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Higher Body Mass Index is Associated with Reduced Posterior Default Mode Connectivity in Older Adults

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Abstract: Obesity is a complex neurobehavioral disorder that has been linked to changes in brain structure and function. However, the impact of obesity on functional connectivity and cognition in aging humans is largely unknown. Therefore, the association of body mass index (BMI), resting-state network connectivity, and cognitive performance in 712 healthy, well-characterized older adults of the Leipzig Research Center for Civilization Diseases (LIFE) cohort (60–80 years old, mean BMI 27.6 kg/m^2 ± 4.2 SD, main sample: n = 521, replication sample: n = 191) was determined. Statistical analyses included a multivariate model selection approach followed by univariate analyses to adjust for possible confounders. Results showed that a higher BMI was significantly associated with lower default mode functional connectivity in the posterior cingulate cortex and precuneus. The effect remained stable after controlling for age, sex, head motion, registration quality, cardiovascular, and genetic factors as well as in replication analyses. Lower functional connectivity in BMI-associated areas correlated with worse executive function. In addition, higher BMI correlated with stronger head motion. Using 3T neuroimaging in a large cohort of healthy

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older adults, independent negative associations of obesity and functional connectivity in the posterior default mode network were observed. In addition, a subtle link between lower resting-state connectivity in BMI-associated regions and cognitive function was found. The findings might indicate that obesity is associated with patterns of decreased default mode connectivity similar to those seen in populations at risk for Alzheimer's disease. *Hum Brain Mapp 38:3502–3515, 2017.*

Key words: brain; neuroimaging; obesity; risk factors; cognition

INTRODUCTION

Obesity is a complex neurobehavioral disorder resulting from excessive energy intake and insufficient energy expenditure. It has been associated with abnormal functionality of homeostasis brain networks [Grill et al., 2007] and some studies also reported differences in higher cognitive functions such as reward evaluation [Amlung et al., 2016; Stice et al., 2008], executive functions [Benito-León et al., 2013; Gunstad et al., 2007] and learning and memory [Cheke et al., 2017; Smith et al., 2011], yet underlying mechanisms are far from understood.

Using task-based functional MRI (fMRI), several studies revealed differences between lean and obese participants in regional activation patterns during the processing of rewarding food and non-food stimuli [Rothemund et al., 2007; Stice et al., 2008; Stoeckel et al., 2008]. In addition, using resting-state fMRI, obesity has been linked to selective changes in functional connectivity between brain areas, including attentional and default mode resting state networks (RSN) [Garcia-Garcia et al., 2013; Kullmann et al., 2012]. However, previous findings of obesity-related changes in functional connectivity are mixed [Kullmann et al., 2012] and mostly based on small sample sizes in young participants using non-standardized experimental conditions [Hsu et al., 2015; Tregellas et al., 2011]. Recently, several studies have associated RSN connectivity strength with individual differences in cognitive performance such as executive function [Gordon et al., 2015; Reineberg et al., 2015] and memory [Salami et al., 2016; Wang et al., 2010]. Thus, determining changes in functional connectivity that are attributed to obesity might help to better understand the link between body weight and cognition in humans.

In the present study we therefore aimed to investigate the association of obesity with RSN connectivity in a large population-based cohort of healthy older adults. We hypothesized that a higher BMI would be associated with changes in obesity-related RSN such as frontal, attentional, or default mode networks. As functional connectivity has been linked to differences in cognition we also determined if changes in RSN connectivity would correlate with cognitive performance.

METHODS

Participants

All participants took part in the LIFE-Adult-Study [Loeffler et al., 2015] and were randomly selected, community-dwelling volunteers older than 60 years (see Fig. 1 for details on sample selection). In total, 712 subjects were included, thereof 521 subjects in the main sample (sample 1) and another 191 subjects in the replication sample (sample 2) (see Table I for demographics). Exclusion criteria were stroke, cancer treatment in the last 12 months, neuroradiological findings of brain pathology, intake of centrally active medication and a score below 25 in the Mini Mental State Examination. All subjects underwent medical examination, anthropometric measurements, MRI assessment, and neuropsychological testing.

Standard protocol approvals and patient consents

The study was approved by the institutional ethics board of the Medical Faculty of the University of Leipzig and all participants signed an informed consent form.

Neuroimaging

Brain imaging was performed on a 3T Siemens Verio Scanner with a 32 channel head coil. T1-weighted images were acquired using generalized autocalibrating partially parallel acquisition technique [Griswold et al., 2002] and the Alzheimer's Disease Neuroimaging Initiative standard protocol with the following parameters: inversion time, 900 ms; repetition time, 2.3 ms; echo time, 2.98 ms; flip angle, 9°; band width, 240 Hz/pixel; image matrix, 256 × 240; 176 partitions; field of view, 256 × 240 × 176 mm^3; sagittal orientation; voxel size, 1 × 1 × 1 mm^3; no interpolation.

T2*-weighted functional images were acquired using an echo-planar-imaging sequence with the following parameters: repetition time, 2 s; echo time, 30 ms; flip angle, 90°; image matrix, 64 × 64; 30 slices; field of view, 192 × 192 × 144 mm^3, voxel size of 3 mm × 3 mm, slice thickness of 4 mm, slice gap of 0.8 mm; 300 volumes; total acquisition time, 10:04 minutes. For two participants only 299 volumes and for one participant only 215 volumes were acquired. Preprocessing was implemented in a reproducible pipeline using nipype [Gorgolewski et al., 2011] which is available to the public at https://github.com/fBeyer89/LIFE_rs_ICA_preprocessing.

After removal of the first five volumes in order to allow the magnetization to reach steady-state, rigid body, boundary-based coregistration with 6 degrees of freedom

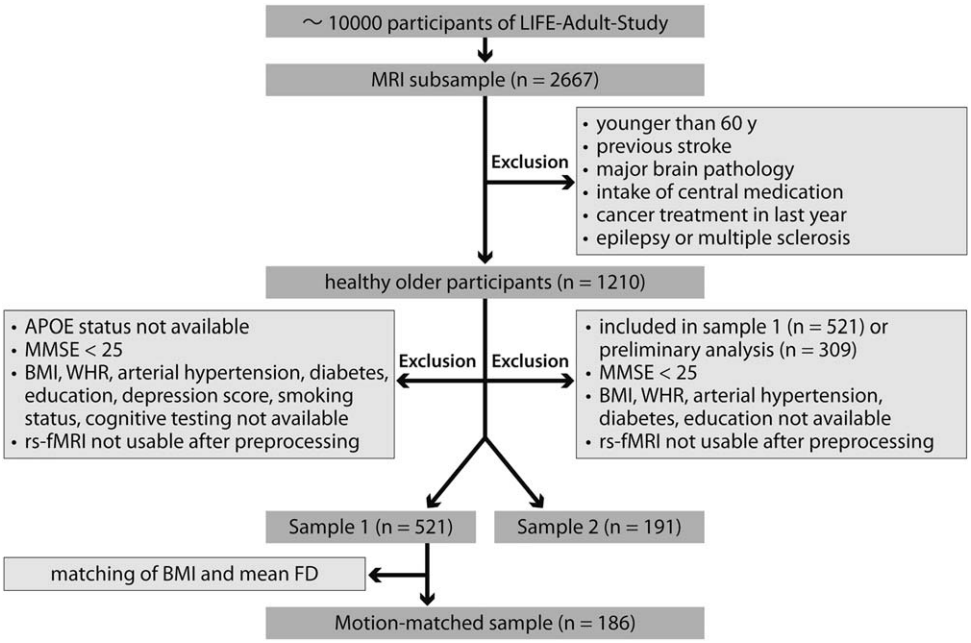

Figure 1.
Flow chart of the study illustrating the exclusion criteria for the selection of sample 1, motion-matched sample, and sample 2.

of the functional scan to the anatomical image, as well as motion and EPI distortion corrections were calculated and jointly applied in a subsequent step to each volume of the functional scan. Scans were slicetime-corrected and non-linearly transformed to MNI space using ANTS Symmetric Normalization (SyN) registration algorithm [Avants et al., 2011], resliced to 3 mm isotropic voxels and smoothed with a gaussian kernel of 6 mm full-width-at-half-maximum. Frame-to-frame head motion was estimated by calculating framewise displacement (FD) [Power et al., 2012]. We excluded 12 participants from sample 1 and 6 participants from sample 2 because of gross motion (maximal FD > 3 mm). Mean FD was calculated across volumes and used as a covariate to correct for head motion in statistical analysis.

All normalized functional images were visually checked and compared with the MNI template which led to the exclusion of 15 and four participants from sample 1 and 2 respectively because of major registration issues (large ventricles, atrophy, or calcified falxes).

A mean functional image was created for the remaining 521 subjects from sample 1 and 191 subjects from sample 2

TABLE I. Demographic characteristics of sample 1 and 2

	Sample 1 n = 521 (230 women)	Sample 2 n = 191 (96 women)
Age (y)	70.1 ± 3.8 (60–79)	68.8 ± 5.4 (60–82)
BMI (kg/m^2)	27.5 ± 4.1 (16.8–41.4)	28.1 ± 4.5 (18.6–43.9)
Mean FD (mm)	0.27 ± 0.12 (0.05–0.87)	0.28 ± 0.14 (0.06–0.92)
q_r	0.95 ± 0.015 (0.86–0.97)	0.93 ± 0.02 (0.79–0.96)
APOE status (% e4 carriers/non-e4 carriers/missing)	20.7/79.3/–	7.3/27.2/65.4
Arterial hypertension (% yes)	60.7	58.6
Diabetes (% yes)	15.7	15.7
Education (% no SS-LD/SS-LD/advanced SS-LD/university-entrance degree)	0.8/52.6/7.7/39	1.6/65.4/11.5/21.5
CES-D (score)/missing	9.3 ± 5.5 (0–34)/–	11.2 ± 5.6 (0–29)/47
Smoker (% current/previous/never/missing)	6.5/32.8/60.7/–	8.4/29.8/37.7/24.1

Data are mean ± SD (minimum–maximum).
BMI, body mass index; FD, framewise displacement; q_r, registration quality; APOE e4, apolipoprotein E epsilon 4 allele; SS-LD, secondary-school leaving degree; CES-D, Center for Epidemiologic Studies Depression Scale.

using the first volume of each subject's time series. A registration quality index q_r was calculated as the spatial cross correlation of each of the subject's first volumes with the mean image and later used as a covariate describing the accuracy of spatial normalization from functional to anatomical subject and MNI space.

To assess RSN, we applied independent component analysis (ICA) which has been shown to reliably identify RSN across subjects [Damoiseaux et al., 2006] using the GIFT toolbox [Calhoun, 2004]. A high number of $n = 75$ components was chosen because such decompositions have been previously shown to yield detailed and nonoverlapping components [Abou-Elseoud et al., 2010; Kiviniemi et al., 2009]. Independent components were selected as reliable RSN if their spatial cross-correlation with publicly available templates [Allen et al., 2011] was higher than 0.4 and they contained mainly low-frequency fluctuations measured with a power ratio above 3 [Robinson et al., 2009]. Subject-specific component maps were calculated using the GICA-approach implemented in the GIFT toolbox [Erhardt et al., 2011].

Gray matter volume (GMV) probability maps were derived from T1-weighted scans using voxel based morphometry in SPM 8 (www.fil.ion.ucl.ac.uk/spm) and averaged within thresholded ICA component maps to correct for local gray matter volume differences within the resting state networks.

Total intracranial volume, cortical white matter volume as well as cortical and subcortical gray matter volumes were derived using FREESURFER (http://surfer.nm.mgh.harvard.edu/) and used to assess and correct for associations of global brain volume measures with BMI.

Neuropsychological Testing and Confounder Definition

Neuropsychological testing was performed using the CERAD-Plus test battery [Morris et al., 1989] and included the trail-making test (TMT) part A and B, semantic and phonemic verbal fluency and verbal memory. The trail-making test is an indicator of speed of cognitive processing and executive functioning [Sanchez-Cubillo et al., 2009] while phonemic and verbal fluency tests measure executive and verbal reasoning [Van Der Elst et al., 2006]. In the verbal memory test, learning was defined as the sum of 3 consecutive learning trials, recall was defined as the sum of correctly recalled words after a delay, in which participants performed a nonverbal task, and recognition was defined as the number of correctly recognized words of a list of 20 mixed words presented afterwards. Test scores were z-transformed and combined to create composite scores for executive function, memory performance and processing speed [Kerti et al., 2013; Van de Rest et al., 2008]. This allowed us to reduce number of comparisons and investigate specific cognitive domains. Composite scores for executive function, memory performance and processing speed were calculated as follows [Kharabian Masouleh et al., 2016]: executive functions = [z_phonemic fluency + z_semantic fluency + z_TMT(part B + part A)/part A]/3; memory = (z_sum_learning þ z_recall þ z_recognition)/3; processing speed = −z (TMT [part A]).

Arterial hypertension was defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg or diagnosis of hypertension or use of antihypertensive medication [Biessels et al., 2006]. Diabetes and hyperlipidemia were binarily defined based on self-reported diagnosis or medication intake. Four levels of education were defined: no secondary-school leaving degree (SS-LD), secondary-school leaving degree (corresponding to 8 years of school), advanced secondary-school leaving degree (corresponding to 10 years of school) and university-entrance degree (corresponding to 13 years of school). Depression score was measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [Radloff, 1977]. Smoking status was defined using self-reported information as never smoker, previous smoker or current smoker. Genotyping of the APOE allele status (E2, E3, E4) was performed on a Roche Lightcylcer 480 according to the method of Aslanidis [Aslanidis and Schmitz, 1999]. APOE-e4 carrier status was then defined as carrying none (0) or at least one APOE-e4 allele (1).

Statistical Analysis

Statistical analysis of the association between obesity and RSN functional connectivity was performed using a multivariate backward model selection approach [Allen et al., 2011] implemented in the MANCOVAN toolbox (http://mialab.mrn.org/software). The primary design matrix contained BMI, age and sex (Model 1). In a second model we additionally added head motion measured by mean FD (log-transformed) and registration quality measured by q_r (Fisher-Z-transformed) as covariates (Model 2). In order to correct for multiple comparison across 18 different RSN that were identified in our sample, the significance level for model selection was set to $0.05/18 = 0.0028$.

After covariate selection, univariate voxelwise testing of multiple regression models was performed as implemented in the MANCOVAN toolbox and results were corrected for multiple comparisons within components using false discovery rate correction (FDR) with $\alpha < 0.05$ [Benjamini and Hochberg, 1995].

In networks significantly associated with BMI we investigated intra-network connectivity using mean cluster connectivity and network eigenvariate (EV) as proposed previously [Glahn et al., 2010]. Statistical analysis on connectivity measures was performed using multiple regression in SPSS 22.0 (IBM). Age, sex, APOE-e4 status, hypertension, diabetes, education, smoking status, and depression score were used as confounding variables.

Associations between BMI, BMI-associated differences in functional connectivity and cognitive performance were

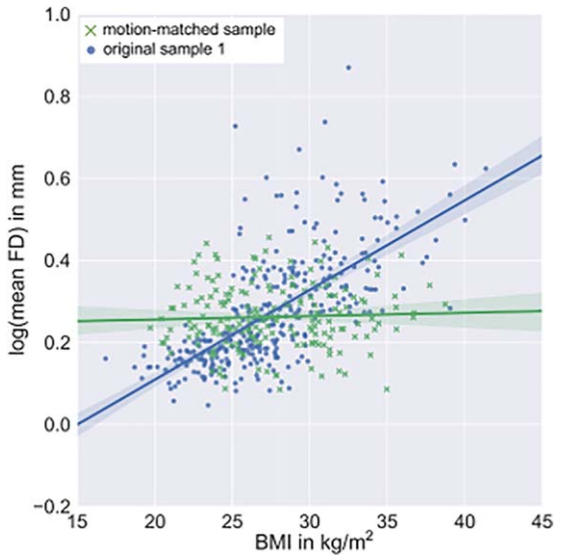

Figure 2.
Correlation of body mass index (BMI) and mean framewise displacement (FD) in the motion-matched sample (green) compared with sample 1 (blue): the strong positive correlation between BMI and mean FD has clearly been reduced. [Color figure can be viewed at wileyonlinelibrary.com]

explored without correction for multiple comparisons using bivariate and partial Pearson's correlations.

Confirmatory analysis

In a replication approach we investigated a second sample including 191 participants who had not been used in any prior analysis and had complete information of BMI, arterial hypertension, diabetes and education (sample 2). Subjects included in sample 2 were on average younger (independent samples *t*-test, $P = 0.005$) while exhibiting a comparable age range, and similar distributions of sex, BMI, mean FD, hypertension and diabetes (independent samples *t*-tests, Chi-squared test, all $P > 0.1$) (see Table I for details). Using FSL's DUAL REGRESSION we calculated subject-specific spatial maps for sample 2 based on components found in the main analysis of sample 1. We extracted the EV of those components that were significantly associated with BMI and calculated a multiple linear regression using a model containing age, sex, BMI, diabetes, arterial hypertension, and education. APOE-e4 status, depression score and smoking status were not available for all participants in the replication sample. Additionally, we estimated a voxelwise multiple regression model with the same covariates using permutation testing implemented in FSL's RANDOMISE. Results were corrected for multiple comparisons using FDR correction with $\alpha < 0.05$.

To overcome the collinearity between BMI and head motion which was noticed during preprocessing, we separated participants from sample 1 into three BMI-groups ($\mathrm{BMI} < 25\ \mathrm{kg/m^2}$, $25\ \mathrm{kg/m^2} < \mathrm{BMI} < 30\ \mathrm{kg/m^2}$, $\mathrm{BMI} > 30\ \mathrm{kg/m^2}$) and matched participants from each group for mean FD with an uncertainty of 0.02 mm. This yielded a sample of 186 participants in which BMI and mean FD no longer correlated (motion-matched sample, see Fig. 2). The resulting sample did not significantly differ from the original sample 1 in age, sex, BMI, APOE-e4 status, hypertension, diabetes, education, depression score, and smoking status (independent samples *t*-tests, Chi-squared test, all $P > 0.1$).

In order to verify that our results were independent of the number of independent components used, we repeated the analysis in sample 1 with 20 instead of 75 components.

RESULTS

RSN Components

Using independent component analysis, we identified 18 RSN components that belong to six commonly described networks, that is, attentional, default mode, frontal, sensorimotor, auditory, and visual network (see Fig. 3 for overview).

Multivariate Results

Multivariate backward model selection analysis of model 1 (including BMI, age, and sex) detected BMI as a significant predictor of functional connectivity strength in the default mode network components 29 and 42, and in the visual network component 25 (see Fig. 4). Backward model selection of model 2 including motion and registration parameters (i.e., FD and q_r) added q_r as a significant predictor for the components 29, 42, and 25.

Univariate Results

Univariate analysis using model 1 showed that higher BMI was significantly associated with decreased functional connectivity within the spatial maps of default mode components 29 and 42 ($P < 0.05$, FDR-corrected, adjusted for sex), more specifically in clusters located in the posterior cingulate cortex (PCC) and precuneus in component 29, and in the precuneus and left parietal cortex in component 42 (see Fig. 5).

We also found a BMI-associated increase of connectivity in visual network component 25. This cluster was located in the right precuneus and left lingual cortex (see Fig. 6).

For model 2 significant BMI effects on voxelwise network connectivity were again found in the PCC and precuneus within the default mode component 29 ($P < 0.05$, FDR-corrected, adjusted for sex and q_r). Effects in component 42 did not survive FDR-correction.

Adding q_r as a covariate into the model for visual component 25 did not change the univariate result showing positive correlations with BMI.

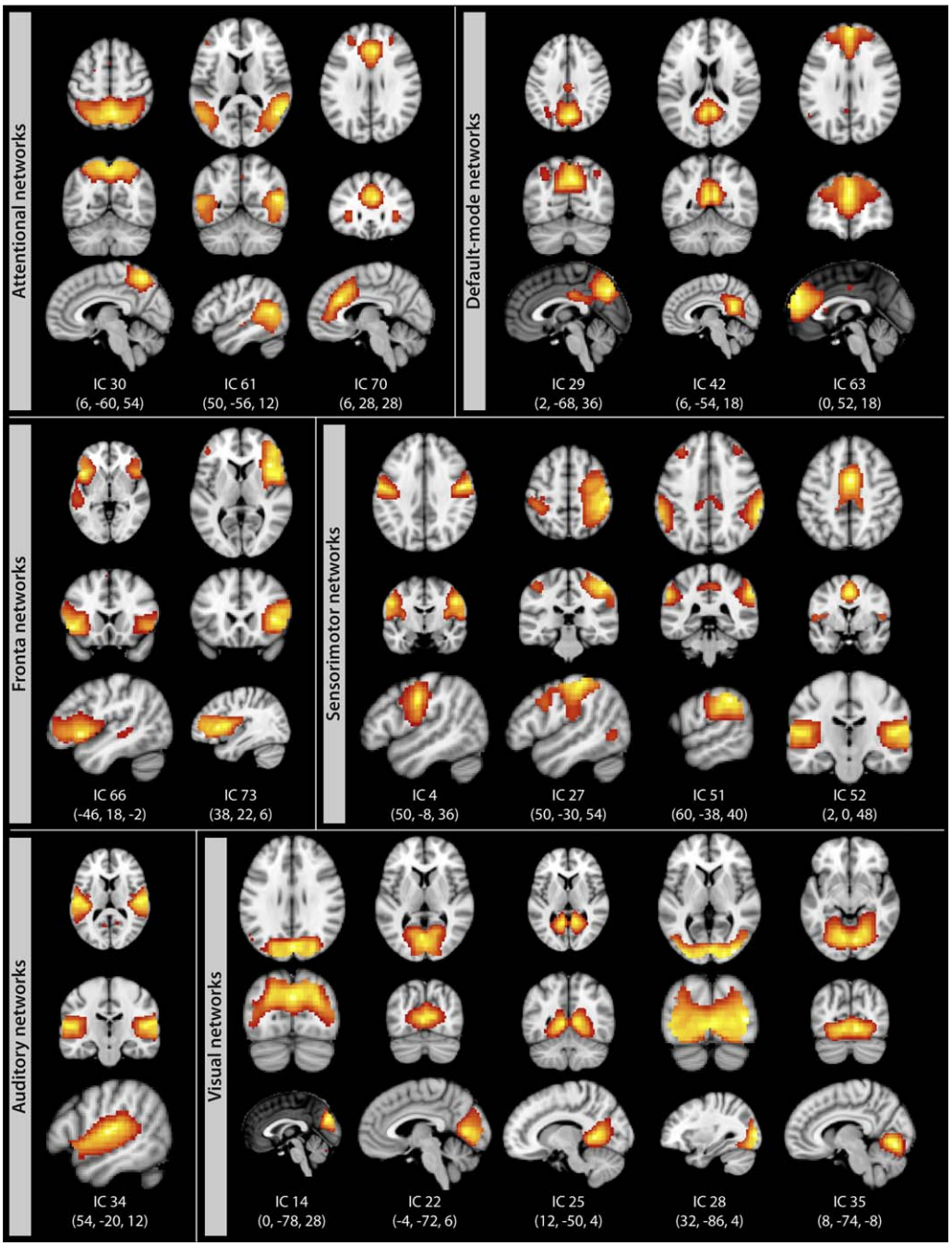

Figure 3.

Spatial maps (SM) of the 18 components identified as resting state networks: SM are plotted as *t*-statistics thresholded at $t > 12$ and displayed at the three most informative slices. Coordinates refer to the maximal *t*-value in MNI-space coordinates. [Color figure can be viewed at wileyonlinelibrary.com]

Analysis of Intra-Network Connectivity

In order to analyze if the association of BMI and posterior default mode network connectivity was independent of further known confounders, we used a multiple linear regression on the intra-network functional connectivity of the spatial maps and corrected for age, sex, APOE-e4 status, diabetes, hypertension, education level, smoking

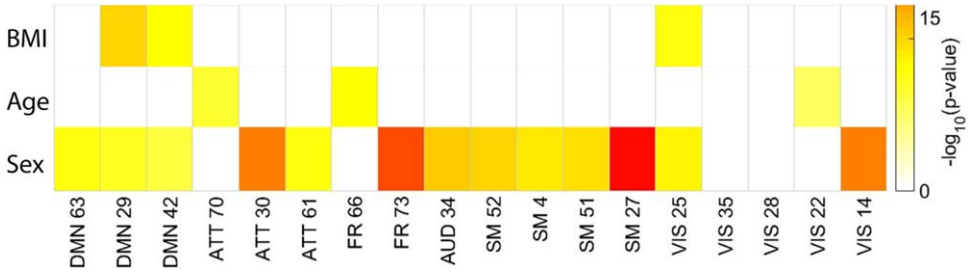

Figure 4.

Results from the multivariate analysis on 18 identified resting state network (RSN) components using Model 1 including BMI, age, and sex ($\alpha < 0.0028$). Colorscale indicates log(*P*), white cells indicate that covariates were removed from the full model during backward selection. [Color figure can be viewed at wileyonlinelibrary.com]

status, and depression score. Accordingly, BMI was significantly negatively associated with intra-network connectivity of default mode component 29, even after adjusting for confounders ($ß = -0.148$, $P = 0.001$, $R^2_{\text{adjusted}} = 0.075$, see Table II and Fig. 7). Age, smoking and APOE-e4 status were all negatively associated with intra-network connectivity (Age: $ß = -0.14$, $P = 0.002$, smoking status: $ß = -0.14$, $P = 0.001$, APOE-e4 status: $ß = -0.1$, $P = 0.018$), while hypertension, diabetes, education, and depression score did not contribute significantly to the model (see Table II).

This result remained stable when additionally including HbA1c as a covariate ($N = 516$, $\beta = -0.14$, $P = 0.002$, correcting for HbA1c, age, sex, APOE-e4 status, diabetes, hypertension, education level, smoking status, and depression score) and correcting for presence of hyperlipidemia ($N = 521$, $\beta = -0.15$, $P = 0.001$, correcting for age, sex, APOE-e4 status, hyperlipidemia, arterial hypertension, diabetes, BMI, education level, smoking status, and depression score). We also included mean GMV within component 29 and total cortical GMV into the model to correct for possible effects of reduced GMV in the region of interest and globally, which did not attenuate the results ($\beta = -0.145$, $P = 0.001$, linear regression on EV of posterior DMN 29, corrected for age, sex, diabetes, hypertension, APOE-e4-status, depression score, smoking-status, education, mean GMV in DMN 29, and mean global GMV). Total mean GMV was significantly associated with BMI (partial correlation coefficient $\rho = -0.12$, $P = 0.005$, corrected for age and sex) while mean GMV within

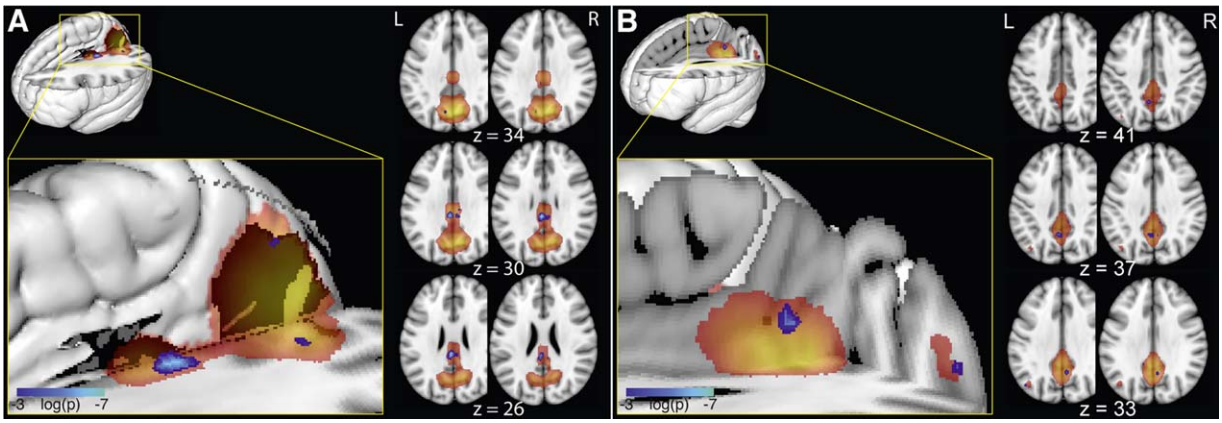

Figure 5.

Higher BMI is associated with decreased posterior default mode network connectivity. A: Decreased functional connectivity in default mode network component 29 is found in clusters in the posterior cingulate cortex (PCC) and precuneus. Blue color map represents log(*P*)-values of significant voxels ($P < 0.05$, FDR corrected, using model 1: main BMI effect correcting for sex). MNI coordinates of peak voxel in component 29 in the PCC is (−3, −33, 27). Red color map represents the spatial map of the component. B: Decreased functional connectivity in default mode network component 42 is found in clusters in the precuneus and parietal cortex. Blue color map represents log(p)-values of significant voxels ($P < 0.05$, FDR corrected, using model 1: main BMI effect correcting for sex). MNI coordinates of peak voxel in the precuneus: (−3, −54, 26). Red color map represents the spatial map of the component. [Color figure can be viewed at wileyonlinelibrary.com]

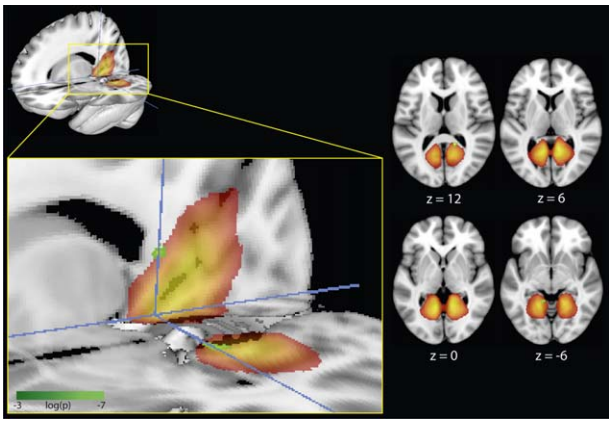

Figure 6.

Association of higher BMI with increased connectivity: In visual network component 25 higher BMI is associated with increased functional connectivity. Green color map represents log(*P*)-values of significant voxels ($P < 0.05$, FDR corrected, using model 1: main BMI effect correcting for sex). MNI coordinates of peak voxel is (15, −45, 22). Red color map represents the spatial map of the component. [Color figure can be viewed at wileyonlinelibrary.com]

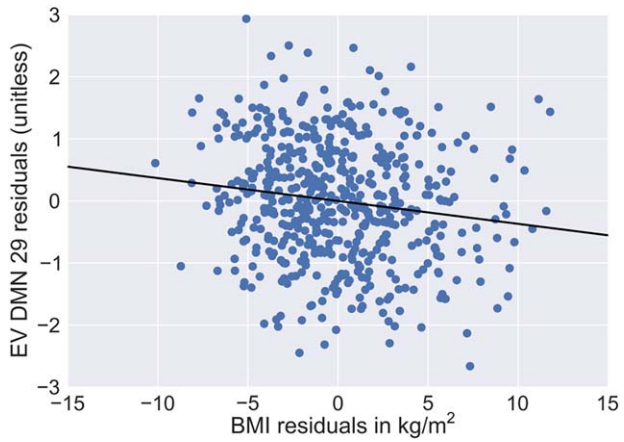

Figure 7.

Association of higher BMI and reduced connectivity after controlling for genetic and environmental confounders: Linear regression of BMI and intra-network functional connectivity of default mode network component 29, controlling for age, sex, APOE-e4 status, hypertension, diabetes, education, smoking status, and depression score. [Color figure can be viewed at wileyonlinelibrary.com]

component 29 was not ($\rho = -0.023$, $P = 0.6$, corrected for age and sex). BMI was not significantly associated with intra-network connectivity of the visual component 25 when correcting for age, sex, APOE-e4 status, diabetes, hypertension, education level, smoking status, and depression score ($\beta = 0.056$, $P = 0.22$, $R^2_{adjusted} = 0.027$).

Associations with Cognitive Performance

Higher BMI was significantly correlated with lower executive performance ($r = -0.11$, $P = 0.015$), even when adjusting for age and sex (partial correlation coefficient $\rho = -0.10$, $P = 0.02$). In addition, higher mean cluster connectivity in the PCC of component 29 was associated with higher executive function ($\rho = 0.10$, $P = 0.03$, corrected for age and sex) although the association became non-significant when additionally controlling for BMI ($\rho = 0.075$, $P = 0.09$). We also observed lower memory performance to be associated with lower PCC cluster connectivity ($r = 0.11$, $P = 0.009$); however, without reaching statistical significance when correcting for age and sex (PCC-ROI: $\rho = 0.06$, $P = 0.17$).

TABLE II. Results of multiple regression performed on EV of DMN component 29 (standardized regression coefficient β, *t*-value *t*, and *P*-value) ($R^2_{adjusted} = 0.074$)

	β	t	P
BMI	−0.15	−3.35	0.001
Age	−0.14	−3.16	0.002
Sex	−0.04	−0.78	0.44
APOE−e4 status	−0.1	−2.37	0.02
Arterial hypertension	0.04	0.81	0.42
Diabetes	−0.034	−0.78	0.44
Education	0.009	0.19	0.84
Smoking status	−0.14	−3.21	0.001
Depression score	−0.06	−1.23	0.21

Confirmatory Analyses

In the replication sample, we found a significant association of higher BMI and lower intra-network connectivity of DMN $29_{sample2}$ (BMI: $\beta = -0.29$, $P < 0.001$, with age, sex, diabetes, arterial hypertension, and education as covariates). In an additional voxelwise analysis we found BMI-associated connectivity reductions to be located mainly in precuneus (significant at $P < 0.05$, whole brain FDR corrected, see Fig. 8) correcting for age, sex, diabetes, arterial hypertension, and education.

We observed in part strong effects of the head motion parameter mean FD on RSN connectivity in the multivariate analysis and found BMI and mean FD to be highly collinear. We, therefore, conducted a sensitivity analysis in a motion-matched sub-sample. Here again, according to linear regression, higher BMI correlated significantly with lower mean connectivity in the cluster previously identified in the PCC ($\beta = -0.18$, $t = -2.48$, $P = 0.014$, correcting for age, sex, APOE-e4 status, diabetes, hypertension, education level, smoking status, depression score, and mean FD). Mean FD was also negatively correlated with reduced connectivity ($\beta = -0.16$, $t = -2.1$, $P = 0.03$).

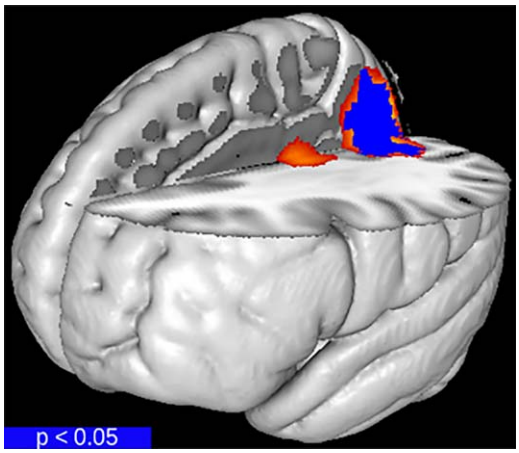

Figure 8.
In the replication sample 2, higher BMI is associated with decreased connectivity of dual-regression derived DMN 29. Blue color map represents p-values of significantly associated voxels ($P < 0.05$, FDR corrected, adjusted for age, sex, hypertension, diabetes, and education). RSN spatial map is shown in red. [Color figure can be viewed at wileyonlinelibrary.com]

We also repeated the ICA with a model order of 20 and found higher BMI to be associated with reduced precuneus and PCC connectivity in a default mode network component (data not shown), which is in line with our initial finding and shows that the result does not depend on the number of extracted independent components.

DISCUSSION

In this study, we detected significant negative associations of BMI and DMN connectivity in the PCC and precuneus using 3T resting-state fMRI in a large cohort of healthy older adults. These findings were independent of age, sex, obesity-associated co-morbidities and other confounders, and remained stable in replication analyses. In addition, posterior default mode connectivity correlated with executive function.

Functional Connectivity and Obesity in Aging

Our main finding is a reduction of posterior default mode connectivity with higher BMI. This effect was found in the main sample (n = 521), in a ROI-based analysis of a motion-matched subgroup (n = 186), as well as in an independent replication sample in the same age range (n = 191), underlining the robustness of the association.

Our finding is in line with and extends a recent report in which lower DMN connectivity was associated with higher BMI in a young sample but no differences of DMN functional connectivity in siblings with differing obesity status were found, indicating the connectivity differences to be subsequent, not prior to the development of obesity [Doucet et al., 2017]. In addition, previous studies on cardiovascular risk factors in middle-aged samples have linked insulin resistance and type 2 diabetes to alterations in default mode connectivity [Buckner et al., 2008; Kenna et al., 2013; Musen et al., 2012]. Notably, decreased default mode connectivity has also been reported in young individuals at risk for Alzheimer's disease (AD) such as APOE e4-carriers, and in older MCI patients [Sheline et al., 2010; Sorg et al., 2007]; moreover several studies suggest that modifiable AD risk factors are linked to alterations in DMN connectivity [Buckner et al., 2008; Kenna et al., 2013; Musen et al., 2012]. Thus, our results suggest an association of obesity and connectivity changes similar to those seen in populations at risk for AD, and support the view of obesity being a risk factor for dementia [Beydoun et al., 2008; Kivipelto et al., 2005].

This view, however, is controversially discussed. While a recent meta-analysis reported that being obese below the age of 65 increased the risk of dementia and being obese above this age lowered dementia risk [Pedditizi et al., 2016], it was also reported that the incidence of dementia decreased with increasing BMI [Qizilbash et al., 2015] and that weight loss in mid-age independent of weight status was associated with increased risk of dementia three to four decades later [Strand et al., 2017]. Selection bias and reverse causation have been proposed to contribute to these contradictory results: obesity is strongly associated with cardiovascular risk factors which are themselves risk factors for dementia [Skoog et al., 1996] as well as overall mortality risk [Stevens et al., 1998] and weight loss 10–20 years before onset of dementia is well known [Knopman et al., 2007]. Our sample solely comprised healthy, cognitively intact older adults with a narrow age range between 67 (1. quartile) and 72 (3. quartile). Half of the sample was younger than the postulated reverse point of 70 years [Gustafson et al., 2009] and only very few were considerably older. This leads us to believe that our sample represents subjects vulnerable to the adverse effects of obesity on cognition who have not yet experienced prodromal dementia-related weight loss. Other studies reporting BMI to be associated with gray matter volume decline and cognitive deficits in old-age [Kharabian Masouleh et al., 2016; Walther et al., 2010] support this association of obesity and brain damage in older subjects.

In line with the literature, we found APOE-4 genotype to be independently associated with precuneus DMN connectivity [Sheline et al., 2010]. Opposed to a previous finding in individuals above the age of 70 years [Bäckman et al., 2015], there was no significant interaction of BMI and APOE-4 status. The modifiable risk factor obesity and the genetic risk factor APOE-4 might thus be associated with similar patterns of decreased posterior DMN connectivity, hinting to a common mechanism such as dysregulated lipid metabolism [Chouinard-Watkins et al., 2015; Romas et al., 1999; Sheline et al., 2010].

Our results remained significant when correcting for age, sex, obesity-associated co-morbidities arterial hypertension and diabetes, and other confounders. This indicates that the association is not primarily due to conditions frequently associated with obesity and known to affect brain structure and function [Jennings and Zanstra, 2009; Moheet et al., 2015].

We found the association of BMI and reduced posterior default mode connectivity to be independent of GMV reductions in the context of pathological aging and did not observe an association of DMN GMV with BMI. In the literature, mixed associations for BMI and precuneus/posterior cingulate cortex gray matter volume have been reported [Willette and Kapogiannis, 2015], leaving the interplay of gray matter volume and functional connectivity strength a matter of debate. Functional connectivity within the DMN is thought to be based on white matter connections between its anterior and posterior regions [Greicius et al., 2008] and decreased functional connectivity could thus be a result of decreased white matter fiber integrity. Obesity has been shown to be associated with reduced indices of white matter microstructure within the limbic system and in other regions [Kullmann et al., 2015] and recently higher BMI was associated with decreased white matter volume in a stereotactic white matter mask of the DMN [Figley et al., 2016]. Upcoming longitudinal studies thus need to further disentangle if obesity-associated white matter microstructural changes within the DMN precede or follow observed obesity-associated decreases in functional connectivity.

Concerning further associations of BMI and functional connectivity, only the visual network was found to be associated with higher BMI, but the extent of increased connectivity was very limited. In our large cohort, we did not observe previously reported increased putamen and insula connectivity [Hogenkamp et al., 2016], decreased insula–anterior cingulate cortex (ACC) connectivity [Moreno-Lopez et al., 2016], increased salience network connectivity [Figley et al., 2016; Garcia-Garcia et al., 2013], reduced temporal lobe network connectivity [Kullmann et al., 2012] or increased DMN connectivity [Kullmann et al., 2012; Legget et al., 2016; Tregellas et al., 2011] with higher BMI. Similar to our results, one study reported reduced precuneus connectivity for obese compared with lean participants, although the results might have been confounded by the significant age difference between groups [Geha et al., 2016]. In a recent study with 496 participants, DMN cohesiveness has been shown to be reduced in young, obese compared with lean individuals, with highest effect size found for the posterior DMN component which is in line with our results. A siblings analysis suggested this to be a consequence rather than a driving factor of obesity [Doucet et al., 2017].

Taken together, our results only partly replicate these findings obtained in young participants (age <40 years); this might be due to an interaction of obesity and aging in the brain potentially involving changes in eating behavior [Elsner, 2002] and levels of circulating hormones such as leptin [Isidori et al., 2000; Moller et al., 1998]. Also, the negative effects of obesity on the brain are probably not detectable at young age but accumulate proportionally to "obesity pack-years" [Abdullah et al., 2011].

The only study investigating obesity and resting state connectivity in aged individuals showed that lower DMN activity during a finger-tapping task in older obese compared with lean participants predicted better working memory performance 12 months later [Hsu et al., 2015]. The authors argued that functional connectivity of the DMN might be a neuroprotective mechanism of higher BMI. Considering the mean sample age of 75 years and the steeper decline in cognitive scores within the normal weight group, we would rather consider this to be an effect of reverse causation. Interestingly, baseline cognitive scores were significantly lower for the overweight and obese groups compared with the lean group which fits to the notion of higher BMI exerting negative effects on the brain in mid-to-late-life.

Cognitive Performance

We observed BMI-associated connectivity changes in a region which is considered to be affected early during cognitive decline [Sorg et al., 2007]. Our results show that both higher BMI and lower mean connectivity in the BMI-associated cluster within the PCC of DMN 29 correlated with slightly worse performance in the memory and more so in the executive domain. Several studies indicate that the DMN plays an important role not only in episodic memory, but also in executive function, as its successful deactivation is predictive of performance in attention and working memory tasks [Daselaar et al., 2004; Wang et al., 2007; Weissman et al., 2006]. Thus, we speculate that a higher BMI in older age might exert negative effects on posterior DMN connectivity, which eventually translate into subtle cognitive impairments. Future longitudinal studies are needed to further test this hypothesis.

Effects of Head Motion

As motion has been shown to exert massive and widespread effects on connectivity [Power et al., 2015] we aimed to account for motion by (1) adding mean FD as a covariate into the multivariate backward model selection and by (2) selecting a sub-sample in which motion and BMI were not correlated. Notably, BMI was retained in the backward model selection process even after including mean FD as a covariate and it remained a significant predictor of reduced PCC intra-network connectivity in the motion-matched sample. This leads us to conclude that there is an association of BMI with posterior default mode connectivity independent of confounding motion effects.

It has also been suggested that by using the common approach of strictly correcting for the effects of motion one might remove information related to the phenotype under study. Along this line, inter-individual differences in motion have been explained by a neurobiological trait of long-range default mode connectivity [Zeng et al., 2014] and head motion has been shown to positively correlate with impulsivity [Kong et al., 2014]. As elevated BMI has been linked to increased impulsivity [Braet et al., 2007], the BMI-related motion increase found in our cohort might not be simply due to increased discomfort during the scan (thereby confounding BMI-related analyses), but reflect an obesity-related trait. This is further supported by recent findings of common genetic factors associated with head motion and BMI that have been reported in two large cohorts [Hodgson et al., 2016]. Thus, disentangling the effects of BMI and motion remains difficult and merits careful investigation in future studies.

Limitations

Several limitations should be considered when interpreting our results. First, our cross-sectional data does not allow us to draw conclusions on the causal relationship between BMI and posterior default mode connectivity and the underlying mechanisms should be carefully studied in longitudinal designs. We demonstrated that the described association of BMI and connectivity was not solely driven by head motion differences, however head motion was a major confounder in this study and it remains unclear whether it is inherently associated with obesity. Physiological parameters [Glover et al., 2000] were not measured and related noise could thus not be controlled for.

In addition, spatial normalization accuracy might be limited in large samples like ours which might have biased our results. However, besides controlling for registration quality as a confounder, we generally achieved a high registration quality through state-of-the-art registration tools [Klein et al., 2009] and careful visual inspection that led to exclusion of subjects with morphological alterations such as calcifications or atrophies/large ventricles as well as brain extraction failures. Another limitation is the definition of obesity by BMI, as this does not reflect age-related changes in body composition, such as conversion of lean body mass to fat [Zamboni et al., 2005]. A more precise measure of body fat (such as MRI-assessment of abdominal fat) would have allowed us to characterize the relationship between obesity and resting-state connectivity more specifically. Our analysis of the associations between BMI, connectivity and cognitive performance was exploratory and should thus be expanded to gain more insight into the cognitive implications of our result. An important strength of this study is that it relies on a large sample size of community-based well-characterized healthy older adults, supplemented by a homogenous replication sample. Also, various potential confounders were comprehensively assessed and controlled for. Our results remained significant when correcting for age, sex, hypertension, diabetes and other confounders, but the high covariance of BMI and obesity-associated comorbidities make it difficult to disentangle their contributions to functional connectivity differences in our cross-sectional design.

CONCLUSION

In the current study we showed that higher BMI is associated with reduced connectivity of the default mode network in the PCC and in the precuneus in a large sample of healthy older adults. This finding was independent of obesity-related comorbidities, changes in regional gray matter volume and APOE-e4 genotype. Moreover, our results indicate that regional changes in default mode connectivity translate into subtle differences in cognitive performance.

Thus, our results support the view that obesity might independently contribute to accelerated brain aging in older individuals without incident dementia, as lower default mode connectivity has been detected in populations at risk for AD, and it has been proposed as an early biomarker for emerging AD [Sorg et al., 2007]. The modifiable risk factor obesity might thus share the pattern of decreased posterior default mode connectivity with the unmodifiable risk factor APOE-e4 allele [Sheline et al., 2010]. Future studies should further investigate potential mechanisms underlying the association of obesity and resting state connectivity and infer obesity-preventing strategies to maintain cognitive function in aging.

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