Cerebral Metabolite Changes and Sleep Correlates in Obstructive Sleep Apnea

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Synopsis

Obstructive sleep apnea (OSA) is a chronic, multisystem sleep disorder that has been linked with dementia, stroke and increased risks of cardiovascular disease. Continuous positive airway pressure (CPAP) is the most common treatment method for OSA patients, but its effect on different organ systems and to reverse the rate of cognitive decline is still unclear. In this study, we evaluated neurochemical changes of untreated and CPAP treated OSA patients versus healthy controls in twelve brain regions using a semi-laser based accelerated five-dimensional (5D) echo-planar J-resolved spectroscopic imaging (EP-JRESI) sequence. We also explored the relationship between brain metabolite ratios and apnea hypopnea index (AHI), a measure indicative of the severity of sleep apnea. We observed significant differences of several metabolites in many brain regions. We also found that, among other metabolites, AHI correlated positively with lactate in right parietal insular cortex. This may be the result of hypoxemia and tissue hypoxia during sleep caused by OSA. To validate our findings, further longitudinal studies using a large cohort of OSA subjects before and after CPAP are required.

Introduction:

Obstructive sleep apnea (OSA) is a chronic, multisystem sleep disorder[1] linked with dementia, stroke and increased risk of cardiovascular disease[2]. Continuous positive airway pressure (CPAP) is the most common treatment method for OSA patients and is partially effective in halting the onset symptoms, and slowing disease progression[3,4]. However, the effect CPAP has on different organ systems and on reversing the rate of cognitive decline is still unclear. Several structural neuroimaging studies have examined the impact of CPAP treatment on OSA patients[5-8]. Although there have been studies showing metabolite changes in untreated OSA[9-12], there are few metabolite study on CPAP treated patients, and those only use 1D MRSI[8]. In this study, we evaluated neurochemical changes of untreated and CPAP treated OSA patients versus healthy controls in several brain regions using a semi-laser based accelerated five-dimensional (5D) echo-planar J-resolved spectroscopic imaging (EP-JRESI)[13] sequence. We also explored the relationship between brain metabolite ratios and apnea hypopnea index (AHI), a measure indicative of the severity of sleep apnea.

Materials and Methods:

We investigated eight healthy volunteers (HV) (age 50.5±15.3years), eight untreated OSA patients (OSA_b) (age 51.8±15.5years), and eight separate OSA patients with minimum 3 months of CPAP (OSA_{CPAP}) (age 57.2±9.0years). All data were collected on a Siemens 3T Prisma MRI scanner running on the VD13D platform using a 16 channel head receive coil. The following parameters were used for water-suppressed 5D EP-JRESI: TR/TE=1.2s/40ms, voxel resolution=1.5x1.5x1.5cm^3, 64Δt_1 increments, 512 bipolar echo pair, FOV=24x24x12cm^3, 1 average, non-uniform sampling=12.5% with a scan time≈20 min. A maximum echo sampling scheme was applied[14] and after postprocessing spectral bandwidths were ±250Hz along F_1 and 1190Hz along F_2. This was followed by a non water-suppressed scan with only the first t_1 increment. The undersampled data were reconstructed as discussed previously[13]. Before each EP-JRESI scan, 3D high resolution T_1-weighted images for localization were collected using an MP-RAGE pulse sequence. Acquired data were post-processed with a custom MATLAB-based program and metabolite ratios with respect to the 3.0 ppm creatine (Cr) peak were calculated using a modified version of ProFit algorithm[15]. The metabolite differences between the three groups were tested in 12 regions with student's t-test (significant level, $p < 0.05$). Additionally, to explore for any relationship between the metabolite ratios and apnea hypopnea index AHI, Pearson correlation was performed on the patient data from the regions where metabolite differences were found. All statistical analysis was done using the SPSS software (Version 24.0, SPSS Inc, Chicago, IL, USA).

Results and Discussion:

Figure 1(A) shows the PRESS-localized volume of interest on a T_1-weighted axial brain MRI of a healthy volunteer brain. Representative 2D *J*-resolved spectra extracted from the right basal ganglia (RBG) and occipital gray (OG) regions of the same subject are shown in Figure 1(B) with 1(C) showing the ProFit fitting results. Figures 2 and 3 show the selected metabolite ratios with respect to Cr in HV, OSA_b and OSA_{CPAP} respectively. Additionally, summaries of the metabolite ratios for the 12 regions are in Table 1. Figure 4 shows the scatter plot of AHI and metabolite ratios in the RPIC and OG in the baseline OSA subjects. We found AHI correlated positively with lactate in right parietal insular cortex, GABA in left parietal insular cortex, and lactate (Lac) in OG. Negative correlations were found with GABA in right parietal insular cortex, glutamine (Gln) in OG and total choline (tCh) in right frontal white.

In summary, we observed changes in OSA with and without CPAP treatment in metabolite ratios of GABA, glucose (Glc), Gln, glycine (Gly), phosphocholine (PCh), scyllo inositol (Scy), glutathione (GSH), glutamate (Glu), Glx (Glu+Gln), Lac, phosphoethanolamine (PE), tNAA (NAA, N-acetylaspartate + NAAG, N-acetylaspartylglutamate, tml (myo inositol + glycine), taurine, and aspartate in different brain regions. Most differences appeared reversed in the OSA patients on CPAP. However, differences in some regions were not reversed completely, perhaps due to residual effects of many years of OSA.

Lactate is considered to be a marker of tissue hypoxia. Our observation of increased lactate in OSA patients and positive correlation with the degree of hypoxia is in agreement with previous findings[16,17]. This may be the result of hypoxemia and tissue hypoxia during sleep caused by OSA. Also, it is noted that in the pressure of sleep-associated hypoxemia in OSA patients, conversion of pyruvate to lactate by the process of anaerobic glycolysis conversion of pyruvate to lactate occurs[17].

Conclusion:

Our findings are consistent with the known phenomenon of oxidative stress in OSA and reversibility of neurofunctional changes after CPAP. Further studies using a large number of longitudinal subjects before and after CPAP are required.

Acknowledgements

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Figures

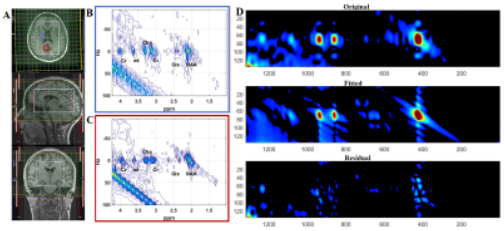

Figure 1: (A) T_1-weighted axial/sagittal/coronal MRI of a female healthy volunteer with the white box indicating the PRESS localization VOI, **(B)** selected 2D *J*-resolved spectra extracted from the right basal ganglia (voxel in blue) and, **(C)** occipital gray (voxel in red), **(D)** example of ProFit fitting results (both x- and y-axis are frequencies (Hz)).

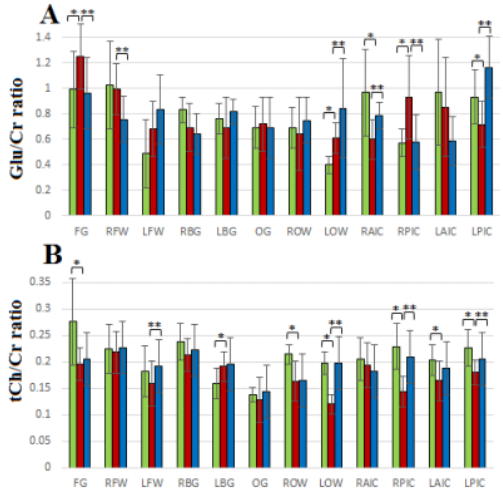

Figure 2: Bar graphs showing mean metabolite ratios (±SD) of **(A)** glutamate (Glu) and **(B)** total choline (tCh) with respect to Cr in 12 different brain regions for the three groups: HV (green), OSA_b (red) and OSA_{CPAP} (blue). *Statistically significant between HV vs OSA_b; **Statistically significant between OSA_b vs OSA_{CPAP}. FG=Frontal Gray, RFW=Right Frontal White, LFW=Left Frontal White, RBG=Right Basal Ganglia, LBF=Left Basal Ganglia, OG=Occipital Gray, ROW=Right Occipital White, LOW=Left Occipital White, RAIC=Right Anterior Insular Cortex, LAIC=Left Anterior Insular Cortex, RPIC=Right parietal insular cortex, LAIC=Left parietal Insular Cortex, tCh=free choline (Ch) + phosphocholine (Pch) + glycerophosphocholine (GPC).

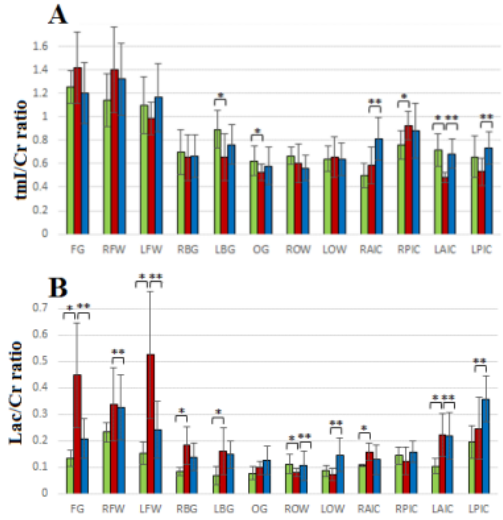

Figure 3: Bar graphs showing mean metabolite ratios (±SD) of **(A)** tmI (myo inositol + glycine) and **(B)** lactate (Lac) with respect to Cr in the same regions as of Figure 1 for the three groups: HV, OSA_b and OSA_{CPAP} . *Statistically significant between HV and OSA_b; **Statistically significant between OSA_b vs OSA_{CPAP}.

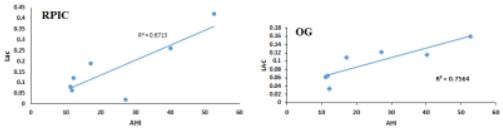

Figure 4: Scatter plot showing Lac correlation with AHI in the RPIC and OG regions.

Regions	Met. Ratios	HV	OSA_b	OSA_{CPAP}	HV vs OSA_b	OSA_b vs OSA_{CPAP}
OG	GABA	0.06	0.17	0.11	0.000	0.021
	Glc	0.28	0.14	0.27	0.004	0.009
	Gln	0.44	0.66	1.01	0.020	0.004
	Gly	0.29	0.16	0.27	0.028	0.002
	PCh	0.05	0.03	0.05	0.017	0.028
	Scy	0.10	0.07	0.16	0.084	0.001
ROW	Gln	0.55	0.43	0.75	0.167	0.000
	GSH	0.25	0.51	0.33	0.001	0.007
LOW	Gln	0.35	0.53	0.84	0.083	0.036
	Glu	0.40	0.61	0.95	0.013	0.003
FG	Gly	0.21	0.65	0.47	0.000	0.049
	Lac	0.13	0.45	0.21	0.011	0.030
RFW	Glx	1.45	1.90	1.07	0.017	0.003
LFW	Lac	0.15	0.53	0.24	0.006	0.020
RBG	Gly	0.26	0.12	0.37	0.036	0.000
	GSH	0.26	0.19	0.33	0.043	0.016
	PE	0.08	0.05	0.03	0.043	0.036
	Scy	0.08	0.22	0.14	0.004	0.029
	tNAA	1.26	1.64	1.37	0.071	0.131
LBG	Scy	0.11	0.26	0.14	0.027	0.016
	Glx	1.50	1.05	1.49	0.023	0.012
RAIC	Glu	0.97	0.60	0.79	0.024	0.047
	PCh	0.04	0.07	0.05	0.003	0.023
	PE	0.08	0.04	0.07	0.037	0.009
	Scy	0.09	0.24	0.09	0.010	0.010
LAIC	GSH	0.27	0.49	0.25	0.026	0.012
	Tau	0.07	0.04	0.06	0.004	0.071
	tmi	0.71	0.48	0.68	0.042	0.002
RPIC	Glu	0.57	0.93	0.58	0.013	0.027
	GSH	0.33	0.54	0.26	0.017	0.003
	Scy	0.22	0.08	0.11	0.000	0.243
	tmi	0.76	0.92	0.88	0.037	0.655
	PE	0.06	0.05	0.05	0.076	0.012
LPIC	Asp	0.42	0.61	0.45	0.059	0.103
	Glu	0.93	0.71	1.16	0.016	0.009
	PCh	0.08	0.05	0.07	0.137	0.075
	tCh	0.23	0.18	0.21	0.027	0.066
	Glx	1.69	1.25	1.79	0.070	0.013

Table 1: Summary of metabolite changes in the 12 regions (described in Figure 2) for the three groups: healthy volunteers (HV), baseline OSA (OSA_b) and CPAP treated OSA (OSA_{CPAP}). Only metabolite showing statistically significant differences in both HV vs OSA_b and OSA_b vs OSA_{CPAP} are shown.