A blood-based lipid profile associated with hippocampal volume and brain resting state activation observed in obese adults from the UK Biobank

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Abstract

Background/Objectives

Obesity is associated with functional and structural brain alterations. Less is known about the mechanisms behind such associations. This study investigates whether hippocampus volume and resting state function are associated with a dyslipidemia profile based on high-density lipoprotein, low-density lipoprotein, and triglyceride levels within obese and non-obese adults. A whole-brain analysis was also conducted to examine the effect of dyslipidemia on resting state function across the brain.

Subjects/Methods

A total of 554 UK Biobank participants comprised three groups based on body mass index (BMI) rankings: adults with obesity with a higher ranked BMI (O_{High}, n=185,), a second obese group with a lower ranked BMI (O_{Low}, n=182,), and non-obese controls (n=187). T1-weighted magnetic resonance imaging (MRI) and functional MRI (fMRI) data were accessed. The fMRI data were reconstructed as the fractional amplitude of low-frequency fluctuations (fALFF) maps to reflect resting-state brain activity. A lipid health score was created using principal component analysis. Linear models tested for associations between the lipid health score and hippocampal volume/fALFF, accounting for age, sex, hemoglobin A1c, total grey matter, and white matter volume.

Results

With a higher lipid health factor corresponding to a lower dyslipidemia risk, we observed a positive correlation between hippocampal volume with the lipid health factor exclusively in group O_{Low} (P=0.01). Meanwhile, we found a positive association between the lipid health factor and hippocampal fALFF in group O_{High} (P=0.02). Additional whole brain voxel-wise analysis to group O_{High} also implicated the premotor cortex, amygdala, thalamus, subcallosal cortex, temporal fusiform cortex, and middle temporal gyrus brain regions.

Conclusion

This study examined three distinct and well-matched groups and highlighted associations between lipids and regional brain volume/resting state function with a primary focus on the hippocampus. These findings support the obesity and brain literature with novel findings regarding the sub-group anthropomorphic differences.

Introduction

Obesity is a chronic disease characterized by excessive accumulation of adipose tissue, which is associated with both structural and functional brain alterations[1]. Past neuroimaging literature has shown that obesity is associated with both structural and functional brain alterations. Body mass index (BMI) is inversely related to subcortical grey matter volume and cortical thickness at midlife[2,3,4]. Brain functional connectivity may be altered in the default mode network, the frontoparietal network, the executive control network, and the salience network among obese adults relative to non-obese controls[5,6,7]. These earlier findings support the use of brain

imaging to characterize obesity-related changes that may contribute to neurodegeneration[8,9]. The hippocampus is a crucial brain region involved in memory, spatial learning, and mood[10]. Hippocampal atrophy is also associated with the early development of Alzheimer's disease[11]. Investigations that link obesity and hippocampal function have been mixed. For instance, data from UK Biobank and Norway report that higher total body fat is correlated with lower hippocampus volume[12]. In contrast, another study found no association between measures of obesity (i.e., BMI, waist-to-hip ratio: WHR) and hippocampus volume (both before and after accounting for global grey matter atrophy)[13]. As the mechanistic insight on drivers of hippocampal changes among obese individuals remains elusive, more research is needed to understand hippocampal and body relationships across different anthropomorphic subgroups, both structurally and functionally.

Obesity is one of the main causes of metabolic syndromes that can lead to dyslipidemia[14]. Both obesity and dyslipidemia are associated with cognitive impairments and brain functional decline[15]. Adiposity-associated dyslipidemia is characterized by lower high-density lipoprotein cholesterol (HDL-C), higher low-density lipoprotein (LDL) particles, and higher triglyceride (TG) levels[15,16,17]. Although the blood-brain barrier restricts the exchange between lipoproteins and the brain, peripheral circulating levels of lipids are still associated with brain health[18,19]. Examples across brain diseases are summarized here. Lower HDL-C levels, increased LDL, and increased TG are all risk factors for Alzheimer's disease[20]. Lower HDL-C level was also a risk factor for stroke within obese adults, and the association is strengthened by increasing BMI[21]. Thus, there is a need to consider participant subgroups based on distinct different BMI levels.

Blood oxygenation level-dependent (BOLD) based contrast is used to probe the brain's innate function through resting-state functional MRI (rs-fMRI). The fractional amplitude of low-frequency fluctuation (fALFF) is one form of rs-fMRI feature mapping that has a proven value and represents the BOLD low-frequency oscillations in the 0.01Hz – 0.1 Hz range that reflect spontaneous regional brain activity[22,23]. The fALFF value is between 0 and 1 since it is defined as BOLD fluctuations over a low-frequency (0.01Hz – 0.1 Hz) range relative to the total amplitude in the entire frequency range[23]. Recent FDG positron-emission tomography imaging supports that the fALFF map is a viable brain function metric since it correlates with brain glucose utilization, cerebral blood volume, and cerebral oxygen metabolism[24]. Another advantage of the rs-fMRI fALFF map is that the low-frequency band may contain less physiological noise due to respiration and cardiac sources and appears to be a better choice compared to the ALFF metric[23,25].

In the current study, we investigated circulating levels of HDL-C, LDL, and TG extracted from non-obese and obese groups. We test whether these lipid variables can uniquely explain regional variance in fALFF maps. Our primary focus was the hippocampus; we hypothesized that a lipid factor of dyslipidemia (HDL-C, LDL, and TG) would be inversely related to hippocampus volume and fALFF. We test the ability to create a lipid factor containing multiple lipid-related variables (HDL-C, LDL, and TG) using principal component analysis (PCA). We also run a sensitivity analysis using the triglyceride-to-HDL (TG/HDL) ratio for comparison. By design, we consider the BMI groups in separate analyses after constructing well-powered and matched samples. In addition to the hippocampal fALFF region-of-interest analysis, we examined lipid to fALFF association in a voxel-wise analysis to look for other regions of brain with functional alterations that happen

along with the hippocampus at resting state. The study would expand the current understanding of how lipid metabolism and dyslipidemia are associated with brain function.

Method

Study population and design

UK Biobank (UKB) is a population-based biomedical initiative that aims to collect data from 500 thousand United Kingdom adults between 38 and 73 years of age[26]. In November 2021, raw and tabular data were accessed using an approved UK Biobank project. Figure 1 summarizes aspects of the current experimental design, namely how individuals were screened for eligibility to the current study. Participants were included if the following were available: T1-weighted MRI, resting-state functional MRI (rs-fMRI), ICD-10 medical history report, and blood biochemistry test reports. Individuals were excluded if required data were incomplete, previous medical reports indicating diabetes, head injury, or 'unspecified brain disease,' MRI scans were not available/collected, or failed MRI image quality as identified by the UK Biobank.

The following describes the methodology to create three groups based on obesity screening to match for age, sex, medical history, HbA1c, grey matter volume, and white matter volume, as well as nearly equal and large sample sizes (see Fig. 1). A total of N = 988 adults met study eligibility. Participants were initially sorted based on BMI > 30 and BMI < 30 (controls). The BMI > 30 individuals (n = 393) were split into two subgroups based on the sorted BMI ranking, and the first n = 200 with higher BMI ranks were assigned to the Group O_{High}, while the remaining n = 193 were assigned to the Group O_{Low}. The third group had a normal BMI, and n = 200 was randomly chosen from a list of 595 control participants. Some participants were later removed when the MRI quality check was deemed poor quality (e.g., raw MR image data were corrupted, incomplete, missing). We collected demographic information for each participant who passed screening, including age, sex, BMI, WHR, frequency of alcohol consumption, and medical history. We collected lipid-related data, including HbA1c, HDL-C, LDL, and TG, through each participant's blood biochemistry report. Finally, brain volume was estimated by adding total grey and white matter volumes from T1-weighted MRI.

Blood biochemistry data acquisition and lipid health factor creation

Peripheral HDL-C, LDL, TG, and HbA1c were measured from participant blood samples during the 2012–2013 assessment visit to the UK Biobank. TG level was measured using a standard clinical biochemistry assay (glycerol-3-phosphate (GPO)-peroxidase (POD) chromogenic method). In contrast, HDL-C was measured using the enzymatic selective protection method, HbA1c was measured using high-performance liquid chromatographic, and the LDL level was measured using the enzyme immunoinhibition method. A detailed UK Biobank biochemistry protocol is available to download at https://www.ukbiobank.ac.uk/

media/oiudpjqa/bcm023_ukb_biomarker_panel_website_v1-0-aug-2015-edit-2018.pdf.

We used blood biochemistry records (UK Biobank Data field 30760, 30780, and 30870 for HDL-C, LDL, and TG, respectively) from the first-repeat assessment visit data (estimated year of collection: 2012–2013). An

omnibus principal component analysis (PCA) was performed using HDL-C, LDL, and TG data from all three groups. A singular principal component was used to create a lipid health score. The eigenvalue and the percentage-variance explanation were noted. The TG/HDL ratio was calculated for each participant as well.

Structural and functional MRI acquisition

We accessed rs-fMRI and the T1-weighted (T1w) data from the first imaging visit to UK Biobank (the estimated year of the collection starts from 2014). T1w images were acquired during a 5-minute scan that used a 3D MPRAGE gradient echo-planar imaging pulse sequence (repetition time/echo time/inversion time = 2000/2.01/880 msec, iPAT = 2, flip angle = 8°). The T1w images had a spatial resolution of 1x1x1 mm and a field-of-view of 208x256x256 mm. The rs-fMRI images were acquired during a 6-minute scan that used a gradient-echo echo-planar imaging pulse sequence (TR/TE = 0.735/39 msec, 8x multi-slice acceleration, no iPAT, and flip angle = 52°) with a spatial resolution of 2.4x2.4x2.4 mm and field-of-view of 211.2x211.2x153.6 mm. A total of 490-time point volumes were collected. DICOM data were converted into NIFTI format using a dcm2niix tool. Additional UK Biobank MR sequence parameters are available at the UK Biobank documentation https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/bmri_V4_23092014.pdf

Image processing and fALFF calculations

In addition to the preprocessing protocol provided by UK Biobank (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/brain_mri.pdf), extra steps were done to calculate fALFF maps. Software from the Analysis of Functional NeuroImages (AFNI) and the FMRIB Software Library (FSL) packages were used for rs-fMRI preprocessing and fALFF calculations. Initial rs-fMRI volumes were removed, and images were de-obliqued to facilitate analysis. As per data cleaning recommendations[27], BOLD timeseries were corrected for head motion, skull removal, de-spiking, detrending, spatially smoothing (FWHM = 6mm), and global intensity normalization.

For fALFF calculation, the square root of the power spectrum of each rs-fMRI timeseries voxel was computed to calculate the amplitude value for each voxel. Then, we calculated fALFF by summing the amplitude data in each voxel, which falls in the 0.01Hz – 0.1 Hz low-frequency range, and dividing by the sum of amplitude in the entire frequency spectrum. (Eq. 1)

$$fALFF = \frac{Sum.Amplitude(0.01\tilde{0}.1Hz)}{Sum.Amplitude(wholefrequencyspectrum)} \quad [1]$$

Brain structure segmentation

T1w and fALFF images were registered to standard space using the MNI-152 template. The FMRIB's Integrated Registration and Segmentation Tool (FIRST) from FSL was used to segment the hippocampus on the T1w images[28]. The number of voxels in the segmented hippocampi masks was counted for volume calculation. The binary left/right hippocampus masks were used for the fALFF region of interest as the mean value in the mask. Estimated brain volumes were downloaded from tabular data (UK Biobank data field 25010).

Statistical analysis

T-statistics were used to test for group differences in demographics and blood lipid variables. A multivariable regression model tested for an association between hippocampus fALFF and lipid score (Eq. 2) along with the following covariates: age, biological sex, HbA1c, and total brain volume. Note that we also replaced the lipid health factor in **Eq. 2** with the triglyceride-to-HDL ratio; this was a pre-defined sensitivity analysis. Participant age was reported by the corresponding assessment center. Biological sex was a categorical variable accessed from the UK Biobank registry at recruitment.

Mean hippocampus fALFF = Age + Sex + HbA1c + Brain volume + Lipid health factor [2]

The beta weights for each regressor were reported, with left and right hippocampus fALFF tested separately. A critical P-value of 0.05 was set to determine the statistical significance. The sensitivity analysis used the same regression model but replaced the lipid health factor by the triglyceride-to-HDL ratio.

The second voxel-wise analysis consisted of non-parametric permutation-based testing for each group separately. This model had the same parameters as the fALFF regional analysis (i.e., as in Eq. 2); the dependent variables were the fALFF voxel intensities. HbA1c was chosen to account for the effect of insulin resistance. Voxel-wise t-statistics and corresponding non-parametric p-value maps were calculated using the 'randomise' program in FSL, based on 10,000 permutations of the data[29]. Threshold-free cluster enhancement (TFCE) (H = 2, E = 5, C = 6) settings were used to produce a p-value corrected for multiple comparisons, and a critical corrected P-value < 0.01 was chosen. Significant clusters were displayed using the t-statistic map, thresholded by TFCE non-parametric P-value smaller than 0.01. Clusters inside the brain stem, cerebellum, and ventricles were excluded from the current analysis. A 'cluster' command from FSL was used to generate a summary of cluster size and location (the latter was deduced using the Harvard-Oxford atlas).

Results

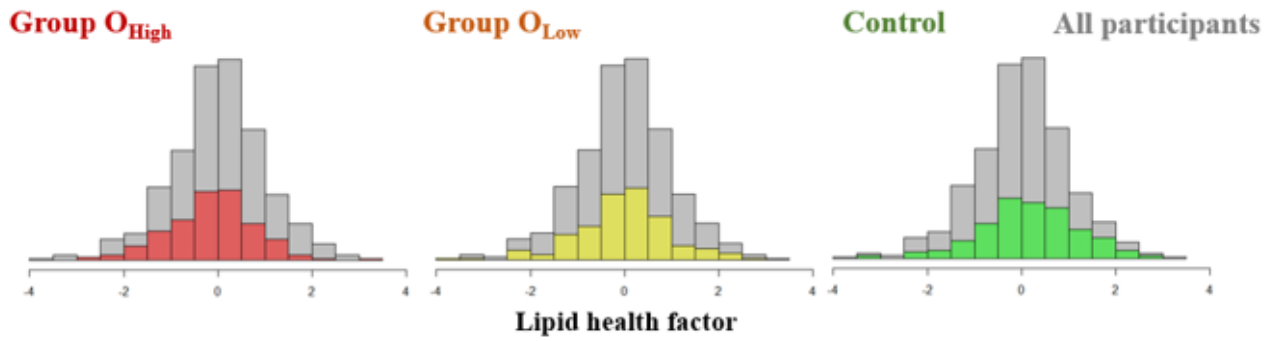
Participant characteristics and blood biochemistry summary

Participant characteristics and blood biochemistry summaries are listed in Table 1. There were no significant group differences in age, total brain volume, LDL, and TG; however, as anticipated, there were group differences in BMI, WHR, HbA1c, HDL-C, and the lipid health factor ($P < 0.05$) (Table 1). An unadjusted correlation map is presented **in supplementary Fig. 1** that shows the raw correlations between variables. Group O_{High} comprised 24 Class III, 78 Class II, and 83 Class I obesity participants (n = 185). Group O_{Low} consisted entirely of Class I obesity participants (n = 182). The lipid health factor explained 48% variance of the original data, with factor loadings of 0.86, 0.09, and − 0.83 for HDL-C, LDL, and TG, respectively; hence a higher lipid score corresponds to a better lipid health profile. The histogram from Table 1 shows the distribution of lipid health factors in the three groups. The PCA analysis detailed results related to the lipid health factor creation are presented in **supplementary table 1.**

Table 1
Group characteristics (mean ± standard deviation) are provided as well as the lipid health factor histograms per group (grey histograms show the whole cohort). The * sign denotes variables that were significantly different compared to controls. (P < 0.05) “Some” alcohol frequency indicates about 3 times a month, while “lots” is more than 3 times a week. Participants who preferred not to answer the ethnic, smoking, and alcohol questionnaire are treated as missing data.

	Obese group O_{High} (n = 185)	**Obese group O_{Low} (n = 182)**	**Control group (n = 187)**
Age *(years)*	62.8 ± 7.6	64.8 ± 7.4	63.3 ± 7.4
Sex *(Male : Female)*	83 : 105 (44.1% : 55.9%)	92 : 92 (50% : 50%)	79 : 108 (42.2% : 57.8%)
BMI $(kg \cdot m^{-2})$	$36.3 \pm 3.5^*$	$31.3 \pm 0.7^*$	27.7 ± 1.1
WHR	$0.91 \pm 0.09^*$	$0.90 \pm 0.08^*$	0.84 ± 0.09
Brain volume (L)	1.17 ± 0.11	1.18 ± 0.13	1.17 ± 0.11
HbA1c $(mmol \cdot mol^{-1})$	$36.40 \pm 3.70^*$	35.87 ± 3.66*	35.15 ± 2.99
HDL-C $(mmol \cdot L^{-1})$	$1.34 \pm 0.32^*$	1.40 ± 0.34	1.46 ± 0.37
LDL $(mmol \cdot L^{-1})$	3.66 ± 0.87	3.77 ± 0.91	3.78 ± 0.89
TGs $(mmol \cdot L^{-1})$	1.99 ± 0.92	2.05 ± 1.00	1.89 ± 1.05
Lipid health factor	$-0.13 \pm 0.92^*$	-0.02 ± 1.01	0.15 ± 1.04
Ethnic background (White/Black/Asian/Mix)	181/2/0/2	180/0/2/0	182/0/2/2

	Obese group O_{High} (n = 185)	Obese group O_{Low} (n = 182)	Control group (n = 187)
Smoking status (Never/Previous/Now)	105/65/14	118/48/16	120/60/7
Alcohol frequency (No/Some/Lots/Daily)	10/52/94/29	6/37/106/33	8/31/95/53



Hippocampus fALFF association with the lipid health factor

Table 2 summarizes the association between the hippocampal volume/fALFF versus age, HbA1c, and the lipid health factor. The lipid health factor was positively associated with left hippocampus volume, a finding observed only in the group O_{Low}. Both left and right hippocampal fALFF were positively associated with the lipid health factor, a finding observed only in the group O_{High}. Age and HbA1c were not significantly associated with either hippocampus volume or mean hippocampus fALFF on both hemispheres within any of the three groups. Examples of the segmented left (yellow) and right (green) hippocampi are included in Table 2. Sensitivity analysis using TG/HDL ratio reveals a consistent pattern of a negative association between TG/HDL ratio and left hippocampus volume for group O_{Low} and another consistent association for left and right hippocampal fALFF for group O_{High} ($P < 0.05$). Details of the sensitivity analysis are available in **supplementary table 2.**

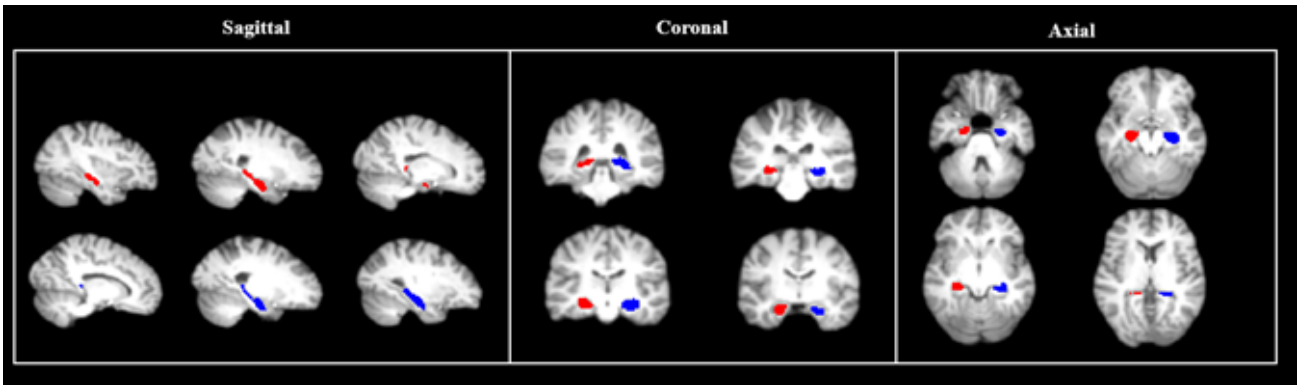
Table 2

Summary of the hippocampal volume statistics and linear regression results. Beta-weights with P-values < 0.05 are denoted with '*' mark and underlined. An example of hippocampal segmentation is provided, superposed on the T1w image (left: blue, right: red).

Hippocampus Volume		**Obese group O_{High} (BMI 36.3 ± 3.5)**			**Obese group O_{Low} (BMI 31.3 ± 0.7)**			**Control group (BMI 27.7 ± 1.1)**		
		Mean(mm^3)	**SD**		**Mean(mm^3)**	**SD**		**Mean(mm^3)**	**SD**	
Left hippocampus		3 741.7	486.1		3 787.8	528.9		3 611.9	593.2	
Right hippocampus		3 906.1	469.6		3 887.2	505.7		3 789.4	543.6	
Linear model: H*ippocampus volume = Age + Sex + HbA1c + Brain volume + Lipid health factor*										
Hippocampus Volume		**Obese group O_{High}** (BMI 36.3 ± 3.5)			**Obese group O_{Low}** (BMI 31.3 ± 0.7)			**Control group** (BMI 27.7 ± 1.1)		
		Age	**A1c**	**Lipid**	**Age**	**A1c**	**Lipid**	**Age**	**A1c**	**Lipid**
Left	Beta	-7.37	16.41	60.13	-7.57	8.41	105.03	3.12	11.97	69.54
	P-value	0.11	0.07	0.11	0.15	0.41	0.008*	0.64	0.44	0.10
Right	Beta	-3.30	16.78	29.28	-7.36	6.91	29.90	-2.21	14.84	9.89
	P-value	0.45	0.051	0.42	0.15	0.48	0.43	0.72	0.29	0.80
Linear model: *Mean hippocampus fALFF = Age + Sex + HbA1c + Brain volume + Lipid health factor*										
Hippocampus fALFF		**Obese group O_{High}** (BMI 36.3 ± 3.5)			**Obese group O_{Low}** (BMI 31.3 ± 0.7)			**Control group** (BMI 27.7 ± 1.1)		
		Age	**A1c**	**Lipid**	**Age**	**A1c**	**Lipid**	**Age**	**A1c**	**Lipid**
Left mean	Beta	< -0.001	<-0.001	0.005	< -0.001	< -0.001	< 0.001	< 0.001	< -0.001	-0.002
	P-value	0.08	0.78	0.02*	0.45	0.22	0.87	0.26	0.47	0.30
Right mean	Beta	< -0.001	< -0.001	0.007	< -0.001	< -0.001	0.001	< 0.001	< -0.001	-0.002
	P-value	0.34	0.69	0.01*	0.61	0.18	0.66	0.45	0.64	0.41

Hippocampus Volume	Obese group O_{High} (BMI 36.3 ± 3.5)		Obese group O_{Low} (BMI 31.3 ± 0.7)		Control group (BMI 27.7 ± 1.1)	
	Mean(mm^3)	SD	Mean(mm^3)	SD	Mean(mm^3)	SD

Example of hippocampus segmentation: Right (Red) and Left (Blue) Hippocampus on T1w MR images.



Voxel-wise brain analysis of fALFF association with the lipid health factor

Within the group O_{High}, we also identified the following fALFF regions that were positively associated with the lipid health factor: premotor cortex, right amygdala, left/right thalamus, subcallosal cortex, temporal fusiform cortex, middle temporal gyrus, right hippocampus, and temporal pole (corrected $P < 0.01$; Fig. 2; clusters reported in supplementary table 3). Within obese O_{Low} and control groups, no significant clusters were detected between regional fALFF with lipid health factors.

Discussion

In this study, we found associations between lipid health and hippocampal measures of function and anatomy that were observed exclusively in the obese groups but not in the controls. Specifically, the group with the highest BMI showed a positive association between the lipid health factor and hippocampal activation. By contrast, the lower obesity group showed a positive association between the lipid health factor and hippocampal volume but not hippocampal function in the resting state. Lastly, we corroborated the use of the lipid health factor by also considering another metric of dyslipidemia, namely the triglyceride to HDL ratio. These findings support the obesity and brain literature with novel findings regarding the pre-selected subgroups. This study focused primarily on the hippocampus as an important region for brain health and benefitted from a relatively large sample size.

The lipid health factor and the sensitivity analysis

Factor loadings showed that the lipid health factors were directly related to the HDL-C, and inversely related to TG, while explaining limited variance in LDL. The factor loadings thus align with the current definition of dyslipidemia. According to the Kaiser rule, the lipid health factor was a valid construct because it exceeded a minimum eigenvalue level for the small number (i.e. three) of input variables[30]. Therefore, it was feasible to use the lipid health factor score as a means of investigating within-group differences in dyslipidemia and the factor loadings aligned with the previous work[31]. The normally distributed lipid health factors within all three groups indicates it is not biased by the obesity class. The sensitivity analysis using TG/HDL ratio also demonstrates high consistency on the TG/HDL ratio and our lipid health factor when observing their associations with hippocampal volume and functional activation. It also indicates our lipid health factors may be related to insulin resistance, and atherosclerosis aside from dyslipidemia as well[32,33].

The lipid health factor is associated with hippocampus anatomy within obese adults within group O_{low}

We demonstrate that a higher lipid health score was associated with larger hippocampal volume exclusively in the obese group O_{Low}. However, we did not observe an association between lipid health score and hippocampal volume for the obese group O_{High}, nor the controls. These findings add to the neuroimaging literature that has historically focused on BMI-to-brain relationships. The literature shows that BMI – as the explanatory variable – was associated with lower hippocampal volume in older adults from the Pittsburgh study, an age-comparable Latino cohort, and younger adults from the Leipzig and Spanish studies[34,35,36,37,38]. To our knowledge, the obesity and brain literature has limited studies on dyslipidemia and brain associations in the manner that we conducted our experiments. With relatively large sample sizes, we were able to show that dyslipidemia was correlated with brain measures in distinct ways based on the subgroups.

Regarding other explanatory variables in the regression model, we note that hippocampal volume was not associated with age or HbA1c for any of the groups. The lack of age-related association with hippocampal volume agrees with one other obesity neuroimaging study[34]; we note our cohort had a relatively narrow age range and therefore does not address population-level brain ageing[35]. Regarding HbA1c, we noted a trending relationship between hippocampal volume and HbA1c for the O_{High} group ($P < 0.1$), but this was not significant. One reason for the lack of HbA1c findings could be the Type 2 Diabetes exclusion in our study. Interestingly, the non-significant association was also reported in an earlier hippocampus and fasting insulin study[34].

The structural analysis also revealed left lateralized findings between hippocampal volume and dyslipidemia, that are noteworthy. The left hippocampal volume was highly correlated with the lipid health factor for the obese low group and showed a non-significant trend for obese high and control groups. Curiously, no associations were found for the right hippocampal volume for any of the groups. Similar results, namely the ‘left-less-than-right’ pattern, was also observed in other neuroimaging studies focused on mild cognitive impairment and depression[39,40]. Our results help to appreciate this phenomenon of left/right hippocampal volumes as it pertains to dyslipidemia. The non-significant findings within O_{High} and control groups may also suggest the association may change dynamically with BMI.

Hippocampal fALFF correlates with dyslipidemia only the high obese group

From the fALFF analyses, we observed bilateral hippocampal resting state activation that was positively correlated with lipid health exclusively in the high obesity group O_{High} but not in O_{low} nor controls. The hippocampal result in the high obesity group aligns with a mood induction paradigm study, albeit we note that this other study focused on BMI as the explanatory variable[41]. Hippocampal function & plasticity are indeed relevant topics with respect to these nuanced findings, as discussed elsewhere[34]. Our study thus further interprets that the possible mechanisms behind such hippocampus-obesity association may be related to dyslipidemia within Class II/III obese adults. Age and HbA1c explanatory variables were not significant in explaining between-subject differences in hippocampal fALFF for reasons that are mentioned above.

Voxel-wise fALFF within O_{High} group further explains the fALFF-dyslipidemia association.

The voxel-wise analysis helped to further elucidate lipid health score and fALFF associations by considering additional brain regions. We found associations with several brain regions within O_{High} group but not for O_{Low} or control groups. The largest cluster was in the premotor cortex (PMC), a brain region that processes information from the posterior parietal and dorsolateral prefrontal cortex and is tied to primary motor cortex execution[42]. We note that decreased PMC activity is being reported in the study of brain diseases, schizophrenia, and Parkinson's disease[43]. Our novel findings add to the neuroimaging literature, and further mechanistic obesity research that attempts to link PMC and dyslipidemia is warranted. The voxel-wise analysis also identified clusters of dyslipidemia-fALFF association in the hippocampus, amygdala, and thalamus; each is involved in eating, reward, memory, and emotional behaviors. These findings align with eating behavior literature. This includes external food sensitivity and binge eating related to inadequate modulations from amygdala, as well as PMC on eating motor planning[44,45]. The reduced sub-callosal gyrus fALFF observed within O_{High} group may also relate to amygdala response due to the circuitry of fearful responses[46].

We failed to detect any voxel-wise associations for the obese group O_{Low} or controls. To our current knowledge, and relative to neuroanatomy, less is known about associations between dyslipidemia and functional neuroimaging. One meta-analysis suggests obesity is associated with disrupted functional connectivity, which may vary by BMI subgroups; however, dyslipidemia was not considered; hence the current study adds new findings[47]. The lack of fALFF findings in the current study for the O_{Low} group and controls may show that dyslipidemia is more relevant for brain activation among higher obese groups. We cannot rule out whether there were 'state-like' differences, i.e. emotions and behaviors on the day of scanning, that could contribute to these subgroup differences; thus, more research is warranted.

Limitations and future directions

There are limitations to this study. We focused on the hippocampus in the primary analysis and used segmentation masks provided by UK Biobank. We acknowledge that additional subcortical grey matter

regions could be of interest and worthy of future investigation. In addition, between-group differences in the image registration quality of the MNI152 brain template could have contributed to experimental errors that would degrade effect sizes. Next, we opted to use fALFF maps from among various choices to characterize resting-state BOLD data. Other approaches would be of interest but were not considered in the current study. Other functional neuroimaging modalities, fMRI-related methods that probe connectivity, or cerebral blood flow MRI techniques each have merit. Finally, despite large sample sizes for each subgroup, we were not powered to include ethnicity as a covariate.

In conclusion, the current study found within-group hippocampus anatomical and functional associations with dyslipidemia for the obese samples, but no such findings were evident in non-obese controls. When considering voxel-wise analysis, similar patterns persisted, whereby the morbidly obese O_{High} group showed activation clusters with dyslipidemia, while the less obese and control groups showed no relationships. These findings suggest that it is important to consider sub-group anthropomorphic differences in brain-based investigations. Future work is warranted to investigate whether these imaging findings align with cognition, behaviours, and persist over time to yield an adverse brain health profile.

Declarations

Competing Interests Statement

We acknowledge funding from the Canadian Institutes of Health Research project grant (165981) and support from the Sandra E Black Centre for Brain Resilience and Recovery. The authors declare no competing interests.

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Author contributions

GJ conceived the study design, conducted data analyses, and drafted the manuscript. JR, SEB, and WS provided critical appraisals of the study, advised on analyses, and made manuscript edits. BJM secured data access, helped conceive of the study, and provided manuscript edits. All authors provided approved the final manuscript.

Statement of competing interests

The authors declare no competing interests.

Data Availability

UK Biobank provides downloads for all subject's CSV data and MRI images with the inclusion criteria described in the method section. The field ID for each variable is included within the method section. Web links for UK Biobank documentation were presented in the method section as well. All other data generated or

analyzed during this study are included in this published paper and its supplementary information files. FSL and AFNI are free-download software for non-commercial users. Resting-state functional MRI analysis script is detailly described step-by-step in the method section, and the code uses part of standard software (FSL, AFNI).

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Figures

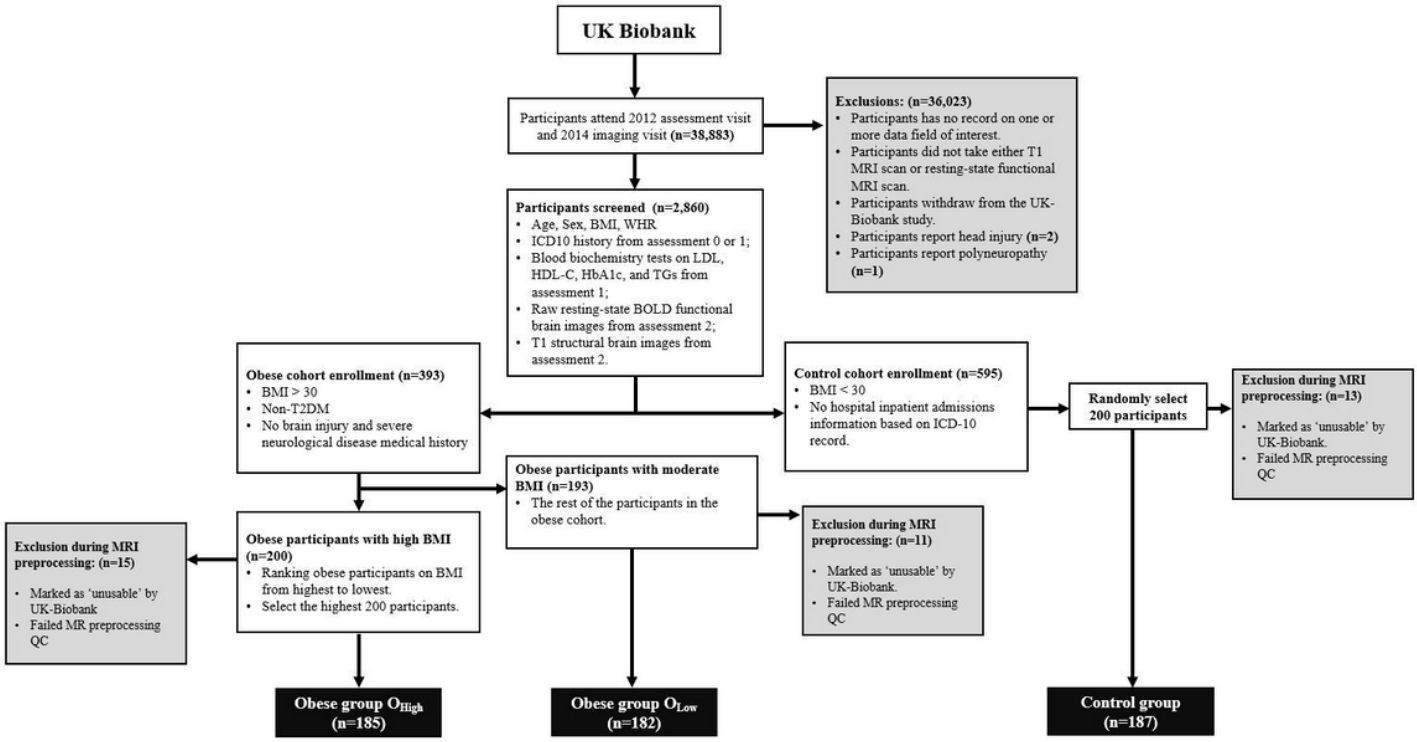

Figure 1

The flow chart describes the participant selection process to create three groups: two obese groups (O_{High}, O_{Low}) and one control group. The screening summary, inclusion, and exclusion criteria for the three study cohorts are listed. BMI: Body mass index. WHR: waist-to-hip ratio. ICD10: International Statistical Classification of Diseases and Related Health Problems. LDL: low-density lipoprotein. HDL-C: high-density lipoprotein cholesterol. TG: triglycerides. BOLD: blood oxygenation level-dependent. HbA1c: Hemoglobin A1c.

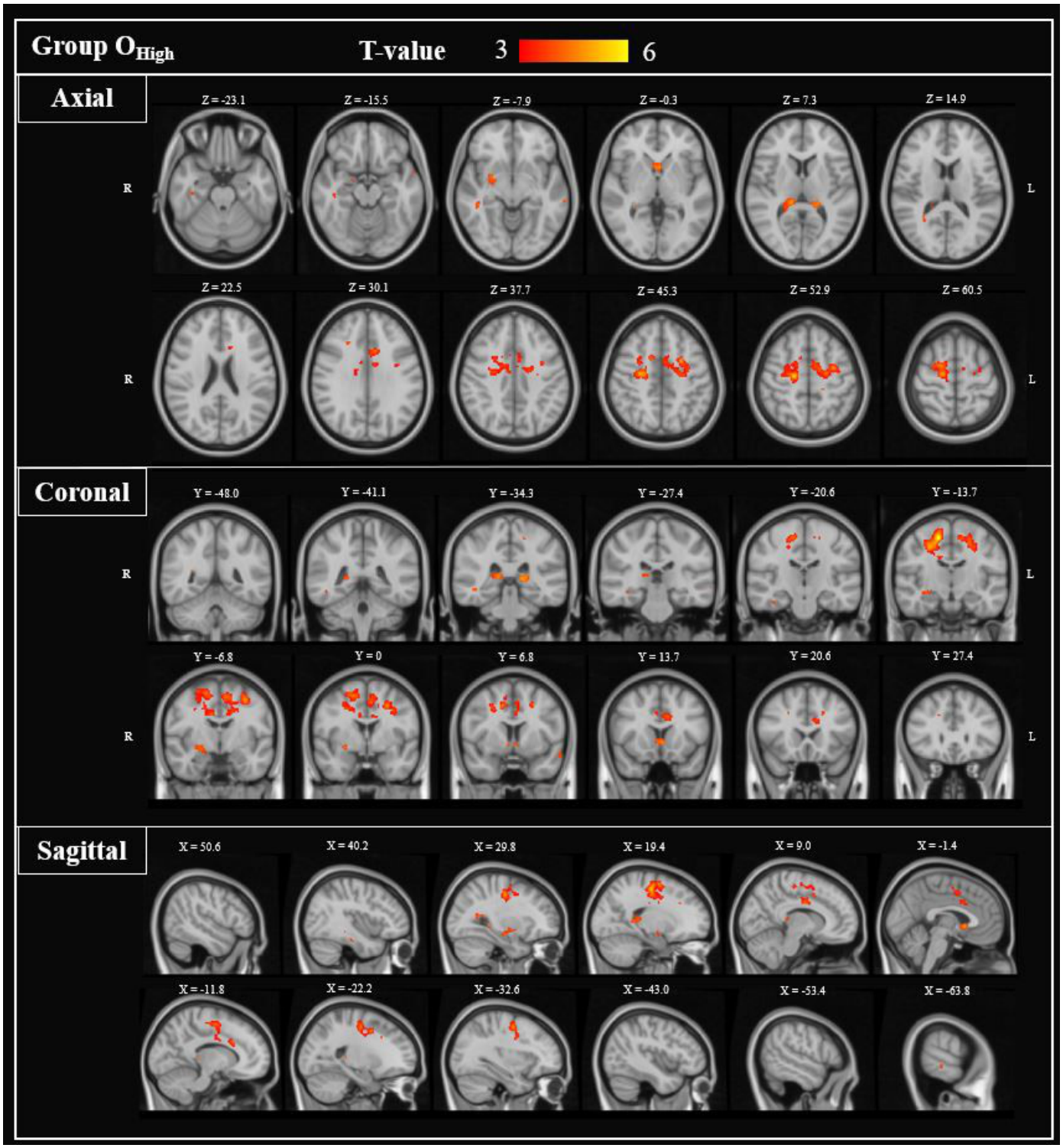

Figure 2

Brain regions and voxel T-values showing a significant correlation between fALFF amplitude and lipid health score were only identified for the obese group O_{High}. Images are arranged in MNI152 brain coordinates.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.pdf