Axial and Radial Diffusion Changes in Recently-Diagnosed Patients with Obstructive Sleep Apnea

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Introduction:
Obstructive sleep apnea (OSA) patients show regional gray matter volume loss (1) and axonal abnormalities (2, 3) in multiple brain sites that regulate autonomic, cognitive, and mood functions, all of which are deficient in the condition. However, it is unclear whether the white matter injury in newly-diagnosed OSA subjects predominantly reflects axonal or myelin changes. Distinguishing axonal and myelin injury will elucidate the nature of tissue pathology in OSA, and may help to identify more effective therapeutic and management strategies. Diffusion tensor imaging (DTI)-based axial diffusivity, which measures water diffusion parallel to axons preferentially indicating axonal changes, and radial diffusivity, which measures diffusion perpendicular to axons preferentially indicating myelin changes, can assist this evaluation. Both measures offer sensitive means to examine subtle tissue alterations, provide pathological information (axonal vs. myelin injury), and may be useful to evaluate tissue pathology in early onset stages of OSA. Here, we examined global and regional brain axial and radial diffusivity changes in newly-diagnosed, treatment-naïve OSA relative to age- and gender-matched controls. We hypothesized that global axial and radial diffusivity values would be reduced in OSA compared to controls, due to the acute nature of the pathology, and that regional declines would appear in multiple brain areas.

Materials and methods:
Twenty-three OSA (age, 44.4±9.3 years; body-mass-index, 30.1±5.4 kg/m²; 20 male; apnea-hypopnea-index, 34.9±24.1 events/hour) and 23 age- and gender-matched healthy control subjects (age, 45.3±11.0 years; body-mass-index, 26.2±3.7 kg/m²; 20 male) were studied. All OSA subjects were recently-diagnosed via overnight polysomnography (apnea-hypopnea-index ≥ 15), treatment-naïve, and recruited from the sleep disorders laboratory at the UCLA Medical Center. Control subjects were healthy, without any brain disorder that might alter brain tissue, had no evidence of sleep disorders (normal score on the Epworth Sleepiness Scale), and were recruited from the Southern California region. All OSA and control subjects provided written and informed consent before the study, and the study protocol was approved by the IRB at UCLA. Brain imaging studies were performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany). High-resolution T1-weighted images were acquired using an MPRAGE pulse sequence (TR = 2200 ms; TE = 2.2 ms; inversion-time = 900 ms; flip-angle = 9°; matrix-size = 256×256; FOV = 230×230 mm; slice-thickness = 1.0 mm). Diffusion tensor imaging data were collected using a single-shot EPI with twice-refocused spin-echo pulse sequence (TR = 10,000 ms; TE = 87 ms; flip-angle = 90°; band-width = 1346 Hz/pixel; matrix-size = 128×128; FOV = 230×230 mm; slice-thickness = 2.0 mm, b = 0 and 700 s/mm², diffusion directions = 12, separate series = 4). Using diffusion-weighted and non-diffusion images, diffusion tensor matrices were calculated, diagonalized, principal eigenvalues (λ1, λ2, and λ3) determined, and axial (λ┴ = (λ1 + λ2)/2) and radial (λ║ = λ3) diffusivity values were derived. We realigned axial and radial diffusion maps, computed from each DTI series, averaged, normalized to Montreal Neurological Institute (MNI) space, and smoothed with a Gaussian filter (10 mm). White matter probability maps of individual subjects, derived from b0 images, were normalized to MNI space, averaged, and a global white matter mask calculated. High-resolution T1-weighted images of all subjects were also normalized to MNI space and averaged to create background images. Using a global white matter mask and normalized diffusion maps, global white matter diffusion values from all subjects were calculated, and compared between groups (ANCOVA; covariate, age; SPSS v20.0 software). The normalized and smoothed axial and radial diffusion maps were also compared between the groups using ANCOVA (covariate, age; SPM8, uncorrected threshold, p < 0.005). The brain clusters with significant differences between OSA and control subjects were overlaid onto background images for structural identification.

Results:
No significant differences in age (p=0.8) or gender appeared between groups. However, body-mass-indices were significantly higher in OSA (p=0.007). Global mean white matter axial (OSA vs controls; 1.27±0.04 vs 1.31±0.06 ×10⁻³ mm²/s, p=0.019) and radial diffusivity (0.69±0.03 vs 0.72±0.04 ×10⁻³ mm²/s, p=0.004) values were significantly reduced in OSA over controls. Multiple brain sites showed reduced axial and radial diffusivity in OSA over controls (Fig. 1). Brain regions with reduced radial diffusivity in OSA included the anterior and mid corpus callosum (d), mid and posterior cingulum bundle (a, c), bilateral inferior fronto-occipital fasciculus, anterior, mid, and posterior thalami (f), putamen and external capsules (e), occipital and frontal (g) white matter, ventral and dorsal temporal white matter, mid and inferior cerebellar peduncles (h, i) and cerebellar cortices, corticopontine tracts, mid and anterior hippocampus extending to the retrolenticular internal capsule, anterior internal capsule, amygdala, and anterior, superior (b), and posterior corona radiata (Fig. 1). Brain sites that showed reduced axial diffusivity in OSA emerged in bilateral anterior and superior (j), and left posterior (k) corona radiata, posterior thalami, extending to the hippocampus (l), globus pallidus (a), putamen, corticopontine tracts (m), and frontal (n) and dorsal temporal (p) white matter.

Discussion:
Global white matter axial and radial diffusivity values were significantly reduced in newly-diagnosed, treatment-naïve OSA over control subjects, indicating axonal and myelin changes. These diffusion changes in OSA subjects were localized in various brain areas critical for cardiovascular and respiratory control, including the medulla, as well as the cerebellum, basal-ganglia, limbic regions, corpus callosum, and multiple regions in the corona radiata. Radial diffusion changes were more widespread than axial diffusion changes in OSA, indicating predominantly myelin pathology over axonal injury. Hypoxemia associated with OSA may contribute primarily to myelin changes; myelin is more vulnerable to hypoxia than axons.

References:

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