

Altered Global and Regional Brain Mean Kurtosis in Recently-Diagnosed Patients with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) patients show brain structural injury, and functional deficits in multiple brain sites observed with various MRI techniques (1, 2). The affected brain regions are principally localized in autonomic control areas, motor sites, limbic regions and interconnecting fibers, and likely contribute to the exaggerated sympathetic tone, hypertension and cardiac arrhythmia, as well as cognitive and mood deficits found in the syndrome. Although the pathological nature of the tissue and fiber injury was initially assessed with diffusion tensor imaging (DTI)-based procedures, the overall extent of the pathological condition in OSA subjects is unclear. Determining the extent of tissue pathology will assist interpretation of the processes contributing to injury in the syndrome. DTI procedures are based on Gaussian diffusion phenomena; however, many brain areas follow non Gaussian diffusion, due to crossing fibers and other complexities. Diffusion kurtosis imaging (DKI) improves on the DTI model by quantifying the degree of non-Gaussian diffusion in both gray and white matter (3), differentiates acute from chronic tissue injury (4), and may be useful to examine the pathological nature of tissue injury in OSA subjects. Our aim was to examine global and regional mean kurtosis values in newly-diagnosed, treatment-naïve OSA relative to controls. We hypothesized that global mean kurtosis values will be increased in OSA, compared to controls, since we expect acute injury in early stages of the syndrome, and that localized increases will appear in multiple brain regions.

Materials and methods: We studied 7 recently-diagnosed OSA (age, 43.9±9.7 years; body-mass-index, 33.4±9.1 kg/m²; 5 male; apnea-hypopnea-index, 35.4±25.7 events/hour) and 14 control subjects (age, 39.6±7.8 years; body-mass-index, 25.1±4.0 kg/m²; 9 male). All OSA subjects were diagnosed via overnight polysomnography with at least moderate severity (apnea-hypopnea-index ≥ 15), treatment-naïve, and recruited from the sleep disorders laboratory at the UCLA. Control subjects were healthy, without any medications that might alter brain tissue, without evidence of sleep disorders (normal score on the Epworth Sleepiness Scale), and were recruited from UCLA and the Los Angeles area. All procedures were approved by the Institutional Review Board at UCLA, and each subject provided written informed consent prior to participation in this study. Brain imaging studies were performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens). High-resolution T1-weighted images were acquired using a magnetization-prepared rapid acquisition with gradient echo 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). DKI data were acquired using an echo-planar-imaging with twice-refocused spin-echo pulse sequence (TR = 7000 ms; TE = 90 ms; FA = 90°; bandwidth = 2440 Hz/pixel; matrix size = 82×82; FOV = 230×230 mm; slice thickness = 2.8 mm; 60 slices; no interslice-gap; diffusion directions = 30; b values = 0, 1000, and 2000 s/mm²) in the axial plane, and collected two separate series for subsequent averaging. DKI tensor calculations were carried out using Diffusional Kurtosis Estimator (DKE) software, which generates voxel-wise whole-brain various kurtosis maps. At each voxel, diffusional kurtosis tensors were fitted to the diffusion weighted images for b = 0, 1,000, and 2,000 s/mm², and finally, mean kurtosis maps were calculated from kurtosis tensors (5). We realigned mean kurtosis maps, computed from both DKI series, normalized to Montreal Neurological Institute (MNI) space, using the unified segmentation approach, and smoothed with a Gaussian filter (10 mm). High-resolution T1-weighted images of OSA and control subjects were also normalized to MNI space, and normalized images were averaged to create background images for structural identification. Global brain mean kurtosis values from individual OSA and control subjects were calculated using global brain masks and normalized mean kurtosis maps, and compared between groups for significant group differences (ANCOVA; covariate, age; IBM SPSS, v20 software). The normalized and smoothed mean kurtosis maps were compared voxel-by-voxel between groups using ANCOVA (covariate, age; SPM8, uncorrected threshold, p < 0.005). Brain clusters with significant differences between OSA and controls were overlaid onto background images for structural identification.

Results: No significant differences in age (p = 0.29) or gender (p = 0.74) appeared between groups. However, body-mass-indices were significantly higher in OSA (p = 0.008). The global brain mean kurtosis was significantly increased in OSA over control subjects (OSA vs controls; 0.89±0.04 vs 0.86±0.02; p = 0.037). Multiple brain areas in OSA subjects showed increased mean kurtosis values, compared to control subjects (Fig. 1, p < 0.005). No brain sites showed decreased mean kurtosis values in OSA over control subjects. Brain sites in OSA subjects that showed increased mean kurtosis values included the bilateral basal forebrain, extending to the hypothalamus, anterior hippocampus, anterior thalamus, anterior, mid, and posterior insular cortices, cerebellar cortex, inferior cerebellar peduncle, internal capsule, parietal cortices, and putamen. Other areas with increased mean kurtosis values appeared in the cerebellar deep nuclei, right superior cerebellar peduncle, left anterior cingulate cortex, left caudate nucleus, left ventral temporal white matter, brainstem, right amygdala, and right ventral medulla.

Discussion: Global mean kurtosis values are significantly increased in newly-diagnosed, treatment-naïve OSA over control subjects, suggesting that the tissue changes are acute in nature. These brain changes in OSA subjects are principally localized in critical autonomic, cognitive, motor, and respiratory control sites, including the insular cortices, cerebellum, and basal ganglia. The pathological mechanisms contributing to tissue injury likely include hypoxemia-induced processes, leading to acute tissue changes in recently-diagnosed OSA subjects.

References:

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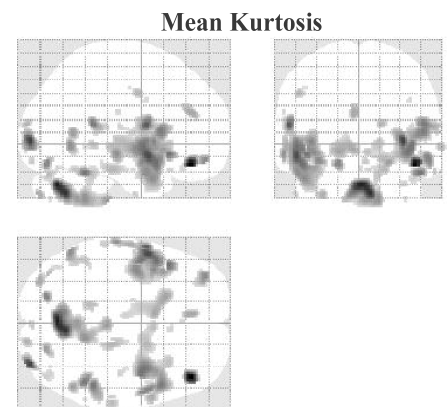


Fig. 1: Brain sites showing increased mean kurtosis values in OSA over control subjects.