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The Cafeteria Diet: a standardized protocol and its effects on behavior

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Highlights

- Cafeteria (CAF) diet has high construct validity.
- CAF diet induces hyperphagia and metabolic syndrome better than other diets.
- A CAF protocol should include different nutrients, tastes, textures, etc.
- A CAF protocol should rotate and be voluntary.
- CAF diet alters reward preferences and tends to reduce stress and spatial memory.

Abstract

Obesity is a major health risk, with junk food consumption playing a central role in weight gain, because of its high palatability and high-energy nutrients. The Cafeteria (CAF) diet model for animal experiments consists of the same tasty but unhealthy food products that people eat (e.g. hot dogs and muffins), and considers variety, novelty and secondary food features, such as smell and texture. This model, therefore, mimics human eating patterns better than other models. In this paper, we systematically review studies that have used a CAF diet in behavioral experiments and propose a standardized CAF diet protocol. The proposed diet is *ad libitum* and voluntary; combines different textures, nutrients and tastes, including salty and sweet products; and it is rotated and varied. Our summary of the behavioral effects of CAF diet show that it alters meal patterns, reduces the hedonic value of other rewards, and tends to reduce stress and spatial memory. So far, no clear effects of CAF diet were found on locomotor activity, impulsivity, coping and social behavior.

Keywords: Cafeteria Diet, Western Diet, Junk Food, Obesity, Animal Model, Systematic Review, Food Preference, Stress, Memory, Reward System

The numbers of people who are overweight or obese have now reached epidemic levels globally and prevalence continues to increase dramatically. Worldwide, one-in-three adults are now overweight

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or obese (Ng et al., 2014; WHO, 2020) and children have a high-risk of becoming so later on (NCD Risk Factor Collaboration, 2017). Being overweight or being obese is a major risk factor for developing numerous diseases, including metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease and certain types of cancer (Klil-Drori et al., 2017; Leggio et al., 2017). Obesity is also linked to an increased risk of developing mental health problems, including depression and, potentially, addiction (Luppino et al., 2010; Ouakinin et al., 2018; Volkow et al., 2017; Ziauddeen et al., 2012). Because of these disease associations, the cost of obesity is overwhelming in terms of both quality of life and healthcare expenses (Malik et al., 2013). For example, the medical cost attributable to obesity in the US alone was $149,4 billion in 2014 (Kim and Basu, 2016). The need to understand the obesity epidemic's underlying causes is, therefore, essential.

There are many reasons for the severe increase in overweight and obesity prevalence in recent decades. While there is high variability in the literature, genetic factors appear to be responsible for 40-70% of the variation in body mass index (BMI) (El-Sayed Moustafa and Froguel, 2013; Pigeyre et al., 2016). However, it is environmental factors that have revealed genetic predispositions to weight gain and to becoming overweight or obese. One of the most important has been the lifestyle changes that have occurred over the last three decades (Blüher, 2019; Van Der Klaauw and Farooqi, 2015). Examples of obesogenic lifestyle changes include living in urban areas, globalization, low levels of physical activity, sedentary leisure activities, and changes in shopping routines (Hruby and Hu, 2015; Malik et al., 2013).

The other major player in this obesity epidemic has been diet. In particular, excessive consumption of highly palatable sugar and fat laden foods, often in the forms of "junk" or "fast" food, plays a central role in the development of obesity in humans (Basu et al., 2013; Mozaffarian et al., 2011; Rosenheck, 2008). Epidemiological studies have shown that an increase in junk food consumption is associated with weight gain and greater risk of type 2 diabetes (Fraser et al., 2011; Pereira et al., 2005). The excessive consumption of junk food is due mainly to its hedonic component and junk food's influence on the reward system (Leigh and Morris, 2018). Therefore, understanding how junk food

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consumption affects the nervous system to affect emotion, cognition and behavior promises to provide key insights into the etiology of overweightness and obesity.

In this review, we will introduce the obesogenic animal model of Cafeteria (CAF) diet and compare this diet with the traditional diet-induced obesity model: high- fat, sugar and/or carbohydrate diets. Then, we will propose a *standardized* CAF protocol and, finally, evaluate the effects of consuming a CAF diet on behavior. We note here that while genetic models are very useful for obesity research, they are beyond the scope of this review. For an excellent review of genetic models, we refer the reader to Kleinert *et al.* (2018). For this review of diet-induced models, we begin with the importance of animal models and their validity for studying the obesity epidemic.

Animal models to induce obesity

Animal models play a crucial role in both basic and clinical research. It is fundamental to have valid animal models to approach and mimic human's disorders, including neuropsychiatric conditions (Belzung and Lemoine, 2011). Willner classified three validity criteria: predictive, face and construct validity (Willner, 1984).

Predictive validity evaluates the effects of therapeutic agents in laboratory animals. Predictive validity is high, if a treatment works for both animals and humans, and thus a drug's effects in animals predict its actions in humans. In other words, the effectivity of the treatment in animals has to correspond with the effectivity in humans. However, predictive validity focuses in particular on pharmacological treatments and does not consider the bio-psychological mechanisms that induces the pathological state in the animal. The forced swim test is for example a good screening test for antidepressant pharmacological treatments, because antidepressant drugs systematically increased active coping behavior (climbing) in this test, and has therefore a high predictive validity. However, the biological underground of the behavioral despair in the forced swim test, as well as its behavioral interpretation, cannot be totally and exclusively linked to "depression". Therefore, the forced swim test has low face and construct validity (Commons et al., 2017).

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Face validity is based on phenomenological, behavioral and physiological similarities, in a sense; does the animal model look like the human condition, reproducing the key symptoms of the disorder? But since face validity in the Willner's model also includes some treatment characteristics, we prefer the definition of Nestler and Hyman (2010) that postulates face validity as "the recapitulation in an animal model of the important anatomical, biochemical, neuropathological or behavioral features of a human diseases". In order words and paraphrasing Belzung and Lemoine (2011) "face validity corresponds to an attempt to mimic diagnostic criteria of the psychiatric conditions". The only details that these definitions are missing are the biological and/or the environmental mechanism that causes the pathology, disorder or psychophysiological alteration modeled in laboratory animals. Olfactory bulbectomy, for example, is a model of depression with high predictive and face validity, because it causes several depressive-like behaviors like anhedonia and antidepressant drugs reverse that symptomatology (Morales-Medina et al., 2017). However, even though rodents rely on olfactory information on numerous psychophysiological processes, depression is just not caused by the olfactory bulb ablation, lesion or dysfunction.

Finally, construct validity considers if the apparent symptoms and other manifestations of a disease that are observed in an animal model are generated via the same mechanisms that cause them in humans. Construct validity is, for that reason, related to a sort of "etiological validity" – are the underlying causative mechanisms shared between disease and model? Therefore, the greatest construct validity is achieved when an animal model is generated by the same factors that cause the human disorder. In other words, an animal model with high levels of construct validity should ideally be recreated by the same causes that afflicts humans (Belzung and Lemoine, 2011; Nestler and Hyman, 2010). For example, sleep deprivation in rodents has been established as a valid model for bipolar mania, because sleep changes and circadian rhythm alteration can often trigger maniac episodes in humans (construct validity), but also produce mania-like behaviors like aggressiveness or hypersexuality (face validity) and lithium or haloperidol (*two pharmacological treatments*) reverse these symptoms (predictive validity) (Logan and McClung, 2016). Another example is cannabis administration as a model for schizophrenia, which exhibits good levels of construct validity, because cannabis is a risk factor for schizophrenia mostly in youngsters (Chesworth and Karl, 2017).

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Because the animal models that will be presented herein are designed to mimic the current western society's dietary pattern and induce obesity rather than to treat it, predictive validity is not considered in this review. Notably, existing pharmacological treatments and lifestyle interventions for reducing obesity have been proven not to be effective or are difficult to maintain (Reinehr, 2018; Van Gaal and Dirinck, 2016). This lack of effective treatments for obesity underscores the importance of generating valid animal models that induce weight gain and obesity so as to allow the development of effective new treatment approaches for either preventing or reversing obesity in the human population (Nilsson et al., 2012). Therefore, one must choose the most adequate animal model based on its advantages and disadvantages related to the scientific objective.

High fat/high sugar diets

Traditionally, high-fat and/or high-sugar (HF/HS *for high-sugar, high-fat or the combination of both*) diets have been the preferred way to induce obesity and its associated pathologies (for a review, Kleinert et al., 2018). This type of diet has a high face validity as it induces the same metabolic consequences found in humans, for example, obesity, metabolic syndrome, and an insulin-resistant phenotype. In models using HF/HS diets, animals are fed pellets with a high content of nutrients that are associated with obesity, such as fat, sugar, oil and/or carbohydrates (Small et al., 2018). The main advantage of this model, compared to other diets to induce obesity, is that it allows the experimenter to have control over all the nutrients and energy that an animal receives. For example, with a HF/HS, you can determine the amount, percentage and type of proteins, minerals and vitamins in each pellet and, in consequence, consumed by each animal.

However, a large disadvantage of HF/HS diets is that they do not mimic actual human behavior. Humans do not consistently consume the same ultraprocessed food (Box 1) with the same extra sugar and/or extra fat as found in HF/HS pellets. Instead, they typically eat unhealthy products due to their taste, texture, novelty, and variety (McCrickerd and Forde, 2016). In addition, since HF/HS diets often contain higher levels of fat than humans usually consume (>45% energy/calories -*%kcal*- from fat in animal models versus ~30-35% in humans (Bennett et al., 2018; Bergström et al., 2020; Vadiveloo et

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al., 2014), HF/HS diets do not model human fat intake appropriately. In order to mimic the current nutritional profile of junk or ultraprocessed food and solve the unbalanced percentage of fat, there are special HF/HS pellets, often called "Western Diet", with higher levels of carbohydrates and lower levels of fat than traditional HF/HS pellets (e.g. Research Diets: D12079B or Envigo/Teklad: TD.88137; Holton et al., 2019; Pistell et al., 2010). Finally, hypophagia (*a reduction in food intake*) is often seen in studies using HF/HS models compared to other diet-induced obesity models like CAF diet, which could be a result of a lack of variety in the sensory properties of the HF/HS pellets. It was found, for instance, that rats start to consume less calories over time when exposed to HF/HS pellets for several weeks. But when a novel aspect was added to the pellets, the presentation of food on different dishes and the free choice between HF/HS and standard (STD) chow, the caloric intake of the HF/HS diet was not reduced (La Fleur et al., 2014). This suggests that willingness and variety are important elements as well. A study that compared obesogenic diets interestingly found that only CAF diet, but not high-fat pellets, increased caloric intake compared to STD chow (Oliva et al., 2017). In a recent review, Leigh *et al.* (2018) explained that palatable food can increase eating due to stimulation of both sensory and rewarding brain areas, as well as regions involved in food intake. Thus, it could be hypothesize that the uniformity and lack of sensory variety of the HF/HS pellets may explain the hypophagia for this sort of diet compared to other diet-induced obesity models.

Hence, although the HF/HS model is a useful diet-induced obesity model and has the advantage of controlling all the nutrients and energy that animals receive, it does not demonstrate good levels of construct validity, because it does not mimic the current human's dietary pattern involved in the obesity epidemic.

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Box 1: From the tree to the factory: the NOVA classification

A classification system (NOVA) has been proposed according to the level of industrial elaboration of a food (Monteiro et al., 2017). *Unprocessed or minimally processed food* are those products that are consumed without any industrial manufacturing or addition of nutrients, such us fat or sugar, e.g. fresh eggs or an avocado. *Processed culinary ingredients* are extracted from unprocessed products, for example olive oil. *Processed food* contains nutrients added to the original food, but with minimal industrial manufacturing, examples include cheese or natural canned beans. In other words, processed food contains "processed culinary ingredients" added to the "unprocessed food". *Ultraprocessed food* has been industrially manufactured and artificial or processed nutrients have been added. Junk food, and so CAF diet, is classified as *Ultraprocessed food*.

Cafeteria Diet

Scientists started to use CAF diets to study obesity in the 1970s (Sclafani and Springer, 1976), but the popularity of CAF diets has increased in the last decade. As stated above, it entails giving lab animals unlimited access to a varied diet of foodstuffs that human consume as junk food. Here, we argue that the model has excellent construct and face validity.

First, we will consider construct validity. In this model, laboratory rodents eat the same ultraprocessed, unhealthy but tasty, products that humans consume (e.g. bacon, muffins and cookies), and which can be easily obtained from supermarkets and fast food restaurant. For this reason, it is also called the "Junk Food Diet", "Supermarket Diet" or "Western Diet". Therefore, the CAF diet model mimics a certain pattern of problematic human consumption. Importantly is recapitulates the orosensory properties (such as smell and texture) and palatability of the foodstuffs that promote overconsumption. Using CAF diet, the metabolic and behavioral causes of eating junk food are the same in rodents and humans, as both shares the same etiology.

Indeed, food preference and overeating are triggered by more than merely the nutritional composition of food. The hedonic properties of food types must be taken into account when evaluating obesogenic models. The CAF diet model, unlike the HF/HS, considers these hedonic properties by

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offering the orosensory response of the type of food in addition to its nutritional components. The hedonic properties of junk food products activate the primary and secondary gustatory cortices and also stimulate the reward system in a way similar to how drugs of abuse activate the reward system (Kenny, 2011a; Volkow et al., 2017).

The CAF model also has a good face validity as an obesogenic model. It has been proven to not only increase body weight and induce obesity, but to also cause metabolic syndrome, severe diabetic symptoms, liver inflammation, and other metabolic dysregulations (Gomez-Smith et al., 2016; Lalanza et al., 2014; Lewis et al., 2019; Macedo et al., 2012; Morris et al., 2008; Mucellini et al., 2014; Romero et al., 2014; Suárez-García et al., 2017). In fact, CAF diet induces obesity and its comorbid metabolic dysregulation and pathologies more efficiently than HS/HF diets (Buyukdere et al., 2019; Gual-Grau et al., 2019; Sampey et al., 2011; Zeeni et al., 2015a).

Furthermore, as overeating is a prominent factor in the development of obesity, a valid model for obesity must also induce overeating itself. The CAF diet, indeed, produces hyperphagia in rodents just as observed in humans consuming junk food (Goularte et al., 2012; Sampey et al., 2011; Shafat et al., 2009; South et al., 2012). For example, a study investigating energy intake found that human participants ate ~500kcal more per day in the ultraprocessed diet condition than in the unprocessed diet condition (Hall et al., 2019). This difference was seen despite both diets containing the same amounts of total calories and nutrients. The study, hence, eliminated these factors as underlying reasons for the difference in energy intake, and showed that industrial food processing altered consumption.

Therefore, the CAF diet is a valid model to mimic the current food system, full of junk and ultraprocessed food products, because the CAF model is composed of exactly this type of food. Furthermore, the CAF diet has been demonstrated to be a good model not only for inducing metabolic alterations, but also for studies investigating neurobehavioral changes. However, depending on the research question, HF/HS, CAF diet or other obesogenic model will be the best choice.

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Objective of this review

Notwithstanding these promising features of the CAF model, there is still a lack of consensus regarding the exact ingredients and food products that should be included in the diet, as well as disagreement over the way the food is administered (Barrett et al., 2016; Nilsson et al., 2012). Each research laboratory uses a different CAF protocol. Critically, the additives contained in the ultraprocessed food products are typically unknown and could, in theory, significantly alter study outcomes (Bortolin et al., 2018). Although cultural and regional differences are relevant for translational approaches, a *gold standard* of the basic ingredients is necessary for inter-laboratory comparisons, as well as increasing nutritional control. Therefore, the first objective of this review is to propose a standardized protocol for CAF models based on the most used food products and ways of administration.

Next, since the CAF diet has only recently become a widely used obesogenic model, its effects on behavioral outcomes are not yet well-established. Thus, the second objective of this review is to summarize and evaluate the main impact of CAF diet on rodent behavior.

The CAF diet model

The first part of this review evaluates the procedures used to provide a CAF diet in studies that assess the effects of CAF on behavior. And it has the goal of proposing a new standardized CAF protocol.

We followed a systematic review methodology in order to increase the validity of the proposed protocol and to reduce search bias. In September 2019, we searched in PubMed, Scopus and Web of Science databases with the following search syntax: (“Cafeteria Diet” or “Junk Diet” or “Cafeteria Food” or “Junk Food” or "Western Diet" or "Western-Style Diet" or "Western-Style Dietary Pattern" or "Supermarket Diet") and (Behavior or Behavioural or Neuroscience or “Behavioural Neuroscience” or “Behavioral Neuroscience” or Psychobiology) and (Rat or Rats or Mouse or Mice or Rodent or Rodents). We restricted our search to rats and mice, because these are the most commonly used species for obesity studies. We also searched for studies in the reference list from the main reviews and included studies from databases.

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Ultimately, we included 50 studies regarding CAF diet and behavior assessment in wild type rats or mice that included at least one experimental group fed exclusively with CAF diet (minimum two products) and one control group fed with STD chow.

Because variety in food products is an important component of the CAF diet – so that animals are able to choose what they prefer to consume – studies using only one product were not included in this review. For example, using only sandwich cookies with cream in a binge addiction-like model (de Jong et al., 2013) or chocolate for partially counteracting the effects of stress (Krolow et al., 2010) was not sufficient to be included. The main findings regarding the CAF protocol in each included study are shown in Table 1.

Type of animal, housing, and age

90% of studies (45/50) were carried out in rats, with Sprague-Dawley and Wistar rats being the most commonly used strains. That rats are so often used, might be cause by the fact that traditionally, rats are widely used in behavioral studies due to its enhanced cognitive skills, tendency for additive-like behaviors and impulsivity, and richer social structure. Mice, on the other hand, are primarily used in biomedical science and genetic research (Ellenbroek and Youn, 2016). In general, there are no significant metabolic differences between mice and rats (Buettner et al., 2007; Hariri and Thibault, 2010; Kleinert et al., 2018).

In behavioral research, Sprague-Dawley and Wistar are the preferred strains (Ellenbroek and Youn, 2016). Interestingly, when comparing the effect of long-term (17 weeks) HF/HS diet exposure between the two strains, beginning at a young age, the HF/HS diet induced obesity in both strains, but the metabolic consequences were more pronounced in Wistar rats (Marques et al., 2016). However, one should always take into account that Sprague-Dawley and Wistar rats are albino rats, and have thus reduced the visual acuity compared to pigmented strains such as Long-Evans (Prusky et al., 2002). Studies using visuo-behavioral test such as Morris water maze or brightly arenas like open field can better try to make use of the pigmented strains.

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Around two-thirds of studies used exclusively male animals, while nine studies used only females, and ten studies used both sexes. Notably, none of the included studies using females controlled or accounted for effects of the estrous cycle. Since it has been demonstrated that the females (despite their estrous cycle) does not show more variability in females than found in males in terms of behavioral and neurophysiological variables (Becker et al., 2016; Prendergast et al., 2014), neither for food intake (Smarr et al., 2019), the estrous cycle might just not play such a relevant role. In fact, housing conditions cause more variability (~37%) in behavioral and neurophysiological variables than the estrous cycle (Prendergast et al., 2014). Still, it would be interesting to study the actual effects of the estrous cycle during CAF diet paradigms in the future.

Housing conditions were also heterogenous: eleven studies single-housed the animals, eight kept them in pairs, 27 in groups of three or more animals, while three studies did not report this information. Interestingly, one study investigated the effect of housing condition, in addition to the diet, on locomotor activity in a home-cage activity test (Sahakian et al., 1982). This showed that CAF increased locomotor activity in single-housed rats (measured by *distance moved* during 30 minutes test), but decreased activity in grouped-housed rats. These differences ceased to exist in a 24-hour test though.

Considering that social isolation is a stressor that alters the neuroendocrine system, dysregulates monoaminergic signaling and modifies behavioral responses (Mumtaz et al., 2018; Walker et al., 2019), we strongly recommend housing animals in pairs or groups. As social isolation at early age could increase the preference for psychostimulants (Walker et al., 2019), it is probable that social isolation may affect junk food intake as well. Studies with HF/HS diet are however inconsistent regarding food intake and metabolic changes due to social isolation (Arcego et al., 2014; Blanco-Gandía et al., 2018; Krolow et al., 2013; Schipper et al., 2020). Because the effects of social isolation are so far unknown, it is better to avoid confounding factors and house animal in pairs or groups. At least, in studies where the objectives are not related to metabolism or nutritional analysis that need a precise control over the amount of food consumed per each animal. One could then just determine the amount of pair/groups of rats have consumed together, combined with the individual measures of body weight increases and other metabolic parameters.

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There may be reasons to keep experimental animals single-housed, e.g.: 1) to avoid fights between animals for food or for other ethological reasons like territorial or hierarchical disputes; 2) to prevent only one animal taking all of the provisions of one food product; or 3) to assess the exact food intake of each animal. However, these concerns can be resolved by: 1) putting more food than the animals are able to consume, so all of them are able to eat all types of products, while also meeting the *ad libitum* condition of CAF diet; 2) putting as many containers with food as animals to avoid the dominance of one animal over a single food container, 3) dividing the total amount of consumed food between the number of animals per cage to obtain an approximate value of food intake per animal. Finally, it is recommended that the experimenter regularly checks each animal's body weight in order to assure that all animals housed together are gaining a similar percentage of weight and, thus, probably eating in a similar way.

Regarding the age of experimental animals, studies displayed differences in the stage of development at the start of the CAF administration. Based on the classification of Sengupta (2013) for laboratory rats, we classified animals within the following categories: infancy (pre-weaning, 0-3w postnatal), childhood (puberty, 3-6w postnatal), adolescence (sexual maturity, 6-9w postnatal), adulthood (general maturity, 9-76w postnatal) and old age (reproductive senescence, 76w-death). According to this, in rats, we found ten studies starting in infancy (pups from gestational and lactation studies), ten in childhood, twelve in adolescence and three in adulthood. In mice, one in infancy, one in childhood, one in adolescence and two in adulthood. To our knowledge, there are no studies assessing the behavioral effects of starting CAF during old age. Eight studies did not report the exact age of the animals at the start of feeding; although six of them indicated the weight and we could predict adolescence-adulthood.

Behavioral outcomes can differ in developmental stages, just as the timing of manipulations can affect outcomes later in life. It is, therefore, relevant to address the age at the start of diet manipulations, and the time of testing. Warneke *et al.* (2014), for example, found that CAF diet caused more alterations in anxiety-like behavior during adulthood than at younger ages – this effect being sex-dependent. On

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the other hand, CAF does not seem to affect impulsivity depending on age (Robertson and Rasmussen, 2017).

Additionally, we would like to note that only 58% of the included studies indicated the animals' initial body weight. As CAF is an obesogenic model, the initial weight could be just as important as the final weight or the weight gain, as the initial weight could give an indication of the health status of the animals at the start of experiment. The relative weight gain could be, in theory, more relevant than the absolute weight gain. We, therefore, recommend authors also report the initial weight of animals in future studies.

Ingredients and nutrients

Number of food products and categories of nutrients

There was a large variation in the number of products used for the CAF diet between studies. While some studies used only three products (Kendig et al., 2016; Rogers, 1985), one study used an impressive 96 different products (Palframan and Myers, 2016). The median number of products per CAF diet protocol was between eight and nine. Similarly, the number of food products administered per day varied widely, and while most studies rotated the food products that were administered each day, not all did. We believe that rotation is beneficial, because varying the available products has been shown to increase food consumption in rats (Oliva et al., 2017; Rolls et al., 1983), non-human primates (Moore et al., 2013), and humans (Johnson and Wardle, 2014). Rotation will therefore increase the construct validity of the CAF model as humans do not always eat the same junk food products.

When considering the variety of the products that should be included in the CAF model, it is relevant to combine high fat and high carbohydrate (mostly sugar) food products, as well as including both salty and sweet tastes. Using only high-fat or high-sugar food products is not as effective as combining a variety both types of food in order to induce hyperphagia and its metabolic consequences (Rodríguez-Correa et al., 2020). We recommend that a CAF diet should include both sweet and salty junk food in order to increase its validity as a translational model. For example, people would pay more for a food product containing both fat and carbohydrates rather than containing only one of them, even

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though the three products (fat + carbohydrate, fat, carbohydrate) are equally caloric and liked (DiFeliceantonio et al., 2018).

Furthermore, most junk food products consumed by humans are considered ultraprocessed (Box 1), so natural food products should be excluded from a CAF diet. Natural foods must be avoided, because they are lower in salt, sugar and fat, and thereby lower in their palatability compared to ultraprocessed food. Moreover, ultraprocessed foods contain unnatural fats and sugars, such as refined sugar or saturated fats, which may affect human and rodent metabolism and central nervous system function (Francis and Stevenson, 2013; San-Cristobal et al., 2020). Thus, optimally, the CAF diet protocol should also be mainly composed of ultraprocessed food products. Nevertheless, not all people suffering from overweight/obesity eat exclusively junk or ultraprocessed food, and would also consume natural food products as part of their diet. Therefore, we also recommend adding STD chow in a CAF study.

The food products used in the studies we analyzed for this review are indicated in Table 1. We have created categories of food to simplify its presentation and have indicated only the type of product, not the commercial brand. We classified the food products according to taste, nutritional value and texture. This proposal to separate tastes (sweet/sugar) and textures (hard/soft/liquid) is based on the findings that neurons in different brain regions and pathways respond to the various sensory properties of food (for a review, see Kenny, 2011a; Rolls, 2005).

The two most used categories were “cakes and biscuits”, for example muffins or donuts, and “processed meats”, for instance, bacon or hot dogs. Both categories were present in more than 75% of the included studies, and together accounted for more than one-third of the total amount of administrated products. Other categories that were used in many of the studies were “candies” (e.g. marshmallows or gumdrops), “potato chips” (such as nachos or cheese-flavored puffed cornmeal), “cookies” (like sandwich cookies with cream or digestive cookies), and “breads” (such as crackers or bagels). Finally, categories that were only used in a few studies were: cheese, sauces, drinks, packaged frozen meals, fruits and vegetables, sweets bars, sweet cereals, and special pellets. This long list of products (Table 1) demonstrates the high variability across studies using CAF diets and mirrors the huge junk food

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availability in the supermarkets. As there are so many options of food products available for inclusion in a CAF protocol, we strongly recommend that authors are precise in describing exactly what food items were used, avoiding ambiguous terms such as "snacks" or "sweets". This will allow replication and improve the understanding of the experimental methodology.

Chocolate

Chocolate was not considered as its own category because many different products contain chocolate as an ingredient. In those studies that directly added chocolate bars or chocolate bonbons, we counted these products under the category "candies". We felt that a separate category would get too complex since chocolate can be combined with milk, and cacao can be obtained as butter, powder or mass, involving industrial processes that change chocolate's natural properties. To make matters even more complicated, chocolate containing 85% cacao has a healthier nutritional composition than chocolate with 30% or less (Box 2).

The Maya civilization named chocolate the "food of the Gods" because of its perceived medical benefits (Araujo et al., 2016) and it remains a foodstuff whose effects are difficult to categorize simply. Chocolate consumption has been associated with reduced cardiovascular disease and diabetes (Veronese et al., 2019), and has also been suggested to improve mood and cognitive function in humans (Socci et al., 2017; Tuenter et al., 2018). Because chocolate often forms part of a human junk food diet, we recommend adding chocolate to the CAF diet, but only as a supplement rather than a separate category, e.g. in the form of chocolate cookies. However, we also suggest avoiding products that contain chocolate with high cacao levels, because such chocolate could partially protect against the unhealthy effects of a CAF diet.

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Box 2: Checking the label

Sometimes food products confuse us as consumers. Two products that appear superficially similar can be quite different at nutritional level, mostly due to its degree of industrial elaboration (Box 1). Here, we consider two examples.

There are different amounts of cacao in commercially available chocolate bars. We are going to compare, from the same brand, one at 85% of cacao and another at 30%. *Lindt Excellence 85%* has per 100g: energy: 2413kj, fat: 46g -saturated fat: 28g-, carbohydrates: 19g -sugar: 11g-, protein: 12.5g, salt: 0.02g. Whereas *Lindt Excellence Extra Creamy Milk (30%*) has per 100g: energy: 2387kj, fat: 37g -saturated fat: 23g-, carbohydrates: 51g -sugar: 50g-, protein: 6.4g, salt: 0.28g. The high cocoa chocolate has more fat, but the creamy milk chocolate has 4.5 times more sugar, which makes it unhealthier.

Now, we compare a processed food (cheddar cheese) with an ultraprocessed food (cheesecake). *Cathedral City Mature Cheese* has per 100g: energy: 1725kj, fat: 34.9g -saturated fat: 21.7g-, carbohydrate: 0.1g -sugar: 0.1g-, protein: 25.4g, salt: 1.8g. While *Tesco New York Cheesecake* has per 100g: energy: 1453kj, fat: 23.7g -saturated fat: 13.4g-, carbohydrate: 28.3g -sugar: 15.9g-, protein: 5.1g, salt: 0.3g. The ultraprocessed food again contain a large amount of sugar, this time 159 times more, even though fat levels are slightly higher in the processed food.

These two examples support the idea that the industrial ultraprocessing of junk food is more harmful for our health than other "processed culinary ingredients" like fat.

These ultraprocessed food also contain more additives, whose effects on health remain still largely unknown (Maffini et al., 2017). The 85% cacao chocolate and cheddar cheese contain relative few additives (from the online nutritional label: *cocoa mass, fat-reduced cocoa, cocoa butter, demerara sugar, vanilla / pasteurized cow's milk, salt, dairy products, coagulant;* respectively). Whereas the 30% cacao chocolate and cheesecake contain many more (from the online nutritional label: *sugar, cocoa butter, milk powder, cocoa mass, anhydrous milk fat, lactose, skimmed milk powder, barley malt extract, emulsifier (soya lecithin), flavouring (vanilla), cocoa / full fat soft cheese (milk) (34%), cream (milk) (17%), wheat flour, pasteurised egg, vegetable margarine (palm oil, water, rapeseed oil, emulsifier (mono- and di-glycerides of fatty acids), acidity regulator (citric acid)), sugar, soured cream (milk) (6%), brown sugar, flavouring, invert sugar syrup, wheat starch, maize starch, raising agents (sodium bicarbonate, ammonium bicarbonate*; respectively).

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Cheese

Arranging products according to their popularity in CAF protocols, we find near the middle, "cheese", most commonly cheddar. This product is often chosen due to its high levels of fat and protein, and its appealing smell and texture. Nevertheless, based on the NOVA classification, cheese should not be considered a junk food, because it is not ultraprocessed and it does not contain the same amount of "extra" nutrients, such as additives. As previously discussed for chocolate, when "pure" cheese is compared to an ultraprocessed food product that contains cheese, the latter would be considered unhealthier than the pure cheese (Box 2). However, it is still unclear exactly which nutrients or industrial processes, or both, are the primary triggers for the unhealthy consequences of junk food (Poti et al., 2017). Therefore, we propose to avoid using cheese as single component, but could be used as part of a foodstuff.

Fruit and Vegetables

Fruit and vegetables are rarely used as part of a CAF diet, probably because natural products are often considered far away from junk food. The main reason to include them is to assure that rats receive all the nutrients (including vitamins) they need (Moore, 1987), especially at young ages (Lalanza et al., 2014). An alternative is to give animals vitamins directly as supplements (Ferreira et al., 2018; Prats et al., 1989). Surprisingly, most of the included studies make no mention of this issue, even though most studies were carried out with young animals. The accessibility of STD chow or special pellets is another option to guarantee that the right vitamins and nutrients are available to ensure correct development. Thus, we strongly recommend adding STD chow or special pellets to the CAF diet animals. In addition, the availability of a STD chow guarantees that animals actually freely choose to eat the CAF diet.

Textures

Beyond the nutritional composition of a food product, its texture is also an important feature to consider when selecting food products for the CAF diet. For example, even though, a chocolate muffin and a chocolate cookie have similar nutritional compositions, they are quite different in terms of texture. The muffin is much softer and fluffier than the hard and dense cookie. Including different textures in a

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CAF diet adds novelty, which increases animals' motivation to eat the various food products. To reflect their different textures is why we divided sweet products into two main categories, "cakes and biscuits" for soft-fluffy-wet textures and "cookies" for hard-dense-dry textures.

Liquids represented another interesting texture that was sometimes used in studies applying the CAF diet. This category includes different kinds of "drink" products such as soda, full fat milk, and sucrose water (one study even included restricted access to beer (Kitchell, 1984). Though, we believe – as to most researchers – that due to their intoxicating and rewarding effects, alcoholic drinks should be avoided in CAF diet protocols). Interestingly, one study compared the effects of CAF diet plus a cola-soft drink or orange-soft drink on recognition memory, but the results were not clear enough due to methodological issues (*see below*, Feijó et al., 2019).

Overall, "drinks" or "sauces" (such as condensed milk, peanut butter or mayonnaise) were not popular categories and were each only included in one-third of studies. The lack of popularity of "sauces" is probably caused by practical and hygiene issues. Some sauces, such as mayonnaise, should not kept outside the fridge for too long. Besides, sauces are easily contaminated with sawdust and other bedding from a cage, which makes it messy and hinders an accurate assessment of the amount consumed.

Ways of administrating

When designing an experiment, the researcher must choose how the CAF diet will be administrated. Questions include: How long will the CAF diet be available to the animals for? How much of each food products is available at any given time? Will the animals continue to be fed the CAF diet during behavioral experiments? With respect to these issues, the protocols of the studies included in this review again varied widely, each with its advantages and disadvantages. The chosen protocol will likely depend on the specific aims of a study, but here we will discuss the main elements that should be considered when designing an experimental plan.

First, how long do you need to administer the diet before starting behavioral experiments? However, before answering this question, we must separate the included studies into two categories: 1)

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studies that fed the animals directly (*classical*) with CAF diet and 2) those that fed the dams (*gestational*), before behaviorally testing the offspring (*indicated in Table 3 in "other factors" column*). "Gestational" studies included those where the CAF diet was administered to the dams before pregnancy, during pregnancy, during lactation or during a combination of these phases. Since the gestational and lactational phase both last three weeks in rats and mice, this will be a limiting factor when designing the timeline of the CAF diet protocol. One should also consider whether or not the CAF diet will be kept available to the offspring after weaning. In a "classical" design, where the CAF-exposed animals are also the behaviorally tested animals, the number of weeks for CAF administration will depend on the objective of the study, whether it is seeking to look at long- or short-term effects of junk food consumption, and on the age of the animals.

In any case, a minimum of some weeks of CAF administration is necessary to ensure the presence of the effects of this diet on animals. A previous review (Small et al., 2018) suggested a duration of 4 to 16 weeks to observe differences in body weight and fat mass. This large variety in the recommended number of weeks resulted from the exact type of diet being used and also on which pathologic aspects of the metabolic syndrome the researcher was studying. For example, 3 weeks of HF/HS diet was induced skeletal muscle insulin resistance (Park et al., 2005), but 6-8 weeks were necessary to achieve a stably obese body in rodents (Heyne et al., 2009). Studies investigating the metabolic effects of the CAF diet also found that 6-8 weeks induced obesity (e.g. Buyukdere et al., 2019; Gual-Grau et al., 2019), although other studies have found shorter times to also be effective (e.g. Morris et al., 2008; Romero et al., 2014; Sampey et al., 2011; Zeeni et al., 2015a).

The next question is whether the experimenter should provide continued access to the CAF diet during behavioral testing. Again, the answer lies in the aim of the study and the type of design. For "gestational" studies testing the effects of maternal diet on the pups later in life, the CAF diet must be withdrawn after weaning, and thus before behavioral testing. However, when the experimental animals themselves are exposed to the CAF diet, there are more factors that should be considered. These include whether the researcher is interested in the acute or long-term effects of CAF diet consumption and the

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type of behavior that will be assessed. For instance, continuation of the CAF diet during behavioral testing may be needed in short-term administration designs, as the effect of the CAF diet may be less stable when it has only been given short-term compared to chronic effects following long-term administration.

On the contrary, behavioral tests that use food rewards usually make use of food deprivation to motivate the animals. Such behavioral tests thus require ceasing or restricting access to the CAF diet. The main disadvantage of stopping feeding before or during testing is that there may be withdrawal effects that could disrupt behavior. For example, withdrawal of a CAF diet has been shown to impair associative learning (Chen et al., 2014) and activate the hypothalamic pituitary adrenal (HPA) axis (Martire et al., 2014). Withdrawal also partially reversed the negative metabolic effects of CAF diet (Lalanza et al., 2014).

An alternative is to separate the different behavioral tests in time. Doing so enables the CAF diet to be taken away shortly before and during the experimental testing, then reintroduced immediately after the test to stabilize animal conditions before the next behavioral test. Using this experimental design, one has both the advantage of CAF diet not acutely affecting the animals during testing, while at the same time avoiding long-term withdrawal effects. As an additional benefit, separating tests in time prevents the induction of order effect on test outcomes, whereby successive, closely spaced testing can lead to early tests impacting performance in later tests. One should be cautious, though, regarding the amount of time inserted between behavioral tests, because long delays could result in different outcomes due to greater exposure to the effects of the CAF diet. For example, Maniam and Morris (2010a) found that 2 weeks of CAF diet counteracted the anhedonia induced in young rats by maternal separation, while 8-9 weeks of CAF diet resulted in a reduction of anxiety. In this example, the counteracting of anhedonia could be considered a short-term effect of CAF diet, while the anxiety reduction could be a long-term effect.

Another methodological decision concerns the amount of time that rodents are given access to the CAF diet each day during the weeks prior to behavioral testing and/or metabolic analysis. One could decide to give *ad libitum* access to the CAF diet, or provide access for only 1 or 2 hours per day. Another

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option is to alternate between days with access to the CAF diet and days offering STD chow. Only a few of the included studies limited access to the CAF diet. This is probably because limiting access to food has been proposed as a model for binge eating (Corwin et al., 2011) or yoyo dieting (Martire et al., 2015).

Four of the included studies used a restricted CAF diet defined by administering only a small quantity of CAF diet items without any time limitation. In each case, the stated aim of the study was not to generate obesity by CAF diet, but to investigate other effects of junk food consumption such as associative learning (Boakes et al., 1987; Kendig et al., 2016; Palframan and Myers, 2016; Pérez et al., 1999). Overall, we think that when the CAF diet is used to model human eating patterns, it should be given *ad libitum*.

We also believe that in order to best model actual human consumption patterns that the CAF diet should *also* not be mandatory to the animals. In a supermarket or canteen, people can choose between healthy and junk food, so, animals should be afforded the same option. To provide this choice to the animals, one can combine the CAF diet with STD chow. The consumption of the CAF diet is then no longer mandatory, and could be alternated with STD chow upon choice.

It is possible to manufacture pellets that are composed of junk food itself, which immediately triggers the next consideration for CAF protocols. A CAF diet consisting of actual human junk food products results in certain shortcomings. For example, animals may prefer one product over other items, the experimenter may have difficulty assessing the ingested nutrients, and there may be issues with introducing junk food products into an animal facility. Mashing junk food into pellets solves these problems, because all pellets will have the same nutritional composition, and the pellets are easier to weigh and to administer than real human food products. In addition, these “mashed CAF pellets” retain the advantage of having the taste of junk food. Some researchers have thus started to use them as an alternative to both HS/HF diet and CAF diet (e.g. de la Garza et al., 2019; Derman and Ferrario, 2018; Estadella et al., 2004; Lesser et al., 2017; Schimidt et al., 2018). Notwithstanding this good alternative solution, we have not included “mashed CAF pellets” studies in this review, because real human

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products improve the construct validity of the CAF diet, for we, as a society, do not eat pellets. In addition, providing a selection of different products replicates the variety, novelty and mixed texture that make the CAF diet so appealing.

Now that we have established what kind of products should be included in the CAF diet, we also need to determine what kind of control diet should be used. In our opinion, this issue has not been sufficiently addressed in the literature. The vast majority of studies we included used STD chow as the control diet, but we argue that the actual type of control diet used should be determined by the aim of the study.

For instance, in a CAF diet study one might consider using a HF/HS diet as the control diet if one wants to control for the nutritional components consumed. However, when a control is needed for the orosensory properties of CAF food or the variety offered in the CAF diet, alternative control diets are required, such as a variety of natural and healthy food. As an example of how different aspects of novel diets affect rodent eating behavior, Palframan and Myers (2016) compared the effects of a CAF diet, a natural food diet and STD chow on food preferences and sucrose intake. They found that both natural food and the CAF diet increased preferences for novel flavors and reduced sucrose intake compared to the STD chow group. It could thus be hypothesized that some effects of a CAF diet or natural food are caused by the environmental enrichment introduced by offering the animals a varied and novel diet, rather than by the products themselves. Despite these considerations, STD chow remains the most used control diet, probably because it is easy to administer and control. After all, it is the diet that is available as standard in animal research facilities and considered the “normal laboratory rodent diet”.

To disambiguate the various effects of giving rodents a CAF diet, the best option might be to add two control groups: one, a STD chow group, the other either a HS/HF diet or natural food group. Again, the final decision on which control diet is most useful depends on the aim of the study and on practical considerations.

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To summarize, having reviewed published studies that employed a CAF diet to study the effects of junk food consumption on rodent physiology and behavior, we propose a general experimental design for such studies, that might act as a standard protocol in the field. Our main goal in proposing the following is to model human eating patterns with maximal construct validity. The main features of our proposed protocol are as follows, with greater detail provided below. Animals are housed in pairs or in group; and provided with, at least, as many separate containers as there are animals, providing more than enough junk food, hence limiting aggressive behavior over access the food. The CAF diet should be given *ad libitum*; it should be rotated with new food elements regularly introduced; and it should provide a free choice of food with a minimum exposure of 4-6 weeks. As far as possible, the CAF diet should be continued before and after behavioral testing to mitigate potential possible withdrawal effects. The only exception to this would be if there are good reasons to believe that junk food consumption has acute effects on the behavioral parameters being tested. Careful consideration should be given to what diet is provided to the control group or groups, with special attention paid to whether increased food variety or altered nutrient consumption need to be controlled for. We believe that the adoption of a standardized methodology would facilitate comparisons between studies in this field and aid in generating consistent insights into the effects of junk food consumption. Nevertheless, all of the suggested parameters should be weighed against the specific research aims and overall experimental design of any given study.

A standardized CAF *recipe*

The standardized CAF *recipe* (or protocol) we propose is shown in detail in Table 2.

A *gold-standard* CAF protocol must take into account: 1) palatability, 2) salt and sweet tastes, 3) different textures, 4) novelty and 5) variety of food products. A systematic and controlled way to combine all of these features can be offered in a "menu" format (Leffa et al., 2015; Mucellini et al., 2019; Pérez et al., 1999; Pini et al., 2017). The menu format entails dividing the total food items that constitute the animals' overall diet into 3 or 4 packages, i.e. "daily menus", and providing animals with a different food choice each day. The daily menus should balance: categories of food, food products,

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textures, energy and nutrient content. By rotating menus on a daily basis, ensures animals experience dietary variety and novelty.

Based on this menu format, we propose a CAF protocol of 16 products divided into four menus (shown in Table 2). Each menu contains one product from the category "cakes & biscuits" and one from "processed meat". In addition, each menu contains two products selected from the other four categories, i.e. "candies", "potato chips", "cookies", and "breads". This results in a 4-product menu. Since for many individual products there is a wide variety of different brands available, and since nutritional values differ somewhat between brands, each of our proposed menus gives two brands of each item that have relatively similar nutritional values (data obtained from two online supermarket websites, Tesco / Bon Preu - Esclat).

Finally, the average of the nutritional balance of the four proposed menus together is presented in Figure 1 and for each of the four menus separately in Supplementary Figure S1. In addition to the CAF diet, we also propose give all animals *ad libitum* access to STD chow and water. We believe that there would great benefits if this proposed standardized CAF protocol could be widely adopted. If necessary – owing to a certain product being unavailable in a given country, for example – the exact food products could be adapted for individual laboratories. However, in the case of such modifications, it would be important that the nutritional values of the category of products are kept as constant as possible, just as we have designed the average nutritional values of each menu to be.

Behavioral effects of the CAF diet

The purpose of the second part of this review is to evaluate the main ways in which consuming a CAF diet affects behavioral and neurophysiological variables in rodents. Table 3 summarizes the included studies and their main findings. As we explained above, studies were either "gestational studies" – in which the diet was administered to mothers, and their offspring were tested – or they were "classical studies", in which the experimental subjects themselves consumed the diet. For each section, we will consider the effects of the CAF diet in gestational and classical studies separately.

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Weight gain

Since the CAF diet is proposed to be an obesogenic model, we first need to determine whether the CAF diet does, in fact, induce overweight and obesity. Several physical and metabolic variables are used regularly to indicate the existence of obesity. Besides the most common parameter of increased body weight (or body mass index, BMI), other measures that could also indicate obesity include rises in abdominal circumference, waist-hip ratio, body fat distribution, and abdominal fat mass. These additional variables are beyond the scope of this review, but, as an example, it has been shown that the CAF diet increases abdominal circumference and levels of retroperitoneal adipose tissue compared to control diet (STD chow), but not relative to a HF/HS diet (e.g. Pini et al., 2017). When evaluating body weight, we conclude that the CAF diet is an obesogenic model, because most included studies showed that it significantly increased body weight compared to consumption of STD chow.

In most "gestational" studies, CAF diet consumption increased the body weight of dams, but had no effect on pups' body weights (Bayol et al., 2007; Ramírez-López et al., 2016; Ribeiro et al., 2018; Wright et al., 2011a; Wright et al., 2011b; Wright et al., 2014). This is consistent with a recent systematic review of the HF/HS diet which also does not increase fetal growth, and which often does the contrary (Christians et al., 2019). Interestingly, Jacobs *et al.* (2014) found that pups from dams exposed to a CAF diet during gestation had slightly increased body weights at postnatal day (PND) 1. However, this increase in body weight became attenuated with time and was normal at PND90. Another study found that offspring from CAF diet-exposed mothers actually gained less weight during lactation, but, again, recovered in weight during the post-weaning period (Ramírez-López et al., 2016). Therefore, even though CAF diet increased body weight in the dams, we conclude that there was no robust effect on pups' body weight.

When the consumption of the CAF diet was started at childhood, adolescence or adulthood, an overwhelming majority of the studies that assessed body weight (32/36) found that it significantly increased body weight compared to STD chow (see Table 3). Notably, the CAF diet resulted in a significantly greater weight gain than HF/HS diets (Ferreira et al., 2018; Zeeni et al., 2013). The reasons

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for that the other studies did not find an increase in body weight upon CAF diet are unclear (Kitchell, 1984; Kosheleff et al., 2018b; Pérez et al., 1999; Pini et al., 2017), but factors such as age, the exact type of CAF administered and other unaccounted variables interact with CAF diet, to affect body weight.

Regarding age, we found two studies that explicitly compared CAF diet effects when it was started at adolescence or adulthood. Whereas the CAF diet significantly increased body weight in young adult and one-year adult rats compared to STD chow (Robertson and Rasmussen, 2017; Warneke et al., 2014, *respectively*), the effect on body weight during adolescence was only found in one of the studies (Robertson and Rasmussen, 2017). This is an unexpected result as both diet protocols from the two studies were similar, including specie and strain (Sprague-Dawley), and without sex differences. Housing conditions in this particular case might add some light as rats were isolated or grouped in each study respectively.

In terms of how the CAF diet was administered, several studies have shown that *ad libitum* access to CAF diet increases body weight to a greater extent than limited access times to CAF diet and/or STD chow does (Chen et al., 2014; Johnson and Kenny, 2010; Martire et al., 2015; Thompson et al., 2017). Only one study found no differences in body weights between animals exposed to either limited or *ad libitum* CAF diet, although the *ad libitum* CAF group was still heavier than STD chow (Kosheleff et al., 2018a).

Finally, individual differences between animals could also affect behavioral outcomes. Some studies actually select on these characteristics. For example, an interesting study used a mouse's percentage increase in adipose tissue, following CAF diet consumption, to classify it as either obesity prone (heavier) or obesity resistant (lighter) (Gac et al., 2015). Similarly, another study selected only animals at the extreme ends of the body weight spectrum for behavioral testing: taking the least heavy from the STD chow group and the heaviest from the CAF diet group (Robertson and Rasmussen, 2017). Although such selection might reduce the effects of individual variability weight gain, thereby reducing the number of animals needed to see an effect of diet, we believe that it represents a severe selection bias that could result in false outcomes. In this particular case, the authors only selected those obese

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prone animals from the CAF diet group ignoring the hypothetical behavioral effects of CAF diet on the obesity resistant animals. We, therefore, recommend avoiding this method unless the aim of the study requires such a selection.

Locomotor activity and Exercise

The relationship between poor eating habits and undertaking inadequate exercise in leading to obesity still needs further investigation, in particular whether poor diet and weight gain can cause sedentarism. Animal models are useful for examining this relationship.

Additionally, however, investigators need to understand if their experimental manipulation leads to gross changes in locomotor activity in order to interpret behavioral test results in other contexts. Most behavioral tests in rodents are based on animals' locomotor activity. A rodent, for example, *walks away* to avoid a stressful area or *approaches* a reward in a standard experimental context. These locomotor activities are the basis for inferring neurobehavioral outcomes such as reduced anxiety-like behavior or higher motivation for food. As such, a rodent exploring the open arms of the elevated plus maze is interpreted as showing low levels of anxiety-like behavior (Pellow et al., 1985), and a rodent swimming to find the platform in a Morris water maze is a model of spatial memory (Vorhees and Williams, 2006). Therefore, if an experimental manipulation increases or decreases locomotor activity *per se*, it could mask psychiatric-like phenotypes assayed via behavioral tests. Consequently, researchers should always control for overall locomotor activity when drawing conclusions from neurobehavioral experiments. We, therefore, look first at how the CAF diet may affect locomotor activity.

The effects of the CAF diet on locomotor activity in gestational studies have not been uniform. Different results have been obtained depending on the kind of test used and the sex of the pups investigated. Measuring locomotor activity in the open field arena, two studies found no differences between pups whose dams had been fed the CAF diet and those whose dams had been given STD chow (Ramírez-López et al., 2016; Ribeiro et al., 2018). However, another study did find an increase of locomotor activity in the open field due to maternal CAF diet (Speight et al., 2017). Perhaps the variability of the CAF diet products played a role. For the first two studies CAF diet was fixed, whereas

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for the last study CAF diet was composed by the double of products that rotated during the days of diet exposure. Interestingly, the authors of this latter study also tested locomotor activity in the elevated plus maze and found no effects of CAF diet on overall locomotor activity during lactation. It is important to remark, however, that the elevated plus maze, even though it is based on animals' locomotor activity, is more difficult to interpret than the open field as assay of overall locomotor activity. Quantification of locomotor activity in the elevated plus maze is based on the ratio of entries or distance travelled in closed arms or all arms pooled (Walf and Frye, 2007), but as closed arms are the "protected areas", locomotor activity on the elevated plus maze is not an optimal output. Additionally, sex differences have also been observed for the effects of CAF diet on locomotor activity (assessed in both the open field and the elevated plus maze). Maternal CAF diet exposure reduced locomotor activity in male pups, but had no effect in females (Wright et al., 2011a). Only three studies also assessed the effects of the CAF diet on locomotor activity in the dams themselves – two found no effect (Ribeiro et al., 2018; Speight et al., 2017) while one saw reduced activity following CAF diet relative to STD chow administration (Bayol et al., 2007).

Testing the effects of CAF diet on the dams could, in fact, be considered a classical design study, as the animals that ate the diet were tested. And the inconsistent observations in dams, chime with classical experimental design studies, where the effect of CAF diet consumption on locomotor activity has not been uniform. Overall, the majority of studies included here found no significant differences in locomotor activity between animals exposed to CAF diet and STD chow, suggesting the CAF diet does not robustly alter total activity levels (Cigarroa et al., 2016; de Oliveira et al., 2019; Ferreira et al., 2018; Leffa et al., 2015; Sahakian et al., 1982). This is consistent with the observations that HF/HS diets also do not seem to affect locomotor activity (Ferreira et al., 2018).

Among studies that saw significant effects of the CAF diet on locomotor activity, the direction of change was inconsistent. A few studies found that the CAF diet increased locomotor activity (Gac et al., 2015; Sack et al., 2017), of which one found an effect in female but not male rats (Warneke et al., 2014). Some of these studies, however, have some methodological features that could account for the

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changes seen, e.g. one applied the obese prone/resistant model, which could have influenced the outcome. Both mice, prone to obesity and those resistant to it, showed an increase in locomotor activity in home cage activity test (over a 24h period) after 8 weeks of CAF diet compared to STD chow. Interestingly, the obese resistant mice also showed a significantly higher locomotor activity compared to obese prone mice fed with CAF diet (Gac et al., 2015). Thus, it could be hypothesized that there is an interaction effect between diet and weight gain on locomotor activity, although this idea needs more research.

On the other hand, two studies have reported a decrease of locomotor activity upon CAF diet consumption (Kitchell, 1984; Lalanza et al., 2014). One of them, though, assessed activity in an uncommon maze for testing learning ability (*3-choice maze*; Kitchell, 1984), so its results could be difficult to compare with the more standard tests. The other study used the open field and the hole board tests after 8 weeks of CAF diet exposure (Lalanza et al., 2014). As these authors also found a decrease of anxiety-like behavior in these behavioral tests, this study is a good example of the importance of assessing and distinguishing both locomotor and anxiety-like variables.

Altogether, we conclude that the CAF diet – when either consumed directly or indirectly via maternally mediated exposure during gestation – does not consistently affect locomotor activity. However, conflicting observations in this field should not be dismissed and further exploration in future studies is warranted.

Although it is not considered locomotor activity in the strict sense of the term, decreased exercise or physical activity is closely related to becoming overweight and obese, and increased physical activity is often viewed as a potential treatment (Chin et al., 2016). It is therefore pertinent to explore the effects that exercise can exert on the unhealthful consequences of eating a CAF diet. Only two of the included studies addressed interactions between CAF diet consumption and exercise. Sack *et al.* (2017) studied whether running was able to compensate for the memory and hippocampal deficits caused by CAF diet exposure. Although running increased the gray matter volume in the hippocampal formation, there was not an interaction with CAF diet. In the second study, both handling (taking the rat

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out of the homecage as the exercised group) and treadmill exercise partially counteracted impaired coping behavior caused by the CAF diet and also reduced anxiety-related behaviors in the CAF diet group (Cigarroa et al., 2016).

Regarding metabolism, treadmill exercise partially reduced the consequences of the CAF diet. It reduced the amount of retroperitoneal white adipose tissue gained and led to lower increases in triglycerides. However, changes in other parameters, including body weight, were unaffected (Cigarroa et al., 2016). This study is typical of the wider literature where exercise has been seen to counteract some of the metabolic consequences of CAF diet, such as altered insulin levels (Auer et al., 2015; Goularte et al., 2012; Sack et al., 2017) but not all. In addition, methodological differences – such as the exact exercise protocol employed and type of CAF diet provided – between studies again complicate interpretation, and deserve careful attention in future studies. For instance, exercise also partially offset the metabolic consequences of eating a CAF diet in the form of mashed pellets (Estadella et al., 2004; Higa et al., 2014).

In the most basic sense, becoming overweight, then obese, results from an imbalance between energy intake (diet) and energy expenditure (metabolism and physical activity) (Spiegelman and Flier, 2001). However, it remains an open question as to whether being overweight or obese actually induces sedentarism or if sedentarism is only correlated with the unhealthy diet that causes weight gain? Although, alternatively, there may be a more dynamic relationship between the two phenomena leading to a type of vicious circle. Even though basic and clinical evidence points to exercise potentially compensating for the metabolic damage caused by obesogenic diets, like the CAF model, more research is needed to unpick the relationship between diet, exercise and weight gain/altered physiology. Studies of the CAF diet have so far produced mixed results. Future studies should not only focus on brain mechanisms, but also carefully explore the type of, intensity of, and adherence to physical activity, in order to determine which, if any, might provide a genuine treatment for the obesity epidemic.

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Feeding patterns

The next logical step is to ask if the CAF diet impacts eating behavior. In fact, one of the most widely reported behavioral changes related to overweightness and obesity is a lack of control over food intake, or more simply "overeating". This is typically ascribed to the hedonic value of food (Yu et al., 2015). Portion sizes and snacking patterns are risk factors for the development of obesity in humans (Bellisle, 2014; Peter Herman et al., 2015). In animal studies, it has been shown that food-related cues can increase food intake (Johnson, 2013). Nevertheless, feeding patterns analogous to human's – i.e. large meals, snacking and/or varying portion sizes – have been scarcely explored in animal models. Actually, one study that did investigate the effects of portion size on rat feeding behavior found no signs of over-eating, even with highly palatable foods (Naneix et al., 2019).

Only four studies included in this review assessed feeding patterns after CAF diet administration. Overall, they found an increase in snacking – that is, more frequent bouts of eating – with the CAF diet compared to STD chow. This was seen in both a gestational (Wright et al., 2011b) and a classical study design (Martire et al., 2013). Interestingly, limiting exposure to the CAF diet increased this snacking pattern for junk food consumption compared to providing *ad libitum* access to CAF diet (or to STD chow), resulting in rodent behavior akin to binge-eating (Martire et al., 2015). Finally, CAF diet administered to dams also produced hyperphagia (increased amount of food intake) for junk food, but not for STD chow, in their pups (Bayol et al., 2007). To the best of our knowledge, no studies have yet tested portion size effects of the CAF diet in rodents.

Reward system: Hedonic response and Motivation

Given that the CAF diet induces a more compulsive eating pattern for junk food rather than natural or healthy food, what about the rewarding value and motivation for natural or healthy food? Can junk food alter this as well? In fact, studies have found that junk food can, indeed, alter the rewarding and motivational value of natural or healthy food. For example, withdrawal from a CAF diet (even though was little varied and fixed) after ~30 weeks of diet exposure, reduced the amount of STD chow eaten for the subsequent 3-4 weeks compared to rats that were always fed with STD chow (Rogers, 1985). Furthermore, rats fed a CAF diet (more varied and rotated) showed reduced food intake when

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they were exposed to STD chow in a 24h home cage activity system, whereas rats fed with STD chow increased food intake when they were given more palatable food (South et al., 2014). This suggests that motivation for other less palatable foods is reduced by chronic junk food consumption.

These results do not, however, directly demonstrate that a CAF diet reduces motivation to eat, or the hedonic value, of STD chow, because other reasons may explain the observed reduction in food intake. A direct approach is, therefore, necessary to establish a causative relationship. In animal research, a change in hedonic values and/or motivation can be investigated using associative learning paradigms that teach rats to associate a cue or context with palatable food (for a review see Johnson, 2013). It is well established that contextual and environmental cues contribute to overeating and constitute a risk factor for junk food consumption and for obesity. Indeed, a recent meta-analysis in humans found that food cues trigger a medium effect on craving and overeating and, subsequently, weight gain, independent of age, gender, BMI and dietary restraint (Boswell and Kober, 2016). It is thus important to explore the role of contextual cues in the development of obesity, but behavioral tests using associative learning are also useful by themselves to dissect the links between motivation for consuming a food type, the hedonic value of different food types, and the role of satiety.

Demonstrating how strongly junk food consumption can affect behavior, studies have shown that it can markedly reduce fear-related behavior. Rats fed *ad libitum* CAF diet did not reduce junk food intake in the presence of cues that predicted shocks, demonstrating the high rewarding level of junk food (Johnson and Kenny, 2010; Thompson et al., 2017). Consequently, it was hypothesized that motivation for eating junk food is greater than the fear of shocks.

Kendig *et al.* (2016) trained rats to consume CAF diet in one context and STD chow in another. They then trained the rats to lever press for pellet or sucrose food rewards, and tested lever-pressing behavior when rats were sated – after 1 hour of *ad libitum* food access, that had thereby decreased the value of the rewards. Rats tested in the CAF diet-associated context were insensitive to the devaluation of the food reward, but expressed the expected devalued response (less lever presses in an operant

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chamber) in the STD chow context. In order words, cues associated with the CAF diet stimulated persistence to consume more food.

A similar effect was found with a chocolate and condensed milk food rewards, whereby the CAF diet group failed to distinguish between rewarded and non-rewarded cues and pressed the lever, to obtain chocolate and condensed milk, equally for both types of cue (Kosheleff et al., 2018a, 2018b). Thus, it was demonstrated that junk food consumption stimulated a continued want for more junk food.

Going a step further, might a CAF diet not only stimulate a general motivation for further food rewards, but also impair satiety for specific tastes? The answer also seems affirmative. The effect of the CAF diet on sensory-specific satiety learning was tested in rats by pre-exposing CAF diet and STD chow-fed rats to one rewarding drink solution *ad libitum*, then testing their preference for a second rewarding solution in a post-exposure trial. CAF diet rats, unlike STD, showed no preference for the second solution, indicating a failure to develop satiety to the initial solution, even though all rats equally drank these two solutions in a baseline session (Reichelt et al., 2014). Moreover, rats fed with the CAF diet did not prefer the flavor associated with calories (glucose), meaning that this diet had also impaired flavor learning (Boakes et al., 1987). Another study, though, found no difference between CAF diet and STD chow in flavor preference, both diet groups choosing the flavor conditioned with the nutritional content (Perez et al., 1999). Nevertheless, this lack of an effect of the CAF diet could be due to the CAF diet group not having become heavier than the STD chow group, and because the CAF diet was restricted as opposite in the study of Reichelt *et al.* (2014). Altogether, these results suggest that the CAF diet alters the preference for, or the perception of, other tastes and other food rewards.

However, this support for the hypothesis that the CAF diet alters contextual and cued responses toward food rewards, as well as sensory-specific satiety learning, should be interpreted cautiously. Different factors could alter these rewarding responses. Some of these studies, for example, required food restriction before testing, which could interact with the CAF diet as an experimental manipulation owing to the withdrawal effect of withholding this diet. In addition, as we explain in the following paragraphs, a CAF diet reduces the hedonic value of other rewards, so sucrose or chocolate pellets used

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in these studies might not interest an animal that has previously been fed a CAF diet. In fact, CAF diet rats consumed less food reward pellets during training for a self-administration task than STD chow fed rats did (Chen et al., 2014) whereas *ad libitum*, but no restricted, CAF diet rats took less condensed milk (Kosheleff et al., 2018a). Therefore, studies addressing these methodological problems are needed to establish the relationship between obesity and associated stimuli or cues.

Up to now, we have discussed about the devaluation effects of the CAF diet towards food rewards (e.g. natural food, chocolate pellets or condensed milk), but what about other types of rewards? Might a CAF diet also change preferences for other rewards, such as ethanol? Or is it solely affecting the hedonic value of – and motivation for – food rewards?

From the included studies, the balance of evidence shows that the CAF diet reduces preference for and/or the hedonic properties of other rewards. Cook *et al.* (2017), for example, found that 4 weeks of CAF diet reduced ethanol intake compared to STD chow. Interestingly, since a CAF diet could alter metabolic processes, the authors confirmed that ethanol was metabolized at the same rate in CAF diet and control rats, meaning that the decreased ethanol intake was not caused by altered alcohol break down. Therefore, it can be argued that the reduction in ethanol consumption is caused by the CAF diet decreasing the rewarding properties of ethanol. This hypothesis is consistent with the reduced ethanol preference found after HF/HS diet exposure compared to STD chow (Takase et al., 2016). In addition, similar results were found with sucrose, another substance with rewarding properties: eating a CAF diet also reducing intake of sucrose (Cook et al., 2017; Gac et al., 2015).

These studies, however, only demonstrated that the CAF diet reduced the consumption of other rewards. They leave open the question whether there was a lack of motivation, or willingness to work, for the reward. Only a few studies investigated the motivational and hedonic value of other rewards after CAF diet exposure. For example, when rats needed to work for a sucrose reward in an operant chamber, the CAF diet group learnt and pressed the lever in the same ratio as the natural food and the STD chow groups. However, both the CAF and the natural food groups reduced the intake of an *ad libitum* sweet solution (Palframan and Myers, 2016). The difference in *ad libitum* intake together with the fact that all

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groups had the same lever press ratio could be explained by the "liking" and "wanting" theory (for a review see Berridge, 2009). In short, liking can be considered the hedonic aspect of the reward, the feeling of pleasure, while wanting is the motivational value of the reward, the *incentive salience* or the desire to obtain the reward. Hence, CAF diet could decrease the liking, or the hedonic properties of other rewards, but leave the "wanting" or the motivation for other rewards unaltered. In line with this hypothesis, Martire *et al*. (2015) found that both STD chow and limited (or cycled) CAF diet groups had more licks for the sucrose solution than the *ad libitum* CAF diet, which is considered a measure of liking, while there were no differences in the number of clusters (that is, bouts or groups of licks), which is considered a measure of wanting.

However, it could be that the CAF diet interacts with sucrose metabolism. Interestingly, using direct electrical stimulation of the lateral hypothalamus as a reward (which should not be affected by any changes in metabolism), Johnson and Kenny (2010) found that rats from the CAF diet group needed higher levels of brain stimulation to obtain the same hedonic or rewarding responses as the STD chow group. This study therefore provided evidence that junk food consumption directly changes brain reward systems.

The foregoing studies were classical, however, similar findings have also come from a gestational study, in which maternal CAF diet reduced the preference for chocolate in pups during adolescence and adulthood (Ramírez-López et al., 2016).

Together, these behavioral outcomes are in line with the hypothesis of *Reward Deficiency Syndrome* proposed by Kenneth Blum and colleagues (for a review, Blum et al., 2014). In short, this hypothesis states that individual's inability to obtain pleasure from natural or everyday stimuli like STD food or sucrose is caused by a deprivation or hyposensitivity of the dopaminergic system due to epigenetic changes. In terms of CAF diet and based on the behavioral results it means that animals fed with junk food show reduced preference and/or hedonic responses to other rewards such ethanol or sucrose.

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The general hypothesis of a hyposensitive reward system (*like the Reward Deficiency Syndrome)* is also supported by neurophysiological alterations produced by a CAF diet. Long-term administration (>4 weeks) to the CAF diet downregulates dopamine receptors and decreases dopamine extracellular levels in the reward system (Cook et al., 2017; Geiger et al., 2009; Johnson and Kenny, 2010; Ong et al., 2013). This dopamine downregulation or reward hypofunction is hypothesized as a neuroadaptive response to an overconsumption of junk food (Johnson and Kenny, 2010). Both obese humans and rodents show reduced levels of dopamine receptors in the striatum (Kenny, 2011b). This dopamine reduction could partially explain the reduced response towards other rewards, but also the impairment in associated learning for cues related to junk food and satiety (*see above*) as well as hyperphagia for junk food (Kenny, 2011b). In addition, it has been suggested that drugs of abuse and junk food share neurophysiological mechanism for example both increasing ΔFosB in the striatum, and palatable food could trigger addictive response in order to alleviate the negative reward state (Kenny, 2011a; Volkow et al., 2017). However, this hypothesis is not accepted by all scientific community (Fletcher and Kenny, 2018).

Following short-term administration, however, the CAF diet seems to *hyper*sensitize the reward system. For example, after 9 days of CAF diet exposure, rats that had previously been fed STD chow for 16 weeks increased the expression of dopamine receptors in the ventral tegmental area (VTA) compared to rats switched from CAF diet to STD diet or rats always fed with CAF diet (South et al., 2012).

Gestational studies of the CAF diet also show interesting long- and short-term effects depending on the duration of administration. For example, CAF diet in dams during lactation increased dopamine in the reward system of their offspring at adulthood in both males and females (Wright et al., 2011b). In this study, the offspring were kept on STD chow after weaning, so lactation could be considered a short-term exposure to CAF diet. At adolescence (6 weeks), offspring of CAF diet dams also had higher levels of dopamine in the nucleus accumbens and VTA (caused by reduced dopamine transporter expression) (Ong and Muhlhausler, 2011). However, the offspring of this study were fed with CAF diet or STD chow after weaning. Again, a short-term exposure to the CAF diet (during the 3 weeks after weaning)

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hypersensitized the reward system (at adolescence), but a long-term administration of the CAF diet after weaning (until adulthood) reversed the increase in dopamine in the reward system found at adolescence. In fact, at adulthood and after ~10 weeks of CAF diet, pups from CAF diet dams downregulated dopamine levels in the major areas of the reward system, as was found in classical studies of long-term exposure. Therefore, a hyposensitive reward system appears to develop when animals are directly exposed to CAF diet (classical) for several weeks, but the opposite (hypersensitization) happens when animals are either indirectly exposed (gestational) or exposed for only a few weeks (classical). In conclusion, the CAF diet clearly has interesting bidirectional effects on reward system, but more studies regarding its effects at both short- and long-term timeframes are needed to refine and further clarify the hypersensitization and hyposensitive hypothesis depending on timing exposure to CAF diet.

Another important component of the reward system is endocannabinoid and endogenous opioid signaling (for a review, Le Merrer et al., 2009; Wenzel and Cheer, 2018). As with dopamine, long-term exposure to a CAF diet also causes a reduction in the expression of cannabinoid and opioid receptors (CB1 and μ-opioid) in the VTA and nucleus accumbens (Martire et al., 2014; Ong et al., 2013). Similarly, long-term administration of HF/HS diet also reduced the expression of μ-opioid receptors (Vucetic et al., 2011). Regarding these systems, similar results were found in gestational studies as well: the endocannabinoid and opioid systems were downregulated in pups whose dams had been exposed to a CAF diet (Gugusheff et al., 2016; Ramírez-López et al., 2016).

Finally, the CAF diet also alters neuronal structure and plasticity in the lateral orbitofrontal cortex, a brain area involved in decision-making, reward valuation and integrating sensory information with expected outcomes (Thompson et al., 2017). This study found a reduction of GABAergic inputs to the orbitofrontal cortex, leading the authors to suggest that these junk food-induced alterations might contribute to overeating and explain the devaluation of food rewards as well as losing control over eating behavior and attributing an inappropriate incentive value to food (for a review, Seabrook and Borgland, 2020).

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Altogether, both behavioral and neurophysiological data indicate that CAF diet consumption reduces the preference for other rewards and their hedonic properties, causing a deprivation or hyposensitivity of the reward system (see Table 4 for a summary of the behavioral and neurophysiological effects of CAF diet). The motivational drive for rewards, however, seems to remain intact after CAF consumption. In order to further validate this hypothesis, more research will be needed. In future studies, it might be relevant to also investigate sex differences, because there is some evidence suggesting that males and females respond differently (Gugusheff et al., 2016; Ong et al., 2013).

Impulsivity

Impulsivity and compulsivity are important components of junk food eating, and are major personality traits associated with being overweight or obese, with high levels of impulsive behavior found in overweight and obese population (Emery and Levine, 2017; Fields et al., 2013; Rasmussen et al., 2010). Nevertheless, the cause and effect relationship between impulsivity and obesity is unclear: does obesity predispose to impulsivity or does impulsivity predispose to obesity?

Although this question is clearly important, surprisingly, only one of the included studies applied a behavioral test aimed at assessing impulsive behavior. Robertson and Rasmussen (2017) used a delay-discounting task in which animals, after training, got to choose between an immediate but small reward and a delayed but larger reward. In addition, the role of dopamine in this process was investigated. After determining a stable baseline for reward choices, no differences between diet groups were found. Interestingly, following the injection of a vehicle solution, rats on CAF diet made significantly more delayed-larger choices compared to rats on control diet, indicating a reduction in impulsivity upon CAF diet exposure. It was suggested that this change, in effect, might be a result of the stress caused by the injection, but that remains a hypothesis. Either way, when rats were injected with a dopamine receptor antagonist (haloperidol) the number of delayed-larger choices declined in CAF diet rats. This suggests that dopamine plays a role in reduced impulsivity following junk food exposure. Even though similar and opposite results were found by HF/HS diets (e.g. Boomhower and Rasmussen, 2014; Steele et al., 2017), the decline in impulsivity in the vehicle condition is surprising,

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because it contradicts most human studies (Emery and Levine, 2017; Fields et al., 2013; Rasmussen et al., 2010). It might be explained, though, by the use of normal pellets in this one study as reward as there low-valued by CAF animals as explained in the previous section. In addition, the authors selected the animals depending on the body weight (*see above*) what could have altered the effects of CAF diet on impulsivity behavior. More work is clearly required to address this important aspect of eating patterns.

Mood: Anxiety- and Depression-like Behaviors

Food and mood are closely related. While stress in some cases induces a reduction in the amount of food consumed, in others, stress increases eating, and often the eating of highly palatable food. This phenomenon is colloquially referred to as eating "comfort food", and it applies to both humans and rodents (Dallman et al., 2003; Pecoraro et al., 2004). Comfort food can be defined as food that is eaten as an attempt to reduce anxiety and for its well-being effects rather than its nutritional value, owing to humans and other animals obtaining pleasure due to emotional relief (Dallman, 2010; Dallman et al., 2003).

Consistently, stress is considered a risk factor for obesity (Sinha and Jastreboff, 2013), and epidemiological and longitudinal studies have found a bidirectional relationship between mood disorders and obesity (Gariepy et al., 2010; Luppino et al., 2010). A recent meta-analysis found that the prevalence of anxiety and depressive symptoms were significantly higher in overweight and obese children and adolescents than in the non-overweight/obese (Wang et al., 2019). This comorbidity is, however, not fully understood yet and it could be strongly affected by genetic predisposition and environmental factors (Mansur et al., 2015).

If there is a causal relationship between junk food and mood in humans, one would expect that exposure to the CAF diet should also affect anxiety- and depression-like behaviors in rodents. Regarding gestational designs, only a few studies assessed the effects of dams receiving CAF diet on stress responses in their pups. Superficially, these studies seem to have reported opposing effects – two studies finding reduced anxiety levels in pups fed a CAF diet in the open field (Speight et al., 2017; Wright et

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al., 2011a), while a third study found a decrease in the amount of time spent in the center, suggesting an increase in anxiety (Ramírez-López et al., 2016). However, a more detailed examination of the methods employed appear to offer an explanation of the differences observed. Specifically, the studies differed in how strongly the open field environment in which anxiety-related behavior was illuminated – light levels being a key determinant of how anxiogenic the environment is. Hence, Wright *et al.* and Speight *et al.*, used high (i.e. strongly anxiogenic) levels of illumination above the test set-up (130 and 70 lux, respectively) compared to Ramírez-López *et al.* (30 lux). Illumination in an open arena could be a critical factor for the visual system and as discussed before, albino rats may experience more disturbances than pigmented strains. Nevertheless, all these three studies used the same albino strain Wistar, so the strain does not seem the cause of this discrepancy. Therefore, we hypothesize that the low illumination was insufficient to induce significant anxiety, at least in the open field test.

Regarding tests of anxiety-related behavior in the elevated plus maze, the lack of effects seen in the study by Speight *et al*, can be explained at least by the age at testing, since they looked at rats on PND23, 2 days after weaning, while the rats in the other studies were tested 9-10 weeks after weaning (Ramírez-López et al., 2016; Wright et al., 2011a). Ramírez-López *et al.* (2016) saw increased levels of anxiety-like behavior in the elevated plus maze, whereas Wright *et al.* (2011a) found the decreased levels in the same test in males. It should be noted though that Wright *et al.* (2011a) compared pre-gestational, gestational and lactation periods, and the reductions in anxiety were not generalized to all experimental groups.

Finally, increased levels of anxiety-like behaviors were also seen in the light-dark test, as mice pups from dams on a CAF diet entered the dark (and less anxiogenic) compartment faster and more often from the light (and more anxiogenic) compartment (Ribeiro et al., 2018).

Therefore, indirect CAF diet exposure via their mothers may result in both an increase and a reduction in anxiety-related behavior. As mentioned before, pups showed more anxiety when their dams were fed CAF diet in some studies (Ramírez-López et al., 2016; Ribeiro et al., 2018), however these studies administered a little varied CAF diet compared to the studies that found reduced anxiety-like behavior. In addition, it is possible that increased stress levels in pups were not produced directly by gestational CAF diet exposure but by abnormal maternal care, because the CAF diet can alter maternal

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care behaviors (Ribeiro et al., 2018; Speight et al., 2017) (see Social Behavior section below). Therefore, after considering these methodological differences, we tentatively conclude that indirect CAF diet exposure via their mothers may result in a reduction in anxiety-related behavior, even though more studies are required in order to further validate this conclusion.

In classical design studies, where subjects were fed CAF diet themselves, the effects of this diet on behavioral and neurophysiological measures of anxiety levels also remain unclear. When we look at effects in male rats and mice, four studies found reduced anxiety levels, in either the open field or elevated plus maze test (de Oliveira et al., 2019; Lalanza et al., 2014; Leffa et al., 2015; Pini et al., 2017), while four studies found no changes in anxiety (Beilharz et al., 2018; Ferreira et al., 2018; Sack et al., 2017), or an increase upon CAF diet consumption (Ferreira et al., 2018; Warneke et al., 2014). Again, all studies conducted with rats chose an albino strain (Wistar or Sprague-Dawley), so the albinism of the animals cannot explain these differences. In female rats, two studies found a reduction in anxiety levels (Lalanza et al., 2014; Warneke et al., 2014) with more pronounced effects in adult females (Warneke et al., 2014), while two studies found no changes (Cigarroa et al., 2016; da Costa Estrela et al., 2015). Since illumination levels during behavioral tests were not properly reported in most of these classical studies, we cannot determine whether this might have contributed to the different findings. Social isolation is neither an alternative factor, as single and grouped-housing protocols are found in both outcomes. It is, thus, difficult to draw any conclusions on whether CAF diet has an effect on anxiety.

Interestingly, CAF diet exposure shortly after weaning did not, at first, reduce anxiety in the elevated plus maze and in the light/dark test, but it did significantly attenuate the anxiogenic effect of maternal separation (Maniam and Morris, 2010a). Attenuating effects on stress levels due to maternal separation were also seen in the dams (Maniam and Morris, 2010b). These results might suggest that CAF diet, and junk food in general, exerts significant anxiolytic effects in stressed subjects.

The hypothesis of junk food consumption reducing stress is supported by the effects of the CAF diet on neurophysiological measures. Maniam and Morris (2010a, 2010b) also found that a CAF diet

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reduced the expression of glucocorticoid receptors (GR) and corticotropin-releasing hormone (CRH) after maternal and litter separation. Similarly, the CAF diet also reduced ACTH (adrenocorticotropic hormone) and corticosterone after chronic stress exposure (Gustaityte et al., 2019; Zeeni et al., 2015b; Zeeni et al., 2013) and CAF diet in rats reduced adrenal gland weight gain following restrain stress (Macedo et al., 2015). Finally, it was also shown that switching from STD chow to CAF diet exposure reduced corticosterone levels after restraint-induced stress (South et al., 2012) and also reduced amygdala GR receptors mRNA expression compared to chronic (15 weeks) CAF diet (Martire et al., 2014).

Overall, we conclude that CAF diet consumption can attenuate stress responses. This clear effect of a CAF diet on the neurophysiology of stress is not a surprise, given that the neural circuits mediating stress responses, reward processing and those regulating feeding behavior and metabolism are intimately connected (for a review, Meye and Adan, 2014; Rabasa and Dickson, 2016; Sinha, 2018). There is overlap and mutual influence between these systems, for instance, the paraventricular nucleus of the hypothalamus is a hub connecting feeding and stress by regulating food intake and activation of the HPA axis, these actions being sensitive to both glucocorticoids and insulin (for a review, Koob and Schulkin, 2019; Morris et al., 2015).

The association between CAF diet consumption and depression-like behaviors has also been assessed. In male rats, it was shown that a fixed CAF diet does not induce depression-like behavior as assayed by the forced swim test and the sucrose preference test (Ferreira et al., 2018; Macedo et al., 2015). In male mice, though, a rotated CAF diet reduced immobility time in both the forced swim and the tail suspension test, suggesting a reduction of certain aspects of depressive-like behavior (Leffa et al., 2015). This latter finding is in line with the observation of increased levels of the neurotrophins BNDF (brain-derived neurotrophic factor) and NGF (nerve growth factor) in the hippocampus, both which are considered as anti-depression markers (for a review, Björkholm and Monteggia, 2016).

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In female rats, a rotated CAF diet has also been shown to reduce some signs of depression-like behavior in the forced swim test (Maniam and Morris, 2010b). These results highlight the importance of considering both the specie – mouse is not a small rat – and the sex of experimental subjects, especially when studying mood disorders which display pronounced sex biases (for a review, Altemus et al., 2014).

Interestingly, in male rats exposed to stressors (either maternal and litter separation or chronic variable stress), the CAF diet compared to STD chow reduced depression-like behaviors (Maniam and Morris, 2010a, 2010b;) and tend to reduce them (Zeeni et al., 2013). This would suggest that a CAF diet exerts its antidepressant effects on animals already suffering from a mood disorder, as we noted in the stress sub-section. On the other hand, however, da Costa Estrela *et al.* (2015) found the opposite effect, whereby the CAF diet reduced the climbing time in the forced swim test (climbing is considered a non-depressive-like behavior) in female rats previously exposed to restraint-induced stress. However, in the STD chow group, the restraint-induced stress did not induce the expected depression-like behaviors, which might indicate that animals were, indeed, not depressed.

To conclude, the CAF diet has been shown to have anxiolytic and antidepressant-like effects on animals that were placed in higher stressful states. For non-stressed animals, the effects of a CAF diet on anxiety and depression have been less clear, but there seems to be a trend towards an anxiolytic effect overall (Table 4). Thus, the idea of eating junk food as a comfort food to relieve negative mood states may be valid. Nevertheless, more research is needed for a better understanding of the bidirectional relationship between junk food eating and negative mood states.

Coping Behavior

The aforementioned behavioral tests, such as the elevated plus maze, light/dark test and the forced swim test are all assays based on unconditioned responses, and are said to involve passive responses. That is, there is not an active solution for the animals to take in order to avoid the stressor (Bourin et al., 2007). The elevated plus maze, for example, has a safe zone, the closed arms, and there is no need for the animal to move to the rest of the maze beyond its natural instinct to explore. So, the

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animal can avoid the stressful situation passively. The same principle applies to the forced swim test, where there is not an active approach that would be beneficial to the rodent. In the real world, however, rodents and humans face complex problems that can usually be solved with active, complex and brave actions. For example, giving a speech as introvert is a hard situation that requires an active confrontation with one's own fears. In other words, one needs to cope with it.

Two studies have investigated the effect of the CAF diet on this kind of coping behavior in rodents. Mucellini *et al.* (2019) used the step-down inhibitory avoidance task to study the effects of gestational exposure at puberty and adult age, while Cigarroa *et al.* (2016) used the two-way avoidance task in a classical design.

The step-down inhibitory avoidance task consists of an arena with a glass platform elevated above the floor. This platform triggers an anxiety-like response in rats. Consequently, the natural urge is to leave the platform and return to the floor. However, since the floor is electrified, the rat has to fight against its fear of highness in order to avoid the electroshock. The latency to get down is therefore a measure of aversive memory or coping. Compared with a more passive light-dark test with the absence of punishment for entering the comfortable zone, this inhibitory avoidance test requires a coping strategy from the animal. As we have discussed, the CAF diet has no effects on locomotor activity, which could impair a coping response due to excessive or deficit motion. On the other hand, CAF tended to reduce stress, mainly in stressed animals, so CAF diet could be beneficial for facing stressful situations calmly. However, CAF diet did not affect coping in the gestational study and reduced coping in the classical study. Methodological differences in both studies might explain these distinct results.

It was found that exposure to CAF diet did not affect coping behavior in step-down inhibitory avoidance task. The latency to get down significantly increased from training to test session, which means that rats learned to cope with the fear of heights. However, this effect was found in both STD chow and CAF diet groups at both ages, puberty and adulthood (Mucellini et al., 2019). Therefore, indirect CAF diet exposure does not affect coping behavior in rats.

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Cigarroa *et al.* (2016) tested adolescent female rats that were directly exposed to a CAF diet in the two-way avoidance task. This task makes use of a fear-mediated conflict between a tendency to freeze and a tendency to escape from an electroshock. The box is composed of two compartments separated by an open door. In order to escape or avoid the upcoming foot shock, signaled by a light and/or a tone, the animal must learn to change between the two compartments. So, when the light/tone signals the incoming electroshock, the animal should come back to the compartment where previously the animal received an electroshock. As there is not a safe compartment, the animal has to face its fears of returning to the compartment where it previously received a punishment in order to avoid the following electroshock (Lalanza et al., 2015). Interestingly, and different from the absence of gestational effects, when female rats were exposed to the CAF diet directly, they displayed impaired coping behavior. CAF diet fed rats had a smaller decrease in the number of avoidances and a smaller increase in the escape latencies.

Two studies are not enough to draw general conclusions, but they indicate that a CAF diet does not improve coping behavior and one suggests it may do the contrary. The differences found between the gestational and the classical study could simply be caused by the timing of CAF diet exposure, but the sex of the subjects could also have played a role, because the gestational study looked at male offspring, while the classical study examined females. Future studies will have to shine more light on this topic.

Cognition and Memory

Human studies suggest that diets rich in fat and sugar are a risk factor for cognitive impairment in adults, for increasing vulnerability to dementia and, even, for slowing the development of children's cognitive skills (Davidson et al., 2019; Morris et al., 2015). Consistently, similar impairment effects were also found in rodents exposed to HF/HS diets (Cordner and Tamashiro, 2015). Therefore, it is expected that the CAF diet will impair cognitive function. Memory could be investigated with different approaches. In this review, based on the types of behavioral tests used, we differentiate between spatial and contextual memory, recognition memory and executive function.

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In gestational studies, to the best of our knowledge, the only assay so far deployed has been the object recognition test. It was found that indirect CAF diet exposure via their dams reduced recognition memory in female pups, although for male pups this impairment was less robust (Moreton et al., 2019; Mucellini et al., 2019; Wright et al., 2014). There is a need for more studies that further characterize these sex differences, and we strongly encourage researchers to go deeper into the question of how perinatal exposure to a CAF diet might affect the cognitive abilities of offspring.

In classical studies, the CAF diet has been found to impair spatial and contextual memory, but no effects on recognition memory or executive function have been observed. Spatial memory is a hippocampus-dependent memory that relies on remembering a location with the help of environmental cues. In three studies that assessed spatial memory in the Morris water maze, two found that the CAF diet reduced spatial memory (Ferreira et al., 2018; Lewis et al., 2019), whereas the other found no effect compared to STD chow and HF/HS diets (Pini et al., 2017). However, this apparent discrepancy might be explained by methodological differences. Pini *et al.* (2017) applied a shorter and more intense learning phase (2 days, 12 trials per day) in the Morris water maze, compared to the standard procedure of 4 to 6 days with only 4 to 5 trials per day (Bromley-Brits et al., 2011; Vorhees and Williams, 2006). Furthermore, in that study, the CAF diet did not induce obesity indicating that their CAF diet protocol was not an effective obesogenic model, maybe because CAF diet was limited only for one-hour a day. In addition, the rats were single-housed while were grouped in the first studies (Ferreira et al., 2018; Lewis et al., 2019). Spatial memory can also be assessed by the Barnes maze, which is a less stressful version of the Morris water maze, without water. Interestingly, the CAF diet did not affect spatial memory in such a Barnes maze, but as the authors reported, this lack of effect could be explained by the lower levels of stress. It is known that stress can reduce the motivation to learn, which could then explain the differences in results between the Barnes and Morris water mazes (Gomez-Smith et al., 2016). All of these studies were carried out with albino strains, what could have interfered with rat's performance in visuo-behavioral measurements like the Barnes and Morris water mazes (Prusky et al., 2002). Further

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studies using pigmented strains will confirm the detrimental effects of CAF diet on spatial memory without the inconveniences of visual acuity.

The CAF diet also reduced contextual memory as assessed by both the object recognition test and the fear conditioning test (Beilharz et al., 2016, 2014; Reichelt et al., 2015). Interestingly, these behavioral tests are able to assess different types of memories depending on the exact protocol used. In the object recognition test, for example, one can assess contextual memory by changing the positions of the objects instead of the objects themselves. Applying this paradigm, it was found that consuming a CAF diet reduced the time spent exploring the object placed in a new position (Beilharz et al., 2016, 2014), Thus, and similar to the Morris water maze, animals fed with the CAF diet did not distinguish between different locations. In another experiment, the same researchers surprisingly found no effects of CAF diet on contextual memory compared to STD chow using the same protocol for the object recognition test. However, and like the previous studies, the exploration ratio between the old and the new position was very close to 50% in the CAF group, which indicates low levels of contextual memory. The exploration ratio indicates the amount of time spent exploring the two different objects or positions, so a ratio of 50% means that both objects/positions were explored a similar amount of time, without preferences for the new one. Interestingly, when the CAF diet was combined with probiotics (evidence suggests that the gut-brain axis and the microbiota could affect the central nervous system), the exploration time of the object placed in the new position actually increased (Beilharz et al., 2018). This interaction between CAF diet and probiotics suggests that CAF diet could have reduced the exploration time of the object in the new position even though the comparison with the STD chow group did not reach significance.

The fear conditioning test can be used to assess recognition memory with an associative learning paradigm or contextual memory, using a contextual learning paradigm. One study found that the CAF diet impaired contextual memory in the fear conditioning test, as shown by CAF diet-fed rats displaying reduced freezing, compared to STD chow controls, in the context associated with the electroshock (Reichelt et al., 2015). However, a second study found no effects of a CAF diet in the contextual version of the fear conditioning test (Ferreira et al., 2018). However, in this second case, only the training context

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without the conditioned stimulus was used to test contextual memory, which could explain the lack of significant difference between the diet groups.

More consistently, the CAF diet has not been found to impair recognition memory using the "new object" version of the object recognition or the associative learning paradigm of the fear conditioning test in multiple studies (Beilharz et al., 2018, 2016, 2014; Ferreira et al., 2018; Leffa et al., 2015; Reichelt et al., 2015). Surprisingly, in a study comparing two CAF diet groups, one with free-access to cola-based soft drink and another with orange-based soft drink, opposite effects were found on recognition memory (Feijó et al., 2019). While the CAF + cola group increased the time exploring the new object, the CAF + orange reduced it compared to the control group. However, the soft drink groups were not compared to each other and the control group was different for the CAF + cola and CAF + orange. Therefore, this result must be taken carefully and does not represent a clear evidence of CAF diet impairing recognition memory.

Finally, executive function was only tested in one study using a puzzle box test, which consists of a subdivided arena with different obstacles to make progress more difficult (e.g. an underpass filled with sawdust) that change each trial. The animal needs to overcome the obstacles to leave the anxiogenic compartment and get into the small and covered safe compartment. The general analysis of the puzzle box, based on the latency to reach the save compartment, showed that executive function was not affected by the CAF diet, even though increased CA1-CA3 volume (Sack et al., 2017).

At a neurophysiological level, the hippocampus is a logical candidate for the impairment of spatial and/or contextual memory caused by the CAF diet, since this brain region also regulates eating behavior (Davidson et al., 2019). It has been shown that a CAF diet increases neuroinflammation and reduces neurogenesis in the hippocampus, which, in most of the studies, correlated with a spatial/contextual memory impairment at a behavioral level (Beilharz et al., 2016, 2014; Ferreira et al., 2018; Gomez-Smith et al., 2016; Reichelt et al., 2015). Interestingly, a gestational study did not found impairment of maternal CAF diet on pups, but neither effects on hippocampal BNDF (Mucellini et al.,

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2019). Similar results regarding impairment of spatial memory and disruption of the hippocampal formation have also been found with HF/HS diets (Boitard et al., 2014; Molteni et al., 2002; Stranahan et al., 2008).

In aggregate, we conclude that direct exposure to a CAF diet seems to be a risk factor for spatial and contextual memory deficits, while indirect exposure via dams may impair recognition memory, which was not affected by direct exposure to CAF diet in classical studies. Although preliminary studies indicate a potential role for changes to the hippocampus in mediating these cognitive declines (Table 4), further work is needed to more fully reveal the brain mechanisms underlying the changes in spatial/contextual and recognition memory produced by a junk food diet.

Social behavior

The concept of social behavior is complex and it includes many types of interactions, including behaviors such as social approach, social play behavior, sexual behavior, and maternal care. A few of the studies we reviewed tested the effects of the CAF diet on some of these social behaviors.

Sexual behavior is itself a multifaceted social behavior (for a review of sexual behaviors, Heijkoop et al., (2018)) consisting of numerous behavioral components that are under regulated by complex hormonal systems, including the estrous cycle. High-fat diets and obesity are able to affect reproductive functions, and obesity is a risk factor for infertility in both women and men (Broughton and Moley, 2017; Kahn and Brannigan, 2017). Therefore, it is possible that the CAF diet also affects sexual behavior.

In female rats it was indeed found that eating a CAF diet affected the estrous cycle: the CAF diet reducing ovulation rates and release of luteinizing hormone, while also increasing the frequency of the diestrus phase and the release of prolactin (Sagae et al., 2012). Interestingly, however, these changes to the estrous cycle did not have consequences for sexual behavior itself, the CAF diet not altering sexual paracopulatory or receptive behaviors, i.e. hops, darts, ear wiggling, solicitations and lordosis.

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The effects of the CAF diet on male sexual behavior, on the other hand, have only been investigated in a gestational study. This study showed that CAF exposure altered male rat sexual behavior with less intromission behavior. This change in behavior was potentially due to decreased production of reproductive hormones (luteinizing hormone, follicle-stimulating hormone, and testosterone) (Jacobs et al., 2014). More research is needed to determine whether the CAF diet affects male and female sexual behavior differently, or whether these apparent differences were caused by the timing and/or way of administration.

Social play behavior is a rewarding and widespread social activity among mammals (for a review, Vanderschuren et al., 2016). As social play is crucial during the early phases of development, the two studies applying CAF diet and assessing social play were carried out on young animals. A gestational study found a reduction in social play in pups of dams fed with CAF diet (Ribeiro et al., 2018). Whereas a classical study with adolescent rats found that a CAF diet resulted in more social play compared to STD chow, with females being more playful than males (Lalanza et al., 2014).

This discrepancy in effects on social play could actually also be explained by changes in maternal care behavior. As mentioned above, maternal care might have more influence on pups than the diet itself, because abnormal maternal care is a risk factor for social dysfunction. For example, in a recent meta-analysis, Bonapersona *et al.* (2019) found that aberrant maternal care behavior reduced social behavior mainly in males. In other words, when a CAF diet is administered to dams, this could influence pups' behavior through changes in maternal care. Surprisingly, only two studies analyzed the effects of a CAF diet on maternal care, and both found alterations in maternal care, including increased licking/grooming (Speight et al., 2017) and arched nursing and nesting (Ribeiro et al., 2018).

Maternal CAF diet exposure is, therefore, a risk factor for the pups as has been discussed in this review. High fat diets and obesity are also risk factors for the abnormal fetal development (Wentzel et al., 2019) and human studies have also found evidence that maternal obesity is a risk factor for future neurodevelopmental and psychiatric disorders in offspring during adolescence and adulthood (for a review, Baker et al., 2017; Rivera et al., 2015).

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Limitations and Conclusions

The aim of this review was twofold. First, we have aimed to establish a standardized CAF diet protocol that would help the field avoid the current wide-ranging disparities in CAF diet protocols. Second, we have evaluated the current state of knowledge regarding the behavioral effects of exposure to a CAF diet on rodents.

The large amount of inconsistency in results has made it difficult to draw firm conclusions on the effects of this diet on behavioral outcomes. However, overall, we believe we can reasonably conclude that a CAF diet: 1) does not change locomotor activity, 2) increases snacking behavior, and 3) reduces the hedonic value of other rewards such as sucrose and ethanol, a principle similar to the hypofunction or deficiency of the reward and dopaminergic system (Blum et al., 2014; Johnson and Kenny, 2010). In addition, exposure to a CAF diet 4) impairs spatial and contextual memory, and 5) tends to have an anxiolytic and antidepressant effects mainly in animal previously exposed to stress. We are, however, very cautious in drawing these general conclusions, because different studies have used widely varying methodologies. Even leaving aside the specifics of how a CAF diet was given, studies varied in terms of age, species, and behavioral tests, all of which could have affected the outcomes. Such differences could well be the reason that we did found insufficient evidence to draw clear conclusions regarding impulsivity, coping behavior and social behavior. The findings suggest that CAF diet altered these behaviors as well, but more research is needed to control for the methodological variations, which hope would lead to more consistent conclusions.

Furthermore, a limitation of this review and the obesogenic diets in general is the difficulty of distinguishing the neuropsychophysiological effects caused by palatable food intake from those derived from the consequently induced overweight/obesity. To illustrate this problem, a negative correlation has been found between the amount of dopaminergic receptors and body weight (de Weijer et al., 2011; Michaelides et al., 2012; Wang et al., 2001). Taking into account that palatable diet in the form of junk and ultraprocessed food is a major cause of obesity (Rosenheck, 2008), it is likelythat the food–body weight interaction is a vicious circle phenomena, because long-term consumption of junk food also

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affects the dopaminergic signaling (*as mentioned above*). For instance, women who gained weight during the last six months had a lower striatal response towards palatable food compared to stable-weigh women. This could increase the vulnerability for overeating (*as a compensatory mechanism of stimulating a hypofunctional reward system*) and result in increases in body weight (Stice et al., 2010).

The large variation in the feeding protocols used to study the effects of CAF diet exposure could also have caused the different behavioral outcomes. In order to improve coherence between experiments, and thereby allow comparisons between studies, we propose that researchers will use a standardized protocol. Therefore, we propose that future CAF protocols should: 1) combine different tastes, textures and nutrients; 2) include salty and sweet products as well as products containing chocolate elements; 3) rotate and vary the diet each day, with the menu structure as an excellent tool; 4) give animals *ad libitum* access to the CAF diet*;* and 5) offer a healthy (or standard) alternative, since a CAF diet must be available voluntarily and chosen due to its palatability.

Nowadays, junk food is highly prevalent in Western societies and plays a key role in the epidemic of overweightness and obesity, which underlies the corresponding epidemic in non-communicable diseases such as diabetes and cardiovascular disease. Basic animal research is necessary to understand not only the physiological and behavioral effects of junk food, but also to comprehend the triggers and risk factors for overeating these kinds of food products. They will also inform the development of potential treatments for obesity. As we have argued, the CAF diet is an excellent model for recapitulating current problematic human eating patterns due to its high construct validity. The standardized CAF diet protocol proposed herein would enhance comparisons between research laboratories, thereby aiding the understanding of the obesity epidemic and developing ways to mitigate it.

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Table 1: The CAF protocols of the included studies (n=50).

Reference	Strain (Specie)	Sex[1]	Age[2] (weeks)	Animals per cage	Weeks of CAF[3]	CAF conditions[4]	Main Ingredients[5]	Products or types of products (number of / number per day)
Bayol et al., 2007	Wistar (rat)	Female (Both)	12-14 (0)	1 (3)	6 (7)	AL, V, F	ST, SW, LCT, MT, CH	(8 / 8): Biscuit, Marshmallow, Cheese, Jam doughnut, Chocolate chips muffin, Butter flapjack, Potato crisps, Caramel and/or chocolate bar.
Beilharz et al., 2014	Sprague-Dawley (rat)	Male	302-467g	4	3	AL, V, R	ST, SW, MT, LQ	(4 / NI): Cakes, Biscuits, Lard, 10% sucrose bottle.
Beilharz et al., 2016	Sprague-Dawley (rat)	Male	192-222g	3	1,5	AL, V, R	ST, SW, MT, CH, LQ	(10 / NI): Chocolate mud cake, Jam roll, Lamingtons, Chocolate chips, Monte Carlo, Scotch fingers, Party pie, Dim sims, Dog roll, 10% sucrose bottle.
Beilharz et al., 2018	Sprague-Dawley (rat)	Male	200g	2	3.5	AL, V, R	ST, SW, MT, CH, LQ	(10 / NI): Chocolate mud cake, Jam roll, Lamingtons, Chocolate chips, Monte Carlo, Scotch fingers, Party pie, Dim sims, Dog roll, 10% sucrose bottle.
Boakes et al., 1987	Hooded Lister (rat)	Male	4.5-8	3-4	3	RST, V, R	ST, SW, LCT, FV	(6 / 1): Sweet cereals, Tinned spaghetti in tomato sauce, Peanuts, Cheese, Banana, Tinned corned beef.
Chen et al., 2014	Long-Evans (rat)	Female	4-5	1	9	AL or LA, V, R	ST, SW, LCT, MT, CH	(9 / 2): Potato chips, Corn snack, Chocolate cake, Peanut butter cookies, Pepperoni, Pretzels, Chocolate sandwich cookies, Chocolate chips cookies, Breakfast pastries.
Cigarroa et al., 2016	Sprague-Dawley (rat)	Female	3	2	8	AL, V, R	ST, SW, LCT, MT, FV, LQ	(8 / 6): Bacon, Hot dog, Biscuits with pâté, Biscuits with cheese, Muffin, Ensaïmada, Carrot, Milk with sugar.
Cook et al., 2017	Wistar (rat)	Male	3-5	1	4	LA, V, R	ST, SW, LCT, MT, CH	(12 / 4): Cheesecake, Bacon, Cream sandwich cookies, Chocolate chips cookies, Sugar wafer cookies, Potato chips 1, Potato chips 2, Sweet cereals 1, Sweet cereals 2, Marshmallow, Chocolate candy, Chocolate bar.
da Costa Estrela et al., 2015	Wistar (rat)	Female	6-7	1	15	AL, V, R	ST, SW, LCT, MT, CH, FV	(49 / 3): Bacon cracker, White chocolate candy, Honey bread, Salami, Lemon wafer cookies, Sweet cereals, Coated Peanuts, Vanilla mini-cake, Dulce de leche, Mini bread roll, etc.
de Oliveira et al., 2019	Wistar (rat)	Male	8-9	3-4	8	AL, V, F	ST, SW, LCT, MT, LQ	(6 / 6): Cracker, Sausage, Snack food, Wafer, Condensed milk, Soft drink.
Feijó et al., 2019	Wistar (rat)	Male	12	2-3	16	AL, V, R	ST, SW, MT, CH, LQ	(9 / 3): Cake, Salty snacks, Biscuits, Potato chips, Cream wafer, Sausage, Mortadella, Chocolate, Soft drink (cola or orange-based).
Ferreira et al., 2018	Wistar (rat)	Male	4	2	12	AL, M, F	ST, SW, MT, CH, LQ	(5 / 5): Chocolate cake, Biscuit, Dog roll, High-fat chow, Sucrose water.
Gac et al., 2015	Balb/c (mouse)	Male	8-12	1	8	AL, V, R	ST, SW, LCT, MT, CH	(11 / 2): Vanilla wafers, Peanut butter, Fruity cereals, Candy bar, Cream sandwich cookies, Milk chocolate, Cheese puffs, Crackers, Cheese tortilla chips, Fried crackers, Cheese.

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Table 1: Continue.

Reference	Strain (Specie)	Sex[1]	Age[2] (weeks)	Animals per cage	Weeks of CAF[3]	CAF conditions[4]	Main Ingredients[5]	Products or types of products (number of / number per day)
Gomez-Smith et al., 2016	Sprague-Dawley (rat)	Male	3	2	14	AL, V, R	ST, SW, LCT, MT, CH, LQ	(17 / 3): Sweet cereals, Chocolate and cream biscuit, Chocolate chips cookies, Peanut butter cup, Peanut butter candy, Butter tart, Cheese puffs, Cheese tortilla chips, Cream sandwich cookies, Vanilla wafers, Brownies, Potato chips, Pre-cooked bacon, Blue ribbon bologna, All beef hot dog, Cheese cracker, Water with sucrose.
Jacobs et al., 2014	Wistar (rat)	Female (Male)	3 (0)	5 (5)	16 (0)	AL, V, R	ST, SW, MT, CH, LQ	(12 / 4): Biscuit, Ham, Cake, Marshmallow, Sausage, Salami, Bread, Snack, Gumdrop, Wafer, Candy, Soft drink.
Johnson and Kenny, 2010	Wistar (rat)	Male	300-350g	1	5.5[6]	AL or LA, V, F	ST, SW, LCT, MT, CH	(6 / 6): Bacon, Sausage, Cheesecake, Pound cake, Frosting, Chocolate.
Kendig et al., 2016	Hooded Wistar and Long-Evans (rat)	Male	NI	4 and 2-4	2	LA, RST, V, F	ST, SW	(3 / 3): Cream sandwich cookie, Potato chips, Jelly snack.
Kitchell, 1984	CD-1 (HaM/ICR) (mouse)	Male	38	3	10	AL, M, R	ST, SW, LCT, MT, LQ	(9 / NI): Potato chips, Pizza, Doughnut, Cheese, Mayonnaise, Cream sandwich cookies, Peanut butter, Beer, Soft drink.
Kosheleff et al., 2018a	Sprague-Dawley (rat)	Male	10	2	6	AL or LA, V, R	ST, SW, LCT, MT, CH	(12 / 2): Cheese puffs, Cheese, White bread, Hot dog, Potato chips, Cracker, Peanut butter, Strawberry pop tart, Sugar shredded wheat, Cream sandwich cookie, Chocolate chips cookie, White chocolate.
Kosheleff et al., 2018b	Sprague-Dawley (rat)	Male	8	2	6	AL or LA, V, R	ST, SW, LCT, MT, CH	(12 / 2): Chocolates, Chocolate bar, Cream sandwich cookie, Chocolate chips cookie, Donut, Brownie, Cracker, Cheese puffs, Tortilla chips, Bagel, Hot dog, Cheese.
Lalanza et al., 2014	Sprague-Dawley (rat)	Both	3	1	8	AL, V, R	ST, SW, LCT, MT, FV, LQ	(8 / 6): Bacon, Hot dog, Biscuits with pâté, Biscuits with cheese, Muffin, Ensaïmada, Carrot, Milk with sugar.
Leffa et al., 2015	Swiss (mouse)	Male	5-6	6	13	AL, V, R	ST, SW, LCT, MT, CH, LQ	(13 / 4-5): Chocolate cracker, Wafer, Marshmallow, Mortadella, Hot dog, Cheese, Bacon chips, Cheese chips, Tortilla chips, Peanut candy, Calf's foot jelly, Soft drink 1, Soft drink 2.
Lewis et al., 2019	Sprague-Dawley (rat)	Male	6-8	3	20	AL, V, F	ST, SW, LCT, MT, LQ	(8 / 8): Cheese, Vienna sausage, Corned beef, Cookie 1, Cookie 2, White hops bread, Cracker, Soft drink.
Macedo et al., 2015	Wistar (rat)	Male	8.5	4	12	AL, V, F	ST, SW, LCT, MT, LQ	(6 / 6): Cracker, Wafer, Sausage, Chips, Condensed milk, Soft drink.
Maniam and Morris, 2010a	Sprague-Dawley (rat)	Both	3	3-5	16	AL, M, R	ST, SW, LCT, MT	(5 / 5): Cakes, Biscuits, Dim sim, Meat pies, Special high fat chow.
Maniam and Morris, 2010b	Sprague-Dawley (rat)	Female	4	4-5	16	AL, M, R	ST, SW, LCT, MT	(5 / 5): Cakes, Biscuits, Dim sim, Meat pies, Special high fat chow.
Martire et al., 2013	Sprague-Dawley (rat)	Male	7-8	2	16	AL, V, R	ST, SW, LCT, MT, CH	(9 / 4): Meat pies, Dim sim, Pasta, Potato Chips, Oats, Dog food roll, Cakes, Biscuits, Special fat pellets.

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Table 1: Continue.

Reference	Strain (Specie)	Sex[1]	Age[2] (weeks)	Animals per cage	Weeks of CAF[3]	CAF conditions[4]	Main Ingredients[5]	Products or types of products (number of / number per day)
Martire et al., 2015	Sprague-Dawley (rat)	Male	6-8	4	13	AL or LA, V, R	ST, SW, LCT, MT, CH	(9 / 4): Meat pies, Dim sim, Oats, Dog food roll, Lamington cake, Mud cake, Chocolate chips cookies, Scotch finger biscuit, Special fat pellets.
Moreton et al., 2019	Wistar (rat)	Female (Both)	0[7]	8	3	AL, V, R	ST, SW, LCT, MT, CH, FV	(10 / 4): Shortbread, Golden syrup, Plain chocolate, Pork pie, Pâté, Cocktail sausage, Cheese puffs, Crisps, Peanuts, Strawberry jam
Mucellini et al., 2019	Wistar (rat)	Female (Male)	3 (0)	4	30 (14)	AL, V, R	ST, SW, MT, CH, LQ	(13 / 5): Salami, Bread, Snack 1, Snack 2, Deliket jellybean, Smoked sausage, Chocolate cake, Biscuit maizena, Marshmallow, Ham, Wafer biscuit chocolate, Gumdrop gomets, Soft drink.
Palframan and Myers, 2016	Sprague-Dawley (rat)	Female	8	2	12	RST, V, R	ST, SW, MT, FV, NI	(96 / 2-3): Pastries, Favored granolas, Sweet cereals, Snack chips, Canned backed beans, Ready-to-eat pasta, Fried plantain chips, Canned pie fillings, etc.
Pérez et al., 1999	Sprague-Dawley (rat)	Female	207-285g	1	6	RST, V, R	ST, SW, LCT, MT, LQ, FV	(18 / 4): Bologna, Canned green peas, Oatmeal cookie, Whole yogurt, Hard salami, White bread, Raisins, Non-fat yogurt, Cheese, Cracker, Dried apricot, Pineapple slice, Boiled ham, Sweet cereals, Graham cracker, Apple sauce, Fat milk, Skim milk.
Pini et al., 2017	Wistar (rat)	Male	3	1	11	LA, V, R	ST, SW, LCT, MT, CH, FV	(28 / 4): Toast, Marshmallow, Sweet peanuts, Salami, Chocolate chips straw, Biscuit maizena, White chocolate, Cheese, Sweet cereals, Chocolate cream sandwich, etc.
Ramírez-López et al., 2016	Wistar (rat)	Female (Male)	175-183g (0)	1 (2-3)	14 (0)	AL, V, F	SW, CH	(4 / 4): Chocolate bar 1, Chocolate bar 2, Chocolate bar 3, Chocolate.
Reichelt et al., 2014	Sprague-Dawley (rat)	Male	6	4	2, 3 or 10	AL, V, R	ST, SW, MT	(6 / 4): Cookies, Cakes, Biscuits, Beef pie, Dim sims, Jam roll.
Reichelt et al., 2015	Sprague-Dawley (rat)	Male	6	4	10	AL, V, R	ST, SW, MT, CH	(4 / 4): Meat pies, Chocolate chip cookie, Cream sandwich cookies, Jam roll, etc.
Ribeiro et al., 2018	Swiss (mouse)	Female (Both)	9 (0)	1 (NI)	3 (0)	AL, V, F	ST, SW, LCT, MT, CH	(5 / 5): Chocolate, Cheese, Potato chips, Bacon, Wafer biscuit.
Robertson and Rasmussen, 2017	Sprague-Dawley (rat)	Male	3 or 10	1	8	AL, V, F	ST, SW, LCT, MT, CH	(6 / 6): Cooked sausage, Cheesecake, Potato chips, Frosting, Chocolate candy, Bar.
Rogers, 1985	Hooded Lister (rat)	Female	NI	NI	32	AL, V, F	ST, SW, CH	(3 / 3): White bread, Chocolate, Digestive cookie.
Sack et al., 2017	C57BL/6N (mouse)	Male	8	1	8	AL, V, R	ST, SW, LCT, MT, CH	(14 / 2)[8]: Cocos biscuit, Peanut caramel bar, Chocolate biscuit, Peanut snack, Salted cracker, Puffpaste cheese snack, Pretzel snack, Mini salami, Wiener sausage, Cheeseballs, Cheese, Chocolate, Chocolate candy, Coconut chocolate bar.
Sagae et al., 2012	Wistar (rat)	Female	3	3-5	9	AL, M, F	SW, CH, LQ	(7 / 6): Wafer, Snacks, Cake, Biscuit, Special CAF mash pellet, Soft drink 1, Soft drink 2[9].
Sahakian et al., 1982	Hooded Lister (rat)	Female	2,5	1 or 4-5	4	AL, V, F	SW, CH	(4 / 4): Bar, Cheese, Ginger cookies, Marzipan

Table 1: Continue.

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Reference	Strain (Specie)	Sex[1]	Age[2] (weeks)	Animals per cage	Weeks of CAF[3]	CAF conditions[4]	Main Ingredients[5]	Products or types of products (number of / number per day)
South et al., 2014	Sprague-Dawley (rat)	Male	275-300g	3	10	AL, V, R	ST, SW, LCT, MT, CH	(6 / 3): Cakes, Cookies, Dim sims, Pasta, Meat pies, Special fat pellets.
Speight et al., 2017	Wistar (rat)	Female (Both)	NI (0)	1 (4)	3 (0)	AL, V, R	ST, SW, LCT, MT, CH, FV	(10 / 4): Pork pie, Pâté, Cocktail sausage, Cheese, Crisps, Jam, Fruit and nut chocolate, Golden syrup cake, Shortbread, Peanuts.
Thompson et al., 2017	Sprague-Dawley (rat)	Male	8-9	1	6	AL or LA, V, F	ST, SW, MT	(5 / 5): Beef hot dog, Sweet cereals, Donut holes, Peanut butter, Tortilla chips.
Warneke et al., 2014	Sprague-Dawley (rat)	Both	6 or 52	4	6	AL, V, R	ST, SW, LCT, MT, CH	(7 / 4): Cake, Cookie, Chocolate, Raisin bread, Cooked noodles, Sausage, Cheese.
Wright et al., 2011a	Wistar (rat)	Female (Both)	3 (0)	NI (grouped)	11 (3)	AL, V, R	ST, SW, LCT, MT, CH, FV	(11 / NI): Biscuit, Potato crips, Fruit and chocolate, Chocolate bar, Cheese, Golden syrup cake, Pork pie, Cocktail sausage, Liver and bacon pâté, Strawberry jam, Peanuts.
Wright et al., 2011b	Wistar (rat)	Female (Both)	12 (0)	1 (8)	3 (0)	AL, V, R	ST, SW, LCT, MT, CH, FV	(11 / 4): Biscuits, Potato crips, Fruit and chocolate, Chocolate bar, Cheese, Golden syrup cake, Pork pie, Cocktail sausages, Liver and bacon pâté, Strawberry jam, Peanuts.
Wright et al., 2014	Wistar (rat)	Female (Both)	NI (0)	1 (4)	3 (0)	AL, V, R	ST, SW, LCT, MT, CH, FV	(10 / 4): Pork pie, Pâté, Cocktail sausages, Cheese, Potato crips, Jam, Fruit and nut chocolate, Golden syrup cake, Shortbread, Peanuts.
Zeeni et al., 2013	Sprague-Dawley (rat)	Male	8-10	4	6	AL, M, F	ST, SW, CH	(4 / 4): Bar chocolate, Digestive cookies, Peanut butter, High carbohydrate pellets.

[1] In gestational (and lactation) studies, the sex of pups is indicated in brackets. [2] "Age" refers to the age of starting feeding, for gestational or lactation studies we indicate the age of the dam and, in brackets, the age of the pup's (other information in brackets refers to pups as well). In case the age was not reported, we indicate the initial body weight. [3] Total or maximal weeks of the CAF diet administration without taking into account different previous assessments. [4] AL=ad libitum, LA=limited access, RST=restriction, V=voluntary, M=mandatory, F=fixed, R=rotate. [5] ST=salty, SW=sweet, LCT=lactose product, MT=meat product, CH=including chocolate or a product with chocolate, LQ=liquid or special drink, FV=fruits or vegetables. [6] or, depending on the experiment, until a significant increase in body weight was reached compared to standard chow group. [7] CAF diet started during lactation. [8] Information taken from supplementary information of Auer *et al*., 2015. [9] Only drinks were daily rotated.

For *ad libitum*, limited access or restriction and rotating variables, in case authors did not indicate it, we assumed the standard (*ad libitum*, no limited access and no rotation). Regarding the number of products, when authors did not report it directly, we just counted the number of different foodstuff indicated in the paper or considered more than one type if it was wrote in plural (standard chow and tap water not included). Only those cases where a "selection of products" was reported, but the exact number was not reported, "NI" (not informed) appears in the table. Commercial brands are not mentioned and in those studies where only commercial brands were reported, we wrote the type of product. NI=not informed.

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Table 2: A 4-day menu CAF diet protocol proposal

Menu	Category	Product	Brand	Energy	Fat (Saturated)	Carbohydrate (Sugar)	Fiber	Protein	Salt	Other
1	Cakes & Biscuits	Doughnuts	Tesco Ring Doughnuts	1744 / 419	28.4 (14.7)	33.6 (8.7)	2.1	6.2	0.3	29.4
			Donut Glacé	1754 / 420	23.0 (12.0)	47.0 (24.0)	1.9	5.2	0.53	22.37
	Processed Meat	Bacon	Woodside Farms Smoked Back Bacon	999 / 241	20.3 (7.9)	0.0 (0.0)	0.0	14.6	2.6	62.5
			Schara	947 / 228	18.0 (6.7)	0.24 (0.24)	0.6	16.3	1.75	63.11
	Candies	Gumdrop	Haribo Goldbears	1459 / 343	<0.5 (0.1)	77.0 (46.0)	0.0	6.6	0.07	15.83
			Chupa-Chups Gomis	1430 / 336	0.0 (0.0)	77.0 (56.0)	0.0	6.0	0.0	17.0
	Potato Chips	Cheese corn chips	Doritos Tangy Cheese Tortilla Chips	2092 / 501	25,9 (3,4)	57,5 (2,7)	5.6	6.5	1.19	3.31
			Cheetos Puffs Cheese Flavour	2025 / 484	24.3 (3.3)	59.4 (4.9)	2.7	5.6	2.1	5.9
2	Cakes & Biscuits	Brownie	Betty Crocker Chocolate Fudge Brownie	1729 / 409	5.7 (2.9)	83.3 (61.2)	3.4	4.4	0.85	2.35
			Milka Choco Brownie	1971 / 473	29.0 (12.0)	48.0 (38.0)	1.7	4.8	0.3	16.2
	Processed Meat	Pâté	Eastmans Ardennes Pate	950 / 229	17.6 (6.2)	5.3 (2.6)	0.6	12.0	1.7	62.8
			La Piara Tapa Negra	1111 / 269	24.0 (8.2)	1.4 (0.4)	0.0	11.0	1.7	61.9
	Cookies	Chocolate Cookie	Fox's Extremely Milk Ch. Chunkie Cookies	2129 / 509	25.0 (14.0)	63.0 (41.0)	2.6	5.6	0.53	3.27
			Chips Ahoy	2110 / 504	24.0 (12.0)	64.0 (34.0)	3.4	5.5	0.75	2.35
	Breads	Flavor Cracker	Jacobs Cracker Crisp Smokey BBQ	1973 / 470	19.3 (4.8)	67.1 (8.1)	2.6	5.5	1.8	3.7
			Lu TUC Bacon	2010 / 480	22 (9.9)	61 (7)	2.9	7.9	2.58	3.62
3	Cakes & Biscuits	Pastries	Jus-Rol Croissants Dough	1559 / 372	21.8 (11.5)	35.1 (6.9)	1.0	7.0	1.47	33.63
			BonPreu "Small Croissant"	1959 / 469	28.0 (14.0)	47.0 (12.0)	1.1	6.8	0.73	16.37
	Processed Meat	Salami	Counter Italian	1635 / 394	32.3 (11.4)	0.5 (0.5)	0.0	25.4	4.0	37.8
			BonPreu Salami Extra	1841 / 445	41.0 (17.0)	3.0 (1.8)	0.0	15.0	2.9	38.1
	Candies	Marshmallow	Princess	1392 / 328	0.0	78.5 (62.3)	0.0	3.4	0.05	18.05
			Haribo	1414 / 333	<0.5 (<0.1)	80.0 (68.0)	0.0	3.5	0.002	16.0
	Breads	Flavor Breadsticks	Tesco Cheese Twists	2120 / 507	26.4 (14.5)	52.1 (2.5)	2.8	13.8	1.7	3.2
			Snatt's Cheese	2026 / 484	22 (3.6)	57 (1,9)	4.0	12.0	1,9	3.1
4	Cakes & Biscuits	Chocolate Muffins	Betty Crocker Chocolate Chunk Muffin	1774 / 421	11.7 (6.5)	71.0 (45.4)	3.1	6.4	1.82	5.98
			Impanasa "Double Chocolate Muffins"	1813 / 434	22 (4.6)	51.0 (27.0)	3.1	5.2	0.57	18.13
	Processed Meat	Hot Dog	Herta Jumbo Frankfurters	1174 / 284	25.0 (9.8)	2.0 (2.0)	1.4	12.0	1.6	58.0
			Oscar Mayer Hot Dog Classic	1072 / 259	23.0 (7.7)	2.0 (2.0)	0.0	11	2.0	62.0
	Cookies	Cream cookie	Oreo Vanilla Original	2010 / 480	20 (9.8)	69 (38)	2.5	5.0	0.9	2,6
			Schär Mini Sorrisi	2129 / 508	24 (14)	66 (33)	2,5	5,8	0,75	0.95
	Potato Chips	Classic Chips	Pringles Original	2153 / 514	33.0 (3.6)	51.0 (1.2)	2.7	4.0	1.3	8.0
			Lay's "Salted"	2176 / 522	31.8 (4.3)	50.1 (0.6)	4.6	6.7	1.5	5.3

Standard (STD) chow and water is always available for the animals in the CAF diet group.

Values expressed in kj / kcal and grams (g) per 100g of the product. Nutritional information has been obtained from 2 online webpages of big supermarkets: (1st row) Tesco (UK) https://www.tesco.com/groceries/ (2nd row) Bon Preu – Esclat (ES): https://www.compraonline.bonpreuesclat.cat/products/ When one value was not available, we checked the original label.

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Table 3: Main behavioral results of the included studies (n=50).

Reference	Increased body weight?[1]	Other Factors	Effects CAF[2] LA	FP	RS	IMP	STS	DP	COP	CM	SoB	Brief Summary of the main results[3]
Bayol et al., 2007	Yes (No)	Gestational + Lactation Study	↓	↑	·	·	·	·	·	·	·	CAF reduced locomotor activity (HCA) in dams. CAF during gestation and/or lactation and post-weaning increased junk food preferences and hyperphagia in pups (HCA), but not gestation or lactation period alone.
Beilharz et al., 2014	Yes	Sugar in CAF diet	·	·	·	·	·	·	·	=↓	·	CAF reduced exploration time in the novel place in the place task recognition (OR), but no effects on recognition task (OR).
Beilharz et al., 2016	Yes	Sugar in CAF diet	·	·	·	·	·	·	·	=↓	·	CAF reduced exploration time in the novel place in the place task recognition (OR), but no effects on recognition task (OR).
Beilharz et al., 2018	Yes	Probiotics	·	·	·	·	=	·	·	=	·	CAF did not affect stress (EPM) or memory (OR).
Boakes et al., 1987	Not Informed	No	·	·	↓	·	·	·	·	·	·	CAF impaired flavor associative learning (SkB).
Chen et al., 2014	Yes	CAF access	·	·	↓	·	·	·	·	·	·	CAF feeding reduced food pellet self-administration and decreased extinction response (SkB).
Cigarroa et al., 2016	Yes	Exercise	=	·	·	·	=	·	↓	·	·	CAF impaired coping behavior (SB), which was partially reversed by treadmill exercise and control handling. CAF did not affect locomotor activity and anxiety in the OF.
Cook et al., 2017	Yes	No	·	·	↓	·	·	·	·	·	·	CAF reduced ethanol and sucrose intake (HCA-SPT).
da Costa Estrela et al., 2015	Yes	Stress	·	·	·	·	=	=	·	·	·	CAF exerted no effects on stress (OF, EPM) and depression-like behavior (FST). CAF potentiated the negative effects of restrain stress on EPM and FST.
de Oliveira et al., 2019	Yes	Transcranial Stimulation	=	·	·	·	↓	·	·	·	·	CAF did not affect locomotor activity (OF), but reduced stress (EPM). CAF did not interact with the transcranial stimulation at a behavioral level.
Feijó et al., 2019	Yes	Type of soft drink	·	·	·	·	·	·	·	↓↑	·	CAF + cola soft drink increased recognition memory (OR), but CAF + orange soft drink reduced recognition memory (OR).
Ferreira et al., 2018	Yes	HF/HS diet	=	·	·	·	=↑	=	·	=↓	·	CAF increased stress in EPM and reduced memory in the MWM, but no effects on locomotor activity (OF), stress (OF), depression-like behavior (FST) and memory (FC and OR).
Gac et al., 2015	Yes (in obese prone mice)	Obese prone or resistant mice	=↑	·	=↓	·	·	·	·	·	·	CAF increased locomotor activity (HCA) in obese-resistant mice. STD chow and obese-resistant mice (CAF diet) preferred more sucrose (SPT), while obese-prone mice (CAF diet) reduced sucrose intake.
Gomez-Smith et al., 2016	Yes	No	·	·	·	·	·	·	·	=	·	Neither CAF nor CAF withdrawal affected spatial memory (BM).
Jacobs et al., 2014	Yes (Yes at PND1, No at PND90)	Gestational + Lactation Study	·	·	·	·	·	·	·	·	↓	CAF reduced sexual behavior (intromissions) (HCA) and reproductive hormones.

Table 3: Continue.

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Reference	Increased body weight?[1]	Other Factors	Effects CAF[2] LA	FP	RS	IMP	STS	DP	COP	CM	SoB	Brief Summary of the main results[3]
Johnson and Kenny, 2010	Yes	CAF access	·	·	=↓	·	·	·	·	·	·	Extended CAF access did not reduce junk food eating due to shock-predicting cue and increased brain stimulation rewarding threshold (SkB).
Kendig et al., 2016	Not Informed	Context	·	·	↓	·	·	·	·	·	·	Context associated with CAF impaired devaluating learning (SkB).
Kitchell, 1984	No	No	↓	·	·	·	·	·	·	·	·	CAF reduced locomotor activity (3CM).
Kosheleff et al., 2018a	Yes	CAF access	·	·	↓	·	·	·	·	·	·	CAF rats were insensitive to reward-paired cues and limited CAF rats generalized the rewarded cue to non-rewarded cue (SkB).
Kosheleff et al., 2018b	No	CAF access	·	·	↓	·	·	·	·	·	·	Both CAF diet conditions impaired distinction learning between rewarded and non-rewarded cues (SkB).
Lalanza et al., 2014	Yes	Sex	↓	·	·	·	↓	·	·	·	↑	CAF reduced locomotor activity (HB, OF), reduced stress (EPM, HB, OF) and increased social behavior (SoP). These effects were dependent on sex.
Leffa et al., 2015	Not Informed	No	=	·	·	·	↓	↓	·	=	·	CAF reduced stress (EPM) and depression-like behavior (FST, TST), but did not alter locomotor activity (OF, EPM) or memory (OR).
Lewis et al., 2019	Yes	No	·	·	·	·	·	·	·	↓	·	CAF diet reduced spatial (MWM) and recognition (OR) memory.
Macedo et al., 2015	Yes	Stress	·	·	·	·	·	=	·	·	·	CAF did not affect anhedonia (SPT), and it was not able to counteract the anhedonia induced by restrain stress neither.
Maniam and Morris, 2010a	Yes	Maternal Separation Stress	·	·	·	·	=↓	=↓	·	·	·	CAF did not affect stress and anhedonia itself (EPM, LDT, SPT) in pups, but reduced stress in the long maternal separation group (EPM, LDT) and anhedonia (SPT, only in males).
Maniam and Morris, 2010b	Yes	Litter Separation Stress	·	·	·	·	=↓	↓	·	·	·	CAF did not affect stress by itself (EPM) in dams, but reduced depression (FST). CAF reversed the negative effects of litter separation on stress and depression.
Martire et al., 2013	Yes	Weeks of CAF exposure	·	↑	·	·	·	·	·	·	·	CAF diet altered eating pattern. CAF rats ate more often (snacking) and more amount of junk food (HCA).
Martire et al., 2015	Yes for *ad libitum*, No for limited access	CAF access	·	↑↓	·	·	·	·	·	·	·	Limited CAF rats ate junk food more quickly. Both limited CAF and STD groups had more sucrose licks than *ad libitum* CAF (HCA), which is interpreted as a reduced "liking" for sucrose. Different patterns of consumption.
Moreton et al., 2019	Not Informed	Lactation Study	·	·	·	·	·	·	·	↓	·	CAF impaired recognition memory (OR) after 30 and 60min, but no after 5min. STD chow also impaired memory at 60min, but presented better recognition ratio at 5min.

Table 3: Continue.

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Reference	Increased body weight?[1]	Other Factors	Effects CAF[2] LA	FP	RS	IMP	STS	DP	COP	CM	SoB	Brief Summary of the main results[3]
Mucellini et al., 2019	Not Informed	Gestational + Lactation Study	·	·	·	·	·	·	=	↓	·	CAF impaired recognition memory (OR) during adolescents, and partially during adulthood. No effects of CAF on aversive memory (coping) (SDIAT).
Palframan and Myers, 2016	Yes	NF (Natural Food)	·	·	= ↓	·	·	·	·	·	·	CAF did not affect lever pressing for a sucrose rewards (SkB) compared to STD and NF (natural food). CAF and NF reduced sucrose intake and licks/bout ratio (SPT), and increased preference to novel tastes (HCA)
Pérez et al., 1999	No	No	·	·	=	·	·	·	·	·	·	CAF did not impair nutrient-conditioned flavor preference learning (SkB).
Pini et al., 2017	No	HF/HS diet	·	·	·	·	↓	·	·	= ↑	·	CAF slightly reduced stress (EPM), improved training in spatial learning, but no effects on the spatial memory test session (MWM).
Ramírez-López et al., 2016	Yes (No)	Gestational + Lactation Study	=	·	↓	·	↑	·	·	·	·	CAF increased stress (EPM, OF) on pups, but no differences were found on locomotor activity (OF). CAF pups preferred less chocolate than STD during adolescence and adulthood.
Reichelt et al., 2014	Yes	No	·	·	↓	·	·	·	·	·	·	CAF impaired palatable and sensory-specific satiety association learning (SkB).
Reichelt et al., 2015	Yes	No	·	·	·	·	·	·	·	↓ ↑	·	CAF exerted a double effect on memory: impaired contextual fear-learning, but increasing freezing response in associative fear-learning (FC).
Ribeiro et al., 2018	Yes (Not Informed)	Gestational Study	=	·	·	·	↑	·	·	·	↓ ↑	CAF did alter locomotor activity (OF) neither in dams nor in pups, CAF increased stress (LDT) and reduced social play (SoP) in pups. CAF also altered few maternal behaviors.
Robertson and Rasmussen, 2017	Yes	Age and dopaminergic antagonist	·	·	·	= ↓	·	·	·	·	·	No effects of CAF on impulsivity at baseline, but CAF increased larger and later reward response (DDT) for vehicle condition. The dopaminergic antagonist (Haloperidol) reduced this response. No age effects.
Rogers, 1985	Yes	Effects of CAF withdrawal	·	·	↓	·	·	·	·	·	·	CAF withdrawal reduced STD food intake as well as meal frequency and body weight (HCA).
Sack et al., 2017	Not Informed	Exercise	=↑	·	·	·	=	·	·	=	·	CAF did not impair executive function (PB), increased locomotor activity (WR) and exerted no effects on locomotor activity and stress (OF). No interaction with exercise regarding memory, but exercise reduced locomotor activity (OF).
Sagae et al., 2012	Yes	No	·	·	·	·	·	·	·	·	=	CAF did not alter sexual receptiveness (lordosis/mounts; HCA), but altered reproductive physiology.

Table 3: Continue.

Reference	Effects CAF[2]

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	Increased body weight?[1]	Other Factors	LA	FP	RS	IMP	STS	DP	COP	CM	SoB	Brief Summary of the main results[3]
Sahakian et al., 1982	Yes	Social Isolation	=	·	·	·	·	·	·	·	·	No main effects of CAF on locomotor activity (HCA, 24h), but CAF increased locomotor activity only in isolated rats. (HCA, 30min)
South et al., 2014	Yes	Weeks of CAF exposure	·	·	↓	·	·	·	·	·	·	CAF rats reduced food intake when the stimulus was STD food (HCA).
Speight et al., 2017	No (No)	Lactation Study	= ↑	·	·	·	= ↓	·	·	·	↑	CAF increased locomotor activity (OF) and decreased stress (OF), but no effects on EPM (locomotor activity and stress). CAF increased maternal behavior (grooming/licking), but also exerted no effects on locomotor activity (HCA) in dams.
Thompson et al., 2017	Yes	CAF access	·	·	↓	·	·	·	·	·	·	*Ad libitum* CAF increased junk food eating in the presence of shock-predicting cue (SkB).
Warneke et al., 2014	Yes in adult, No in young rats	Age + Sex	= ↑	·	·	·	↓ ↑	·	·	·	·	CAF increased locomotor activity in females, but not in males (OF), and no effects of locomotor activity in the EPM. CAF decreased stress in females (EPM, OF), but increased stress in males (EPM).
Wright et al., 2011a	Yes (No)	Gestational + Lactation Study	= ↓	·	·	·	= ↓	·	·	·	·	CAF mostly affected during lactation, decreasing locomotor activity (EPM, OF) and stress (EPM, OF) in males. No generalized effects on females.
Wright et al., 2011b	Not Informed (No)	Lactation Study	·	↑	·	·	·	·	·	·	·	CAF pups ate more palatable food, showing more bouts (shorter in males and longer in females) than STD chow (HCA).
Wright et al., 2014	Yes (No)	Lactation Study	·	·	·	·	·	·	·	=↓	·	No effects of CAF on recognition memory (OR) in male pups, but CAF reduced recognition memory (OR) in females.
Zeeni et al., 2013	Yes	Stress, HF/HS diet	·	·	·	·	·	=	·	·	·	No effects of CAF on sucrose intake (SPT). CAF slightly counteracted the effects of chronic variable stress avoiding anhedonia (SPT).

[1] After CAF diet administration and compared to STD (standard chow diet). In brackets, the pup's body weight. [2] Behavioral effects of CAF diet compared to STD chow. For gestational and lactation studies, we reported pup's behavior and maternal care behavior. LA=locomotor activity, FP=feeding pattern or amount of CAF food eaten, RS=reward system: motivation for food rewards, other sort of rewards and expected cue/contextual associations with rewards such as flavor preference or satiety, IMP=impulsivity, STS=stress, anxiety and negative mood, DP=depression, COP=coping behavior, CM=cognition and memory, SoB=social behavior. ↑: CAF diet administration increased this behavior significantly, ↓: CAF diet administration decreased this behavior significantly, =: no significant differences in this behavior, · : this behavior has not been assessed. Two symbols together means different effects depending on the behavioral test, age or sex. [3] 3CM=3 choice maze, DDT=delay discounting task, EPM=elevated plus maze, FC=fear conditioned, FST=forced swim test, HCA=home cage activity or similar methods like observational box, LDT=light dark test, MWM=Morris water maze, OF=open field, OR=object (or novel object) recognition and place recognition, PB=puzzle box, SB=shuttle box, SDIAT=step-down inhibitory avoidance task, SkB=skinner box, self-administration box, operant box, etc., SoP=social play, SPT=sucrose preference test, TST=tail suspension test, WR=wheel running.

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Table 4: A summary of the main behavioral effects evoked by neurophysiological alterations due to CAF diet*

Behavioral Effect	Neurophysiological mechanisms	Reference and type of study	
Reward system: Hedonic response and Motivation			
At long-term, CAF diet **reduces the hedonic value of other rewards** and **impairs** the association between cues **predicting shock and junk food.**	*(only behavioral studies)*	Gac et al., 2015	B
		Martire et al., 2015	B
		Palframan and Myers, 2016	B
		Rogers, 1985	B
		South et al., 2014	B
	Downregulation of DAergic receptors and decreased DA extracellular levels	Cook et al., 2017	B, N
		Johnson and Kenny, 2010	B, N
		Geiger et al., 2009	N
		Ong and Muhlhausler, 2011	N
		Ong et al., 2013	N
	Downregulation of cannabinoid receptors and anandamide	Martire et al., 2014	N
		Ramírez-López et al., 2016	B, N
	Downregulation of μ-opioid receptors	Gugusheff et al., 2016	N
		Martire et al., 2014	N
		Ong et al., 2013	N
	Reduced GABAergic inputs into the OFC	Thompson et al., 2017	B, N
At **short-term** CAF diet increases **snacking**	Upregulation of DAergic receptors and DA extracellular levels	Wright et al., 2011b	B, N
		Ong and Muhlhausler, 2011	N
		South et al., 2012	N
Mood: Anxiety- and Depression-like Behaviors			
CAF diet **increases anxiety-like** behaviors	*(only behavioral studies)*	Ferreira et al., 2018	B
		Ribeiro et al., 2018	B
		Warneke et al., 2014	B
	Downregulation of anandamide (endocannabinoid)	Ramírez-López et al., 2016	B, N
CAF diet **reduces anxiety-like** behaviors	*(only behavioral studies)*	de Oliveira et al., 2019	B
		Lalanza et al., 2014	B
		Leffa et al., 2015	B
		Pini et al., 2017	B
		Speight et al., 2017	B
		Warneke et al., 2014	B
		Wright et al., 2011a	B
CAF diet **does not affect anxiety-like** behaviors	*(only behavioral studies)*	Beilharz et al., 2018	B
		Cigarroa et al., 2016	B
		da Costa Estrela et al., 2015	B
		Ferreira et al., 2018	B
		Sack et al., 2017	B
		Speight et al., 2017	B
		Wright et al., 2011a	B
CAF diet **reduces anxiety-like** behaviors after a **stressful situation**	Reduced GR and CRH expression	Maniam and Morris, 2010a	B, N
		Maniam and Morris, 2010b	B, N
	Reduced ACTH and/or corticosterone	Gustaityte et al., 2019	N
		Zeeni et al., 2013	N
		Zeeni et al., 2015b	N
Switching **from STD chow to CAF** diet…	Reduced amygdala GR	Martire et al., 2014	N
	Reduced corticosterone	South et al., 2012	N
CAF diet **reduces depressive-like** behaviors	*(only behavioral studies)*	Maniam and Morris, 2010b	B
	Increased neurotrophic factors in hippocampus	Leffa et al., 2015	B, N
CAF diet **does not affect depressive-like** behaviors	Reduced neurogenesis in the hippocampus	Ferreira et al., 2018	B, N
	Reduced BDNF in the hippocampus	Macedo et al., 2015	B, N
	Reduced adrenal gland weight	Macedo et al., 2015	B, N
CAF diet exposure **reduces depressive-like** behaviors after an **stressful situation**	*(only behavioral studies)*	Maniam and Morris, 2010a	B
		Maniam and Morris, 2010b	B
Cognition and Memory			
CAF diet **reduces recognition memory**	*(only behavioral studies)*	Lewis et al., 2019	B
		Wright et al., 2014	B
	No effects on hippocampal BNDF	Mucellini et al., 2019	B, N
	Increased 5-HT metabolism, but decreased DA metabolism in the PFC	Moreton et al., 2019	B, N
CAF diet **does not affect recognition memory****	Increased neuroplasticity genes expression	Beilharz et al., 2018	B, N
	Increased hippocampal BDNF	Leffa et al., 2015	B, N
CAF diet **reduces contextual and spatial memory**	*(only behavioral studies)*	Lewis et al., 2019	B
	Increased neuroinflamatory markers in hippocampus	Beilharz et al., 2014	B, N
		Beilharz et al., 2016	B, N
	Reduced expression of a hippocampal marker of neuroplasticity (reelin)	Reichelt et al., 2015	B, N
	Reduced neurogenesis in the dentate gyrus	Ferreira et al., 2018	B, N
CAF diet **does not affect contextual and spatial memory**	*(only behavioral studies)*	Pini et al., 2017	B
	Increased hippocampal neuroinflamation	Gomez-Smith et al., 2016	B, N

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CAF diet **does not affect executive function**	Increased CA1-CA3 volume	Sack et al., 2014	B, N

* This table is based on the included and selected studies in this review and summarizes the main effects of CAF diet exposure on both behavioral and/or neurophysiological levels: B=behavioral study, N=neurophysiological study. BDNF=brain derived neurotrophic factor, CA=cornu ammonis, CRH=corticotropin-releasing hormone, DA=dopamine, GR=glucocorticoid receptors, OFC=orbitofrontal cortex, PFC=prefrontal cortex. ** See the main text for those studies that does not find behavioral changes in recognition memory, but are included in the spatial memory row.

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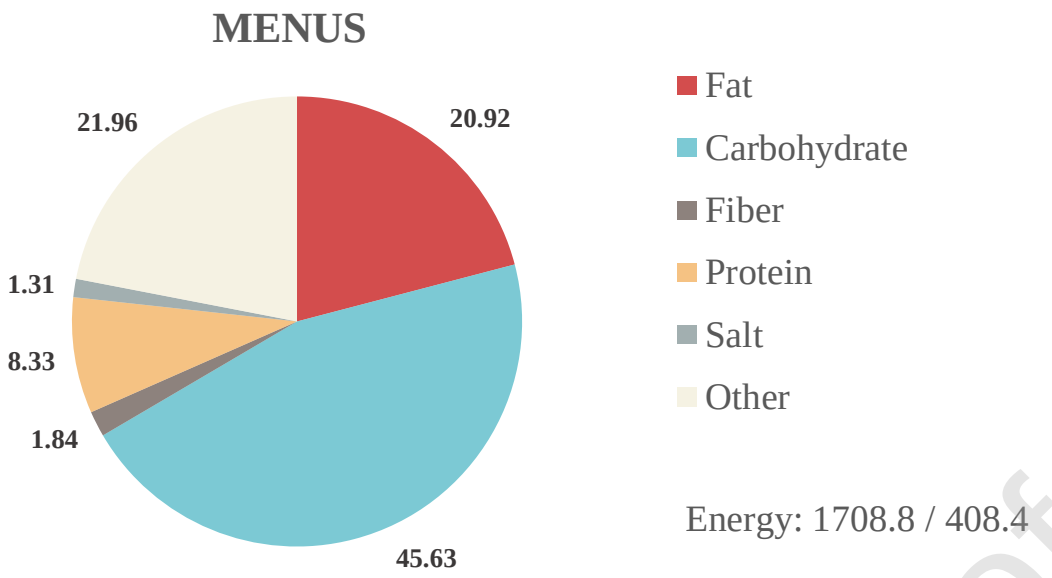

Figure 1: The average of nutritional composition (grams per 100g) and energy (kj/kcal) of the four proposed "Menus" of the CAF diet protocol proposal.

[figure in color]

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