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Brain putamen volume changes in newly-diagnosed patients with obstructive sleep apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is accompanied by cognitive, motor, autonomic, learning, and affective abnormalities. The putamen serves several of these functions, especially motor and autonomic behaviors, but whether global and specific sub-regions of that structure are damaged is unclear. We assessed global and regional putamen volumes in 43 recently-diagnosed, treatment-naïve OSA (age, 46.4 ± 8.8 years; 31 male) and 61 control subjects (47.6 ± 8.8 years; 39 male) using high-resolution T1-weighted images collected with a 3.0-Tesla MRI scanner. Global putamen volumes were calculated, and group differences evaluated with independent samples t-tests, as well as with analysis of covariance (covariates; age, gender, and total intracranial volume). Regional differences between groups were visualized with 3D surface morphometry-based group ratio maps. OSA subjects showed significantly higher global putamen volumes, relative to controls. Regional analyses showed putamen areas with increased and decreased tissue volumes in OSA relative to control subjects, including increases in caudal, mid-dorsal, mid-ventral portions, and ventral regions, while areas with decreased volumes appeared in rostral, mid-dorsal, medial-caudal, and mid-ventral sites. Global putamen volumes were significantly higher in the OSA subjects, but local sites showed both higher and lower volumes. The appearance of localized volume alterations points to differential hypoxic or perfusion action on glia and other tissues within the structure, and may reflect a stage in progression of injury in these newly-diagnosed patients toward the overall volume loss found in patients with chronic OSA. The regional changes may underlie some of the specific deficits in motor, autonomic, and neuropsychologic functions in OSA.

1. Introduction

Obstructive sleep apnea (OSA) patients show multiple neurobehavioral difficulties, including deficits in attention, psychomotor and executive functioning, memory, and affect (Beebe et al., 2003). However, the principal deficits in the syndrome involve the loss of motor control over the upper airway muscles, which fail to discharge in a timely fashion, when they should dilate the airway during diaphragmatic descent, and a loss of control over autonomic motor activity, with chronic, exaggerated sympathetic discharge (Somers et al., 1995), and inappropriate lagged or muted dynamic sympathetic responses to blood pressure or ventilatory challenges (Harper et al., 2003; Henderson et al., 2004; Macey et al., 2006). Those somatic and autonomic motor defects suggest central injury in motor and autonomic regulatory structures, and gross damage has been found in multiple sites, based on manual and voxel-based morphometry of high-resolution T1-weighted images (Kumar

Abbreviations: OSA, Obstructive sleep apnea; 3D, Three dimensional; MRI, Magnetic resonance imaging; AHI, Apnea–hypopnea index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; BDI-II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; PD, Proton density; MNI, Montreal Neurological Institute; CSF, Cerebrospinal fluid; TIV, Total intracranial volume; MPRAGE, Magnetization prepared rapid acquisition gradient-echo; TR, Repetition time; TE, Echo time; FA, Flip angle; FOV, Field of view; GRAPPA, Generalized autocalibrating partially parallel acquisition.

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et al., 2008; Macey et al., 2002), diffusion tensor imaging (Kumar et al., 2012; Macey et al., 2008), and T2-relaxometry procedures (Cross et al., 2008; Kumar et al., 2009b). Several of the affected brain sites include structures that serve both somato motor and autonomic motor roles; one such structure is the putamen, which shows overall injury, metabolic abnormalities, and functional deficits (Alkan et al., 2013; Emin Akkoyunlu et al., 2013; Kumar et al., 2012; Macey et al., 2006).

The evidence for putamen roles in autonomic regulation is well-known, especially from pathological conditions with dysautonomia, such as Multiple Systems Atrophy (Pastakia et al., 1986). Such a role is expected, considering the major projections received from the autonomic regulatory insular cortices (Saper, 1982). The putamen somatic motor role appears to incorporate sensory and other signals to initiate effective motor action, with putamen stroke inducing conditions of "motor neglect" (Sapir et al., 2007). OSA represents a prime example of how signals fail to initiate and maintain upper airway muscle discharge, and the putamen may be playing a significant role in that upper airway muscle "neglect," particularly considering its projections to brain areas regulating oral motor functions (Kunzle, 1978; Miyata and Sasaki, 1984).

The putamen also contributes to regulation of other neuropsychologic, cognitive, and learning functions which are deficient in OSA. These functions include memory, mood, language, and motivation, show differential topographic organization (Alexander and Crutcher, 1990; Badgaiyan et al., 2008; Booth et al., 2007; Bowman et al., 1996; Husain et al., 1991; Saper, 1982), and the sub-regions within that organization receive information from prefrontal, insular, and thalamic areas, and send dopaminergic projections to the ventral tegmentum, substantia nigra, and globus pallidus (Avendano et al., 2006; DeVito et al., 1980; Ferry et al., 2000; Gorbachevskaya, 1997; Saper, 1982; Schultz and Romo, 1987). Putamen volumes are reduced in depressed patients (Husain et al., 1991), and over half of OSA patients are depressed (Asghari et al., 2012); the majority of OSA subjects also show learning deficits (Wallace and Bucks, 2013).

Regional structural changes within the putamen can thus alter information transfer between various brain sites. Manual volumetric procedures, using high-resolution T1-weighted images, can evaluate global putamen volume (Kumar et al., 2011), and 3D surface morphometry techniques can assess regional tissue changes, as well as extent of changes within the structures (Butters et al., 2009; Sabattoli et al., 2008; Shi et al., 2013; Thompson et al., 2004). Both procedures have been used to examine global and regional basal ganglia structures (Kumar et al., 2009a), including the putamen (Kumar et al., 2011). The extent of tissue changes within putamen sub-regions which serve specialized functions, or project to other brain areas serving unique roles, is unclear in OSA. Knowledge of localized changes is essential to disclose functional outcomes, since the functional topography of the putamen is not uniform.

Our aim was to examine global and regional putamen volumes in OSA relative to control subjects using high-resolution T1-weighted images with manual volumetric and 3D surface morphometry procedures, and to determine the nature of any volume changes. We selected newly-diagnosed, untreated OSA patients to avoid confounding measures with treatment interventions, and to determine tissue changes as early as possible in the syndrome development. Since OSA subjects show overall putamen damage, altered metabolites, and functional deficits (Alkan et al., 2013; Emin Akkoyunlu et al., 2013; Kumar et al., 2012; Macey et al., 2006) and severe autonomic, behavioral and motor deficits appear in the condition, we hypothesized that both left and right global and regional putamen integrity would be altered in OSA, compared to control subjects.

2. Materials and methods

2.1. Subjects

We studied 43 recently-diagnosed (based on overnight polysomnography; apnea–hypopnea-index ≥ 5) OSA subjects before any treatment, and 61 healthy control subjects. Both OSA and control subjects included here were subjects in previously-published manuscripts related to other issues in OSA (Cross et al., 2008; Kumar et al., 2008, 2009b, 2012; Macey et al., 2008, 2010, 2012, 2013). All OSA subjects were recruited from the Sleep Disorders Laboratory at UCLA, and control subjects were recruited from the UCLA campus and West Los Angeles area. OSA subjects were not taking any medications (β-blockers, α-agonists, angiotension-converting enzyme inhibitors, vasodilators, or serotonin reuptake inhibitors), and were without any diagnosed history of stroke, heart failure, or mental illness that might influence brain tissue composition. Control subjects were in good health, without any brain disorder which may induce brain tissue changes. We interviewed the control subjects, as well as their sleep partners, when available, to determine the potential for sleep disordered breathing, and subjects suspected of having such disturbed patterns underwent an overnight sleep study. OSA and control subjects with body weight more than 125 kg (scanner limitation), or with MRI incompatible metallic implants were excluded, as described at the MRI safety website (http://www.mrisafety.com/). All OSA and control subjects gave written and informed consent prior to the study, and the study protocol was approved by the Institutional Review Board at the University of California at Los Angeles.

2.2. Overnight polysomnography (PSG)

Overnight sleep studies were performed on all OSA subjects at the UCLA Sleep Disorders Center and Laboratory, and consisted of a 7–10 hour period (9:00 PM to 6:00 AM) monitoring of electroencephalogram (EEG — central and occipital), digastric electromyogram (EMG), electrocardiogram (EKG — lead II), right and left extra-ocular eye movement (EOG), thoracic and abdominal wall movement, air flow, O_2 saturation, end-tidal CO_2 levels, snore volume, bilateral leg movement, and sleep position. Acquired data were digitized, and stored on a computer for sleep evaluation.

2.3. Examination of daytime sleepiness and sleep quality

We used the Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI) questionnaires to examine daytime sleepiness and sleep quality, respectively, in both OSA and control subjects (Johns, 1991; Knutson et al., 2006). These commonly-used measures were self-administered, either before or after MRI data acquisition.

2.4. Assessment of depression and anxiety symptoms

We administered the Beck Depression Inventory (BDI)-II to examine depressive symptoms, and the Beck Anxiety Inventory to assess anxiety symptoms in OSA and control subjects (Beck et al., 1988, 1996), either before or after MRI data collection. Both inventories are self-administered questionnaires, with scores between 0 and 63, based on the severity of symptoms (Beck et al., 1988, 1996).

2.5. Magnetic resonance imaging

Brain studies were performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany), with a receive-only 8-channel phased-array head-coil, and a whole-body transmitter coil. Foam pads were used on both sides of the head to reduce head motion related artifacts, and subjects lay supine during data collection. We collected two high-resolution T1-weighted image scans using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence [repetition time (TR) = 2200 ms; echo time (TE) = 2.2 ms; inversion time = 900 ms; flip angle (FA) = 9°; matrix size = 256 × 256; field of view (FOV) = 230 × 230 mm; slice thickness = 1.0 mm; slices = 176]. Proton density (PD) and T2-weighted images were collected using a dual-echo turbo spin-echo pulse sequence (TR = 10,000 ms; TE1,