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Brain structural differences in monozygotic twins discordant for body mass index

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A B S T R A C T

Background: Substantial efforts have been made to investigate the neurobiological underpinnings of human obesity with a number of studies indicating a profound influence of increased body weight on brain structure. Although body weight is known to be highly heritable, uncertainty remains regarding the respective contribution of genetic and environmental influences.

Methods: In this study we used structural magnetic resonance imaging (MRI) data from the Human Connectome Project (HCP). Voxel-based morphometry (VBM) was applied to study BMI-associated differences in gray matter volume (GMV) within monozygotic (MZ) twin pairs discordant for BMI ($\Delta BMI > 2.5\ kg*m^{-2}$, $n = 68$ pairs). In addition, we investigated the relationship of ΔBMI (entire range) with GMV differences within the entire sample of MZ twin pairs ($n = 153$ pairs).

Results: Analyses of BMI discordant twin pairs yielded less GMV in heavier twin siblings ($p < 0.05\ FWE_{TFCE}$; paired *t*-Test) within the occipital and cerebellar cortex, the prefrontal cortex and the bilateral striatum including the nucleus accumbens. A highly converging pattern was found in regression analyses across the entire sample of MZ twin pairs, with ΔBMI being associated with less GMV in heavier MZ twins.

Conclusion: While MZ twins share the same genetic background, our findings indicate that non-genetic influences and the mere presence of a higher BMI constitute relevant factors in the context of body weight related structural brain alterations.

1. Introduction

Overweight and obesity remain a worldwide health concern, particularly in industrialized countries (Abarca-Gómez et al., 2017).This obesity epidemic can be largely ascribed to an obesogenic environment that promotes a behavioral phenotype characterized by unhealthy eating patterns and a sedentary lifestyle (Cecchini et al., 2010; Chaput et al., 2011). With behavior being the driving force behind the development of adiposity, increasing efforts have been made to enhance our understanding of associated neurobiological mechanisms. Considerable evidence indicates altered function of mesolimbic and mesocortical dopaminergic reward pathways as a potential mechanisms which - on a behavioral level – results in compensatory increases in reward-related behavior (e.g. eating palatable foods; Berridge et al., 2010; Kenny, 2011; Volkow et al., 2013). Evidence exists that the neurobiological underpinnings that underlie body weight homeostasis and associated behavioral phenotypes are somewhat genetically determined (e.g. Heni et al., 2014; Ho et al., 2010; Vainik et al., 2018; Weise et al., 2017), yet a number of intervention studies point to a dynamic interaction of potential mechanisms (e.g. Dunn et al., 2010; Karlsson et al., 2016; Prehn et al., 2016; Rullmann et al., 2018; Tuulari et al., 2016). In the past decade numerous studies investigated body weight related brain morphological changes, mostly showing reduced gray matter volume (GMV) of distinct brain regions in overweight and obese but also underweight individuals (e.g. Horstmann et al., 2011; Kurth et al., 2013; Pannacciulli et al., 2006; Taki et al., 2008; Walther et al., 2010; Titova et al., 2013). However, the cross-sectional design of the majority of these studies does not allow drawing any conclusions regarding the origin of these changes. We previously showed that brain regions associated with adiposity underlie varying degrees of heritability, indicating that some of these regions might constitute risk factors for obesity in the sense of a predisposing endophenotype (Weise et al., 2017). Nevertheless, due to the descriptive nature of these observations, a cautious interpretation is required, as this approach does not have the potential to establish causality. In contrast, studies of MZ twins discordant for a specific trait have the potential to identify environmental effects in the absence of genetically determined differences.

Therefore, we sought to follow up on our previous study by investigating brain structural differences in MZ twins discordant for body mass index. However, this approach implies the analyses of sibling pairs where both individuals may share – according to BMI criteria - a similar weight status. Therefore, our findings primarily reflect brain structural

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differences in relation to BMI differences - independently of genetic predispositions - but not structural differences between lean and obese siblings in the narrower sense. Here, we hypothesized that heavier MZ siblings – compared to their leaner counterparts - would exhibit reduced gray matter volume of brain regions within mesocorticolimbic pathways involved in eating and reward related behavior. To do so, we analyzed data from the Human Connectome Project, a large-scale study of twin and non-twin individuals with the goal to identify genetic and environmental influences on the central representation of behavioral aspects by applying multimodal neuroimaging methods (Van Essen et al., 2013).

2. Methods

2.1. Study population

For this study, we analyzed data from the publicly available Human Connectome Project (HCP) database (www.humanconnectome.org). The HCP sample is composed of a total of n = 1206 healthy young to middle-aged adults and contains data from non-twin siblings, monozygotic (identical) and dizygotic (fraternal) twins. For a detailed description of eligibility criteria and study protocols, we refer to previously published work (Van Essen et al., 2012, 2013). Complete structural MRI and BMI data of each individual monozygotic twin sibling were available for n = 153 twin pairs. Twin status was defined based on selfreport (n = 15) and genetic testing (n = 138). All individuals' height and weight were measured upon intake on the first visit day and BMI was calculated as body weight divided by height squared (kg/m^2). In addition, BMI deltas were calculated as BMI MZ1 minus BMI MZ2. Measures of submaximal cardiovascular endurance were obtained by a 2-min walking test (i.e. walking distance; unadjusted scale score with mean = 100) as part of the NIH toolbox (for details see www.healthmeasures.net). For this study, we analyzed data from the entire sample of n = 153 MZ twin pairs and from a subsample of n = 68 BMI-discordant MZ twin pairs. Here, BMI-discordance was defined as an absolute BMI difference of $\geq$2.5 $kg*m^{-2}$ (Robciuc et al., 2011). All participants gave written consent and experimental procedures were approved by the institutional review board (IRB # 201204036; Title: 'Mapping the Human Connectome: Structure, Function, and Heritability'). No additional approval for the analyses of openly available data was required by local institutions.

2.2. Imaging procedures

Structural imaging protocols are specified in previous publications (Van Essen et al., 2013) and can be found on the website of the HCP (www.humanconnectome.org). In short, two separate high resolution T1-weighted, 3D MPRAGE anatomical images with 0.7-mm isotropic voxels were acquired on a customized Siemens 3-T Skyra system (32-channel head coil; Siemens, Germany). Imaging parameters were the following: FOV = 224 mm, matrix = 320, 256 sagittal slices per single slab, TR = 2400 ms, TE = 2.14 ms, TI = 1000 ms, FA = 8°, Bandwidth (BW) = 210 Hz per pixel, Echo Spacing (ES) = 7.6 ms. For our study, data from the first scan only were analyzed.

2.3. Data analysis

We used VBM8 (http://dbm.neuro.uni-jena.de/vbm.html) and the Statistical Parametric Mapping package (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm) for voxel-based morphometry of anatomical images. Preprocessing of T1 MPRAGE images was performed with default settings, which include high-dimensional DARTEL normalization algorithms and modulation for non-linear components, thus not requiring additional correction for potential differences in intracranial volume. Preprocessing steps include the segmentation of whole brain images into gray matter (GM), white matter, and cerebrospinal fluid and the normalization to the DARTEL template in MNI space (voxel size: 1.5 mm × 1.5 mm × 1.5 mm). Next, GM data was smoothed with an 8 mm full-width half-maximum isotropic Gaussian kernel. Quality control was performed automatically as implemented in the VBM8 toolbox and by visual inspection of the preprocessed images via SPM's CheckReg function. In order to identify relevant artifacts all images were perused in the axial, sagittal and coronal plane. Paired t-tests of smoothed GM data were used to investigate differences in regional GMV between BMI discordant twins (i.e. leaner sibling vs. heavier sibling). In addition, for each twin pair, delta images were acquired by subtracting the individual smoothed GM images using SPM's ImCalc function. Multiple regression analyses were used to investigate the associations between the BMI delta of each twin pair with the respective delta image of GMV differences. Here, age and gender were included as regressors of no interest to account for the corresponding nuisance variance. Additional post-hoc analyses were performed with measures of endurance as further covariate (i.e. absolute values for paired t-tests and delta values for regression analyses). Detailed results are provided as supplementary material. Statistical significance was determined using the Threshold-Free Cluster Enhancement (TFCE) toolbox (dbm.neuro.uni-jena.de), which offers a nonparametric permutation-based statistical approach that does not require arbitrarily defined voxel-wise or cluster thresholds (Smith and Nichols, 2009). TFCE-based analyses were performed with 5000 permutations and results were considered significant at $p < 0.05$ family-wise-error (FWE) corrected for the entire brain volume. Anatomical locations of VBM results were determined using MNI to Talaraich Coordinate conversion as implemented in GingerAle (www.bioimagesuite.org) and the Talaraich Client (Lancaster et al., 2000). Non-imaging data was analyzed with SAS Software (SAS Institute Inc., version 9.4, Cary, NC).

3. Results

From 153 pairs of MZ twins we identified 68 pairs with a BMI difference >2.5 $kg*m^{-2}$. Table 1 lists basic subject characteristics for weight discordant MZ twins and the entire sample of MZ twins. Expectedly, BMI was significantly different in weight discordant MZ twins ($p < 0.0001$) but no significant differences were observed for education, measures of fluid intelligence and measures of endurance (all $p \geq 0.49$).

Paired t-tests of weight discordant MZ twin pairs showed reduced GMV of several cortical and subcortical brain regions ($p < 0.05$ FWE_{TFCE}) in heavier MZ twin siblings compared to their leaner siblings, most prominently within the occipital cortex and the cerebellum, the ventromedial prefrontal cortex (i.e. subgenual cingulate) and neighboring subcortical structures (i.e. bilateral caudate nucleus and nucleus accumbens). Further regions included the right medial frontal gyrus together with adjacent parts of the cingulate gyrus and the left middle frontal gyrus within the orbitofrontal cortex (see Fig. 1 and Table 2 for detailed results). In contrast, no significant reductions in GMV were

Table 1
Descriptive statistics of all monozygotic twins and BMI discordant monozygotic twins.

	All MZ (n = 306/153 pairs)	BMI discordant MZ (n = 136/68 pairs)
Age in years	29.40 (±3.37)	29.60 (±3.17)
Gender (m/f)[a]	120/186	44/92
Ethnicity (white/non-white)[a]	258/48	116/20
BMI (kg/m^2)	26.30 (±4.69)	27.54 (±4.93)
ΔBMI (kg/m^2)[b]	−2.77 (±2.59)	−4.84 (±2.59)
Education, years	14.99 (±1.87)	14.79 (±1.94)
Fluid Intelligence (PMAT)	16.91 (±4.56)	16.21 (±4.71)
Endurance	111.37 (±12.27)	107.50 (±10.80)
ΔEndurance [b]	0.03 (±11.30)	0.87 (±10.33)

Results are listed as mean ± SD except for[a]. [b] Mean differences (leaner sibling minus heavier sibling). *PMAT* Penn Progressive Matrices (number of correct responses; for details see www.humanconnectome.org).

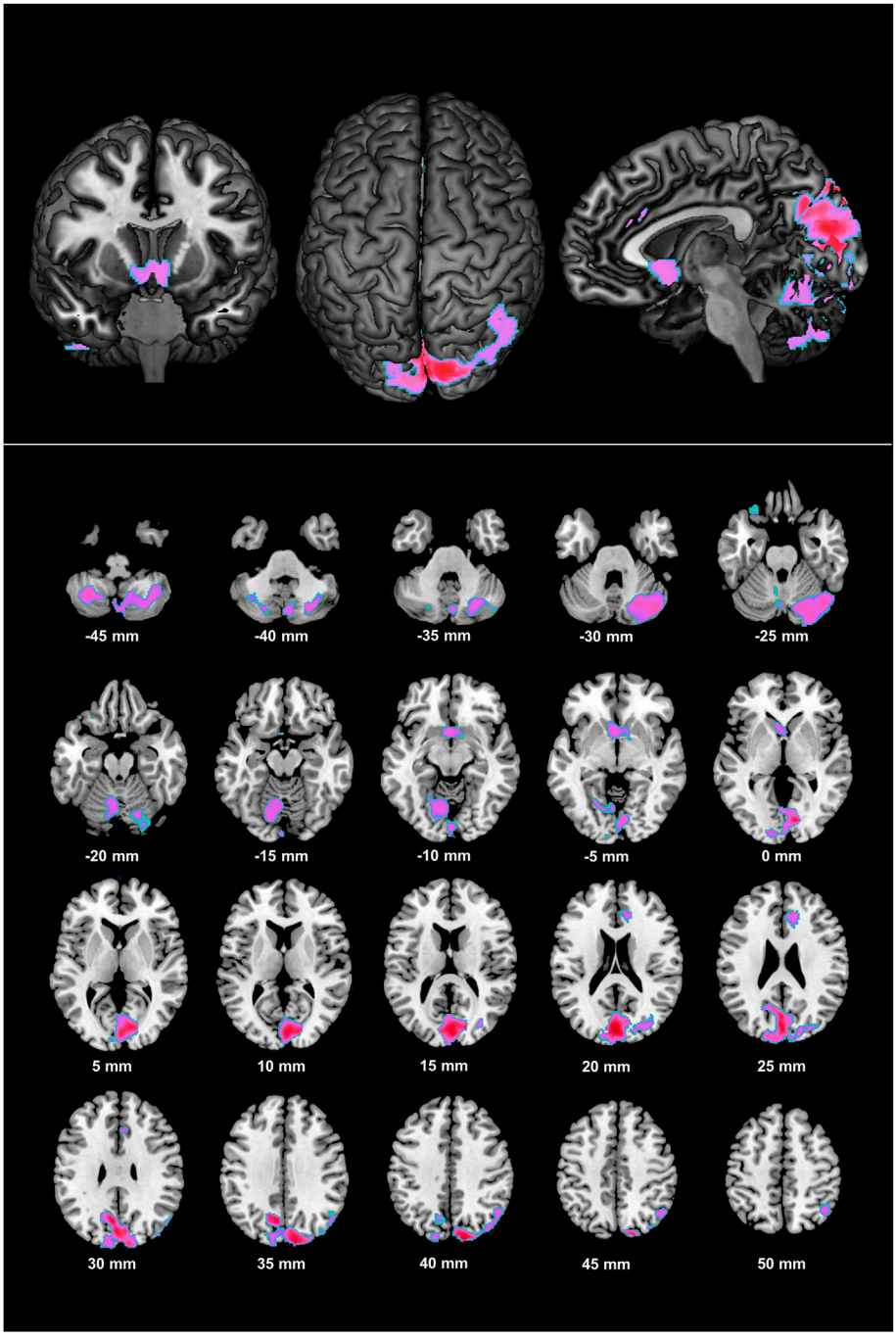

Fig. 1. Brain morphometric differences in weight discordant monozygotic twins. The upper panel shows brain regions with significantly lower GMV (paired T-test; $p < 0.05$ FWE_{TFCE}) in heavier vs. leaner MZ twins on a three-dimensional rendered brain. The lower panel illustrates the results in the axial plane with the corresponding locations on the z-axis indicated below each section.

observed in leaner MZ twin siblings compared to the heavier sibling. Removal of MZ twin pairs without genetic verification (N = 8 pairs) did not significantly change these results (data not shown).

Within the whole group of MZ twin pairs (n = 153 pairs), additional multiple regression analyses using the GMV delta images of each individual MZ twin pair (i.e. ΔGMV) yielded a very similar pattern of inverse associations with the BMI difference (i.e. ΔBMI) of the respective twin pair (see Fig. 2 and Table 3 for detailed results).

Further adjustment for measures of endurance did not significantly change these results (see Supplementary Figs. S1–2 and Supplementary Tables S1–2).

4. Discussion

One prevailing question in obesity research is to which extent the obese phenotype is driven by heritable as compared to environmental influences. In order to address this question, we investigated differences in brain structure of 68 pairs of MZ twins discordant for BMI. Here, heavier MZ twins compared to their leaner siblings presented reduced GMV within brain regions involved in valuation and reward processes – important cognitive mechanisms required to control food choices and eating behavior (Hollmann et al., 2013).

Significant GMV differences were found in the (pre-)frontal cortex and subcortical structures, such as the subgenual cingulate together with

Table 2
Brain morphological differences in weight discordant monozygotic twins.

	Brain Region, BA	*k*	pFWE[a]	MNI x	MNI y	MNI z
Leaner Twin > Heavier Twin						
L	**Cuneus, BA 18**	**10201**	**0.001**	**0**	**−82**	**19**
R	Cuneus, BA 19		0.001	14	−88	40
R	Lingual Gyrus, BA 18		0.002	3	−87	9
R	**Cerebellum, Tuber**	**4845**	**0.011**	**44**	**−73**	**−29**
R	Cerebellum, Pyramis		0.012	26	−69	−29
R	Cerebellum, Uvula		0.013	32	−81	−26
L	**Cerebellum, Cerebellar Tonsil**	**799**	**0.012**	**−30**	**−57**	**−45**
L	Cerebellum, Cerebellar Tonsil		0.026	−20	−61	−47
L	Cerebellum, Inf. Semi-Lunar Lobule		0.042	−22	−72	−41
L	**Anterior Cingulate, BA 25**	**797**	**0.022**	**−2**	**9**	**−11**
R	Caudate		0.037	10	8	−8
R	**Medial Frontal Gyrus, BA 9**	**383**	**0.026**	**16**	**35**	**25**
R	Cingulate Gyrus, BA 32		0.026	8	33	25
L	**Middle Frontal Gyrus, BA 11**	**56**	**0.040**	**−27**	**27**	**−24**

BA Brodmann area; MNI Montreal Neurological Institute.
Bold data indicate primary peak within a cluster; Non-bold data indicate secondary peaks.
[a] Results are listed at a threshold of $p < 0.05$ FWE TFCE corrected.

bilateral caudate nucleus and nucleus accumbens (NAcc). The subgenual cingulate is densely connected to a number of brain regions implicated in the regulation of food intake and energy balance - including the hypothalamus and the solitary nucleus - and is thought to have a central function in visceromotor control (Freedman et al., 2000). The NAcc – a dopamine-rich region within the mesolimbic pathway and part of the ventral striatum – is a crucially important brain structure in the context of food intake and reward related motivated behavior in general (Corbit and Balleine, 2016; Salamone et al., 2016; Volkow et al., 2013), playing a preferential role in encoding the value of food related cues (Small et al., 2008, 2001). Consequently, NAcc activation in response to food cues has been shown to predict snack consumption and higher BMI in subjects with low self-control (Lawrence et al., 2012). The caput caudatum on the other hand - as part of the dorsal striatum - rather responds to ingestion of food and has been implicated in its devaluation by food intake in the absence of hunger (Small et al., 2001). Intriguingly, its activation in response to food intake has been related to current and future increases in body mass (Stice et al., 2008). Obesity and addictive disorders appear to share pathophysiological mechanisms with similar striatal responses in the presence of food related rewards and drugs of abuse (Volkow et al., 2013). Increased craving and blunted reward responses to palatable, high-caloric foods have been observed in obese subjects, a constellation believed to promote compensatory overeating (Stice et al., 2008), presumably due to dopaminergic dysfunction. Making use of an HCP subsample, a recent fMRI study showed stronger network connectivity in low-BMI MZ twins, including brain regions within mesocorticolimbic dopaminergic pathways (Sadler et al., 2018), while rodent studies found reduced dopamine release within the NAcc and the dorsal striatum in rats with diet-induced obesity as compared to normal weight animals (Geiger et al., 2009). Collectively, these and our findings suggest a dynamic development of dopaminergic dysfunction in relation to body weight increases with environmental influences being a relevant factor. Within the frontal lobe, we also identified effects in the medial frontal gyrus reaching into adjacent parts of the cingulate gyrus. This area is involved in cognitive processes spanning from short-term memory (Babiloni et al., 2005) and selective attention (Nakai et al., 2005) to error detection (Chevrier et al., 2007). The attenuated GMV in this area in heavier MZ twins may point to an impaired cognitive control and error processing, a constellation possibly supporting unhealthy eating behaviors (Hsu et al., 2017). Additionally, BMI-associated attenuated GMV was found in the medial OFC, reaching into the frontal pole. Being part of the brain's valuation system, the medial OFC is required to code rewarding properties of incentives (Rolls, 2011), thus having a pivotal role in motivational behavior such as food intake and related disorders, including obesity.

While the above mentioned brain regions are well established in the context of reward-related behavior and obesity, we also found extensive GMV reductions within the occipital cortex including the bilateral cuneus, parts of the posterior medial cortex (i.e. precuneus) and the cerebellum. Despite being primarily implicated in visual information processing, a number of structural and functional neuroimaging studies have highlighted the occipital cortex in the context of obesity and food intake (e.g. Alkan et al., 2008; García-García et al., 2015; Killgore and Yurgelun-Todd, 2007; Kullmann et al., 2013; Pannacciulli et al., 2006). Additional support for these and our findings is furthermore provided by Sadler et al. who reported differential connectivity of occipital regions (i.e. between different occipital regions and between the occipital pole and precentral, insular and prefrontal regions) in BMI discordant MZ twins with stronger connectivity in leaner MZ twins (Sadler et al., 2018). Complex behaviors do require the integration of sensory inputs such as visual information. Consequently - via the ventral visual pathway - dense connections exist between the visual cortex and the NaCC, amygdala and the PFC, brain regions that also showed GMV reductions in our sample of heavier MZ twin siblings. These networks are thought to support a number of cognitive functions prerequisite in the context of food intake, including valency attribution of visual stimuli, habit formation and reward processing (Kravitz et al., 2013). Interestingly, fMRI studies found striatal availability of dopamine transporters (DAT) to be associated with BOLD measured regional activity of occipital structures including the cuneus and precuneus (Tomasi et al., 2009a). Considering the substantial anatomical overlap between our results and Sadler et al. - particularly with respect to occipital brain regions (see Supplementary Fig. S3) - and assuming that attenuated GMV indexes attenuated activity, our findings may indeed point to a down regulation within the reward and valuation system in heavier MZ twins as compared to their lower-weight siblings. In contrast however, we observed decreased cerebellar GMV in heavier MZ siblings, whereas Sadler et al. reported increased connectivity for similar cerebellar regions in heavier MZ siblings (Sadler et al., 2018). Hence, a one-sided perspective in a sense of "less connectivity equals less GMV" (or vice versa) will likely oversimplify the intricate relationship between morphological and functional features of the brain.

With respect to the cerebellum's contribution to body weight/energy homeostasis, obesity and food intake, comparably little is known, although both structural and functional cerebellar alterations have been consistently reported in this field (e.g. Alkan et al., 2008; Pannacciulli et al., 2006; Raschpichler et al., 2013; Smucny et al., 2012; Tomasi et al., 2009b; Weise et al., 2017; García-García et al., 2019). Considering its well established role in motor control, the here observed reductions in cerebellar GMV likely may be the consequence of less physical activity and/or physical fitness in heavier siblings although additional post-hoc analyses did not support fitness as driving factor behind our results, with highly comparable patterns after adjustments were made for basic measures of endurance. Yet, a more detailed characterization of cardiorespiratory fitness and average physical activity may allow to further narrow down causal dependencies in obesity related brain changes. Nevertheless, increases in body weight are related to substantial changes in energy homeostasis (e.g. higher energy demands; Ravussin et al., 1982) and have been associated with worse performance in distinct cognitive measures (Yang et al., 2018). Considering that the cerebellum is densely connected to the hypothalamus, the homeostatic center of the brain (Zhu and Wang, 2007) and also forms part in the modulation of several non-motor cognitive processes (Guell et al., 2018), other factors – next to motor control - may be relevant in the context of this finding and should be adressed in future studies.

Considering the large body of evidence with respect to the neurobiological features of obesity and the fact that body weight and obesity are highly heritable traits, only few studies did attempt to provide an

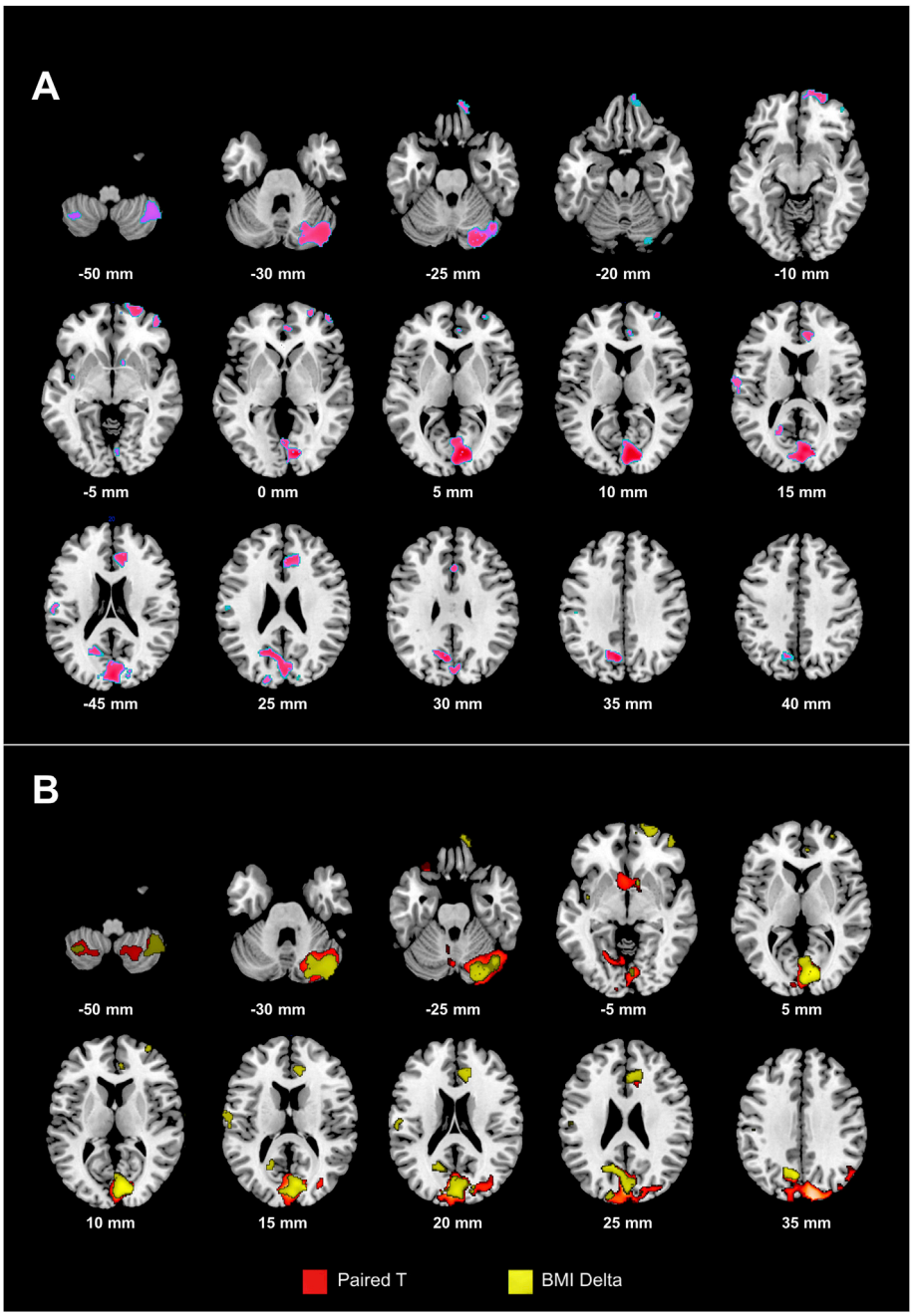

Fig. 2. Fig. 2A: Negative associations between regional differences in GMV (ΔGMV) and differences in BMI (ΔBMI) within all identical twins (paired T-test; $p < 0.05$ FWE_{TFCE}). Fig. 2B illustrates the regional overlap (at $p < 0.05$ FWE_{TFCE}) of GMV reductions in heavier BMI discordant identical twins (red blobs) and the negative associations of ΔGMV with ΔBMI across all identical twins (yellow blobs). Numbers below each section indicate the corresponding location on the z-axis.

integrated perspective on the interaction of genetic risk factors and brain structural alterations. Addressing this issue, a recent study by Opel et al. found that both polygenic risk for obesity and higher BMI were related to orbitofrontal gray-matter decreases, which in turn was shown to act as a mediator between polygenic risk factors and BMI (Opel et al., 2017). This particular medial orbitofrontal region was not included in the GMV pattern that we identified by comparing MZ twins discordant for BMI, suggesting complimentary heritable and environmental influences on different key regions implicated in reward and valuation processes. In a previous study (Weise et al., 2017), we investigated the heritability of physiologically relevant brain structures associated with obesity. To this end, we applied VBM to structural MRI data of MZ and dizygotic twins. Like in the present study, data was taken from the Human Connectome Project, but analyzed by applying the additive genetic, common environmental and residual effects model to determine heritability of brain regions that were associated with BMI. Our model revealed mostly negative associations of BMI with regional GMV, predominantly within prefrontal, temporal/mesotemporal, subcortical and cerebellar brain regions. While these brain regions yielded varying degrees of heritability, highest heritability estimates are found for GMV within the cerebellum and subcortical brain region including - amongst others - the dorsal and ventral striatum (Weise et al., 2017). Previous and present findings together, based on partly the same participants point to common effects in same subcortical brain structures (e.g., ventral and dorsal striatum) suggesting that corresponding BMI-associated morphological alterations are driven by both, heritable and environmental factors. In this context we see the strength of our analyses, since the comparison of MZ twins discordant for a specific trait allows identifying environmental effects in

Table 3
Negative associations of brain regional differences in GMV (ΔGMV and differences in BMI (ΔBMI) between identical twins.

	Brain Region, BA	*k*	pFWE[a]	MNI x	MNI y	MNI z
R	**Lingual Gyrus, BA 18**	**3610**	**0.007**	**12**	**−79**	**3**
L	Precuneus, BA 31		0.009	−8	−66	34
R	Cuneus, BA 17		0.010	15	−81	16
R	**Cerebellum, Uvula**	**1537**	**0.020**	**26**	**−81**	**−24**
R	Cerebellum, Tuber		0.023	44	−72	−30
R	Cerebellum, Tuber		0.023	36	−76	−29
R	**Anterior Cingulate, BA 32**	**671**	**0.021**	**9**	**34**	**22**
L	Cingulate Gyrus, BA 32		0.023	2	26	28
R	Anterior Cingulate, BA 32		0.040	3	46	−0
R	**Superior Frontal Gyrus, BA 10**	**516**	**0.023**	**24**	**63**	**−8**
R	Superior Frontal Gyrus		0.025	15	70	−9
R	Middle Frontal Gyrus, BA 10		0.041	33	58	10
L	**Cerebellum, Cerebellar Tonsil**	**311**	**0.025**	**−34**	**−60**	**−47**
R	**Cerebellum, Cerebellar Tonsil**	**495**	**0.025**	**42**	**−51**	**−50**
R	Cerebellum, Cerebellar Tonsil		0.032	36	−58	−48
R	Cerebellum, Inferior Semi-Lunar Lobule		0.041	27	−70	−45
R	**Middle Frontal Gyrus, BA 10**	**144**	**0.038**	**45**	**58**	**−2**
R	**Medial Frontal Gyrus, BA 11**	**109**	**0.042**	**10**	**58**	**−26**
R	Superior Frontal Gyrus, BA 11		0.045	14	51	−26
R	Superior Frontal Gyrus, BA 10		0.049	10	64	−20
L	**Transverse Temporal Gyrus, BA 42**	**219**	**0.042**	**−63**	**−9**	**13**
L	Postcentral Gyrus, BA 43		0.042	−56	−13	19
L	Postcentral Gyrus, BA 40		0.045	−60	−21	16
L	**Middle Occipital Gyrus**	**65**	**0.046**	**−16**	**−88**	**24**
R	**Medial Frontal Gyrus, BA 10**	**2**	**0.049**	**9**	**62**	**−6**
L	**Claustrum**	**7**	**0.049**	**−40**	**−3**	**−6**
R	**Caudate**	**13**	**0.050**	**10**	**10**	**−5**
L	**Postcentral Gyrus, BA 2**	**4**	**0.050**	**−50**	**−21**	**36**

BA Brodmann area; MNI Montreal Neurological Institute.
Bold data indicate primary peak within a cluster; Non-bold data indicate secondary peaks.
[a] Results are listed at a threshold of $p < 0.05$ FWE TFCE corrected.

the absence of genetic differences. Nevertheless, some limitations apply. Most importantly, no information was available on body composition. Since BMI does not allow to differentiate between tissue classes we do not know whether differences in BMI were the result of excess adipose tissue, an uncertainty that may be even more relevant in lower BMI twin pairs with only slight differences in body weight. Thus, more detailed anthropological measures should be applied in future studies in order to enhance our understanding of involved mechanisms. Also, analyses of BMI discordant MZ twins is not tantamount to comparisons of lean vs. obese siblings since – despite BMI discordancy – both siblings may share the same weight status according to BMI criteria. Still, GMV reductions in heavier siblings were located within brain regions implicated in the neurobiology of obesity and regression analyses showed BMI differences are linearly related to GMV differences of the same brain regions, thus collectively supporting the interpretation of our results in the context of weight gain and body weight differences.

In summary, we applied VBM to compare brain structure in MZ twins discordant for BMI. Here we find attenuated GMV in heavier twin siblings within cognitive brain regions involved in valuation and reward processing, potentially pointing to a downregulation within these systems in heavier MZ twins as compared to their lower-weight siblings. Present together with previous findings (Opel et al., 2017; Weise et al., 2017) suggest that some of those BMI-associated characteristics are determined by heritable or environmental factors alone, whereas in other brain regions they rather seem to be driven by a combination of both factors together.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.07.019.

Conflicts of interest

The authors declare no conflict of interest.

Data and code availability statement

Raw imaging data and non-imaging measures are made publicly available by the Human Connectome Project (HCP). Code and processed data is available upon request to the authors.

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