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Sex-specific hippocampus volume changes in obstructive sleep apnea

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) patients show hippocampal-related autonomic and neurological symptoms, including impaired memory and depression, which differ by sex, and are mediated in distinct hippocampal subfields. Determining sites and extent of hippocampal sub-regional injury in OSA could reveal localized structural damage linked with OSA symptoms.

Methods: High-resolution T1-weighted images were collected from 66 newly-diagnosed, untreated OSA (mean age ± SD: 46.3 ± 8.8 years; mean AHI ± SD: 34.1 ± 21.5 events/h;50 male) and 59 healthy age-matched control (46.8 ± 9.0 years;38 male) participants. We added age-matched controls with T1-weighted scans from two datasets (IXI, OASIS-MRI), for 979 controls total (426 male/46.5 ± 9.9 years). We segmented the hippocampus and analyzed surface structure with "FSL FIRST" software, scaling volumes for brain size, and evaluated group differences with ANCOVA (covariates: total-intracranial-volume, sex; $P < .05$, corrected).

Results: In OSA relative to controls, the hippocampus showed small areas larger volume bilaterally in CA1 (surface displacement ≤0.56 mm), subiculum, and uncus, and smaller volume in right posterior CA3/dentate (≥ − 0.23 mm). OSA vs. control males showed higher bilateral volume (≤0.61 mm) throughout CA1 and subiculum, extending to head and tail, with greater right-sided increases; lower bilateral volumes (≥ − 0.45 mm) appeared in mid- and posterior-CA3/dentate. OSA vs control females showed only right-sided effects, with increased CA1 and subiculum/uncus volumes (≤0.67 mm), and decreased posterior CA3/dentate volumes (≥ − 0.52 mm). Unlike males, OSA females showed volume decreases in the right hippocampus head and tail.

Conclusions: The hippocampus shows lateralized and sex-specific, OSA-related regional volume differences, which may contribute to sex-related expression of symptoms in the sleep disorder. Volume increases suggest inflammation and glial activation, whereas volume decreases suggest long-lasting neuronal injury; both processes may contribute to dysfunction in OSA.

1. Introduction

The hippocampus shows both damage and dysfunction in obstructive sleep apnea (OSA), which may contribute to memory, autonomic and depressive symptoms in the disorder. Early findings indicate volume reductions and other structural changes in or adjacent to the hippocampus (Macey et al., 2002; Dusak et al., 2013; Morrell et al., 2003; Tummala et al., 2017; Tummala et al., 2016), and metabolite levels suggestive of inflammation and glial activation (O'Donoghue et al., 2012; Sarma et al., 2014; Alkan et al., 2013; Kizilgoz et al., 2013; Algin et al., 2012; Bartlett et al., 2004). Patterns of activity within the structure are modified in OSA, as measured by functional neuroimaging (Henderson et al., 2003; Harper et al., 2003; Macey et al., 2003; Macey et al., 2006; Castronovo et al., 2009; Fatouleh et al., 2014; Li et al.,

Abbreviations: AHI, apnea-hypopnea index; CA, cornu ammonis; OSA, obstructive sleep apnea

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2016a; Li et al., 2016b), and are reflected in symptoms such as elevated sympathetic tone, high levels of depressive and anxiety symptoms, and memory difficulties (Narkiewicz and Somers, 2003; Hoth et al., 2013; Rezaeitalab et al., 2014). The particular areas of injury in the hippocampus are not well defined, nor are patterns of volume increase or decrease understood; inflammation and glial activation should produce volume increases, whereas neuronal death or damage to cells should cause volume decreases. Moreover, the symptoms expressed in OSA differ by sex, and it is unclear whether structural changes differ between males and females in a way that reflects those characteristics. Finally, hippocampal roles in some functions, such as regulation of blood pressure, are highly lateralized, and it is unclear whether OSA damage is equally expressed in both left and right hippocampi.

Knowing the location and nature of hippocampal volume changes would provide insights into mechanisms of pathology which accompany OSA. The multitude of potentially damaging processes occurring in OSA makes predicting volume changes in the disorder difficult, since neuronal death results in volume loss, but glial responses to hypoxia can increase tissue volume. Both of these effects are visible in the putamen in OSA (Kumar et al., 2014a), and similar patterns may occur in the hippocampus. Precise volumetric assessment is possible, but sensitivity is limited by small subject samples. However, a combination of publically-available MRI databases and analytic software now allow hundreds of subjects to be used as a population reference. Early hippocampal analyses required manual, time-consuming tracing of structures (Morrell et al., 2003; Macey et al., 2009; Thompson et al., 2004). Automatic segmentation methods include FreeSurfer (Fischl et al., 2002), its subsequent improvements (Clerx et al., 2015; Iglesias et al., 2015), and FSL FIRST (Patenaude et al., 2011), and these approaches allow analysis of large numbers of subjects in an objective, repeatable manner. In particular, FSL FIRST allows for shape analysis with group and regression analyses, and using conventional anatomical MRI scans can distinguish between hippocampal subregions of volume change measured as surface displacement at sub millimeter resolution.

Our objective was to assess OSA-related differences in regional hippocampal volume, relative to a large reference population, and to assess laterality, regional site, and sex-specific effects of OSA on hippocampal structure. Based on symptoms found in OSA patients, we hypothesized volume changes would appear in memory-, autonomic-, and mood-related subfields of the hippocampus. However, we did not hypothesize a direction of change, since available evidence suggests the potential for both acute (volume increases from inflammatory and other processes) and long-term (volume decreases and cell death) injury.

2. Methods

2.1. Subjects

We performed high-resolution T1-weighted imaging in 66 newly-diagnosed, untreated OSA (mean age ± SD: 46.3 ± 8.8 years; mean AHI ± SD:34.1 ± 21.5 events/h; 50 male) and 59 healthy age-matched control (46.8 ± 9.0 years; 38 male) participants. Further sleep and demographic details are in Tables 1 & 2. Sleep scoring was per the 1999 AASM criteria (Author, 1999). The study was approved by the UCLA Institutional Review Board, and all subjects provided written informed consent. To improve sensitivity, we combined our healthy control sample with two large datasets, IXI (https://www.nitrc.org/projects/ixi_dataset/) and OASIS (http://www.oasis-brains.org/; Marcus et al., 2007), resulting in a control group of 979 age-matched subjects (426 male, 46.5 ± 9.9 years) representative of the general population. These studies were approved by their governing ethics committees, and all subjects provided written informed consent.

Table 2
Polysomonographic characteristics of OSA patients.

	Mixed	Female	Male
	OSA N = 65	OSA N = 15	OSA N = 50
	Mean ± std	Mean ± std	Mean ± std
AHI events/hour	30.6 ± 20.7	23.0 ± 22.4	33.0 ± 19.5
SaO2 (minimum %)	81.9 ± 9.1	86.9 ± 6.0	80.2 ± 9.4
SaO2 (baseline %)	94.7 ± 2.3	94.7 ± 2.4	94.7 ± 2.4

2.2. Implications of using a large reference dataset

While including the IXI and OASIS subjects means the control group will likely include some people with OSA, the large number of subjects leads to improved sensitivity to detect OSA-related effects. For example, a sensitivity analysis for ANCOVA shows that 125 subjects with a two group, three covariate model at alpha = 0.05 and power of 0.95 is sensitive to an effect size f of 0.46, whereas the same model with 1045 subjects is sensitive to an effect size f of 0.15. The main consequence of the undetected OSA in the control group would be to reduce the OSA-control group differences, and hence underestimate the magnitude of any effect. A further advantage of using these datasets as a population reference is that other researchers can compare their findings against a common standard.

2.3. MRI protocol

Image volumes for the UCLA subjects were acquired on a Siemens 3 Tesla Trio scanner with magnetization prepared rapid acquisition gradient echo protocol product sequence (MPRAGE; TR = 2200 ms, TE = 2.34 ms, inversion time = 900 ms, flip angle = 9°), with 320 × 320 matrix size, 230 × 230 mm field of view (FOV), 0.9 mm slice thickness, 192 sagittal slices, and two repeats. An acceleration factor of two was applied with generalized-autocalibrating-partially-parallel-acquisition parallel imaging (GRAPPA).

2.4. Analysis

All T1-weighted image scans were visually inspected for artifact and

Table 1
Characteristics of OSA and control subjects. Group differences assessed with independent samples *t*-tests for continuous variables, and chi-square for sex. Gray cells indicate not applicable.

	Mixed			Female			Male		
	OSA N = 65	Control population N = 980	OSA vs Control	OSA N = 15	Control population N = 553	OSA vs Control	OSA N = 50	Control population N = 426	OSA vs Control
		Mean ± std	P		Mean ± std	P		Mean ± std	P
Age (years)	47.5 ± 9.9	47.5 ± 18.8	0.6	51.4 ± 10.2	49.6 ± 19.2	0.7	44.9 ± 9.4	44.9 ± 17.7	1.0
Sex	16 ♀, 50♂	553 ♀, 426♂	< 0.001						