Diffusion Tensor Imaging Detects Early Microstructural Hypothalamic Changes Associated with Cognitive Dysfunction in Obese Subjects

Abstract No:

O-94

Submission Number:

2611

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Purpose:

Despite progress in understanding the neurobiology of energy homeostasis, little is known regarding how brain systems that promote weight stability are altered in obesity. Growing evidence implicates hypothalamic inflammation in the pathogenesis of diet-induced obesity and cognitive dysfunction in rodent models. Few studies have addressed the association between obesity and hypothalamic damage in humans and its relevance. We sought to evaluate obesity-associated hypothalamic damage by diffusion tensor imaging (DTI) together with its impact on cognitive function.

Materials and Methods:

We prospectively studied 24 consecutive middle-aged obese subjects (13 women; 49.8±8.1 years; BMI 43.9 ± 0.92 Kg/m2) and 20 healthy volunteers (10 women; 48.8±9.5 years; BMI 24.3 ± 0.79 Kg/m2). All patients underwent 1.5 T MRI (Intera, Philips Healthcare, Best, the Netherlands) including axial FLAIR and DTI sequences. Diffusion-sensitized gradients were applied along 15 noncollinear directions with a b-value of 1000 s/mm2. Diffusion tensor images were coregistered, and a neuroradiologist blinded to all clinical information placed free-hand regions of interest in the right and left sides of the hypothalamus using dedicated software (Olea Sphere V.2.0, Olea Medical, La Ciotat, France). Primary (λ1), secondary (λ2), and tertiary (λ3) eigenvalues, FA, and mean diffusivity (MD) were calculated. Cognitive function was evaluated with neuropsychological tests. Receiver operator characteristic curves were used to calculate the DTI-metrics cutoffs to predict obesity-associated hypothalamic damage.

Results:

Mean λ1 values for the hypothalamus were significantly lower in obese subjects (P<0.001). The mean hypothalamic λ1 cutoff point that best discriminated obese and control subjects was 1.072, yielding 75% sensitivity, 87.5% specificity, 83.3% PPV, and 80.7% NPV for hypothalamic damage (AUC, 0.854; 95% CI, 0.742-0.96) (Figure). No significant differences were found for λ2, λ3, FA, or MD (Table). Patients with hypothalamic λ1<1.072 had significantly increased BMI and blood inflammatory markers. Loss of hypothalamus gray matter defined as λ1<1.072 significantly correlated with cognitive impairment. Combined BMI and alanine aminotransferase was the strongest predictor of obesity-associated hypothalamic damage (AUC=0.89).

Conclusions:

Our preliminary data indicate that λ1 could be a useful DTI-metric for assessing hypothalamic damage in obese individuals. Further studies are needed to validate the quantification of DTI-metrics as a noninvasive tool for detecting obesity-induced damage in the hypothalamus.

Adult Brain:

Functional Imaging (fMRI, MEG, MRS, PET, DTI, SPECT, connectivity studies)

Anatomy - Secondary:

Brain

Keywords:

Cognitive Deficit

Diffusion Tensor Image

Hypothalamus

	Obese (n=24)	**Control (n=20)**	**p-value**
Sex (male/female)	11/13	10/10	0.783
Age (years)	49.875(8.158)	48.85(9.511)	0.706

BMI (kg/m2)	43.987(4.548)	24.305(3.548)	<0.001
Waist circumference (cm)	115.896(37.612)	84.35(10.261)	0.001
Systolic blood pressure (mmHg)	142.625(20.334)	120.9(11.947)	<0.001
Total cholesterol (mg/dl)	190.75(46.731)	202.9(30.953)	0.309
HDL–cholesterol (mg/dl)	46.875(11.078)	63.35(15.618)	<0.001
Triglyceride (mg/dl) log transformation	4.61(0.532)	4.203(0.454)	0.009
HOMA-IR (mean ± SD)	4.838(3.149)	0.97(0.906)	<0.001
Ultrasensitive CRP (mg/dl)	0.877 (0.843)	0.137(0.152)	<0.001
Primary eigenvalue	1.014(0.984 – 1.040)	1.112(1.046 – 1.162)	<0.001
Secondary eigenvalue	0.673(0.611 – 0.728)	0.767(0.665 – 0.812)	0.105
Tertiary eigenvalue	0.395(0.334 – 0.433)	0.440(0.351 – 0.535)	0.096
Fractional anisotropy	0.393(0.369 – 0.444)	0.410(0.380 – 0.440)	0.427
Mean diffusivity	0.755(0.724 – 0.817)	0.802(0.727 – 0.843)	0.337

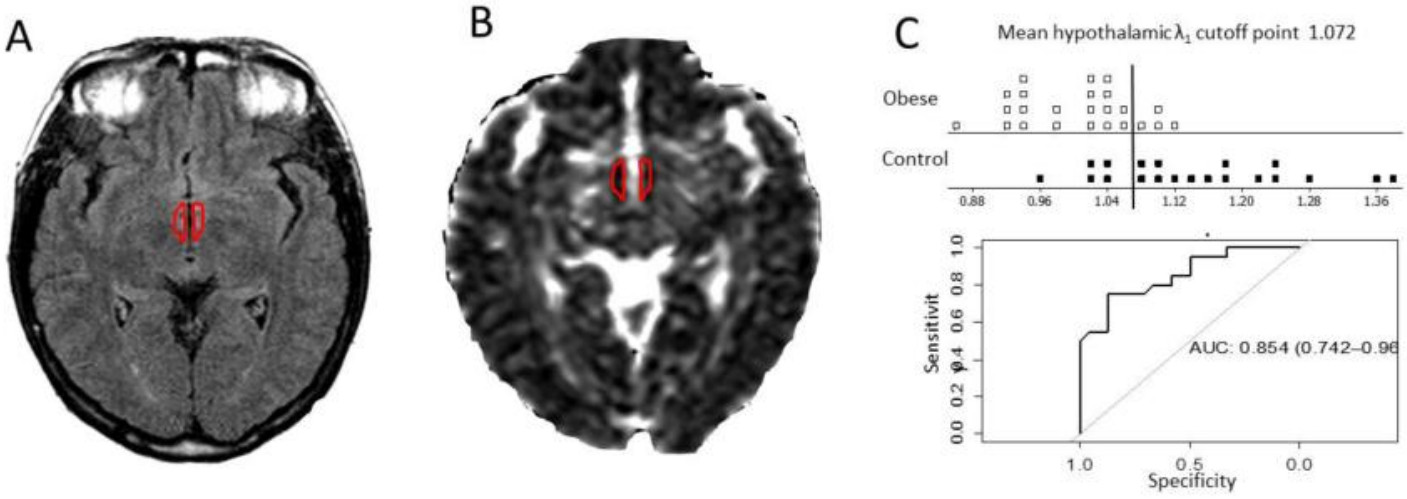

Figure. FLAIR images (**a**) and diffusion tensor images (**b**) were coregistered and a free-hand region of interest was placed on the hypothalamus. **c**, Primary eigenvalues (λ_1) for the hypothalamus were lower in obese subjects (P<0.001). We calculated the λ_1 cutoff to predict hypothalamic damage with receiver operator characteristic curves.