Aberrant Brain Resting-State Functional Connectivity in Patients with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) patients show impaired autonomic, affective, executive, sensori-motor, and cognitive functions. Brain tissue injury and functional deficits, expressed as altered white matter integrity, free water content, brain metabolites, regional gray matter integrity, and impaired functional MRI signal responses to autonomic and breathing challenges, appear in multiple regions serving these functions (1,2). Regional brain tissue injury in OSA may alter overall spontaneous functional organization, as well as changes in resting-state functional connectivity in the condition (3), but these resting-state interactions remain unclear. Resting-state functional MRI (rs-fMRI) procedures are used to assess inter-regional functional connectivity (FC), a term which refers to temporal correlations between neuronal activity of anatomically-distinct brain regions, and graph-theoretical approaches can characterize such complex brain networks with various topological properties. Our aim was to investigate the functional interactions and complex organization of brain networks across the whole-brain in OSA subjects over healthy control subjects using FC and graph-theoretical analyses procedures. We hypothesized that OSA subjects would show intrinsically abnormal FC that may result from previously-described impaired brain regions. We further hypothesized that these abnormal functional connections may lead to deficient global integration (level of flow information efficiency between any node pairs) and local segregation (level to which regions in a network tend to locally cluster together) in serving deficient brain functions in the condition.

Materials and methods: We investigated 69 recently-diagnosed, treatment-naïve OSA (age, 48.3±9.2 years; body-mass-index (BMI), 31.0±6.2 kg/m^2; 52 male; apnea-hypopnea-index (AHI), 35.6±23.3 events/hour) and 82 control subjects (age, 47.6±9.1 years; BMI, 25.1±3.5 kg/m^2; 58 male). All OSA subjects had a moderate-to-severe diagnosis (AHI ≥15 events/hour), no history of neurological illness or psychiatric disorders other than OSA condition, and were recruited from the Sleep Disorders Laboratory at the UCLA Medical Center. Control subjects were healthy, without any evidence of sleep disorders (normal Epworth Sleepiness Scale scores) or neurological issues, and were recruited from the UCLA campus and West Los Angeles area. All participants gave written informed consent before data acquisition and the study protocol was approved by the Institutional Review Board at the UCLA. Brain imaging of all participants was performed using a 3.0-Tesla MRI scanner (Siemens, Magnetom Tim-Trio). Rs-fMRI data were acquired with an echo planar imaging-based blood-oxygen-level-dependent sequence in the axial plane [TR = 2000 ms; TE = 30 ms; FA = 90°; FOV = 230×230 mm^2; matrix size = 64×64; slice thickness = 4.5 mm; volumes = 59]. Rs-fMRI data were acquired while participants lay resting with eyes open, without focusing on any specific thoughts or sleeping. High-resolution T1-weighted images were collected from each subject using a magnetization prepared rapid acquisition gradient-echo pulse sequence (TR = 2200 ms; TE = 2.2, 2.34 ms; FA = 9°; FOV = 230×230 mm^2; matrix size = 256×256, 320×320; slice thickness = 0.9, 1.0 mm). After discarding the initial 3 volumes to avoid signal saturation issues, rs-fMRI data were preprocessed with SPM8, consisting of realignment of EPI brain volumes, co-registration to T1-weighted images, and spatial normalization to a standard common space using nonlinear transformation procedures. Rs-fMRI time series were averaged across all voxels in each region, based on 116 distinct sites defined by automated anatomical labeling atlas. For each regional averaged fMRI time series, we applied canonical rs-fMRI signal processing procedures, including band-pass filtering (0.009–0.08 Hz) and removing effects of six rigid motion, the first derivatives of the rigid body motion variables, and global signal changes in white matter, cerebrospinal fluid, and whole-brain. Individual whole-brain FC was defined as an inter-regional correlation map among 116 preprocessed regional time series, and transformed to z-scored maps with Fisher's r-to-z transformation. We compared the z-scored maps connection-by-connection between OSA and control subjects (ANCOVA; covariates, age and gender). We also investigated individual brain networks' graph-theoretical properties, including network centrality, segregation, and integration.

Results: No differences in age (p=0.7) or gender (p=0.4) appeared between OSA and control subjects. However, BMI values were significantly higher in OSA vs controls (p<0.001). OSA subjects showed decreased (Figure 1a, Blue) or increased (Figure 1b, red) FC in cerebellar, frontal, parietal, temporal, occipital, limbic, and basal-ganglia regions, (FDR, p<0.05). Topological properties for functional whole-brain network centrality, segregation, and integration properties of OSA subjects were significantly reduced in regions showing altered FC, and these reductions were further summarized as reduced global network efficiency in OSA, suggesting aberrant brain network organization (p<0.05; permutation test).

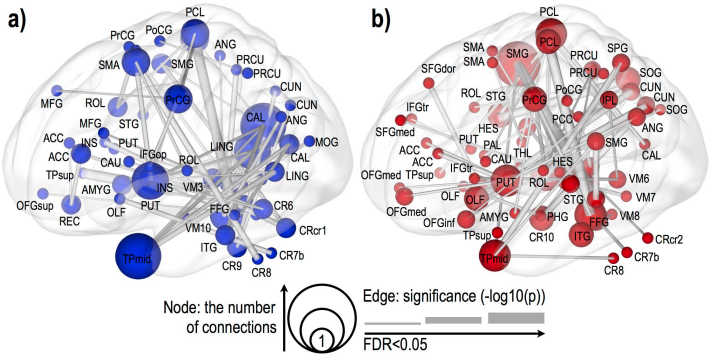

Fig. 1: Significantly decreased (a) or increased (b) FC in OSA over control subjects. Node sizes and edge thicknesses represent more number of connections and significance levels, with increasing sizes and thicknesses, respectively.

Discussion: OSA subjects showed abnormal resting functional connections in brain regions largely related to autonomic, affective, executive, sensori-motor, and cognitive regulatory functions, and abnormalities were apparent in aberrant brain network organization. Earlier studies show altered functional responses to evoked autonomic, motor, or ventilatory challenges; the findings here suggest that the dysfunction extends to spontaneous resting conditions, and impaired responses in autonomic, cognitive, and sensori-motor functions may stem from altered FC and brain network organization. The outcomes likely result from the prominent structural changes in both axons and nuclear structures reported-earlier in the condition.

References:

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