ORIGINAL ARTICLE

The Birth of Obesity Neuroscience during the 20th Century

Abstract

Increasing obesity rates are an enduring concern for the health sector globally. By the beginning of the 21st century, neuroscientists began to assert that obesity is primarily a brain disorder. The resulting field of obesity neuroscience has become an influential lens through which to research the pathogenesis of diet-induced obesity, with important implications for both public health and bioethics. This historical analysis aims to trace the intellectual origins of the obesity neuroscience discipline by examining two historical events: the United States' war on drugs, and the nutrition transition. Major historical milestones associated with each of these events are analyzed. Then, the convergence of these events is characterized, by an analysis of how this transformed neuroscience research on hunger. This analysis demonstrates how the US war on drugs discovered new neurobehavioral epistemologies, predominately around addiction, that were then grafted onto the existing neuroscience of hunger. The resulting analysis provides an illustrative explanation of the close epistemological relationship between obesity neuroscience and addiction.

Key words: Diet-induced Neuroplasticity, Addiction Neuroscience, Nutrition Transition, Obesity, Hunger, Bioethics

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Introduction

The world's attention has long been gripped by the rising body weights of its populace. Globally, rates of obesity, as defined as a body mass index ≥ 30 kg/m2, have steadily risen since the mid-20th century (Figure 1). These consistent increases in body weight resulted in the declaration of an obesity epidemic by central United States (US) health organizations at the turn of the 21st century and the reduction of obesity levels as a crucial public health goal (Flegal, 2006, pp. 72-74). In 2021, the US spent an estimated $3.3 billion on the research, prevention, and management of obesity (Estimates of funding for various research, condition, and disease categories, 2022). Despite this extensive investment, the 'war on obesity' continues with little visible progress. The excess adipose tissue, characterizing obesity, often results in several comorbid conditions, both from physiological metabolic alterations (Sharma, et al., 2019, pp. 1341-1349) and the social stigma suffered by obese people (Muennig, 2008, pp. 1-10). Understanding the history of obesity medicine is, therefore, crucial to alleviate the increasing burden these trends place on the healthcare systems globally.

While obesity may be caused by a variety of genetic or hormonal deviations (Yeo, 2018, pp. 3-25), excessive adipose accumulation is most often a result of energy imbalance, resulting from some combination of excessive caloric intake and insufficient caloric expenditure (Hall, et al., 2022, pp. 1243-1254). Both of these factors have drastically changed in modern society. Technological automation has reduced the everyday need for humans to exercise, and rates of exercise globally have been decreasing (Park, et al., 2020, p. 366). While these trends are undoubtedly an important contributing factor to rising obesity rates, in this article I instead focus on the other key variable driving increases in body weight: excessive caloric intake due to shifts in the modern diet.

Obesity neuroscience examines the organ responsible for choosing overconsume food: the brain. This field has expanded rapidly in the 21st century; over half of US and Australian citizens surveyed believed that obesity should be treated as a brain disease (Lee, et al., 2013, p. 3). However, the debate has recently emerged questioning the efficacy of obesity neuroscience in developing obesity treatments, as well as highlighting the fields' potential for increasing weight-based stigma (Santiago, et al., 2022, pp. 1-23; Throsby, 2020, pp. 12-16). Despite this, there are relatively sparse historical examinations of obesity neuroscience as a field. The purpose of this article is to examine the relevant neuroscience research that occurred parallel to the beginnings of the obesity epidemic in order to illustrate the intellectual origins of obesity neuroscience.

Methodology

Peer-reviewed literature, policy documents and archived conference proceedings that were developed in response to the emerging obesity crisis were examined. An analysis of neuroscience advances paralleling this period was also conducted. Particular milestones considered are the identification of specific nutrients in obesity pathogenesis, the US war on drugs and the discovery of the mesolimbic dopaminergic

system. These findings are then synthesised to demonstrate how their shared temporal history gave rise to the modern field of obesity neuroscience.

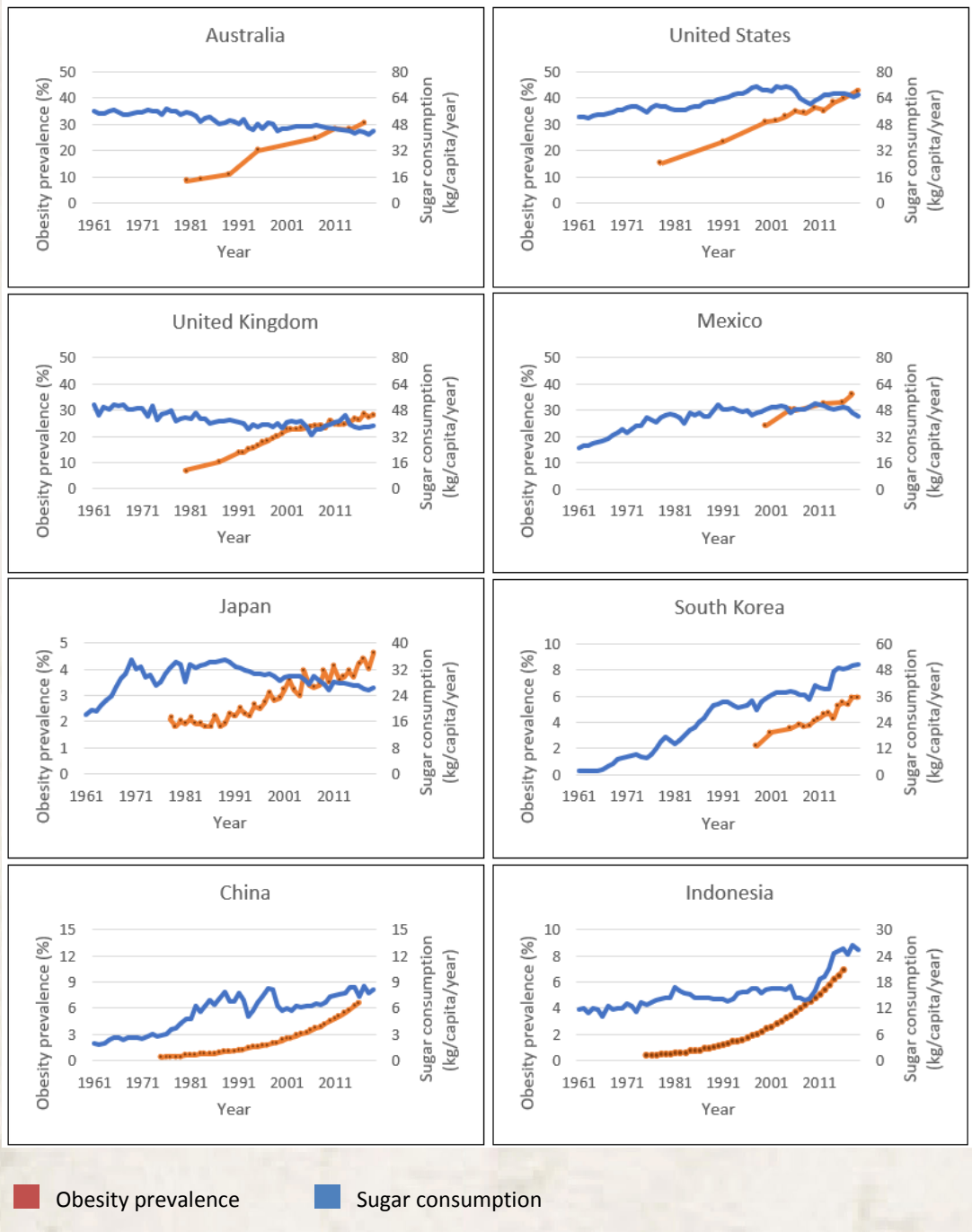

Figure 1. Estimated obesity prevalence (defined as a BMI above 30 kg/m2) and sugar consumption in selected Western and non-Western countries from 1961to 2019. Data were sourced from the Food and Agriculture Organization of the United Nations (2022) and downloaded from the OECD (2022).

The emergence of the obesity epidemic

In the past, diet was studied mainly only in the context of malnutrition (Carpenter, 2003, pp. 975-984). The dangers of excessive nutrition were first considered when non-communicable, chronic diseases began rising in developed countries with ageing populations around the beginning of the 20th century. In 1928, the UK Registrar General redefined stroke mortality to highlight atherosclerosis as the underlying pathology responsible for death (Bartley, 1985, p. 295; The Registrar General's statistical review of England and Wales, 1928, p. 84). Deaths due to atherosclerosis were increasingly reported in the following decades (Michaels, 1966, pp. 258-264). The intuitive cause of atherosclerosis was dietary fat, given that these diseases coincided with fatty arterial plaque. Dietary fat was considered to be a predominant cause behind the emerging obesity epidemic and a public health crusade followed in an attempt to reduce the public's dietary fat intake (Keys, et al., 1966, pp. 1-392). The validity of these nutritional claims was the subject of bitter debate in the medical community (Olszewski, 2015, pp. 218-249). However, public health authorities decided to ignore these debates to ensure a simple message to the public: reduce saturated fat intake. Low-fat food items became a staple of the late 20th century and dietary fat consumption decreased nationally across both the US and the UK; "99% fat free became a health claim" (Thornley and McRobbie, 2012, p. 61).

Decades after its research was applied to public health initiatives, the medical research underpinning the villainization of dietary fat was found to be biased. Food industries that produced and marketed high-sugar products were repeatedly found to have influenced the design and reporting of major studies (Moss, 2014, pp. 292-321), as well as public opinion. The willingness of the industry to intervene in nutritional research can be seen in several correspondences from Henry Hass, director of the Sugar Research Foundation (1949-1961):

> *"The ignorance about sugar on the part of even intelligent, well-educated people is astonishing. It often includes a great deal of misinformation. It needs to be removed. It is for these reasons that I am unhappy about advertising which implies that sugar is in some unique sense the cause of obesity. I do not think that coal-tar sweeteners are, in themselves, of surpassingly great importance to the sugar industry. The attitudes toward sugar which No-Cal advertising fosters will, unless vigorously opposed by efforts of the sugar industry, make it impossible for us to grow into the place in the American diet which we should rightfully occupy."* – (Hass, 1954, p. 21)

The sugar industry's efforts resulted in underestimating the health risks of sugar overconsumption and overestimating the health risks of fat overconsumption (Kearns, Schmidt, and Glantz, 2016, pp. 1680-1685). Reporting guidelines for large-scale epidemiological studies were also not mature, resulting in some researchers omitting data that did not fit the prevailing narrative (Ramsden, et al., 2016, pp. 13-15). Historical analyses ultimately confirm that much of this early research implicating dietary fat as the predominant cause of the obesity epidemic was warped and inaccurate (DuBroff and Lorgeril, 2021, pp. 3-7). At the time, however, these false

findings formed the basis of a public health strategy to "Blitzkrieg the community" (Skrabanek, 1994, p. 87; Yanchinski, 1981, p. 223) with messaging to reduce their dietary fat intake. Given the high cost of protein, dietary fat was instead replaced with dietary carbohydrates, often in the form of sugar (Connor and Connor, 1997, pp. 562-563; Thornley and McRobbie, 2012, pp. 33-59). As a result, sugar consumption rose in the 2nd half of the 20th century, marking a secular shift in the Western diet likely underpinning the enduring obesity epidemic to this day.

Sugar intake, rather than dietary fat, predicts the prevalence of obesity in epidemiological studies (Bentley, Ruck, and Fouts, 2020, pp. 1-7; Faruque, et al., 2019, pp. 219-233). Globally, sucrose consumption is predicted to rise in a vast majority of countries (OECD-FAO Agricultural Outlook 2021-2030, 2021, pp. 150-162; Sugar: World markets and trade, 2022; Figure 1). The consumption of sucrose greatly exceeds public health recommendations; Americans currently consume triple the recommended maximum daily amount of sugar (Faruque, et al., 2019, p. 225). The percolation of sugar into global diets is rooted in its discovery by the British Empire in the 16th century (Mintz, 1985, pp. 51-60; Thomas, 1968, pp. 30-45). Before this period, sugar was perceived as a luxury product similar to spices, and reserved for the world's elite. However, given its cheap production, long storage life and ability to avoid inducing satiation when consumed, the production and consumption of sugar were massively upscaled (Mintz, 1985, pp. 51-60). This particular scenario is associated with the rise of capitalism more broadly, given that sugar was one of the first products that customers could increasingly consume (Mintz, 1985, pp. 75-150; Wells, 2016, pp. 283-291). As globalisation advances, sugar consumption has increased in developing nations (Figure 1). Such a fast dietary shift supports the hypothesis that a sudden obesity epidemic can be more greatly attributed to sugar overconsumption than fat overconsumption.

Dietary choices are made by the brain

Despite vast research conducted on sugar's capacity to generate obesity, there has always been an obvious strategy to avoid obesity: limiting the intake of obesogenic foods such as sugar. Regardless of the specific dietary advice provided, eating less will result in weight loss. Public health campaigns have successfully percolated this message, and it is common knowledge amongst most. Therefore, why are obesity rates still high? Why are so many people seemingly choosing to consume excess food against their health interests? The obesity epidemic survives as a result of the widespread choice to overconsume. Descartes would consider these choices orchestrated by the *res cogitans* (the mind/spirit), rather than the *res extensa* (the material body) (Descartes, 1649, pp. 1-83). This dualist view of mind and brain heavily influenced neuroscience in the 17th century. Over the past century, neurophilosophical developments deny such Cartesian dualism, instead providing compelling theses that consciousness, behaviours and choices are an emergent property of the physical body (Churchland, 1989, pp. 242-317; McCulloch, and Pitts, 1943, pp. 115-133; Ryle,

1949, pp. 1-13; Smart, 1959, pp. 141-156; Turing, 1950, pp. 433-460); the mind and the body are currently considered one. Therefore, a bottleneck in the war on obesity lies in the organ responsible for coordinating our motivations and choices to overeat: the brain. The interactions between food overconsumption and the brain must be considered to understand how food overconsumption persists despite its clear danger.

The brain's basis for hunger

Hunger has long been thought to be centrally coordinated by the brain and not the stomach (Boring, 1915, pp. 306-331). Seminal work distinguished the acute, gastrointestinal sensation of hunger from the less tangible desire of appetite (Carlson, 1916). Lesioning and electrical stimulation studies in the mid-20th century discovered key 'feeding centres' in the brain ; damage to these regions would drastically alter feeding, causing the animals to either starve or become obese (Anand and Brobeck, 1951, pp. 323-325; Delgado and Anand, 1952, pp. 162-168; Hetherington and Ranson, 1942, pp. 609-617). These feeding centres were all localised within the hypothalamus, an evolutionarily conserved diencephalic structure which surrounds the 3rd ventricle. The position of the hypothalamus allows it to sense peripheral metabolic cues from the adjacent cerebrospinal fluid (Langlet, 2014, pp. 753-760), as well as afferent projections from neurons encoding the status of the gastrointestinal tract (Aklan, et al., 2020, pp. 313-326). Various nuclei within the hypothalamus then coordinate with other brain regions to regulate feeding behaviour accordingly, maintaining homeostasis. While this simplistic model explains how hunger is broadly regulated, it cannot explain why many people have an excessive appetite and overconsume food beyond their homeostatic limits.

The brain's basis for appetite

By the end of the 20th century, Schultz and colleagues (1997) discovered the neural substrates underpinning a circuit that reinforces goal-directed behaviours: the mesolimbic dopaminergic system . This system includes the ventral tegmental area, which contains dopaminergic neurons that encode reward prediction (Lüscher, and Janak, 2021, pp. 173-195). Upon activation, these neurons release dopamine at the nucleus accumbens and the prefrontal cortex (Figure 2). This system has a conserved evolutionary function to facilitate the compulsion for behaviours that increase survival, such as drinking, mating, and feeding (Scaplen, and Kaun, 2016, pp. 133-148). Each of these activities results in a release of dopamine into the nucleus accumbens and simultaneously produces a qualia described as pleasure, increasing the animal's motivation to repeat the same activity in the future (Ikemoto, and Panksepp, 1999, pp. 6-41). Most knowledge of this system did not stem from appetite research, as obesity was not a public health priority when this circuit was first characterised. Instead, public health efforts in the nation that dominated neuroscience research into reward were preoccupied with "*public health enemy number one*" (Nixon, 1971; archived by Richard Nixon Foundation, 2016): addictive drugs.

In the early 1970s, under the presidency of Richard Nixon, the United States began to expand its funding for preclinical research into the neural regulation of motivation and reward (Vrecko, 2010, pp. 52-67). Such action was justified by citing increased rates of heroin use in returning Vietnam War Veterans (Holloway, 1974, pp. 108-113), but motivated by drug use in the expanding, politically-opposed counterculture movement (Kuzmarov, 2009, pp. 1-303; Rodrigues and Labate, 2016, pp. 11-32). The resulting research constructed the enduring paradigm that drugs of abuse, such as morphine, cocaine, alcohol and nicotine, all 'hijack' the evolutionarily conserved mesolimbic dopaminergic system and increase dopamine release within the nucleus accumbens (Di Chiara and Imperato, 1988, pp. 5274-5278; Roberts, Corcoran, and Fibiger, 1977, pp. 615-620; Wikler, Norrell, and Miller, 1972, pp. 543-557). In addition, their chronic use induces enduring neuroplastic changes in this system which reinforce addicts' experiences of craving, tolerance and withdrawal (Huang, et al., 2018, pp. 331-339; Wise and Robble, 2020, pp. 79-106; Xiong, et al., 2018, pp. 289-303). Addiction had accordingly shifted from previously being considered a moral deficiency, to a brain disease (Leshner, 1997, pp. 45-47). Such a conceptualisation of addiction is still endorsed by major governmental bodies, such as the National Institute of Drug Abuse (2020), empowering it as the orthodoxy view in clinical practice. To this day, drugs that counter this hijacking of the mesolimbic dopaminergic system are being developed and used to treat people with drug addiction (Burnette, et al., 2022, pp. 251-274). Increasingly, the brain disease model of addiction is being adopted to analyse the excessive appetite assumed to underpin obesity. This overlap is best summarised by Foddy's (2011) paper title: "addicted to food, hungry for drugs".

Obesity as an addiction to food

Prior to the war on drugs, food addiction was only scantly discussed by neuroscientists (Hebb, 1949, p. 203; Randolph, 1956, pp. 198-224). After the mesolimbic dopaminergic system became implicated in drug addiction, a handful of seminal experiments investigated the potential for food to stimulate pleasure through similar biological mechanisms. Colantuoni (2001, 2002) measured the neurological effects of palatable food intake in animal models. The intake of sugars appeared to mimic the dopamine-stimulating effects of drugs of abuse. These findings generated significant interest in the addiction frame of obesity and sparked further studies seeking to identify whether sugar consumption similarly affected the mesolimbic dopaminergic system to drugs of abuse. Subsequent data supported the addiction frame. For example, when sugar is ingested, dopamine release in the nucleus accumbens is initiated by both the activation of sweet receptors on the tongue as well as taste-independent processes (Ren, et al., 2010, pp. 8012-8023). These data ultimately bolstered hypotheses of sugar addiction as a contributing culprit to the obesity epidemic. As a result, obesity research became a neuroscientist's domain.

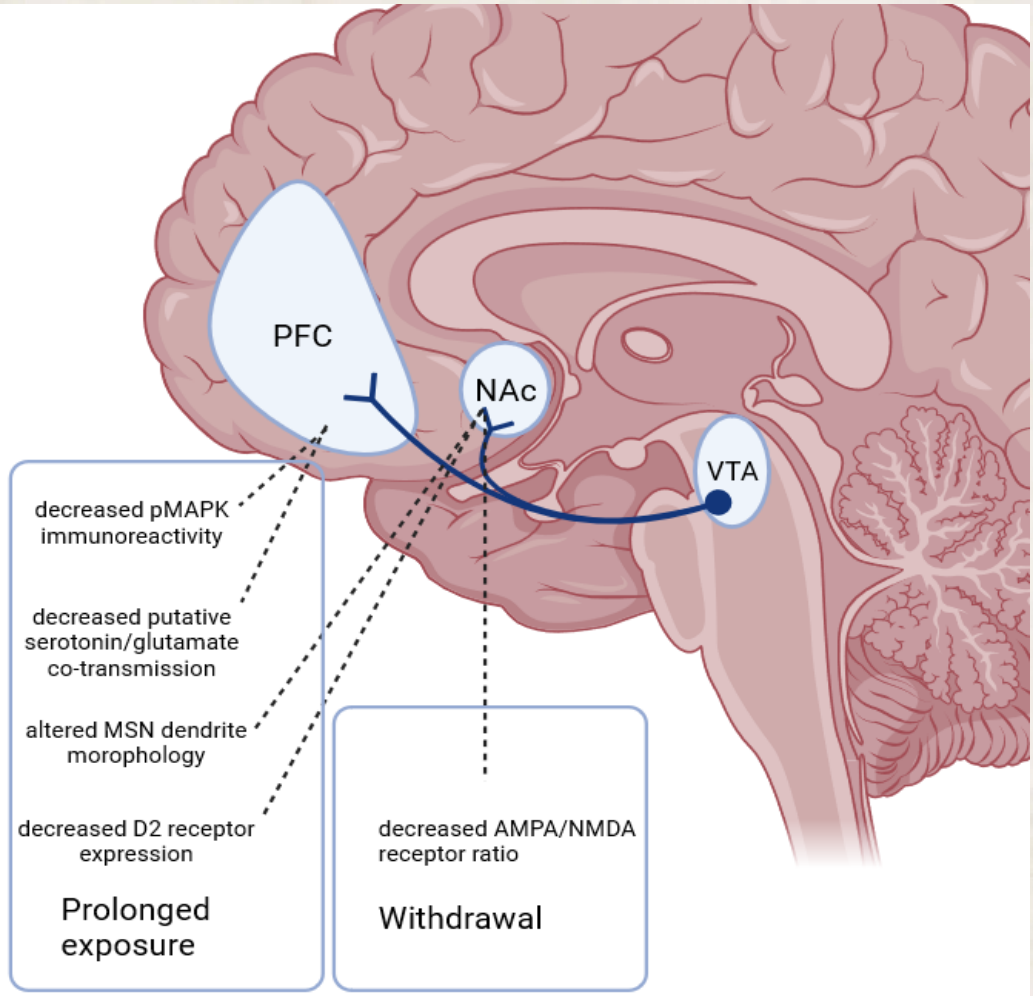

Figure 2. Basic schematic of the mesolimbic dopaminergic system. Neurons from the ventral tegmental area (VTA) release dopamine at the nucleus accumbens (NAc) and prefrontal cortex (PFC) in response to pleasurable stimuli. Prolonged exposure to dietary sucrose alters several aspects of this system. Sugar induces plasticity in the PFC, for example, through alteration in pMAPK signalling and potentially through glutamate/serotonin co-transmission (Beecher, et al., 2021b, pp. 1-11). In a rat model, a high-sucrose diet reduced dopamine type-2 receptor expression in the NAC shell (Bello, Lucas, and Hajnal, 2002, pp. 1575-1578). Prolonged sucrose consumption alters the dendritic morphology of median spiny neurons in the NAC shell, likely increasing the excitability of this region (Klenowski, et al., 2016, pp. 1-10). Withdrawal from sucrose in rodents also decreases AMPA/NMDA ratios in NAC neurons that receive input from the PFC in rats (Counotte, et al., 2014, pp. 1675-1684). Figure produced using Biorender software.

As previously discussed, 20th century ablation studies in non-human mammals had already demonstrated that regions of the brain regulated eating. For addiction to persist, the reverse process must also occur – food must regulate the brain. Eventually,

it was discovered that overconsuming palatable, obesogenic foods, like other substances of abuse, prompts enduring neuroplastic changes in the brain's reward system (Figure 2). While these findings cannot be replicated in human studies, attempts have been made to triangulate experimental data on diet-induced neuroplasticity with brain imaging data. For example, compared to non-food-addicted controls, food-addicted humanshave altered activation in the pre-frontal cortex following the anticipation and receipt of a sweet beverage, as detected by functional magnetic resonance imaging (Gearhardt, et al., 2011, pp. 808-816). The vast majority of these studies, human and non-human, either assess the neuroplastic effects of a high-sugar diet, high-fat diet, or a combination of both (Beecher, et al., 2021a, pp. 1-15; Bocarsly and Avena, 2021, pp. 173-185; Wang and Beecher, 2021, pp. 1-9). These studies are all built upon a theoretical and methodological framework used to research the neuroscience of drug addiction.

Conclusion

This article sought to examine the historical convergence of neuroscience and obesity. The field of obesity neuroscience developed due to the simultaneous occurrence of two historical events in 20th-century America: the nutrition transition and the war on drugs. Each of these events was researched separately by the medical community. However, by the end of the 20th century, diet-induced neuroplasticity that mirrored the effect of drugs on addiction was discovered. This discovery connected addiction neuroscience and obesity medicine. The neuroscience of drug addiction was adopted as an explanatory model for continuingly rising obesity rates, and the concept of food addiction remains a popular explanation of obesity pathogenesis in the modern world. It is important for current obesity neuroscience researchers to examine the limitations of its narrow epistemological origin (Wang, et al., 2023, pp. 295-311) in order to explore the reality of obesity pathogenesis more comprehensively.

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Conflict of Interest

None.

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