration and we have developed an approach to group apneas by duration and use the apnea end as a pivot point for the analysis. These methods and the statistical approaches that needed to be adopted in order to demonstrate not only that DCS could indeed be used during sleep but also it provides sufficient signal-to-noise ratio characterize the cerebral blood flow response to apnea, led us to consider only obstructive apneas for the original study. At the time of the original publication, this was a remarkable accomplishment and the results were published.

The original data-set included measurements with frequency-domain near-infrared diffuse correlation spectroscopy (NIRS-DOS) (as described in this manuscript) which had employed two different probes. As described in this manuscript, one was meant to allow us to estimate absolute values of initial optical properties and the other was suitable for overnight measurements. The preliminary analysis of the frequency-domain NIRS-DOS data revealed that we could not rely solely on the continuous measurement which allowed us to only estimate changes in oxy- and deoxy-hemoglobin concentrations. Therefore, we have taken extra care and carried out validation experiments on tissue simulating phantoms to extract the absolute values measured prior to the night study and then adjust the relative changes accordingly. This is detailed in the manuscript (section Methods, subsetion Optical methods and instrumentation).

As described in the manuscript, we have also adopted new approaches, albeit based on the original work, to characterize the response to the apnea events from different parameters. This allowed to reliably compare different parameters measured by different modalities in a more reliable manner.

Once this was accomplished, and we were convinced that this is a reliable method for data analysis, we were able to include both obstructive apnea and hypopnea events in the analysis.

Finally, to be even more specific, the main physiological conclusion in the original manuscript is that microvascular cerebral blood flow shows a biphasic behavior with a first increase followed by a decrease. The

new work follows on its footsteps and demonstrates that cerebral microvascular total hemoglobin concentration and cerebral blood oxygen saturation also show this biphasic behavior. We are now also able to include the analysis of post-apnea recovery parameters. We show a complete and thorough statistical analysis of the relation between cerebral hemodynamics versus polysomnographic parameters. We dive deeply into the clinical parameters of our cohort of patients and the relationship of these with cerebral hemodynamics leading to a comparison between obstructive apnea events and hypopnea events.

2 Tables

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Table 1: The number of obstructive apneic and hypopneic events considered from the polysomnography detection and the events considered for the further analysis in different steps.

Event	Step		CBF	THC	StO_2	SpO_2	HR
1		**Total detected by PSG, n (%)**	3817 (100)	3817 (100)	3817 (100)	3817 (100)	3817 (100)
Obstructive apnea	2	**Detected by PSG, n (%) of step 1**	1365 (36)	1365 (36)	1365 (36)	1365 (36)	1365 (36)
	3	**n (%) of step 2**	1153 (84)	1327 (97)	1327 (97)	1248 (91)	1169 (86)
	4	**After outlier removal, n (%) of step 3**	1047 (91)	1200 (90)	990 (75)	1085 (87)	1069 (91)
Hypopnea	2	**Detected by PSG, n (%) of step 1**	1918 (50)	1918 (50)	1918 (50)	1918 (50)	1918 (50)
	3	**n (%) of step 2**	1558 (81)	1522 (79)	1522 (79)	1859 (97)	1146 (60)
	4	**After outlier removal, n (%) of step 3**	1159 (74)	1115 (73)	1118 (73)	1374 (74)	1060 (92)

Values are reported in frequency (%). Step 1, total events detected by PSG. Step 2, obstructive apneic events detected by PSG. Step 3, obstructive apneic events detected by PSG and recorded by each technique. Step 4, obstructive apneic events detected by PSG and recorded with each technique that are remaining after removing the outliers. CBF, cerebral blood flow; HR, heart rate; SpO_2, arterial oxygen saturation by pulse oximetry; THC, total hemoglobin concentration; StO_2, cerebral blood oxygen saturation; PSG, polysomonography.

Table 2: P-values of the statistically significant linear models between cerebral hemodynamic parameters versus polysomnographic parameters considering obstructive apneic and hypopneic events.

p-value	Event duration (s)	Arterial oxygen saturation, SpO_2					Heart rate, HR				
		1st ext. (min) (%)	2nd ext. (max) (%)	Time-to-1st ext. (s)	Time-to-2nd ext. (s)	Time-to-recovery (s)	1st ext. (max) (%)	2nd ext. (min) (%)	Time-to-1st ext. (s)	Time-to-2nd ext. (s)	Time-to-recovery (s)
Cerebral blood flow, CBF											
1st ext. (max) (%)	<0.001	<0.001					<0.001				
2nd ext. (min) (%)	<0.001	<0.001	<0.001				<0.001	<0.001			
Time-to-1st ext. (s)	<0.001	0.740		0.001			0.202		<0.001		
Time-to-2nd ext. (s)	0.257	0.124			0.015		0.004			<0.001	
Time-to-recovery (s)	0.001	0.009				0.007	<0.001				<0.001
Total hemoglobin concentration, THC											
1st ext. (max) (uM)	0.932	0.015					<0.001				
2nd ext. (min) (uM)	0.001	<0.001	<0.001				0.018	<0.001			
Time-to-1st ext. (s)	0.003	0.698		0.069			0.823		0.082		
Time-to-2nd ext. (s)	0.680	0.128			0.028		<0.001			<0.001	
Time-to-recovery (s)	0.657	0.039				0.654	0.004				0.001
Cerebral blood oxygen Saturation, StO_2											
1st ext. (min) (%)	<0.001	<0.001					<0.001				
2nd ext. (max) (%)	<0.001	<0.001	<0.001				<0.001	0.001			
Time-to-1st ext. (s)	0.011	0.147		<0.001			0.179		<0.001		
Time-to-2nd ext. (s)	0.082	0.015			<0.001		0.002			0.152	
Time-to-recovery (s)	0.001	<0.001				<0.001	<0.001				0.088

CBF, cerebral blood flow; SpO_2 arterial oxygen saturation; HR, heart rate; StO_2, cerebral blood oxygen saturation; THC, total hemoglobin concentration.

Table 3: P-values of the statistically significant linear models between cerebral hemodynamic parameters versus patient polysomnographic and clinical parameters considering the mean (per patient) of obstructive apneic and hypopneic events.

p-value	**Gender effect *(being female)***	**Age (*years*)**	**Smoking *(yes)***	**Mean night SpO_2 *(%)***	**AHI *(n apneas/ hour)***
Cerebral blood flow, CBF					
1st ext. (max) (%)	0.666	0.039	0.235	0.249	0.457
2nd ext. (min) (%)	0.485	0.862	0.334	0.316	0.825
Time-to-1st ext. (s)	0.702	0.202	0.746	0.936	0.849
Time-to-2nd ext. (s)	0.916	0.049	0.655	0.729	0.097
Time-to-recovery (s)	0.982	0.211	0.893	0.641	0.185
Total hemoglobin concentration, THC					
1st ext. (max) (uM)	0.006	0.697	0.087	0.783	0.029
2nd ext. (min) (uM)	0.000	0.593	0.025	0.104	0.045
Time-to-1st ext. (s)	0.036	0.706	0.002	0.387	0.264
Time-to-2nd ext. (s)	0.065	0.460	0.171	0.710	0.008
Time-to-recovery (s)	0.030	0.885	0.173	0.099	0.031
Cerebral blood oxygen saturation, StO_2					
1st ext. (min) (%)	0.232	0.337	0.855	0.432	0.312
2nd ext. (max) (%)	0.444	0.781	0.990	0.875	0.830
Time-to-1st ext. (s)	0.545	0.231	0.860	0.127	0.098
Time-to-2nd ext. (s)	0.634	0.312	0.769	0.024	0.148
Time-to-recovery (s)	0.747	0.136	0.623	0.016	0.019

CBF, cerebral blood flow; SpO_2 arterial oxygen saturation; StO_2, cerebral blood oxygen saturation; THC, total hemoglobin concentration; AHI, apnea-hypopnea index.

Table 4: Student's t-test comparison of the cerebral hemodynamic and polygraphic parameters between obstructive apneas and hypopneas.

p-value	**1st extremum**	**2nd extremum**	**Time-to-1st extremum**	**Time-to-2nd extremum**
Cerebral blood flow, CBF	**<0.001**	**<0.001**	0.253	0.516
Total hemoglobin concentration, THC	**<0.001**	**<0.001**	0.062	0.343
Total oxygen saturation, StO_2	**<0.001**	**<0.001**	0.876	0.174
Arterial oxygen saturation, SpO_2	**<0.001**	**<0.001**	**0.004**	**<0.001**
Heart rate, HR	**<0.001**	**<0.001**	**0.018**	0.142

Numbers in bold indicate that the test remains statistically significant after removing each patient of the analysis and repeating the calculations.