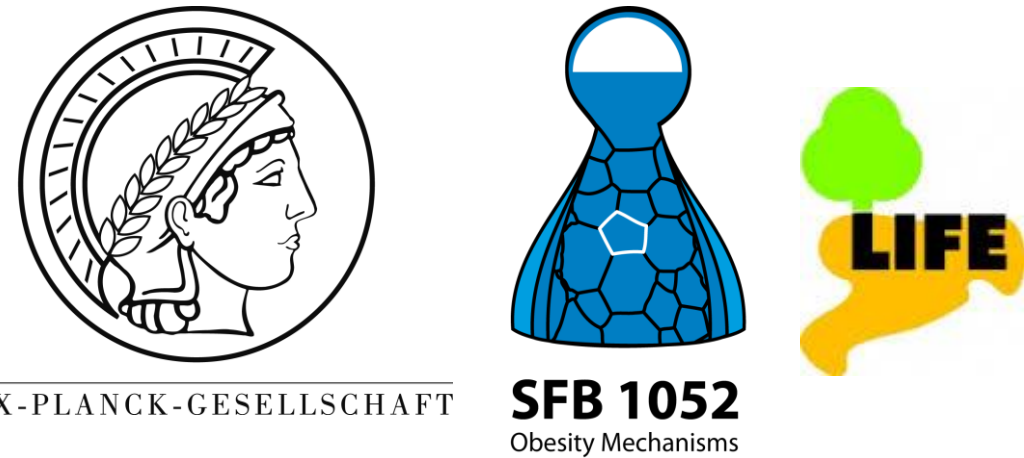# Metabolic obesity profiles and gray matter tissue loss in older individuals

Frauke Beyer[1,5], H. Lina Schaare[1], Shahrzad Kharabian Masouleh[1], Jürgen Kratzsch[4], Joachim Thiery[4], Markus Loeffler[2], Matthias L. Schroeter[1,2,3], Arno Villringer[1,3,5], A. Veronica Witte[1,5]

[1]Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2]LIFE – Leipzig Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany
[3]Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany
[4]Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University of Leipzig, Leipzig, Germany
[5]SFB 1052 – Obesity Mechanisms, University of Leipzig, Leipzig, Germany

fbeyer@cbs.mpg.de

MAX PLANCK INSTITUTE FOR HUMAN COGNITIVE AND BRAIN SCIENCES LEIPZIG

Introduction

Mid- to late-life obesity has been consistently associated with neurodegenerative changes in gray and white matter [1] and might contribute to increased risk of Alzheimer's disease [2]. However, it remains unclear which metabolic mechanisms underlie these findings. Obesity is often accompanied by adipose tissue inflammation, insulin resistance, dyslipidemia and differences in adipokine and gut-hormone signaling and many of the involved hormones, such as insulin and leptin [4] have been shown to independently affect brain tissue and function.

Objectives:
Here, we investigated the covariation of obesity and metabolic markers with gray matter tissue volume in a large sample of healthy older individuals using partial least squares correlation (PLSC), thereby aiming to determine metabolic patterns specific to gray matter volume changes.

Methods

Study sample:
- 320 elderly healthy participants (156 women) from the LIFE-Adult Study [5] without stroke, major brain pathology or intake of centrally active medication
- Age: 60 – 79 years (mean: 67.9 y)
- Body mass index: 17 – 42 kg/m^2 (mean: 28.6 kg/m^2)
- Mini Mental State Examination > 26

Obesity and metabolic measures:
- body mass index (BMI, in kg/m2)
- waist to hip ratio (WHR)
- total blood cholesterol (in mmol/l),
- low/high density (LDL/HDL) lipoprotein (in mmol/l)
- glycated hemoglobin (log(HbA1c), in %)
- interleukin 6 (log(IL-6), in pg/ml)
- C-reactive protein (log(CRP), in mg/ml)
- adiponectin (log, in ng/ml)
- leptin (log, in ng/ml)
- ghrelin (log, in pg/ml).

Magnetic resonance imaging (MRI):
- T1-weighted MPRAGE using 3T Siemens Verio
- Inversion time: 900 ms, repetition time: 2300 ms, field of view: 256 x 240 x 176, voxel size: 1mm^3

Preprocessing of MRI data:
- DARTEL in SPM12 (www.fil.ion.ucl.ac.uk/spm)
- creation of a sample-specific template
- warping of T1-weighted images to the template
- transformation of flowfields into Jacobian determinants showing relative gray matter volume (GMV) differences between individuals and the population average
- regression of age and sex from the morphometric data.

Statistical analysis:
- Spearman's correlation to assess the correlation of anthropometric and metabolic measures
- PLSC, implemented based on a publicly available version of singular value decomposition-PLSC in python (https://libraries.io/github/chrisfilo/pypls).
- PLSC is a multivariate technique to extract latent variables (LV) with maximal covariance [6] which allows to model multiple collinear predictors.
- significance of latent variables (p < 0.05) and reliability (Z-value > 2.3) of contributing obesity measures was based on permutation and bootstrapping (N=5000)
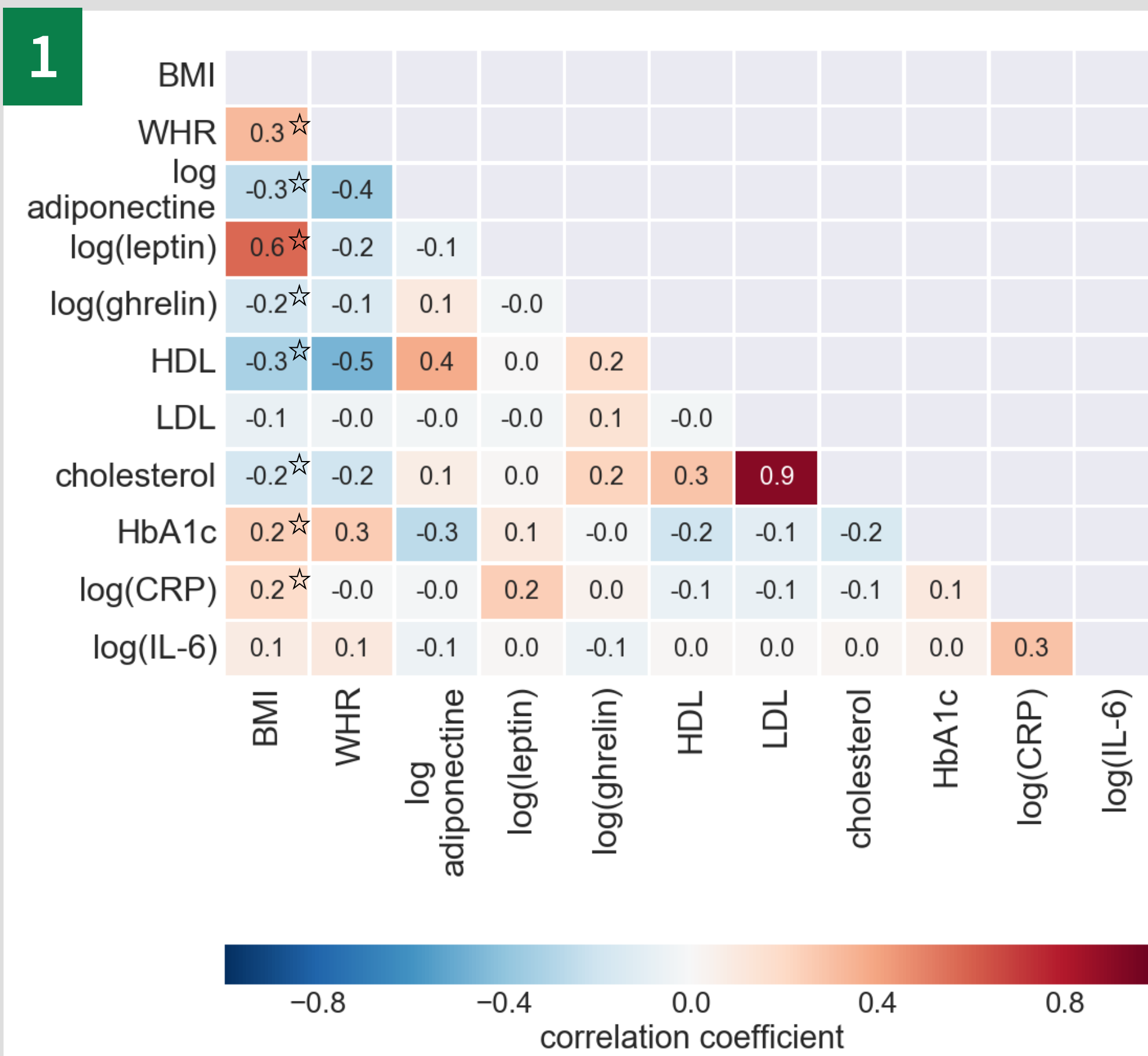
Results

Figure 1: Correlation of anthropometric and metabolic markers associated with obesity (blue/red: negative/positive correlation, ☆ indicates significant correlation (p< 0.05), corrected for age and sex)
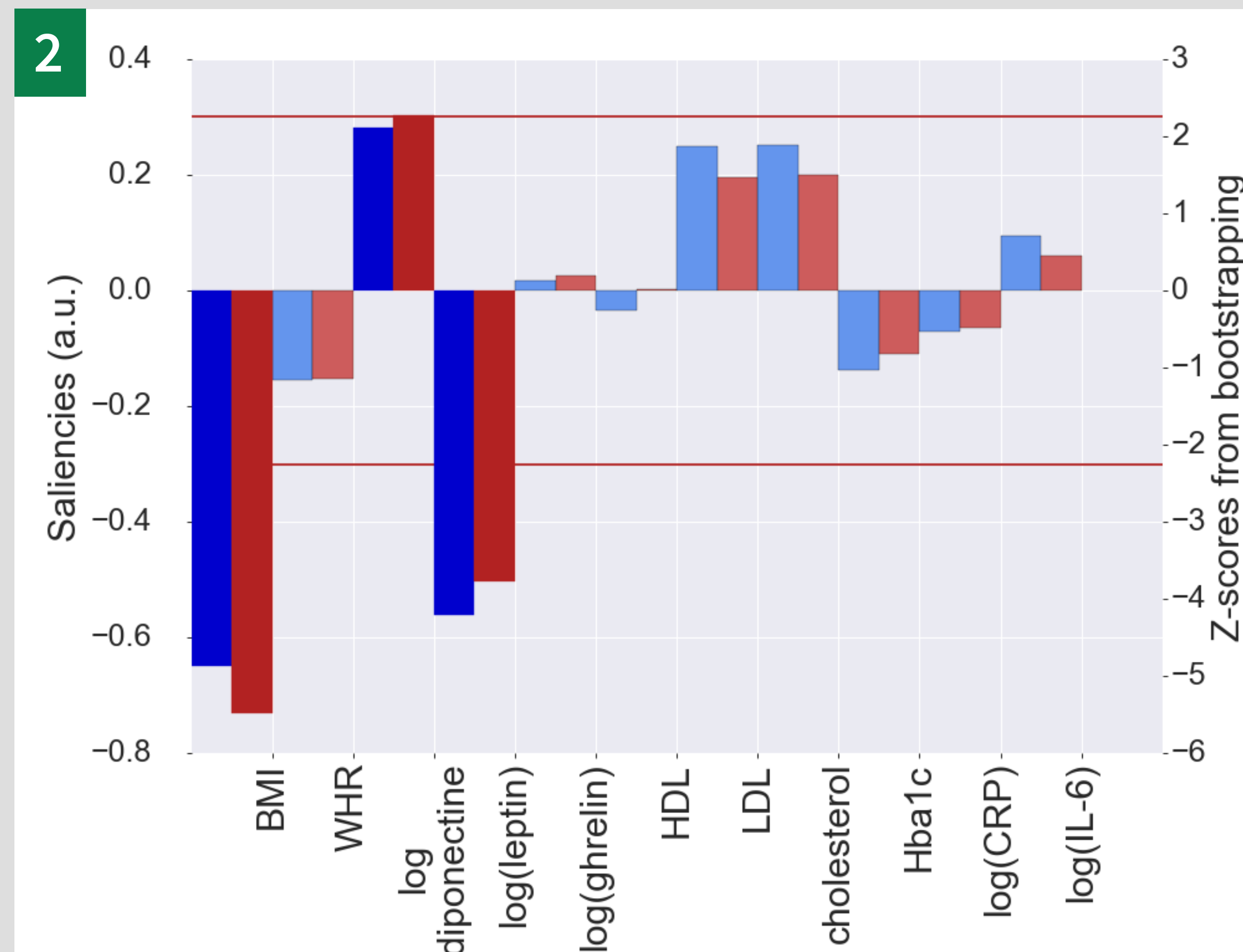

Figure 2: Saliencies of the first latent obesity variable (blue: saliencies of variables, dark blue: saliencies of reliable variables, red: bootstrapped Z-values, dark red: bootstrapped Z-values >2.3)
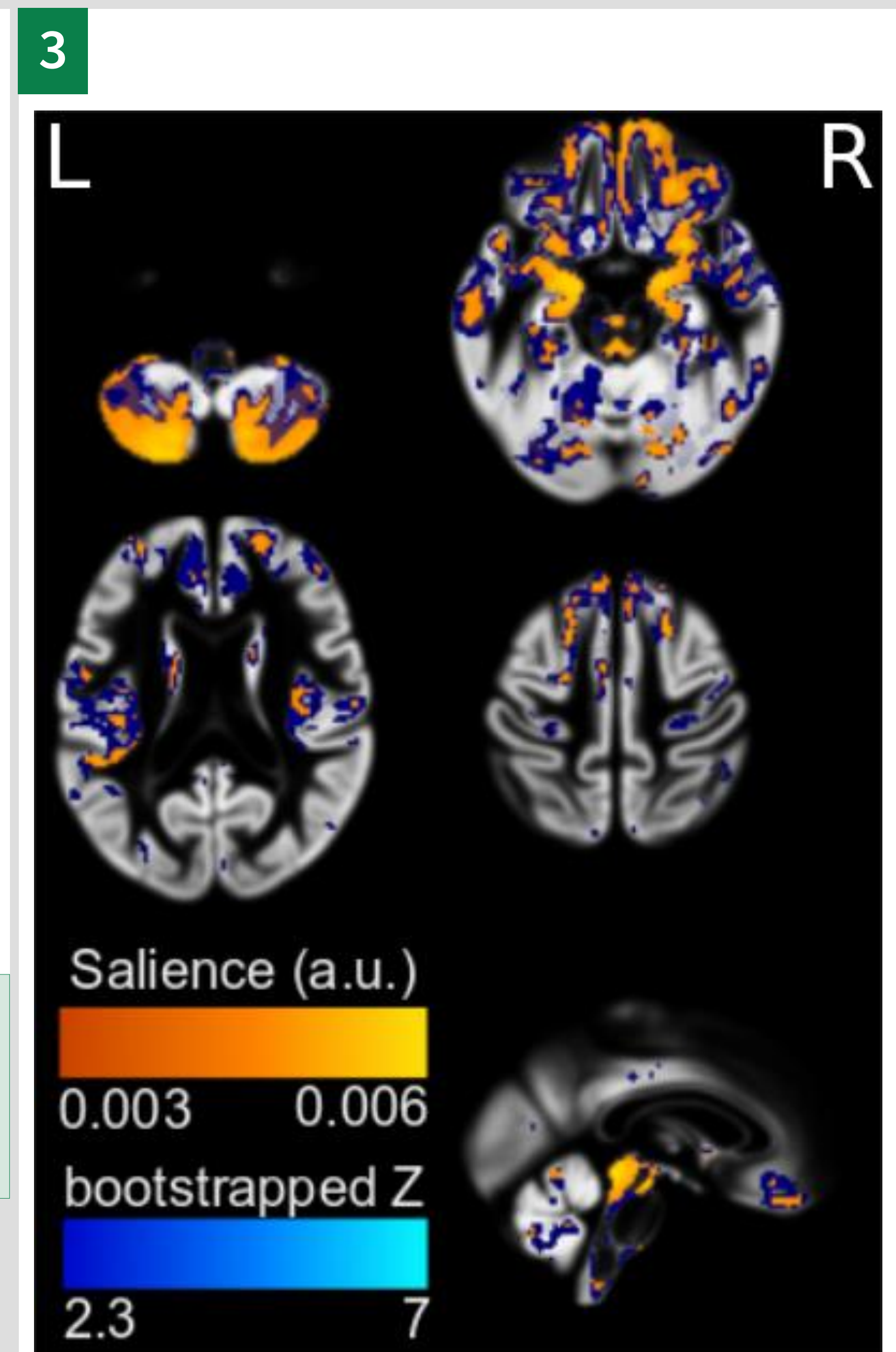

Figure 3: Reliable saliencies for the first latent gray matter volume variable masked for bootstrapped Z-values > 2.3 (yellow = saliencies of reliable voxels, blue = bootstrapped Z-values)

The correlational analysis showed that BMI significantly correlates with most blood measures, even after adjusting for age and sex (see Figure 1). WHR showed a similar correlation pattern with a pronounced difference in the association of leptin.

The first pair of latent variables derived by PLSC explained 26% of variance and was significant according to permutation tests (p=0.0172). The obesity LV included negative reliable contributions of BMI (Sal=-0.65, Z=-5.3) and leptin (Sal=-0.56, Z=-3.6), and a marginally reliable positive contribution of adiponectin (Sal= 0.28, Z=2.2) (see Figure 2). This LV covaried with a latent gray matter volume LV with positive, reliable contributions from widespread brain areas, with highest saliencies in right hippocampus (cluster size= 956 voxel, Sal=0.006, Z=6.2), cerebellum (Crus II, cluster size= 820 voxel, Sal=0.0054, Z=4.2), left hippocampus (cluster size= 696 voxel, Sal=0.0056, Z=5.1), mesencephalon (cluster size=480 voxel, Sal=0.0056, Z=5.5) and thalamus (cluster size= 228 voxel, Sal=0.0052, Z=4.4) (see Figure 3).

Discussion

We found a common covariance structure of higher BMI and leptin, lower adiponectin and lower GMV in cortical and subcortical brain areas. In line with these results, higher BMI has been associated with reduced GMV in a partially overlapping sample of older adults [7]. Here, we additionally found that leptin and adiponectin significantly contribute to explain covariance of obesity measures and GMV. Leptin regulates food-intake via hypothalamic neurons and has also been shown to have neuroprotective properties, e.g. enhancing neurogenesis as well as memory formation in the hippocampus [4]. Higher BMI is associated with higher leptin levels but also lower leptin sensitivity, which is probably due to impaired leptin transport at the blood brain barrier induced by chronically elevated peripheral leptin [3]. Our results thus indicate that lower leptin sensitivity in obesity might contribute to tissue loss in susceptible regions like the hippocampus, possibly by inhibiting its neuroprotective effects. Adiponectin which positively covaried with GMV might counteract adverse effects of obesity, supposedly via its insulin-sensitizing and arterio-protective properties [8]. Adipose tissue and subsequent neuronal inflammation is a possible mechanism of obesity-associated neuro-degeneration, however here, CRP and IL-6 did not significantly contribute to the first latent variable. Similarly, none of the lipid markers had a significant saliency which might indicate that variance in lipid metabolism is already captured by BMI.
In sum, our analysis revealed a complex association of metabolic obesity markers and gray matter volume loss which should be further investigated in longitudinal studies focusing on the impact of different adipokines on the aging brain.

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