Hypothalamic inflammation in humans is not reversed by a profound weight loss and an improved insulin sensitivity due to bariatric surgery

Kreutzer C.1, Peters S.1, Schulte D.M.1, Türk K.1, Wolff S.1, Rohr A.2, Kerby T.1, Riedel C.1, van Eimeren T.2, Franke A.2, Heinsen F.A.3, Freitag-Wolf S.4, Dempfle A.3, Schreiber S.3, Laeuders M.1
1University Medical Center Schleswig-Holstein, Department of Internal Medicine I, Kiel, Germany, 2University Medical Center Schleswig-Holstein, Department of Neuroradiology, Kiel, Germany, 3University Medical Center Cologne, Department of Nuclear Medicine, Cologne, Germany, 4University Medical Center Schleswig-Holstein, Institute of Clinical Molecular Biology, Kiel, Germany

Introduction
Obesity is associated with hypothalamic inflammation (HI) in animal models. The mediobasal hypothalamus (MBH) is a brain region crucial for body weight control as it regulates appetite, which leads to changes in nutritional intake. While MRI studies in obese human subjects also found an increased density in the MBH, it remains unclear (1) if HI causes neuronal death and (2) if HI reverses during weight loss.

Patients and methods
n=50 obese subjects and n=50 age- and gender-matched controls were examined. MRI scans including spectroscopy were performed (s.Fig.1). Also, detailed nutritional questionnaires, serum lipidomics, 16s rDNA microbiome sequencing data as well as SNP genotyping data were obtained. n=10 obese subjects underwent bariatric surgery followed by a second MRI.

Results
1) Obese subjects exhibit an increased density in the left, but not the right MBH compared to non-obese controls.

2) The number of neurons is not altered in the left MBH of obese human subjects despite increased MBH-Density, indicating that neurons might not be negatively affected by the inflammatory process.

3) Weight loss due to bariatric surgery does not influence MBH-Density in obese humans.

4) Increased density in the left MBH of obese humans is associated with systemic inflammation (A) but not with systemic glucose metabolism (B).

Fig.1: Spectroscopy illustration, method: 1H NMR T2 relaxation time
N-Acetylaspartat (NAA) and Creatin (Cr) measurements where used to calculate the NAA/Cr ratio, a marker for neuronal cell count.

Fig.2: Comparison of MBH Density between non-obese and obese human subjects
The MBH/Amygdala ratio revealed significant differences (2-sided t-test) between the two obesity groups within the left hemisphere.

Fig.3: Comparison of neuronal cell count of non-obese vs. obese humans
The NAA/Cr ratio shows no significant differences (t-test) in cell numbers among the weight groups.

Fig.4: Before and after bariatric surgery
BMI and MBH-Density, measured as MBH/Amygdala ratio. Before- and after-comparison via t-test.

Fig.5: 3D-Scatterplot of MBH-Density, IL6 and BMI, within the obesity group
MBH-Density increase is significantly associated with increased IL6 serum levels rather than with BMI (linear model: MBH density – BMI + IL6).

Fig.6: Before and after bariatric surgery
IL6 and HOMA (Homeostasis Model assessment – as a measure for insulin resistance). Before- and after-comparison via t-test.

Discussion
Obese human subjects exhibit an increased MRI-Density of the MBH suggesting HI. While HI and IL6 are not reversed by a significant weight loss due to bariatric surgery, the finding that the number of neurons is not altered in the MBH by HI might suggest that the function of the MBH in terms of appetite regulation might be reversible. Disturbances in the gut-brain-axis induced by an unhealthy diet might in part explain the obesity associated hypothalamic pathology.

Wissen schafft Gesundheit