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Obesity affects brain structure and function- rescue by bariatric surgery?

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ABSTRACT

Obesity has a major impact on metabolic health thereby negatively affecting brain function and structure, however mechanisms involved are not entirely understood. The increasing prevalence of obesity is accompanied by a growing number of bariatric surgeries (BS). Weight loss after BS appears to improve cognitive function in patients. Therefore, unraveling mechanisms how BS influences brain function may be helpful to develop novel treatments or treatments in combination with BS preventing/inhibiting neurodegenerative disorders like Alzheimer's disease.

This review shows the relation between obesity and impaired circulation to and in the brain, brain atrophy, and decreased cognitive functioning. Weight loss seems to recover some of these brain abnormalities as greater white matter and gray matter integrity, functional brain changes and increased cognitive functioning is seen after BS. This relation of body weight and the brain is partly mediated by changes in adipokines, gut hormones and gut microbiota. However, the exact underlying mechanisms remain unknown and further research should be performed.

1. Introduction

It is undeniable that obesity continues to increase around the world. Having tripled over the last 40 years, 39% of adults worldwide are overweight (body mass index (BMI) ≥ 25 kg/m^2) and 13% are obese (BMI ≥ 30 kg/m^2) (WHO, 2018). It is well known that obesity leads to an increased risk of developing metabolic disorders (WHO, 2018; Mitchell et al., 2011) and there is accumulating evidence that obesity negatively affects brain structure and function (Cherbuin et al., 2015; Gunstad et al., 2007; Raji et al., 2010; Gunstad et al., 2010). For example, it has been shown that obese individuals have a decreased regional cerebral blood flow (CBF) in prefrontal brain regions involved in attention, reasoning, and executive function (Willeumier et al., 2011). Moreover, obesity is associated with a lowered gray matter (GM) volume, as well as impaired white matter (WM) microstructure indicating a loss of WM integrity either via demyelination or due to inflammation (Debette et al., 2014; Kullmann et al., 2016). Moreover, obesity during midlife has been associated with accelerated aging of the brain and risk of developing dementia (Ronan et al., 2016).

Body Mass Index (BMI) is the most commonly used, yet indirect measure for obesity. However, in determining the risk of individuals to develop obesity-related comorbidities, such as cardiovascular disease and type 2 diabetes mellitus, it is important to acknowledge the distribution of white adipose tissue (WAT) within the body. Excess body fat mainly accumulates in the abdominal, gluteal and femoral regions in subcutaneous WAT, but can also be stored around the internal organs in visceral WAT (Lee et al., 2013). The latter becomes dysregulated and detrimental in central obesity, while gluteofemoral obesity is associated with a lower risk for metabolic disorders (Lee et al., 2013; Veit et al., 2014a). Therefore, waist circumference or waist-to-hip ratio may be a more informative measure than BMI only, when regarding obesity-related diseases (Lee et al., 2013).

WAT is known to produce adipokines, such as the hormones leptin and adiponectin and proinflammatory cytokines. The production of these adipokines is deregulated in obesity. Especially visceral WAT produces more proinflammatory cytokines in obesity, which increases the risk of developing metabolic complications (Lee et al., 2013). This imbalance of adipokines can also lead to changes in brain function, such

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as impairment of the cerebral blood flow (CBF) and subsequent neurodegeneration (Arnoldussen et al., 2014). Furthermore, adipokines can have a widespread effect on body and brain while they are associated with inflammatory processes, energy balance and hypertension (Kiliaan et al., 2014).

Despite the various ways to visualize changes in the brain, it is not entirely clear via which mechanisms obesity affects brain structure and function. Therefore, it is extremely important that more research is conducted to not only treat obesity, but also to prevent a consequent negative impact on the brain. Undoubtedly, given the compelling evidence that obesity poses a risk for a multitude of comorbidities including those of the brain, it is essential that improved treatment options are available.

Conservative treatment options such as dietary restriction and physical activity, often show disappointing long-term effects, especially in patients with morbid obesity (BMI $\geq$ 40 kg/m^2) (Gloy et al., 2013). Contrarily, bariatric surgery (BS) is known to rapidly and sustainably decrease body mass and lead to a remission of type 2 diabetes mellitus and metabolic syndrome. One of the most commonly used procedures is the Roux-en-Y gastric bypass (RYGB), which results in a reduced stomach volume allowing less food intake, and a shorter small intestine leading to hormonal changes and reduction of nutrient absorption (Berthoud et al., 2011; Shin et al., 2013). Although this procedure facilitates rapid weight loss, there are some important issues associated with the procedure, such as vitamin and mineral deficiencies due to bypassing the first part of the small intestine that absorbs these nutrients (Bal et al., 2012; Dogan et al., 2017). Another commonly performed type of surgery is laparoscopic sleeve gastrectomy (LSG). During this procedure, the greater curvature side of the stomach is removed leaving a tube-shaped remnant. LSG is a technically easier and faster procedure compared to a RYGB. Long-term effects regarding weight loss seem promising, although more studies evaluating the long-term efficacy of LSG are necessary (Peterli et al., 2018).

Recent studies have indicated a possible association between BS and reduction of neurological problems such as cognitive impairment, yet underlying mechanisms are still far from understood (O'Brien et al., 2017; Keshava et al., 2017; Thiara et al., 2017). In order to shed light on the impact of obesity and BS on the brain, this review will provide an overview of the current knowledge on the topic. More specifically, known impact on brain structure as well as cognitive functioning will be discussed. With regard to brain function and structure, this review will focus on CBF and brain atrophy, specifically GM and WM volume reduction as well as a decrease in structural and functional connectivity. We will also focus on cognitive domains such as stimulus processing, reward and memory. Additionally, the potential ability of rapid weight loss after BS to counteract the negative impact of obesity on the brain will be explored and hypotheses about the underlying mechanisms will be shared. This review mainly focuses on human literature, however further research in humans and animals should be exerted to disentangle the mechanisms responsible for (partially) restoring brain structure and cognitive functioning after weight loss. Unraveling underlying mechanisms may be of help to develop novel treatments or treatments in combination with BS. Relevant literature was gathered from Scopus and PubMed published between 1997 and May 2019, using the following search terms in different combinations: 'obesity', 'brain', 'structure', function', 'cerebral blood flow', 'bariatric surgery', 'neuroimaging', 'RYGB' and 'sleeve gastrectomy'. Articles written in English were screened for relevance. Besides, we included relevant additional publications identified from bibliographies from retrieved literature.

2. Influence of obesity on brain structure and function

2.1. Cerebral hemodynamics

Accurate blood flow is crucial for survival and functioning of any organ, however the brain is fully dependent on blood flow for oxygen and glucose, and tissue damage may already occur after a very brief disruption in blood (Cipolla, 2009). Therefore, it is important to understand how obesity influences blood flow to and in the brain. Studies show significant negative correlations between BMI and CBF velocity (CBFV) in the common and internal carotid arteries (Zhang et al., 2006). Lowered CBFV in obesity is associated with reduced cognitive performance independent of comorbid medical conditions. More importantly, the effect of BMI on CBFV seems to be independent of other factors such as hypertension and type 2 diabetes mellitus (Zhang et al., 2006; Selim et al., 2008).

Recently, it was found that obesity (measured as BMI and waist circumference) was negatively associated with resting GM CBF. This is an important finding, as GM CBF is generally correlated with cognitive functioning, implying that obesity may directly affect cognition via changes in CBF (Rusinek et al., 2015). Abdominal obesity is a major risk factor contributing to the metabolic syndrome (MetS). In a late middle-aged MetS group mean GM CBF was decreased compared to the control group (excluding medial and inferior parts of the occipital and temporal lobes). Interestingly, the MetS group also had lower immediate memory function (Birdsill et al., 2013).

Altogether, this implies that obesity may pose a risk for impaired blood flow to and in the brain. Contrarily, studies using positron-emission tomography have shown hypermetabolism in the brain in obesity, which might lead to an imbalance in reward systems and cognitive control (Iozzo et al., 2012). Furthermore, CBF and oxygen metabolism in feeding-related brain regions is higher in obese individuals than in normal-weight persons (Karhunen et al., 1997). Possibly, increased activation in the right parietal cortex may relate to decreased feeding control, which could contribute to development and maintenance of the obese state (Karhunen et al., 1997).

2.2. Brain volume and integrity

It is well-established that obesity affects GM and WM integrity, probably caused by impaired CBF leading to ischemic stress and concomitant neuronal damage within the brain (Bobb et al., 2014).

2.2.1. Grey matter

Although there is increasing awareness that obesity is a risk factor for neurodegenerative diseases and cognitive decline, it is not yet clear how overweight relates to brain structural and functional changes. A large-scale population neuroimaging study showed a negative association between BMI (kg/m2), waist-to-hip ratio and fat index (total fat mass (kg)/height (m)) with overall GM volume (Hamer and Batty, 2019). Another study reported that obese individuals showed decreased GM density in different brain areas, notably those involved in taste, reward and feeding/goal-directed behavior. Contrarily, greater GM density was also seen in obese subjects when compared to lean counterparts (Pannacciulli et al., 2006).

Subsequent studies on GM atrophy have examined volume and cortical thickness rather than density and found that obesity/BMI/waist circumference is as expected, inversely related to GM volume. However, some have focused more on pin-pointing the underlying cause of these GM changes, by distinguishing between different aspects of obesity. For example, one study focused on the underlying cause of these changes, by distinguishing between fat mass and fat-free mass in overweight/obese individuals (Weise et al., 2013). Interestingly, this study indicated that there is an association between excess fat/adiposity and GM atrophy, which is more attributed to the increased fat-free mass in obese individuals than increased body fat mass. Nevertheless, it was found that obesity is negatively related with GM volume, especially in the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC). These structures are involved in decision making and inhibitory control (Weise et al., 2013). On the other hand, Janowitz et al. have linked waist circumference as a measure for abdominal obesity to GM volume changes, rather than simply BMI. With 2344 subjects, this large study has indicated that many brain regions are affected by abdominal

obesity (Janowitz et al., 2015).

Rather than investigating GM density or volume, Shaw et al. focused on cortical thickness as a measure of GM integrity. According to this study, an inverse relationship between BMI and cortical thickness was found (Shaw et al., 2018). However more importantly, an association was discovered between cortical thinning and increased visceral WAT, when adjusted for BMI score (Veit et al., 2014b). This relates well to the study by Janowitz et al. on effects of abdominal obesity, which indicates that these GM changes are possibly caused by inflammatory responses due to adipokine release by central WAT (Janowitz et al., 2015). Similar to other studies, Veit et al. showed an association between increased BMI and increased visceral WAT with reduced GM thickness in several brain areas (Veit et al., 2014a).

In conclusion, there is increasing evidence for obesity measures being associated with GM volumes, although the exact associations and mechanisms are still under debate. Furthermore, many studies are performed cross-sectional, and therefore it is not possible to definitely state the direction of the associations.

2.2.2. White matter

It has become clear that obesity not only influences integrity of GM in the brain but WM and structural connectivity is affected by adiposity as well (Verstynen et al., 2013). Conclusions from adiposity and WM integrity association studies resemble those about GM integrity. Indeed, several studies using diffusion weighted imaging have shown negative correlations between obesity measures and fiber connectivity (Kullmann et al., 2016; Verstynen et al., 2013; Xu et al., 2013; Bolzenius et al., 2015; van Bloemendaal et al., 2016; Alarcon et al., 2016). Interestingly, not all studies have implicated the same regions, although there is some overlap in results. Affected WM structures comprise for example the corpus callosum (genu, trunk and splenium), cerebellar peduncle, corona radiata (Verstynen et al., 2013; Xu et al., 2013), fornix (Xu et al., 2013), and the uncinate fasciculus in older adults (Bolzenius et al., 2015). One of these studies has indicated a decrease in WM volume using voxel based morphometry analysis (van Bloemendaal et al., 2016). Kullmann et al. revealed regionally specific changes in mean diffusivity and a strong decrease in axial diffusivity in obese young adults in the corticospinal tract, anterior thalamic radiation and superior longitudinal fasciculus indicating an increased risk for cognitive decline in obese individuals (Kullmann et al., 2016).

It is important to note that Hamer et al. did not find any association between obesity measures and WM and others even observed a positive interaction between BMI and WM integrity and volume (Hamer and Batty, 2019; Koivukangas et al., 2016; Haltia et al., 2007). In short, there is less conclusive evidence about the associations between obesity measures and WM compared to GM. An increase in WM volume might be due to an abnormal lipid metabolism and therefore fat accumulation in myelin throughout the brain (Haltia et al., 2007). More importantly, it would be interesting to see whether these WM changes affect cognitive impairment.

2.3. Resting state activity

Lastly, several neuroimaging studies demonstrated a marked difference in resting-state functional connectivity (RSFC) between obese and normal-weight individuals. This is indicative of lower functional connectivity in the middle frontal gyrus (Garcia-Garcia et al., 2015). On the other hand, increased activity synchronicity was found in the left putamen of obese men before consumption of a meal. Furthermore, the same study also indicated lower functionality of the (pre)frontal cortex before food intake, possibly leading to decreased inhibition (Zhang et al., 2015).

Table 1 gives an overview of the studies discussed, focusing on the influence of obesity on blood flow, brain structure and resting state activity.

3. Influence of obesity on cognitive functioning

3.1. Food-related stimulus processing

Areas concerning feeding behavior, such as the frontal operculum, post-central gyrus, dorsal striatum, prefrontal cortex and hippocampus, often show a decreased volume in obesity (Pannacciulli et al., 2006; Janowitz et al., 2015). Concurrent with this, obese people do in fact show different responses to visual food cues. When observing high-calorie foods obese women show higher blood oxygen level dependent (BOLD) activation in the dorsal striatum, a brain area that has been implicated in habit learning and addictive behavior (Rothemund et al., 2007). Moreover, obese children, adolescents and adults show higher activation of several brain regions, including the nucleus accumbens and caudate nucleus, compared to normal-weight controls when tasting sweet, bitter and high-calorie substances (Feldstein Ewing et al., 2017; Boutelle et al., 2015; Szalay et al., 2012). In general, it is noteworthy that increased BMI/waist circumference is associated with altered gustatory perception, although it should be investigated whether this is a cause or consequence of obesity.

In addition, obesity has been shown to be associated with aberrant reward responsivity. Several studies have indicated that connectivity in reward-related networks is less strong in obese individuals in comparison to normal-weight counterparts (Garcia-Garcia et al., 2013; Wijngaarden et al., 2015). However, there appears to be a stronger activation of reward-processing areas during tasks such as monetary reward paradigms (Opel et al., 2015). This suggests that disinhibition takes place due to decreased connectivity. Additionally, BMI is positively associated with serotonin availability in areas such as the nucleus accumbens and ventral pallidum, which are involved in reward processing (Haahr et al., 2012). This indicates that obese individuals have a stronger sense of reward after ingestion of palatable foods. Increased serotonin levels have also been found in hippocampus and the orbitofrontal cortex in obese subjects, which are both involved in (food) reward learning and processing (Haahr et al., 2012).

Moreover, obesity is associated with changes in activity of brain regions that are related to feeding behavior and stronger reward activity (Rothemund et al., 2007; Szalay et al., 2012). This suggests that these alterations cause obesity, rather than obesity causes changes in brain activity (Janowitz et al., 2015).

3.2. Cognitive function and control

Obesity has been associated with decreased memory performance and learning ability, as shown through various parameters. For example, it has been found that working memory is decreased in obese individuals when compared to normal-weight counterparts (Stingl et al., 2012). Interestingly, this was associated with an increase in neural activity, rather than a decrease, during the early phase after stimulus presentation. This possibly indicates disinhibition, which has indeed been observed in obesity and can lead to insufficient suppression of unwanted responses, thereby decreasing accuracy and reaction speed (Stingl et al., 2012). Additionally, recent evidence suggests that obese individuals exhibit inadequate implicit learning, for example by failing to apply negative prediction error in tasks requiring adaptation of behavior. This is possibly due to inadequate dopamine signaling (Mathar et al., 2017). It has further been shown that compared to normal-weight individuals, obese participants exhibit decreased activity in regions associated to memory and learning, such as the hippocampus, angular gyrus, precuneus and the parahippocampal gyrus and parts of the prefrontal cortex. Areas such as these have been implicated to be affected by obesity, making this decreased activity consistent with findings of volume and density loss mentioned earlier (Cheke et al., 2017).

Lastly, there are reports on increased impulsivity/lack of inhibitory control in obese individuals, which is in accordance with structural alterations observed in regions associated with cognitive control (Weise

Table 1
Summary of studies based on the influence of obesity on blood flow, brain structure and resting state activity. *mean ± SD. (f)MRI: functional magnetic resonance imaging; DTI: diffusion tensor imaging; BMI: body mass index; FA: fractional anisotropy; SLF: superior longitudinal fasciculus; ILF: inferior longitudinal fasciculus; CBF: cerebral blood flow; GM: gray matter; MetS: metabolic syndrome; VBM: voxel-based morphometry; WM: white matter; WHR: waist-hip ratio; SPECT: single photon emission computed tomography; rCBF: regional CBF; RD: radial diffusivity; CC: corpus callosum; rCBF: regional cerebral blood flow; DBP: diastolic blood pressure; TCD: transcranial Doppler; BFV: blood flow velocities; SBP: systolic blood pressure; CVR: cerebrovascular resistance; T2DM: type 2 diabetes mellitus; VAT: visceral adipose tissue; FFMI: fat-free mass index; FMI: fat mass index; GMV: gray matter volume; vmPFC: ventromedial prefrontal cortex; OFC: orbital frontal cortex; $\lambda 1$: axial eigenvalue; CR: corona radiata; $\lambda_{\perp}$: radial eigenvalue; CBFV: cerebral blood flow velocity; CCA: common carotid artery; CA: carotid artery; ICA: internal carotid artery; mPFC: medial prefrontal cortex.

	Participants (M:F)	Mean Age of Participants	Additional Information	Tests/methodology	Observations
Alarcon et al., 2016	152 (85:67)	14.1 ± 1.3	3 study groups: normal-weight (n = 88), overweight (n = 46), obese (n = 18)	(f)MRI, DTI	BMI correlated to FA ↓ (L SLF/ILF)
Birdsill et al., 2013	69 (26:43)	60.4 ± 6.1	2 study groups: control (n = 40), metabolic syndrome (n = 29)	Arterial spin labelling for CBF, MRI, neuropsychological assessment	GM CBF and immediate memory function ↓ in MetS compared to control. Abdominal obesity and triglyceride ↑ correlate with CBF ↓
Bolzenius et al., 2015	62 (20:42)	62.4 ± 8.44		MRI, DTI, neuropsychological assessment	BMI associated with FA ↓ (uncinate fasciculus)
Garcia-Garcia et al., 2015	41 (15:26)	31.3 ± 6.0 (lean), 33.6 ± 5.6 (obese)	2 study groups: lean (n = 21), obese (n = 20)	Task-related and resting state fMRI	↓ Functional connectivity of the middle frontal gyrus and the lateral occipital cortex in obese compared to lean.
Haltia et al., 2007	46 (20:26)	37 ± 21 (lean), 37 ± 12 (obese)	2 study groups: lean (n = 16), obese (n = 30)	MRI for VBM	WM volumes ↑ in obese compared to lean (temporal gyri, fusiform and parahippocampal gyri, brainstem and cerebellum). WHR and serum free fatty acid concentration correlate with WM volume ↑ in obese group. Dieting/weight loss correlates with WM volume ↓
Hamer and Batty, 2019	9652 (4623:5029)	55.4 ± 7.5		Medical examinations, MRI	↓ GM volume associated with BMI, WHR and fat mass. No associations between obesity and white matter.
Janowitz et al., 2015	2344 (1087:1257)	49.8 ± 9.3 (SHIP-2); 46.3 ± 11.3 (SHIP-TREND)	2 study populations: SHIP-2 (n = 758), SHIP-TREND (n = 1586)	Questionnaire, medical examination, MRI for VBM	Waist circumference associated with GM ↓ (various parts of cerebral cortex, striatum, limbic system)
Karhunen et al., 1997	23 (0:23)	39.8 ± 9.7 (lean); 45.0 ± 10.0 (obese)	2 study groups: lean (n = 12), obese (n = 11)	SPECT for rCBF	No differences in total CBF obese vs. lean; temporal/parietal rCBF ↓ in obese subjects in control situation, L parietal rCBF ↓ in food-exposed situation; rCBF R side > L side of parietal cortex/thalamus of obese women during food-exposure, compared to normal-weight. R temporal and parietal rCBF ↑ between control and food-exposed situation in the obese group compared to the lean. ↑ R parietal rCBF was associated with ↑ feeling of hunger in the obese group.
Koivukangas et al., 2016	88 (29:59)	22.3 ± 0.7 (risk); 22.2 ± 0.7 (control)	2 study groups: familial risk for psychosis (n = 42), control (n = 46)	MRI, DTI	In risk group, BMI correlated with FA ↓ (R parietal and periventricular areas) and RD ↑; In control group, BMI associated with FA ↑ (L hemisphere)
Kullmann et al., 2016	48 (25:23)	subcohort: 26.68 ± 3.68 (lean); 26.12 ± 1.95 (overweight); 26.88 ± 4.45 (obese)	3 study groups: lean (n = 24), overweight (n = 12), obese (n = 12)	MRI for voxel-based quantification and DTI	BMI associated with differences in DTI parameters indication ↓ myelin (parts of L SLF, thalamic radiation, internal capsule, CC), water ↑ (R SLF), iron content alteration (thalamic radiation, CC, cingulum), FA ↓ (cerebellar peduncle, corticospinal tract, thalamic radiation)
Pannacciulli et al., 2006	60 (36:24)	33 ± 9 (lean); 32 ± 8 (obese)	2 study groups: lean (n = 36), obese (n = 24)	PET for rCBF, MRI for voxel-based morphometry	GM density ↓ (cerebellum, L postcentral gyrus, R frontal operculum, putamen, middle frontal gyrus), in obese vs. normal-weight. Higher GM density of the L calcarine cortex, L middle occipital and inferior frontal gyri, and the R cuneus, and higher WM density around striatum, in obesity vs. normal-weight
Rusinek et al., 2015	87 (37:50)	51.8 ± 3.8 (healthy); 50.9 ± 4.5 (insulin resistance); 54.2 ± 5.2 (T2DM)	3 study groups: control (n = 37), insulin resistant (n = 27), diabetes (23)	Medical evaluation, neuropsychological assessment, arterial spin labelling to measure CBF	CBF associated with sex, waist circumference, DBP, end tidal CO2, verbal fluency score and BMI, and was significantly different between the groups.
Selim et al., 2008	197 (90:107)	56.8 ± 13.2 (healthy); 61.3 ± 7.2 (T2DM); 52.9 ± 11.3 (hypertension); 58.2 ± 9.8 (stroke)	4 study groups: control (n = 90), diabetes (n = 30), hypertension (n = 45), stroke (n = 32)	Medical examination, TCD analysis, MR angiography, MRI	Age/BMI associated with mean BFV ↓; SBP associated with BFV in hypertension group; mean BFV ↓ in men vs. women in stroke group; BMI associated with CVR ↑ and atherogenic index
Shaw et al., 2018	792	44–49 (midlife); 60–66 (late-life)	2 study groups: midlife (n = 405), late-life (n = 387)	Medical examination, MRI	BMI associated with ↑ cortical thinning at midlife (posterior cingulate). In late-life, increasing BMI is associated with ↓ cortical thinning (R supramarginal cortex, frontal regions).

(*continued on next page*)

Table 1 (*continued*)

	Participants (M:F)	Mean Age of Participants	Additional Information	Tests/methodology	Observations
van Bloemendaal et al., 2016	46 (24:22)	57.3 ± 1.9 (lean); 57.7 ± 2.2 (obese); 61.4 ± 1.5 (T2DM)	3 study groups: lean (n = 15), obese (n = 15), obese T2DM (n = 16)	MRI for VBM and DTI	WM volume/integrity ↓ in T2DM vs. lean (R corticospinal/fronto-occipital tracts, R SLF/forceps major), BMI associated with WM volume/integrity ↓ (L external capsule, R inferior parietal lobe)
Veit et al., 2014a,2014b	72 (42:30)	29.7 ± 8.2		Medical examination, MRI	BMI/VAT associated with cortical thickness ↓ (parts of R frontal/temporal lobe, L temporal/parietal/occipital cortex)
Verstynen et al., 2013	155 (78:77)	40.7 ± 6.2		Medical examination, DTI	Adiposity correlated with FA ↓ (CC, peduncle, corona radiata), mediated by BP, dyslipidemia, inflammation and glucose regulation
Weise et al., 2013	76 (52:24)	32.1 ± 8.8		Body composition assessment, MRI for VBM	FFMI, and for some parts also FMI, correlated with GMV ↓ of temporal lobes, vmPFC, caudolateral OFC and L mid-posterior insula. FMI correlated with L cerebellar GMV ↓
Xu et al., 2013	51 (30:21)	29.6 ± 10.0	2 study groups: BMI < 25 (n = 22), BMI ≥ 25(n = 29)	DTI	BMI correlated with FA ↓ of CC, λ_1 ↑ of R CR/SLF, and $\lambda_\perp$ ↑ of CC/fornix
Zhang et al., 2006	1323 (474:849)	56.41 ± 8.19		Questionnaire, medical examination, TCD ultra-sound examination	CBFV ↓ associated with age (CCA in men, all CA in women), BMI (ICA in men, CCA and ICA in women), and SBP (CCA)
Zhang et al., 2015	20 (20:0)	24 ± 4 (lean); 24 ± 4 (obese)	2 study groups: lean (n = 20), obese (n = 20)	Resting state fMRI in hunger and satiety states, blood samples.	Before food intake: ↑ synchronicity of activity in l putamen, ↓ synchronicity of activity in OFC and mPFC in obese subjects. ↑ ratings of hunger. After food intake: no differences between obese and lean. In all participants ↑ synchronicity of activity in OFC.

et al., 2013; Skoranski et al., 2013). However, it is difficult to assess whether obesity causes increased impulsivity or vice versa, as it seems more plausible that impulsive individuals have a higher disposition to develop obesity. Nevertheless, this association should be investigated further.

Table 2 gives an overview of the studies discussed based on the influence of obesity on cognitive functioning.

3.3. Underlying mechanisms between obesity and brain structure and function

As mentioned earlier, it has been suggested that especially visceral and abdominal WAT becomes inflamed and dysregulated in obesity, producing adipokines, such as inflammatory cytokines that can cause inflammation (Verstynen et al., 2013). Examples are monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α) and interleukins (IL) such as IL-6 and IL-β (Kiliaan et al., 2014; Jaganathan et al., 2018). This increased secretion of inflammatory factors has been associated with damage to food-intake regulating circuits of the brain (Cazettes et al., 2011). Moreover, the pro-inflammatory IL-6 may especially affects hippocampal volume and function (Kiliaan et al., 2014). These and other adipokines, such as angiotensinogen, serum amyloid A (SAA) and plasminogen activator inhibitor-1 (PAI-1) have adverse effects on the cardiovascular system, such as hypertension, thrombosis, atherosclerosis and endothelial dysfunction which may contribute to the changes observed in the blood circulation and consequently CBF (Arnoldussen et al., 2014; Kiliaan et al., 2014; Verstynen et al., 2013). Additionally, altered CBF itself has a negative effect on cognitive function (Rusinek et al., 2015). Leptin is one of the more well-known adipokines that may contribute to the negative effects of obesity on the brain. Leptin can have various roles in the brain such as energy intake regulation in the hypothalamus, memory, neurogenesis and brain structure (Arnoldussen et al., 2014). It has been shown that concentrations of leptin in the blood are negatively correlated with GM volume (Pannacciulli et al., 2007).

Changes in WM in obesity seem to be related to vascular and inflammatory factors as well (Bettcher et al., 2013). For example, inflammatory cytokines can lead to a cellular response of microglia leading to more water in brain tissue causing loss of WM integrity (Rosano et al., 2012; Kullmann et al., 2015).

Sex differences should be considered when looking at WAT in the relation between the obese phenotype and brain function and structure (Horstmann et al., 2011). There are significant discrepancies in fat distribution between men and women which might lead to different effects on the brain. Most importantly, men typically store more fat in the abdomen, whereas in women, fat is mostly stored in gluteofemoral WAT (White and Tchoukalova, 2014). This is also associated with sex-related differences in adipokine levels (Kiliaan et al., 2014). Therefore, it is important to have equal representation of males and females in studies.

Next to WAT, the gut, gut hormones and its microbiome have large effects on the brain, such as regulating eating behavior (Torres-Fuentes et al., 2017). It has been found that microbiota of obese individuals are different and less diverse compared to lean individuals, with a lower proportion of the bacteria group *Bacteroidetes* and higher proportion of *Firmicutes* (Ley et al., 2006). Additionally, gut microbiota can generate short chain fatty acids (SCFAs) via fermentation of dietary fibers. In obesity, increased SCFA concentrations are observed and these SCFAs can influence the production of neurotransmitters and their precursors (van de Wouw et al., 2017; Schwiertz et al., 2010). Furthermore, gut microbiota can affect gastrointestinal barrier permeability. As shown in diet-induced obese mice, obesity is associated with increased gut permeability (Lam et al., 2012).

Therefore, it is plausible that the obese phenotype is related to changes in the gut as well as changes in WAT, which influence brain function and structure (see Fig. 1a).

Table 2
Summary of studies based on the influence of obesity on cognitive functioning. *mean ± SD. (f)MRI: functional magnetic resonance imaging; IR: insulin resistance; BMI: body mass index; PFC: prefrontal cortex; PET: positron emission tomography; 5-HT4R: 5-hydroxytryptamine receptor 4; NAcc: nucleus accumbens; OFC: orbital frontal cortex; PE: prediction error; vlPFC: ventrolateral prefrontal cortex; SMA: supplementary motor area; EEG: electroencephalography; ERP: event-related potential; ERN: error-related negativity; MEG: magnetoencephalography; RMS: root-mean-square; dlPFC: dorsolateral prefrontal cortex; dACC: dorsal anterior cingulate cortex.

	Participants (M:F)	Mean Age of Participants	Additional Information	Tests/methodology	Observations
Boutelle et al., 2015	23	10.4 ± 0.3	2 study groups: obese (n = 10), healthy (n = 13)	fMRI	↑ response to sucrose in obese compared to healthy weight, and to water in healthy weight compared to obese (paracingulate, medial/middle frontal and lingual gyri, R amygdala, L posterior middle temporal gyrus)
Cheke et al., 2017	32 (18:14)	27.3 ± 5.9 (lean); 27.7 ± 5.7 (obese)	2 study groups: lean (n = 16), obese (n = 16)	Treasure-Hunt task, fMRI	IR but not BMI is associated with task performance (error rate). Activity ↑ in angular and parahippocampal gyrus, hippocampus, L anterior PFC, L precuneus of lean vs. obese. Similar for low vs. high IR. Leptin associated with R parahippocampal/angular gyrus and L precuneus activity.
Feldstein Ewing et al., 2017	24 (20:4)	16.46 ± 1.4	1 study group, all overweight.	fMRI gustatory cue exposure task	↑ response in various regions for high vs low calorie beverages. BMI associated to ↑ response for high vs low calorie beverages.
Garcia-Garcia et al., 2013	37 (13:24)	34.78 ± 4.45 (obese); 32.00 ± 5.87 (normal-weight)	2 study groups: obese (n = 18), normal-weight (n = 19)	fMRI	↓ connectivity in visual, frontal and default mode networks during rewarding stimuli, and occipital, frontal and default mode networks during neutral stimuli, in obese vs. normal-weight.
Haahr et al., 2012	28 (15:13)	41.3 ± 15.4 (normal-weight); 41.0 ± 19.9 (overweight/obese)	2 study groups: normal-weight (n = 16), overweight/obese (n = 12)	MRI, PET for 5-HT4R binding potential	BMI associated with 5-HT4R density in NAcc, ventral pallidum, L OFC and L hippocampus.
Mathar et al., 2017	58 (28:30)	26.6 ± 3.6 (lean women); 28.3 ± 4.7 (obese women); 26.0 ± 3.2 (lean men); 27.2 ± 5.3 (obese men)	2 study groups: lean (n = 30), obese (n = 28)	Weather prediction task (positive/negative prediction error learning), fMRI	Learning performance ↓ in obese vs. lean. Learning strategy more random-like in obese vs. lean. Response consistency and negative PE use ↓ in obese vs. lean. Prediction-related BOLD activation ↓ in L superior frontal gyrus, L vlPFC, precuneus and R premotor cortex of obese vs. lean. Complexity-related BOLD activation ↑ in L putamen, premotor cortex, SMA, R thalamus, precuneus, lingual/parahippocampal gyrus, L inferior parietal lobe of lean vs. obese. PE-related functional connectivity/coupling ↓ between ventral striatum and SMA/motor cortex in obese vs. lean.
Opel et al., 2015	56 (30:26)	42.04 ± 10.17 (normal-weight); 43.79 ± 8.86 (obese)	2 study groups: normal-weight (n = 28), obese (n = 28)	fMRI	BOLD response ↑ for reward vs. control in insula, OFC, putamen, PFC, anterior cingulate cortex, temporal/occipital lobe and cerebellum of obese, compared to normal-weight.
Rothemund et al., 2007	26 (0:26)	29 ± 5.6 (normal-weight); 31 ± 9.4 (obese)	2 study groups: normal-weight (n = 13), obese (n = 13)	Psychometric evaluation, fMRI	Activation ↑ in parts of striatum, L insula, L hippocampus and L parietal lobe under high-calorie condition, in several frontal, occipital and temporal gyri under low-calorie condition, and in L middle frontal gyrus, L cuneus and R inferior parietal lobe under utensil condition, in obese vs. control. ↑ activity in R caudate body under utensil condition in control vs. obese. BMI associated with BOLD signal change in various regions across the brain under high-calorie condition.
Skoranski et al., 2013	60 (23:37)	12.8 ± 2.4 (obese); 12.8 ± 2.5 (control)	2 study groups: obese (n = 22), control (n = 32)	Arrow task, EEG/ERP	ERN amplitude ↓ after errors in obese vs. control. Pe component ↓ in obese vs. control. Error rates ↑ in obese vs. control.
Stingl et al., 2012	68 (20:48)	36.5 ± 9.5 (lean); 38.4 ± 11 (obese)	2 study groups: lean (n = 34), obese (n = 34)	MEG	Weight associated with response accuracy ↓ and reaction time ↑. RMS ↓ in obese vs. lean. BMI associated with neural activity ↓ in occipital area at 250−350 ms. BMI correlated with neural activity in R dlPFC at 100−350 ms.
Szalay et al., 2012	24 (6:18)	38.3 ± 4.2 (obese); 37.1 ± 3.8 (healthy)	2 study groups: obese (n = 12), healthy (n = 12)	Taste stimulation on fMRI, MRI	Pleasantness rating ↑ for sucrose and vanilla, and ↓ for quinine (bitter) in obese vs. control. Taste induced brain activity ↑ in operculum, insula, middle frontal gyrus, OFC, amygdala, striatum and thalamus of obese vs. control. BMI and subjective hedonic sucrose/vanilla ratings associated with activation ↑ for these areas under taste condition. Quinine ratings associated with activation ↓.
Wijngaarden et al., 2015	24 (4:20)	31 ± 3 (obese); 28 ± 3 (lean)	2 study groups: obese (n = 13), lean (n = 11)	fMRI	After 48 h fast, connectivity ↓ between hypothalamus and L insula/superior temporal gyrus, and ↑ between amygdala and L caudate nucleus in obese but not lean. Hypothalamus connectivity to dACC ↓ in obese but ↑ in lean.

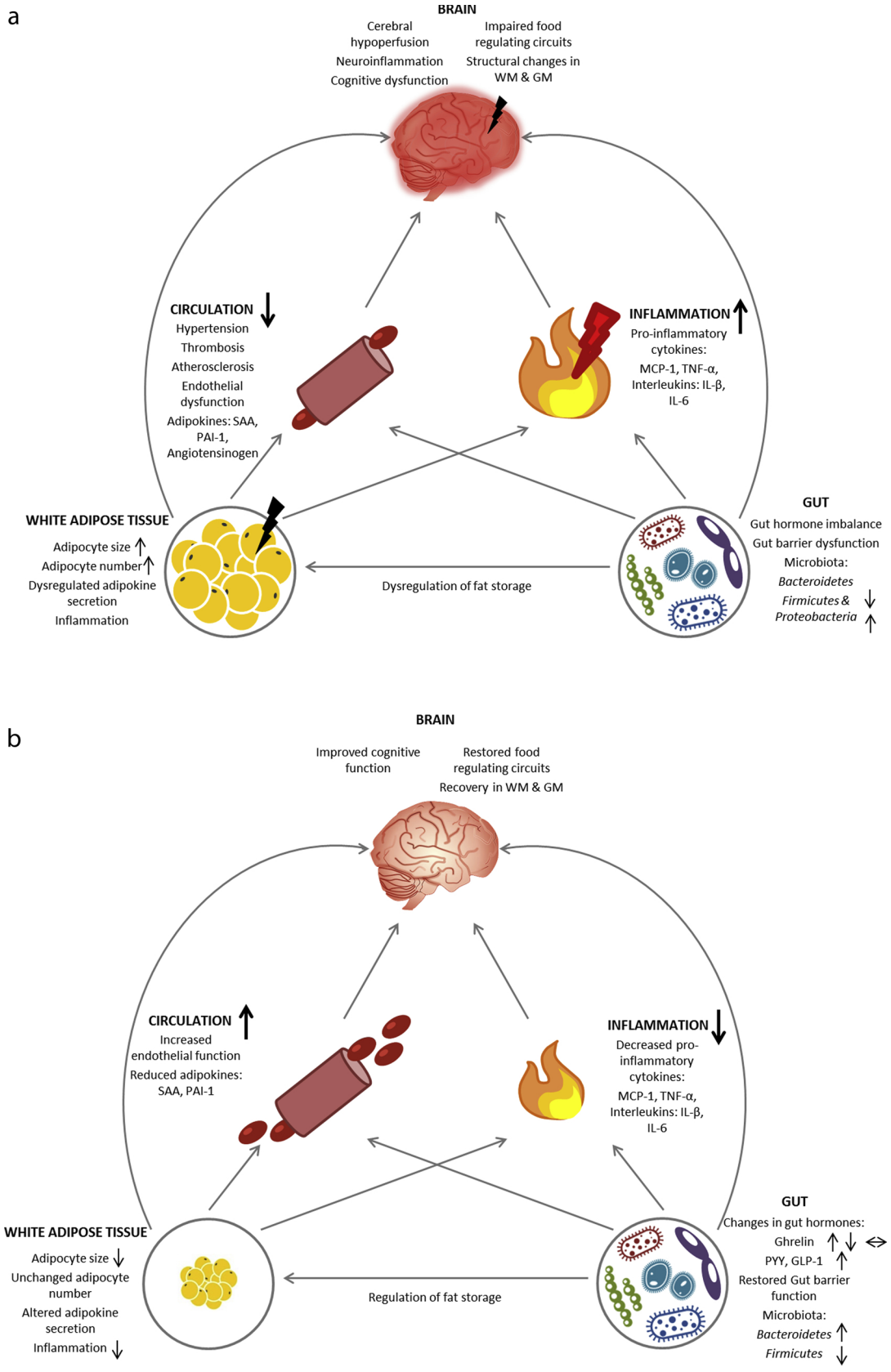

Fig. 1. The potential mechanism between obesity (a) and the potential effect of bariatric surgery induced weight loss (b) on brain function and structure based on changes in adipose tissue and the gut. WM: white matter; GM: grey matter; SAA: serum amyloid A; PAI-1: plasmogen activator inhibitor-1; MCP-1: monocyte chemotactic protein-1; TNF-α: tumor necrosis factor-alpha; IL-β: interleukin-beta; IL-6: interleukin-6; PYY: peptide YY; GLP-1: glucagon-like peptide-1.

4. Effects of bariatric surgery

Given the fact that BS is concomitantly increasing with the number of morbidly obese individuals, it would be interesting to determine whether drastic weight loss measures can reverse the obese-related effects previously explained.

4.1. Structural alteration

Some recent studies investigated the possibly reversing effects of BS on structural alterations in the brain. It has been confirmed that morbid obese individuals showed marked changes in both GM and WM density of various brain regions prior to surgery, in comparison to healthy controls (Tuulari et al., 2016; Zhang et al., 2016). Surprisingly, six months after BS alterations in GM density as well as WM density were shown. Both GM and WM densities recovered after weight loss, being most apparent in WM (Tuulari et al., 2016). Moreover, a study on the effects of LSG showed improvement of WM integrity and connectivity, already one month after surgery (Zhang et al., 2016). The effect on GM is different, as only modest GM recovery is visible six months after surgery. Nevertheless, follow-up in the aforementioned studies is relatively short and long-term follow-up of BS may reveal significant improvement of GM (Tuulari et al., 2016).

4.2. Cognitive improvement

Compared to brain structure, more research has been performed on cognitive changes after BS. It was assumed that surgery itself could pose a risk of (further) cognitive dysfunction due to nutritional deficiencies that can occur after BS. However the study by Gunstad et al. indicated that patients' cognitive functioning in several domains, such as memory, attention, executive function and language had in fact improved after surgery, from below average to (greater than) average (Gunstad et al., 2011). On the other hand, obese controls who had not been subjected to surgery, did not show such improvement, but rather a decline of cognitive performance (Gunstad et al., 2011).

A similar study with three to four year follow-up of patients who underwent BS, also showed that cognitive improvement was maintained for attention, executive function and memory: significantly fewer patients showed cognitive impairment three years after surgery than before, and cognitive functioning improved from low average to average. Moreover, four years after BS, executive function even improved to a high average score. Interestingly, it was shown that when BMI in patients increased again, which was seen mostly between the 2nd and 3rd year after surgery, attention scores were decreased (Alosco et al., 2014). However, this was not observed in all measures of cognitive functioning.

Although, surgically induced weight loss is associated with improved cognitive function, a recent study showed that when compared to healthy controls who had never been obese, ex-obese individuals who had undergone BS still do not perform at the same cognitive level (Tarantino et al., 2017). This implies that some alterations in the brain due to excess weight cannot be restored in the short term. However, the healthy control group still had a significant lower BMI compared to the ex-obese individuals, as BS mostly only reduces the severity of overweight. This might also explain the difference seen in cognition between healthy controls who had never been obese and the ex-obese individuals. Longer follow-up is required to confirm these findings.

4.3. Functional changes

Observed neural activity in patients before and after BS demonstrates changes in brain function. For example, several studies indicate that people show less craving of high calorie (HC) food (Li et al., 2019) and less response to visual HC food cues, especially within the mesolimbic pathway already one month after surgery (Ochner et al., 2012). More importantly, activity within the mesolimbic pathway before surgery seems to potentially predict weight loss 12 months after LSG (Holsen et al., 2018), which may indicate neural activity as a useful biomarker for BS eligibility. Furthermore, differences in activity are seen between LSG and RYGB; BOLD signal in the ventral tegmental area (important for reward processing) for HC food cues declined more after RYGB compared to LSG (Faulconbridge et al., 2016).

As the obese state is associated with altered RSFC, it is interesting to see whether weight loss after BS can reverse these changes. Decreased RSFC within reward processing and cognitive control areas as seen in obesity, has been shown to recover after BS (Li et al., 2018a). Wiemerslage et al. have indeed found changes in RSFC following BS, including the insula and putamen dependent on prandial state (Wiemerslage et al., 2017). These areas affect self-referential processing and learning, therefore changes within these regions might alter control of eating behavior. This is in line with more recent literature showing reduced RSFC within regions affecting self-referential processing (Li et al., 2018b).

The reviewed studies focusing on impact of BS on the brain are summarized in Table 3.

4.4. Underlying mechanisms

Despite the positive influence of BS on brain function, it is not yet entirely clear whether these changes are brought about solely by weight loss. Therefore it will be worthwhile to determine whether 'traditional weight loss' programs which involve dietary modification and exercise show the same positive influence as BS on the brain. However, it has been indicated that especially RYGB may influence gut-brain communication as well as adipokine secretion, which may provide additional benefits to brain function recovery (Berthoud et al., 2011; Ballsmider et al., 2015).

Additionally, after BS altered adipokine secretion is found, with among others reduced angiotensinogen (Ghanim et al., 2018) and PAI-1 levels (Tschoner et al., 2012). These changes may lead to remission of hypertension and reduction of atherosclerosis which has a positive influence on the vascular wall health (Tschoner et al., 2013; Wilhelm et al., 2014). This might contribute to a better blood circulation and therewith higher CBF.

Furthermore, changes in gut hormone levels after BS are related to weight loss (Alamuddin et al., 2017) and functional brain changes (Li et al., 2019; Zhang et al., 2019). In summary, changes in fasting ghrelin levels and postprandial higher levels of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) are seen after BS (le Roux et al., 2006; Field et al., 2010; Kalinowski et al., 2017). These gut hormones play a role in the regulation of energy homeostasis in the brain. Especially the decrease of ghrelin after LSG due to the removal of the gastric fundus in which ghrelin is mainly produced, has shown to directly influence the brain. For example, the study by Li et al. showed that the reduction in ghrelin was associated with less cravings to HC food and reduction in dorsolateral prefrontal cortex activation to food cues along with strengthened connectivity between regions important for self-control and executive functions (Li et al., 2019). Others also demonstrated that ghrelin directly affects the hippocampus via modulating its connectivity with the insula (Zhang et al., 2019). This implies that ghrelin underlies changes in brain reactivity and eating behavior.

Furthermore, recovery of obesity-related brain volume might be due to a reduction of inflammatory cytokines and less metabolic stress (Tuulari et al., 2016). Reduced levels of the adipokines IL-6, TNF-α and MCP-1 (Kelly et al., 2016) are found after BS, and lead to lower WAT inflammation and systemic inflammation (Sams et al., 2016). For example, since an association exists between IL-6 plasma levels and lower hippocampal GM volume, reduction of IL-6 levels possibly mediate memory improvement (Marsland et al., 2008).

Recovery of WM might be due to remyelination (Bhatt et al., 2014). The fact that WM is able to recover due to weight reduction, also

Table 3
Summary of studies based on the effects of bariatric surgery on brain function and structure. *mean ± SD. Wk: week; Mo: month; RYGB: Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy; (f)MRI: functional magnetic resonance imaging; HC: high calorie; VTA: ventral tegmental area; NAcc: nucleus accumbens; DLPFC: dorsolateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex; %TWL: percentage total weight loss; lFCD: local functional connectivity density; VMPFC: ventromedial prefrontal cortex; PCC: posterior cingulate cortex; dACC: dorsal anterior cingulate cortex; BMI: body mass index; RS: resting state; OFC: orbital frontal cortex; MFG: middle frontal gyrus; SFG: superior frontal gyrus; GR: gyrus rectus; FC: functional connectivity; BS: bariatric surgery; LC: low calorie; PFC: prefrontal cortex; EEG: electroencephalography; ERP: event-related potential; RT; reaction time; VBM: voxel-based morphometry; WMV; white matter volume; GMV: gray matter volume; fALFF: fractional amplitude of low-frequency fluctuations; DTI: diffusion tensor imaging; FA: fractional anisotropy; CC: corpus callosum; MD: mean diffusivity; SLF: superior longitudinal fasciculus.

	Participants (M:F)	Mean Age of Participants	Additional Information	Tests/methodology	Observations
Alosco et al., 2014	50 (4:46)	44.08 ± 10.76	Bariatric surgery patients	Neuropsychological assessment (memory, executive function, language)	Cognitive impairment prevalence ↓ at 36mo post-surgery. Attention ↑ from baseline to 12wk, 12 and 24mo post-surgery, but ↓ between 24-36mo. Memory/executive function ↑ from baseline to 12wk, 12, 24, 36 and 48mo. Weight regain between 24-36mo associated with attention ↓ .
Faulconbridge et al., 2016	59 (0:59)	37.2 ± 9.3 (RYGB); 40.3 ± 8.9 (LSG); 36.4 ± 8.2 (obese control)	3 study groups: RYGB (n = 22), LSG (n = 18), obese control (n = 19)	fMRI, fasting blood samples	After RYGB and LSG ↓ liking ratings for HC food. ↓ activity in the VTA to HC in RYGB compared to control. Changes in ghrelin (+) correlated with changes in VTA activity in RYGB and LSG, but not in control group.
Gunstad et al., 2011	150 (25:125)	44.66 ± 11.03 (surgery); 40.42 ± 11.48 (obese control)	2 study groups: bariatric surgery patients (n = 109), obese control (n = 41)	Neuropsychological assessment(memory, attention, executive function, language)	Memory performance ↑ at 12wk post-surgery vs. Baseline, largely irrespective of weight change or medical conditions.
Holsen et al., 2018	18 (2:16)	38.4 ± 10.1	LSG patients	Fasting blood samples, questionnaires, fMRI	After LSG: ↓ reduction in ghrelin, leptin, glucose and insulin, improved maladaptive eating behaviors, ↓ activity in NAcc, caudate, pallidum, amygdala and ↑ DLPFC and DMPFC during desire for HC food enhancement vs. regulation. Baseline activity in NAcc and hypothalamus during HC food enhancement predict %TWL at 12m.
Li et al., 2018a,	41 (21:20)	26.64 ± 1.83 (LSG); 28.63 ± 2.06 (control)	2 study groups: LSG (n = 22), obese control (n = 19)	Fasting blood samples, fMRI	After LSG: ↓ lFCD in VMPFC, PCC/precuneus, dACC/DMPFC. ↓ lFCD in VMPFC and PCC/precuneus was (-) correlated with change in BMI. ↑ connectivity between VMPFC and L DLPFC and between PCC/precuneus and R caudate and L DLPFC. ↓ connectivity between VMPFC and hippocampus.
,2018b	68 (37:31)	27.8 ± 6.9 (surgery); 26.7 ± 6.8 (control)	2 study groups: bariatric surgery patients (n = 34), normal-weight (n = 34)	fMRI	↓ RS activity in regions as OFC, MFG, SFG, GR in preop. subjects compared to controls and ↑ FC in these regions. BMI was associated with these changes. BS recovered this dysfunction.
Li et al., 2019	41 (21:20)	26.64 ± 1.83 (surgery); 28.63 ± 2.06 (obese control)	2 study groups: bariatric surgery patients (n = 22), obese control (n = 19)	Fasting blood samples, questionnaires, fMRI food cue-reactivity task	After LSG: ↓ fasting plasma of ghrelin, leptin and insulin, ↓ cravings for HC food, ↓ brain activation in the RDLPFC in response to HC vs LC food cues. ↓ brain activation in the R DLPFC is (+) correlated to reduction in ghrelin and cravings. R DLPFC had ↑ connectivity with the vACC. Changes in BMI were (-) correlated with changes in connectivity between the R DLPFC and vACC in the LSG group only.
Ochner et al., 2012	5 (0:5)	36 ± 13	RYGB candidates	fMRI	Neural responsivity to HC vs. LC food cues ↓ in insula, PFC and motor/sensory cortices after surgery. Preoperative differences in neural responsivity fasted vs. fed state disappeared postoperatively.
Tarantino et al., 2017	43 (12:31)	40.57 ± 11.05 (patient); 40.18 ± 12.18 (control)	2 study groups: ex-obese bariatric surgery patients (n = 21), normal-weight (n = 22)	EEG/ERP, Stroop/Switching tasks, Sustained attention to response test (SART)	No differences in Stroop accuracy, spatial RT Stroop effect, RT mixing cost, accuracy mixing and switch cost, and accuracy % and RT NoGo trials, between groups. Verbal RT Stroop effect and RT switch cost ↑ in patients vs. controls. Cue-evoked ERPs (switch trials), and target-evoked ERPs, different between patients and controls: positivity ↓ in patients. Early negative peak (N1) ↑ in patient vs. control. Negative N2 peak ↑ on NoGo stimuli in patients vs. controls. Positive P3 peak ↓ on Go trials in patient vs. control.
Tuulari et al., 2016	76 (11:65)	45.9 ± 11.8 (normal-weight); 44.9 ± 9.0 (morbid obese)	2 study groups: normal-weight (n = 29), morbidly obese (n = 47)	MRI for VBM, pre- and postoperative	WMV ↑ throughout the brain, slight GMV ↑ in occipital and temporal lobe, 6 months post-surgery. Presurgery regional GM/WM density associated with postsurgical weight loss.

(*continued on next page*)

Table 3 (*continued*)

	Participants (M:F)	Mean Age of Participants	Additional Information	Tests/methodology	Observations
Wiemerslage et al., 2017	11 (0:11)	42 ± 10	RYGB candidates	fMRI	Resting-state activity (fALFF) ↓ in claustrum, precentral/superior temporal/inferior and middle frontal/supramarginal gyri, thalamus, putamen, cingulate cortex and insula, after surgery. fALFF ↑ in cerebellum, thalamus and superior frontal gyrus, after surgery. Fasted state fALFF ↓ in pre-/postcentral/middle frontal gyrus and insula post vs. presurgery. Sated fALFF ↓ in precentral gyrus and ↑ in superior parietal lobule after surgery.
Zhang et al., 2016	33 (11:22)	25.8 ± 2.2 (obese); 27.0 ± 1.9 (normal-weight)	2 study groups: obese (n = 15), normal-weight (n = 18)	MRI for VBM/DTI, pre- and postoperative	FA ↑ in parts of corona radiata, CC, fornix, stria terminalis, sagittal stratum and fasciculus of obese post vs. pre surgery. MD ↓ in parts of corona radiata, internal/external capsule, SLF and sagittal stratum of obese post vs. pre surgery. GM density ↑ in parts of frontal gyrus, anterior cingulate, PFC, temporal lobe and fusiform/postcentral gyrus of obese post vs. pre surgery. WM density ↑ in caudate, thalamus, frontal/postcentral gyrus, cingulate cortex and precuneus of obese post vs. pre surgery. BMI and food addiction score correlation with MD and GM density disappeared, some negative correlations of BMI with FA and WM density remain.

indicates that initial decrease of WM in obesity is likely an effect of the obese state, rather than a cause for weight gain.

In fact, these changes in the gut, gut hormones, blood circulation and inflammation affect brain structure and function (Fig. 1b). Unfortunately, these changes have not been studied extensively.

With regard to improving brain structure and function, it might also be valuable to consider other confounding health benefits associated with BS. For example, it has been shown that cardiorespiratory fitness is inceased after BS (Tettero et al., 2018), but also directly associated with GM volume increase (Esteban-Cornejo et al., 2017). Moreover, it has been proposed that improved quality of sleep due to alleviation of sleep apnea as well as altered gut hormone levels may aid in improvement of brain structure and function (Tuulari et al., 2016). Therefore, to study the underlying mechanisms it is important to take into account exercise and quality of sleep before and after BS, as this may increase benefits associated with the surgical procedure.

5. Discussion

In this review, a summary on the impact of obesity and surgically induced weight loss on different aspects of neurological health was presented. Multiple studies have shown that obesity, as measured by high BMI, adiposity and/or waist circumference, affects function and structure of the brain, independent from obesity related comorbidities, such as hypertension and type 2 diabetes mellitus. It is clear that individuals with high BMI are more likely to have poorer circulation to and in the brain (Willeumier et al., 2011). There is also a large body of evidence suggesting that obesity is directly linked to brain atrophy. In fact, obese individuals have lower GM and WM volumes and WM integrity, although there is much debate about which areas are predominantly affected (Kullmann et al., 2016; Pannacciulli et al., 2006; Janowitz et al., 2015; Xu et al., 2013; van Bloemendaal et al., 2016). Still, it is clear that obesity is independently and negatively correlated with brain volume, which in turn is highly associated with cognitive functioning (Walther et al., 2010). A multitude of cognitive measures have been found to be altered in the obese brain, such as stimulus and reward processing, as well as memory, learning and cognitive control (Garcia-Garcia et al., 2013; Wijngaarden et al., 2015; Stingl et al., 2012; Cheke et al., 2017; Skoranski et al., 2013). Furthermore, changes in resting-state activity are seen in obese individuals (Garcia-Garcia et al., 2015; Zhang et al., 2015).

As all of the aforementioned effects were associated independently with obesity parameters, such as BMI or waist circumference, it would be interesting to investigate whether these effects are reversible, for example by rapid weight loss after BS. Indeed, recent studies have been able to show a positive effect of procedures such as RYGB and LSG on brain volume and function (Tuulari et al., 2016; Zhang et al., 2016; Gunstad et al., 2011; Alosco et al., 2014; Li et al., 2019; Ochner et al., 2012; Holsen et al., 2018; Faulconbridge et al., 2016; Li et al., 2018a; Wiemerslage et al., 2017; Li et al., 2018b; Alamuddin et al., 2017). Interestingly, these effects occurred relatively quickly after surgery and, more importantly, changes in cognitive functioning were long-lasting.

However, the potential of BS to rescue negative impact of obesity on the brain, especially in the long term, should be investigated further. It would be particularly interesting to follow patients for a longer time period after surgery, as BS is known to have disadvantages as well, such as vitamin deficiencies (Bal et al., 2012; Dogan et al., 2017). Besides, it would be of interest to include gut-microbiota and metabolic parameters in these studies to identify underlying mechanisms. As mentioned earlier, more health related benefits associated with BS, such as improved quality of sleep, should be considered in future studies.

In addition, many studies only use BMI as a measure of obesity, although it has been shown that the location of adiposity is an important factor in the risk of brain impairment. For example central obesity is assumed to have a greater risk of developing metabolic disorders and brain impairment. This difference has not yet been

investigated thoroughly and therefore including several obesity measures and comparing the outcome of these measures is advisable for further research. This will not only support to unravel underlying mechanisms, but will more accurately investigate and represent obesity-related effects.

6. Conclusion

Overall, obesity is associated with functional and structural alterations in the brain. There are indications that rapid weight loss after BS can rescue these various pathological effects. This includes changes in cognitive functions, functional brain changes and GM and WM volume and integrity, which may be related to improvement of blood vessel quality, lower blood pressure and less atherosclerosis (Tschoner et al., 2013; Wilhelm et al., 2014). Furthermore, changes in gut microbiota, gut hormones and less systemic inflammation might counteract some of the pathological effects of obesity on the brain (Berthoud et al., 2011; Ballsmider et al., 2015; Sams et al., 2016). Further knowledge on the underlying mechanisms via which these processes influence the brain could be helpful in the development of treatment and prevention of obesity. In the future, longitudinal studies combining neuroimaging, cognition and biological markers (e.g. gut hormones, adipokines, gut-microbiota) are necessary to provide more insight on the effects of weight loss on brain structure and functioning.

Declaration of Competing Interest

The authors declare no competing financial interests.

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