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Structural changes in the obese brain

Anna R.R. Da Conceicao[#], Marcelo N.N. Vieira[#], Fernanda G. De Felice[*]

Obesity represents a major global health concern, with widespread growing prevalence and severe consequences for the quality of life and life expectancy of affected individuals and for the economic burden of healthcare systems (Prospective Studies Collaboration, 2009). Obesity is a well-established risk factor for a variety of conditions including metabolic, vascular, and heart diseases, and several types of cancer (Prospective Studies Collaboration, 2009). In addition, in the past few decades, accumulating clinical and epidemiological evidence associates obesity with cognitive decline and a higher risk for developing neurodegenerative and neuropsychiatric disorders such as Alzheimer's disease (AD), anxiety, and depression. A recent large-scale cross-sectional study concluded that midlife obesity is now the most prominent modifiable risk factor for developing AD and related dementia in the US (Nianogo et al., 2022). Further evidence from a prospective study with 1 million UK women (mean age of 56 years at baseline) shows that a body mass index (the anthropometric marker for obesity) > 30 kg/m^2 at baseline was associated with a higher incidence of dementia 15 years later (Floud et al., 2018).

It is well known that long-term multi-factorial physiological dysregulation resulting from excessive fat accumulation in obesity affects peripheral organs and systems, ultimately rendering them susceptible to developing other diseases. The dynamics behind these effects have been extensively studied and we now have a solid understanding of the underlying molecular mechanisms. They are primarily mediated by altered profile of circulating lipids, aberrant secretion of hormones, and pro-inflammatory cytokines into the circulation by the obese adipose tissue leading to a chronic low-grade systemic inflammation (Banks, 2019).

However, the more recently discovered link between obesity and brain health is a rather obscure subject and a topic of intense current research. Whereas adipose-derived molecules can directly access and target peripheral organs through circulation, their actions on the brain are not straightforward. To reach target sites in the brain and promote disease, periphery-borne molecular signals must cross the blood-brain barrier, a highly specialized interface separating the brain from the periphery with tight permeability constraints. Several mechanisms have been proposed to explain how obesity-triggered peripheral molecules surpass the blood-brain barrier to affect the brain. Though the matter is far from settled, cytokines and hormones, such as insulin and leptin, are key factors appointed in this crosstalk (for a comprehensive review, see Banks, 2019). Understanding the communication between the periphery and the brain and how such interactions may affect central neurophysiological processes in health and disease has become a major goal for scientists. Such knowledge may hold the key to develop effective tools for treatment, prevention, and diagnostics of obesity-related brain disorders. In addition, it may shed light on previously unknown aspects of neurodegenerative diseases.

The deleterious impacts of obesity on the brain sometimes manifest as macroscopic anatomic changes in cerebral structure. Significant atrophy has been found in different brain regions of cognitively healthy obese individuals (Dekkers, 2019), and important similarities between obesity- and AD-associated grey matter atrophy patterns have been described (Morys et al., 2023). Furthermore, animal models of obesity, including genetically modified mice displaying impaired leptin signaling, as well as wild-type mice fed on a high-fat diet, also develop structural and functional abnormalities in the brain. Cognitive decline, anxiety, brain atrophy, and impaired neurogenesis have been consistently reported in such models (Ogrodnik et al., 2019). These studies provide solid evidence that obesity is associated with detrimental changes in brain structure and function, in agreement with epidemiological data.

Pathological alterations in the brains of obese humans are primarily observed through brain imaging techniques routinely used in diagnostics, such as computerized tomography and magnetic resonance imaging. Although those methods have proven highly effective to detect and measure macroscopic changes in brain anatomy (Dekkers et al., 2019), they offer limited information about crucial aspects of cytoarchitecture and cellular composition. The size of the brain and its substructures depends on several independent variables such as the total number of (neuronal and non-neuronal) cells, the average size of cell bodies, dendritic and axonal arborization, vascular structures and extracellular space (Herculano-Houzel, 2005). Since each of these parameters could be independently affected by obesity, macroscopic morphometry of the brain does not provide a complete picture. A more descriptive characterization of obesity-related changes in brain structure, one that includes microscopical parameters such as cell-type specific numbers and densities in different regions, should provide valuable information to advance the understanding of how obesity affects the brain.

In a recent study, we have used the isotropic fractionation method to determine the cellular composition from different brain regions of obese Lep$^{ob/ob}$ and LepR$^{Null/Null}$ mice (Andrade et al., 2022). The isotropic fractionation method offers a simple and accurate technique to study the cellular composition of brain tissue samples by transforming highly anisotropic brain structures into homogeneous and isotropic suspensions of cell nuclei, which can then be immunocytochemically identified as neuronal or non-neuronal nuclei and counted. Isotropic fractionation has been consistently used to study the cellular composition of the brain in a variety of contexts including comparative neuroscience and brain diseases such as AD (Andrade et al., 2022). The Lep$^{ob/ob}$ mouse holds spontaneous mutations in the obese (ob) gene that encodes for leptin, resulting in failure to produce this hormone. The LepR$^{Null/Null}$ mouse model carries a transcriptional blocker in the leptin receptor (LepR) gene that impairs leptin signaling. Both Lep$^{ob/ob}$ and LepR$^{Null/Null}$ mice develop hyperphagia, transient hyperglycemia, reduced energy expenditure, and accelerated weight gain that results in triplicated body size at the adult age. Importantly, both these animals were shown to develop cognitive decline, neuroinflammation, impaired neurogenesis, and synaptic loss, making them suitable models for studying the central impact of obesity.

We found that 10- to 12-month-old female Lep$^{ob/ob}$ and LepR$^{Null/Null}$ mice have reduced neuronal number and density in the hippocampus as compared to wild-type mice (Andrade et al., 2022). This observation is consistent with compromised hippocampal neurogenesis, a feature that has been previously demonstrated in various murine models of obesity. Remarkably, LepR$^{Null/Null}$ mice showed increased density of non-neuronal cells, mainly glial cells, in the hippocampus, frontal cortex, and hypothalamus compared to either wild-type or Lep$^{ob/ob}$ mice (Andrade et al., 2022). We speculate that such an increase in non-neuronal cell population across different brain regions reflects a state of widespread brain inflammation.

Our observations further support the notion that chronic pathological processes triggered by excessive body fat accumulation result in significant harm to the central nervous system. Previously, unreported absolute quantification of neuronal and non-neuronal cell numbers and densities in brain regions of obese animals showed a marked increase in the population of non-neuronal cells in those regions. This is suggestive of chronic and widespread inflammatory response taking place in the brain. Neuroinflammation is a common feature of obese animal models and is believed to play a key role in a variety of neurodegenerative and neuropsychiatric conditions, including AD. In obesity, it remains to be determined the exact cascade of events through which periphery-borne molecular signals surpass the blood-brain barrier to ultimately harm the central nervous system. A deeper understanding of how neural cells are affected may shed light on new mechanisms involved in neurodegenerative processes induced by obesity and how it relates to the development of dementia.

Chronic mild systemic inflammation in peripheral tissues is a well-known consequence of obesity and underlies many of the deleterious processes that raise the risk for developing metabolic, heart, and vascular diseases. Adipose-driven inflammation is thought to be the primary cause of peripheral insulin resistance in obesity-associated type II diabetes mellitus. Importantly, it has been established over the past few decades that neuronal insulin signaling plays pivotal roles in synaptic plasticity, learning, and memory. Moreover, brain insulin resistance has been described as a key pathological feature of Alzheimer's disease and other neurological conditions. There is strong evidence in the literature suggesting that – as is the case in the periphery – insulin resistance in the brain may result from sustained, low-grade central inflammation (De Felice, 2013). It is plausible, therefore, to suppose that obesity would harm the brain primarily by augmenting central inflammatory tonus and thereby producing central insulin resistance and related pathological mechanisms triggered by neuroinflammatory response.

Neuroinflammation appears to be a common pathological feature shared by many neuropsychiatric and neurodegenerative disorders. To expand our understanding of these conditions and the role played by the immune response in each of them, it is crucial to further dissect the particular aspects of brain inflammatory response

in regard to regional distribution, cell types and major molecular pathways involved, and the components that trigger brain inflammatory response.

Allostatic load, a term introduced by McEwen and Stellar in 1993, refers to the activation of chronic stress pathways in peripheral tissues and brain in response to progressive and prolonged exposure to harmful and unfavorable occurrences throughout life. Insulin resistance has been proposed to be a key component of allostatic load, which has been associated with brain neurological and neurodegenerative diseases, including depression and Alzheimer's disease (McEwen, 1998).

Mechanisms underlying insulin resistance in diabetes and obesity, such as chronic inflammation and oxidative stress, emerge from allostatic overload and are believed to be associated with alterations in the brain, including neuroinflammation. Allostatic load may further be linked to alterations in brain structure in obesity, favoring the decrease in the number of neurons and the increase in the number of glial cells. Indeed, allostatic load may be a central mechanism in obesity-induced insulin resistance, since social factors, lifestyle, and comorbidities, identified as risk factors linked to impaired insulin signaling, have been associated with the development and progression of AD (De Felice et al., 2022). Diabetes and obesity-induced insulin resistance are multifactorial diseases. The underlying mechanisms of pathogenesis and reasons why some individuals appear to be more resilient to develop brain abnormalities and cognitive decline while others are susceptible to developing dementia remain to be fully elucidated. It is likely that differences in individual resilience and the relationship between intrinsic biological factors and the prolonged/cumulative stress associated with social and lifestyle challenges that each individual experience in life will lead to allostatic overload and contribute to the development of insulin resistance and the ensuing deleterious effects in the brain (De Felice et al., 2022).

Hence, obesity affects the central nervous system in different ways, from structural changes involving brain atrophy to molecular changes such as hormonal imbalance, oxidative stress, neuroinflammation, and insulin resistance (**Figure 1**). Modifications in lipid profiles, increased blood-brain barrier permeability, and loss of synapse proteins have also been described in obese models (**Figure 1**). These deleterious events lead to allostatic overload and eventually, may result in the death of neural cells. Strategies aimed at decreasing inflammation and allostatic load in obesity such as healthy diets and exercise hold the potential to effectively counteract the detrimental impacts of obesity on the brain.

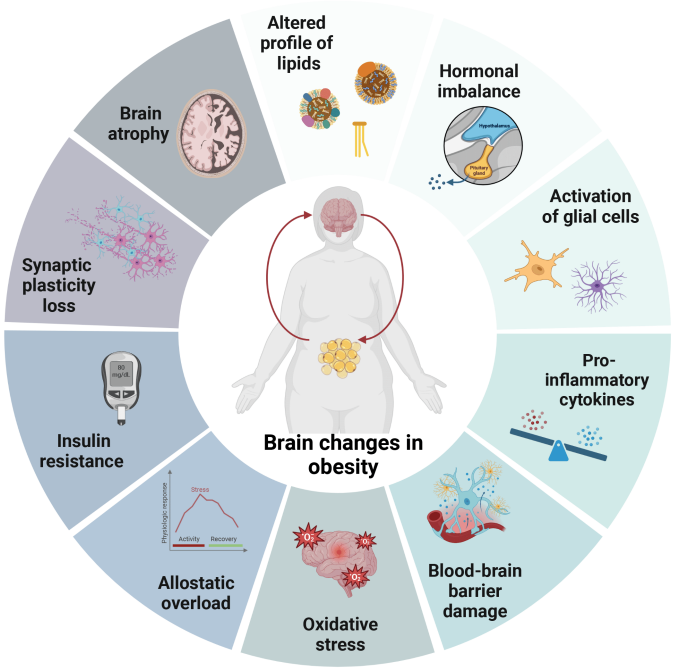

Figure 1 | **Brain changes in obesity.**
Obesity can lead to detrimental effects on the central nervous system. These effects encompass structural modifications and brain atrophy, increases in the number of glial cells, and decreases in the number of neurons. Other alterations include changes in lipid profile, neuroinflammation, oxidative stress, and synapse deterioration, among others. As a consequence, allostatic overload may develop and favor the development of dementia. Created with BioRender.com.

Anna R.R. Da Conceicao[#], Marcelo N.N. Vieira[#], Fernanda G. De Felice[*]
D'Or Institute for Research and Education, Rio de Janeiro, Brazil (Da Conceicao ARR, Vieira MNN, De Felice FG)
Institute of Medical Biochemistry Leopoldo De Meis, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil (Da Conceicao ARR, De Felice FG)
Centre for Neuroscience Studies, Department of Biomedical and Molecular Sciences & Department of Psychiatry, Queen's University, Kingston, ON, Canada (De Felice FG)
***Correspondence to:** Fernanda G. De Felice, PhD, fernanda.defelice@queensu.ca.
https://orcid.org/0000-0001-8358-0589 (Fernanda G. De Felice)
#Both authors contributed equally to this work.
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