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Brain Diffussivity and Neurochemical Changes in Obstructive Sleep Apnea: A Pilot Correlation Study

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Target audience: Researchers interested in obstructive sleep apnea syndrome, spectroscopic imaging and diffusion tensor imaging.

Purpose/Introduction: Obstructive sleep apnea (OSA) is a common disorder characterized by repeated hypoxic episodes during sleep. OSA patients demonstrate daytime sleepiness, diurnal fatigue, mood changes, and altered concentration likely leading to cognitive deterioration[1]. Studies have shown that cognitive dysfunction in these patients are associated with chronic exposure to nightly hypoxic periods[2]. Cerebrovascular risk factors such as hypertension, diabetes mellitus, and obesity are common in OSA[3]. Advanced neuroimaging techniques, such as diffusion tensor imaging (DTI) and magnetic resonance spectroscopic imaging (MRSI), enable non-invasive identification of OSA-induced, structural–neurochemical changes[4-6]. DTI is sensitive to the microstructure of brain tissue; various indices derived from DTI data, including fractional anisotropy (FA), and diffusivity (MD), identify cerebral structural changes in OSA. Although MRSI is used in differentiating a variety of brain lesions, there have been only a limited number of MRSI studies on OSA patients, but identification of chemical alterations associated with DTI changes could help identify the nature of the pathology in the sleep condition. The goals of this study were to examine if there is any correlation between FA and MD with metabolite ratios in various brain regions of OSA patients. We also investigated changes in FA and MD between OSA patients and healthy controls in those regions.

Materials and Methods: We assessed ten moderate-to-severe OSA patients (54.60±10.81 years) and six age matched healthy volunteers (46.66±8.77 years). OSA patients were recruited following a diagnostic sleep study at the UCLA Sleep Disorders Center, based on full overnight polysomonography scored with standard criteria. Evidence of clinical brain pathology was cause for exclusion. All subjects gave informed consent according to an institutionally approved research protocol. All data were collected on a 3T Trio-Tim MRI scanner (Siemens Medical Solution, Erlangen, Germany) using the Siemens VB17a compiler. DTI was performed using a single-shot multi-section spin-echo echo-planar pulse sequence [repetition time (TR) = 10,000 ms; echo-time (TE) = 87 ms; average = 1] in the axial plane, with a 130 x 130 matrix size, 256 x 256 mm^2 field of view (FOV), 2.0 mm slice thickness, 72 slices. For each slice, diffusion gradients were applied along 30 independent orientations with b =1000 sec/mm^2 after the acquisition of b = 0 sec/mm^2 (b0) images. MRSI data was collected using a from a compressed sensing based 4D echo planar J-resolved spectroscopic (EP-JRESI) sequence. For this purpose, the standard EP-JRESI sequence was modified to accommodate for the 25% NUS of the fully sampled data[7]. The following parameters were used for CS EP-JRESI: TR/TE = 1.5s/30ms, 1.5x1.5x1.5 cm^3 voxel for VOI localization, $64\Delta t_1$ increments, 256 bipolar echo pair, FOV= 24x24cm^2, 2 averages, F1 and F2 bandwidths of 1000 Hz and 1190 Hz, respectively. Before applying the NUS based EP-JRESI sequence, 3D high resolution T_1-weighted images for localization were collected using a MPRAGE pulse sequence. EP-JRESI was performed over an axial slice covering frontal/occipital regions. Modified Profit algorithm[8] was applied to process the extracted data and to calculate metabolite ratio with respect to the 3.0 ppm creatine peak (S/S_{Cr}). FA and MD were calculated using the SPM diffusion toolbox[9] and subsequent ROI analysis was done using ImageJ[10]. The FA and MD differences between OSA patients and healthy controls were tested with a two-tailed t-test with statistically significant level $p < 0.05$. To explore for any relationship between the FA/MD values and metabolite ratios, Pearson correlation was performed on the patient data. A Bonferroni-like correction for multiple comparisons was was used to calculate an adjusted alpha level. All statistical analysis was done using the SPSS software (Version 20.0, SPSS Inc, Chicago, IL, USA).

Results: Table 1 shows significant correlations between FA/MD values and MRS indices in left frontal white, right frontal white, medial frontal gray/white and medial occipital gray regions. Left frontal FA correlated with choline (Cho) ratio, and MD correlated negatively with glutamine (Gln) ratio. In the right frontal region, MD correlated significantly with myo-inositol (mI) ratio, and in the medial frontal white/gray FA correlated with N-acetylaspartate (NAA) ratio. Other metabolite ratios showed positive but non-significant correlations with FA and MD. Fig. 1 shows FA (a) and MD (b) values of OSA patients and healthy controls in the left frontal white, right frontal white, medial frontal gray/white and medial, occipital gray regions. Reduced FA and increased MD were observed between OSA and healthy controls in all brain regions ($p < 0.05$).

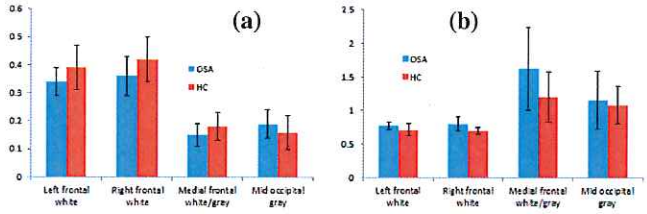

Fig. 1: Bar graphs showing mean (a) FA (±SD), (b) MD (±SD) ($\times 10^{-3}$ mm^2/s) value changes in four selected regions of OSA patients compared to healthy controls (HC) (all $p < 0.05$).

Left Frontal white	Metabolite ratios	Correlation Coefficients	p-value
FA	Cho	0.852	0.031*
	tNAA	0.69	0.058
MD	Gln	-0.756	0.030*
	Glx	-0.676	0.065
Right Frontal white			
FA	Gln	-0.996	0.056
	tNAA	0.754	0.083
MD	mI	0.961	0.002*
Medial frontal white/gray			
FA	NAA	0.765	0.045*
Medial occipital gray			
FA	Cho	0.787	0.063
MD	mI	-0.647	0.116

Table 1: Pearson Correlation between the FA/MD and metabolite ratios significant at 0.05 level. tNAA = NAA+NAAG, tCho = Cho+ PCH+GPC, Glx = Glu+Gln.

Discussion and Conclusion: White matter is extensively altered in OSA patients resulting reduced axonal integrity and changes identified by DTI indicate the underlying pathologies. Our finding of decreased FA and increased MD values are in accordance with earlier studies[4,11]. Lower FA primarily represents axonal groups that are damaged, shrunken, or that have less myelin. Increased MD values can result from subacute processes as well as chronic pathological conditions like chronic ischemia, gliosis, and demyelination. The correlations between FA/MD values and metabolic ratios supports these interpretations of the nature of structural injury in OSA. The use of CS based EP-JRESI sequence has the advantages of acquiring measurements across multiple brain regions, which is important for assessing a condition like OSA as multiple cortical, limbic and lower brains regions show structural and function alterations with other techniques. Furture studies with more OSA patients and controls are required to confirm these findings of abnormalities associated with the sleep disorder.

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