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## Appetite and energy balancing

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### HIGHLIGHTS

- Energy expended meal-to-meal is trivial compared with total body energy reserves.
- Meal patterns are adapted to avoid the performance-impairing effects of recent eating.
- 'Hunger' (appetite) is the absence of fullness and the anticipation of food reward.
- Energy dense foods are more rewarding partly because they are less filling kJ for kJ.
- Erroneous beliefs about 'hunger' and energy depletion undermine attempts to eat less.

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### ABSTRACT

The idea that food intake is motivated by (or in anticipation of) 'hunger' arising from energy depletion is apparent in both public and scientific discourse on eating behaviour. In contrast, our thesis is that eating is largely unrelated to short-term energy depletion. Energy requirements meal-to-meal are trivial compared with total body energy stores, and energy supply to the body's tissues is maintained if a meal or even several meals are missed. Complex and exquisite metabolic machinery ensures that this happens, but metabolic regulation is only loosely coupled with the control of energy intake. Instead, food intake needs to be controlled because the limited capacity of the gut means that processing a meal presents a significant physiological challenge and potentially hinders other activities. We illustrate the relationship between energy (food) intake and energy expenditure with a simple analogy in which: (1) water in a bathtub represents body energy content, (2) water in a saucepan represents food in the gut, and (3) the bathtub is filled via the saucepan. Furthermore, (4) it takes hours to process and pass the full energy (macronutrient) content of the saucepan to the bathtub, and (5) both the saucepan and bathtub resist filling, representing negative feedbacks on appetite (desire to eat). This model is consistent with the observations that appetite is reduced acutely by energy intake (a meal added to the limited capacity of the saucepan/gut), but not increased by an acute increase in energy expenditure (energy removed from the large store of energy in the bathtub/body). The existence of relatively very weak but chronic negative feedback on appetite proportional to body fatness is supported by observations on the dynamics of energy intake and weight gain in rat dietary obesity. (We use the term 'appetite' here because 'hunger' implies energy depletion.) In our model, appetite is motivated by the accessibility of food and the anticipated and experienced pleasure of eating it. The latter, which is similar to food reward, is determined primarily by the state of emptiness of the gut and food liking related to the food's sensory qualities and macronutrient value and the individual's dietary history. Importantly, energy density adds value because energy dense foods are less satiating kJ for kJ and satiation limits further intake. That is, energy dense foods promote energy intake by virtue (1) of being more attractive and (2) having low satiating capacity kJ for kJ, and (1) is partly a consequence of (2). Energy storage is adapted to feast and famine and that includes unevenness over time of the costs of obtaining and ingesting food compared with engaging in other activities. However, in very low-cost food environments with energy dense foods readily available, risk of obesity is high. This risk can be and is mitigated by dietary restraint, which in its simplest form could mean missing the occasional meal. Another strategy we discuss is the energy dilution achieved by replacing some sugar in the diet with low-calorie sweeteners. Perhaps as or more significant, though, is that *belief* in short-term energy balancing (the energy depletion model) may undermine attempts to eat less. Therefore, correcting narratives of eating to be consistent with biological reality could also assist with weight control.

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## 1. Introduction

Human body weight (fatness) is determined strongly by the eating environment [1,2,3]. The phrases ‘toxic food environment’ and ‘obesogenic environment’ are often used in this respect. Of course, without specifying what features of food and its availability are responsible for encouraging consumption, these phrases on their own explain little about obesity. Food energy density and portion size are implicated [4,5], but we suggest that ease of access, which in part is embodied in portion size, is also fundamental (see below). Equally, it is necessary to understand the nature of appetite control that leaves humans ‘susceptible’ to obesity, and that is the main focus of this review. Throughout, we use the term ‘appetite’ to mean desire to eat, and ‘eating’ to refer to food intake.

## 2. Energy balancing

In an obesogenic environment, attempting to maintain energy balance (i.e., matching energy intake with energy expenditure) frequently entails dietary restraint, including conscious calorie-counting [6]. The conscious energy accounting is typically done on a meal-to-meal or daily basis – food labels in the UK currently state the guideline daily amount (for a woman) as 8400 kJ/2000 kcal. However, 8400 kJ is trivial compared with the energy stored in fat tissue, which for a lean individual amounts to approximately 55 day’s supply ([7], based on 65 kg person and an energy expenditure of 10 MJ/day). Therefore, biologically, the time scale of energy balancing is longer than 24 h. The advantage is that there is a considerable buffer against unevenness of food supply, including unevenness of risk and cost of obtaining food [1,8]. The total ‘reservoir’ of body energy, which also includes glucose, glycogen and protein [7], is correspondingly larger than the reservoirs of fluid and oxygen, and accordingly drinking and breathing can be postponed for less time than eating.

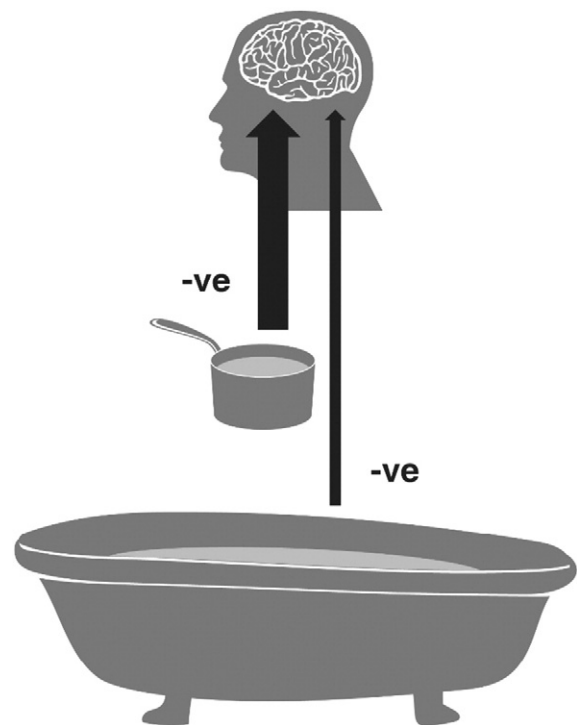
In the case of eating, appetite appears to be reduced by chronic, negative feedback proportional to body fatness [1,9,10,11]. This is presumably an adaptation that diminishes eating as a priority in favour of other activities when energy reserves are high, and protects against possible costs of obesity, including ancestrally, at least, risk of predation [12]. Furthermore, as body fatness increases so to some extent does energy expenditure, including basal metabolic rate and the energy cost of movement [13]. Consequently, all else being equal, fatness balances at a ‘settling point’ with the eating environment [1,10,14,15].

## 3. Saucepan and bathtub

The weak, chronic effect of body fatness on appetite can be contrasted with the very noticeable but acute effects of consuming a meal. Food intake inhibits appetite, although even after a very large meal we might eat again after only a few hours or less. These controls on appetite can be illustrated by a simple analogy or model (Fig. 1), in which the water in a bathtub represents body energy content and

water in a saucepan represents food in the gut. The contents of the bathtub are replenished via the saucepan. It takes hours to process and pass the full energy content of the saucepan to the bathtub. Both the saucepan and the bathtub resist overfilling (representing negative feedbacks on appetite).

The relative energy contents of the saucepan and the bathtub (approximately 1:180, representing a lean adult human who has just finished lunch [7]) demonstrates why appetite is governed primarily by recent eating. Lunch with, for example, an energy content of 3000 kJ is a significant load for the gut (saucepan), but adds very little to total body energy content. Indeed, food ‘preloads’ that differ by only 1000 kJ or less have clearly detectable acute differential effects on appetite, as demonstrated by a variety of studies [16], including studies on effects of consuming low-calorie sweeteners versus sugar [17] that we discuss in Section 8 below. Our model predicts that, in contrast to energy (food) intake, an acute increase in energy expenditure will have



**Fig. 1.** Model of energy balancing and appetite. The thick arrow represents the acute, but relatively strong inhibition of appetite which waxes and wanes as successive meals fill then empty from the upper gut (saucepan). The thinner arrow represents very much weaker, but chronic inhibition of appetite proportional to body fat content (represented by the water in the bathtub), which makes up the major part of body energy stores. Note that the saucepan and bathtub are not to scale: for a lean adult the bathtub contains about 180 times the energy content of an average meal [7].

little impact on appetite, as energy expended is subtracted from the bathtub. And, indeed, this is exactly what is observed. Results of a recent meta-analysis of the effect of acute exercise on subsequent energy intake showed no meaningful difference in energy intake between exercise and control conditions [18]. The median difference in energy expenditure was 2060 kJ, which represents a significant amount of exercise activity, but of course is trivial compared with total body energy reserves (see also [19]). Likewise, as macronutrients move from the gut to body energy stores their impact on appetite wanes. This is demonstrated by decreased energy compensation at longer inter-meal intervals [16].<sup>1</sup>

#### 4. Eating and performance

Whether or not eating has occurred recently, energy supply to the body's tissues is maintained, though the sources and mix of fuels varies with the duration of fasting [7]. Soon after eating, glucose is the primary fuel for muscle and the brain, but as time since the meal passes fatty acids become a significant fuel for muscle. Glucose supply to the brain is maintained from breakdown of liver glycogen and via gluconeogenesis (glucose derived from glycerol and protein), except after prolonged fasting when utilization of ketone bodies, which are products of fatty acid oxidation, becomes increasingly important.

This predicts that recent eating is not necessary for maintenance of physical and mental functioning. Although it is generally believed that missing a meal will lead to impaired cognitive performance, the effects observed are actually rather small and inconsistent [23], even when consecutive meals are missed [24,25]. In one of the earliest studies on this topic, 9- to 11-year-old children who missed breakfast were tested mid-morning 18 h after their last meal [26]. Performance was little affected compared with when they ate breakfast. On a component of one task, performance was improved after missing breakfast, whilst on another task missing breakfast led to impaired performance in a subgroup of the participants. A general problem for such research is that there is no fully adequate placebo for missing breakfast, so it is usually obvious to participants that they have eaten or not eaten. We attempted to reduce this demand effect by using a between-subjects design and a cover story about measurement of time-of-day effects on performance which required us 'to carefully control nutritional state' (i.e., feeding a fixed breakfast of 2510 kJ or 1255 kJ, or nothing). We found that breakfast impaired performance in a dose-related manner on a memory task and a tapping task, with no effect on choice reaction time [27]. Similarly, a large lunch impairs performance [28,29], and sugar consumed in a drink increases sleepiness [30]. These observations are consistent with the notion that a meal is a physiological challenge [31] and that postprandial sleepiness is a controlled process [32]. Indeed, we suggest this is why in the context of a working day, breakfast, despite being consumed after the longest inter-meal interval, and lunch are usually relatively small meals, but with a different pattern perhaps at weekends, and in cultures that take a siesta. In other words, meal size is not adapted to either compensate or anticipate acute energy expenditure, but to minimise the disruptive effects of eating on performance.

<sup>1</sup> That is, the difference in the effect of a low- versus high-energy preload on ad libitum test-meal intake decreases as the length of the preload, test-meal interval increases [16]. However, memory of what has been eaten recently [20,21], and possibly memory of immediate postprandial fullness, also influences subsequent intake, and this may at least partly compensate for the faster declining influence of gut-related signals. The different time courses of physiological feedback and memory for recent eating are evident in the results of our study [22] which manipulated the amount of soup participants saw and remembered consuming independently from the amount they actually consumed (see footnote 6 for more details). It may be that remembering recent meals contributes to efficient foraging, although in food-rich environments memory for recent eating is more likely to underpin dietary restraint.

#### 5. What is hunger?

In contrast to the discussion above, the notion that acute energy depletion is a stimulus for 'hunger' (which causes us to eat) is very apparent in everyday discourse as well as in the past and recent scientific literature on human eating behaviour [33,34,35,36]. A more neutral use of this term is as an intervening variable between independent and dependent variables such as duration of food deprivation and propensity to work for food [33]. Nevertheless, what is usually meant by hunger is the urge to eat arising from an energy deficit. This is embodied in the notion of 'homeostatic hunger' (see Footnote 4), phrases such as 'physiological deficit cues' [37], and the strong tendency for most people, including health professionals, to endorse the view that hunger and eating behaviour are regulated by deviations in body energy reserves [38]. Despite this, when well-nourished participants are asked to explain their hunger ratings (made in the absence of food) they typically refer to the timing and/or size of their last meal, their fullness from recent eating, and proximity to their next mealtime [39]. These are proxies for short-term energy depletion in the sense that they equate roughly to a certain amount of energy that has been expended since the last meal (but a very small amount compared with total body energy reserves), and as such may or may not relate directly to concern about redressing energy depletion. None of these answers, however, include the eating equivalent of the physical sensation of a dry mouth and throat [33,40] that signals thirst, and none of them are at all similar to the irresistible hunger for air that is experienced when breathing is prevented.<sup>2</sup> Instead, it seems that an *absence of fullness* is a salient stimulus underlying the readiness to eat that is expressed in reports of hunger [1,39,44]. This is evident in the explicit references participants make to gastric sensations of fullness (low hunger), and sometimes to a rumbling stomach, when explaining their hunger. Less directly, references to recent eating are consistent with the postprandial return of hunger being a decline in fullness arising from the digestion and assimilation of the meal. It is also the case that hunger and fullness ratings correlate very highly [39], and that some investigators place the words hunger and fullness at opposite ends of the same rating scale [45]. Hunger as the absence of fullness is represented in our model by the gradual attenuation postprandially of the negative feedback going from the saucerpan (upper gut) to the brain (Fig. 1).

We acknowledge that the brain monitors the state of the body's energy stores (e.g., [46]), which is vital for metabolic regulation [7,47], but we suggest that this signalling is only loosely coupled with the control of appetite.<sup>3</sup> Two examples, based on informal discussions with participants serve to illustrate this point. 'Hitting the wall' is well known in endurance sports such as long-distance cycling and running. It is a sudden fatigue and loss of energy caused by depletion of liver and muscle glycogen stores [51], which is remedied fairly rapidly by consuming carbohydrates. Participants familiar with this phenomenon say, however, that it is not accompanied by 'normal hunger' (appetite). The symptoms of

<sup>2</sup> As we noted earlier, these differences correlate with the relative momentary reserves of energy, water and oxygen, and the more compelling nature of thirst than 'hunger'. When asked to describe their experiences of thirst, as well as noting dryness of the lips, mouth and throat, participants also commented on an indistinct, but nonetheless identifiable, mental state of want or need to drink (J. Ferrar and P. J. Rogers, unpublished data). Ultimately, though, both hunger and thirst can be resisted for a strong enough cause [10,41], whereas we are unable to hold our breath to the point of asphyxiation. Moreover, in food-rich environments we overdrink [42] as well as overeat, seemingly encouraged by the false notion that thirst is not an adequate signal for fluid requirements [42], and both independently and together by the caffeine content and sweetness of popular beverages [43]. The consequences of chronic overeating, though, are much more significant than the consequences of overconsumption of (non-alcoholic, non/low-energy) fluids.

<sup>3</sup> We prefer the terms energy intake (and appetite) control and body weight control, because values for these parameters are affected by negative, and positive [48], feedbacks, but have a large range. In contrast, energy supply to the body's tissues and organs is regulated according to ongoing needs (e.g., thinking and running). Thus it can be said that appetite control provides the fuel for metabolic regulation (cf. [49,50]).

hypoglycaemia, which can occur unrelated to exercise, and include sweating, shakiness and weakness, are also removed by eating carbohydrates. Although participants who had experienced hypoglycaemia were aware that they should eat something, again their symptoms did not include 'feeling hungry in the normal way.' In both these situations, eating is instrumental in that it is motivated by removal of unpleasant symptoms, akin to taking paracetamol (acetaminophen) to cure a headache; however this differs from the more typical everyday experience of appetite for a meal or a snack. Paracetamol relieves our headache, but when we get a headache we do not experience an *appetite* for paracetamol.

We suggest then that 'normal hunger' or appetite for food is the product of having an empty, or less than full, upper gut together with the anticipation of the pleasure of eating. In other words, usually when a (well-nourished) person says they are 'hungry,' or even 'starving,' what they are really experiencing and communicating is a momentary desire for food reward. Essentially, this is an incentive model of eating, in which eating is more rewarding in the absence of fullness and when the food is liked [39].<sup>4</sup> In everyday life, the approach of meal-times acts as a reminder of the pleasure of eating and usually coincides with a relatively empty gut, although for example the offer of food between meals can also trigger eating because, as described next, we are rarely too full to eat more. Eating, therefore, is essentially a cycle of reward and (partial) satiety, only indirectly related to energy balancing in that intermittent food intake serves to keep the body's energy reserves topped up.

## 6. Food reward: food energy density and satiety

The pleasure of eating can be equated roughly with food reward [39]. Recent eating reduces food reward [39], which reflects the limited capacity of the stomach and intestines to process the ingesta, but normally only rather rarely is the gut filled to capacity, at least partly to avoid impairment of mental and physical performance that would ensue (Section 4). Consequently, we are almost always ready to eat if the opportunity arises, so we are easily tempted to eat by the offer of (delicious or different-tasting) food, even when we have consumed enough food to make us 'comfortably full' [53] (see also [54,55]). The gut-brain dialogue underlying the fluctuating states of readiness to eat and fullness involves multiple signalling pathways [11]. It is collaterally part of the physiology coordinating food digestion and absorption of nutrients but, like post-absorptive metabolic regulation (Section 4), it is not concerned directly with acute energy balancing.

An important question is then, what features of food contribute to food reward and satiety (the sensation of fullness and the inhibition of further eating)? A variety of studies, some of which we discuss in Section 8, show that the carbohydrate, fat and protein content of food contribute to satiety, as does non-nutritive bulk [16,17,56]. Arguably though, a food's energy (macronutrient) content, and not its fillingness, should determine its reward value, as energy content is of primary biological value and satiety limits further energy intake. This is supported by evidence from studies on rats, from which Sclafani and Ackroff [57] conclude that 'These reward effects (of nutrients) appear separate

from the satiating actions of nutrients, which may actually reduce food reward' (p. 89). In humans, 'satiety index,' that is, the satiating capacity kJ for kJ of foods, is *inversely* related to their palatability [56]. This equates to energy-dense foods, for example fat-rich foods, being the most rewarding. The upshot is that availability of such foods will lead to high energy intake because (1) they are highly desirable and palatable, and (2) they have low satiating capacity kJ for kJ. We suggest that, to a large extent, (1) is a consequence of (2).

A caveat to this discussion is that humans appear under a variety of circumstances to opt for satiety over energy. For example, by choosing energy-dilute foods the dieter reduces the energy content of their meal, whilst maintaining its satiating capacity. The downside is that, compared with energy-dense foods, energy-dilute foods are intrinsically less enjoyable (rewarding) to consume, and the temptation to eat energy-dense foods is hard to resist. Another example of preference for satiety comes from recent studies in our lab. We find that when participants are faced, hypothetically, with the choice of an equi-energetic amount of an energy-dense and an energy-dilute food, with no other food available for several hours, at small portion sizes they choose the energy-dilute food [58,59]. This decision appears, at least in part, to be based on a desire to avoid 'being hungry.' That is reasonable to the extent that choosing the energy-dense food would leave the participant with a relatively empty gut, but that in itself should not be aversive or affect performance and it would leave open the possibility of more fully exploiting an opportunity to eat that arose sooner than anticipated. However, concern to avoid the imagined adverse consequences of 'hunger' (see Section 8) may bias choice towards the less energy-dense, physically larger of two equi-energetic small portions. With larger equi-energetic portions, though, we do observe a switch to choice of the energy-dense option, and at a point that appears to be well below maximum portion size [59]. In other words, when the amount of food approximates typical meal size, energy is favoured over satiety.

Whilst food reward is a function of the fullness of our gut and the nutrient value of the food [39], how hard we have to work to get food also affects when we eat and how much we eat [60]. This is significant, because easy, and often almost effortless, access to food is characteristic of many home, work, leisure, and retail environments in nations where prevalence of overweight and obesity is high. The low barriers to eating extend to the many places and situations in which eating is socially acceptable, the convenience of ready-to-eat products, and even to the act of eating itself – compare, for example, the effort required to consume an apple versus a chocolate bar, which is vastly different kJ for kJ. Furthermore, when a large portion is served eating can continue without the effort (and interruption) of refilling the plate.

## 7. Energy balancing again

From the perspective of our saucepan and bathtub model, the effects of food availability (ease of access) and energy density can be viewed as an opportunity to add to bodily energy reserves at low cost. This cost is composed of the time, effort and monetary cost expended in obtaining, preparing and eating food, plus the acute negative after-effects of food ingestion on performance, all of which are lower per kJ for energy-dense foods. In that sense, 'overeating' under low-cost environmental conditions is an adaptive response, and not the food environment 'overriding' control of energy balance, because there is no need, or corresponding specific mechanism, for short-term energy balancing (Sections 2 and 3). Nonetheless, the temptation to eat can be tempered by dietary restraint, and there is ultimately a limit to the amount of food that the gut can reasonably accommodate and process. (Actually, the latter may mean that it is not possible to avoid negative energy balance under conditions of very high energy demand [61]). Additionally, the weak, but chronic, effect of fatness in reducing appetite also helps curtail energy intake with an accumulating

<sup>4</sup> True hunger might be what is felt when total energy reserves are depleted to the point of emaciation (i.e., the bathtub is very nearly empty). However, appetite rather than hunger, which implies energy-depletion driven eating, better describes the desire to eat regularly experienced by well-nourished individuals. This is also why we reject the distinction between homeostatic and hedonic hunger/eating [34,35,36,52], with the implication that somehow the former is healthy/normal and the latter unhealthy/maladaptive/dysfunctional. First, as described above, there is no need for short-term energy balancing. Instead, eating is opportunistic (see Section 7). Second, there is no sense within the usual experience of eating of separate hunger and hedonic components – for example, of the first 2000 kJ of a 4000 kJ meal being homeostatic, hunger-driven eating, balancing 2000 kJ expended since the last meal, and the second 2000 kJ being pleasure-driven eating surplus to bodily need [39].

energy surfeit (Sections 2 and 3). However, the degree to which these restraints on eating are effective in preventing overweight and obesity appears to be variable. Dietary restraint, for example, is liable to disinhibition [6,62], and in any case exerting dietary restraint is (cognitively) effortful and distracting [1,63,64]. Furthermore, repeated consumption of large meals can result in increased 'tolerance' to the filling effect of food [65] and, similarly, leptin resistance may reduce the negative feedback effect of body fatness on appetite [11,66].

## 8. Implications, including missing a meal, beliefs about hunger and effects of low-calorie sweeteners consumption

Although the non-existence of physiological short-term matching of energy intake to output makes us vulnerable to frequently eating in excess of immediate energy expenditure, it also means that eating less than is needed to maintain energy balance will not be strongly compensated for. A very good illustration of this is the energy deficit carried forward over a day after missing breakfast. When freely-eating participants were required to miss breakfast (mean energy intake = 2595 kJ) they ate somewhat more (an extra 585 kJ) at lunchtime, but subsequent energy intake from afternoon and evening snacks and at dinner was almost the same on days that breakfast was eaten and when it was not eaten. Consequently, missing breakfast led to a 2050 kJ reduction in daily energy intake [2] (see also [67]). From the discussion above (Section 4), we predict that the participants' performance would not have been impaired when they missed breakfast.

These outcomes, however, are at odds with the mantra that 'breakfast is the most important meal of the day,' which extends to advice that breakfast should be eaten even if one is 'not hungry first thing in the morning' [68]. The evidence most often cited in favour of breakfast is the very well established correlation between not eating breakfast and overweight and obesity. However, as Brown and colleagues [69] point out, merely demonstrating this relationship repeatedly with new studies does nothing to establish causation. In fact, intervention studies, including Levitsky's [2,67], indicate that missing breakfast will lead to lower overall energy intake and body weight than would otherwise be the case [69].<sup>5</sup> Presumably, missing other meals or eating occasions in the day will have the same effect, and indeed some popular 'diets' prescribe missing meals on designated days (e.g., 5:2 and 4:3 diets [71]). Missing some meals is a simple regimen that also reduces contact with (and therefore potentially thoughts about) food, which is in contrast to the relative complexity and involvement with food typical of diets that include meal-by-meal calorie-counting. This predicts that intermittent fasting will be superior to daily energy restriction as a method for weight loss, as demonstrated by Harvie et al. [72]. Nonetheless, missing meals means missing out on the pleasure of eating. That might be balanced by the satisfaction of having successfully restrained one's food intake but, ultimately, how the eater construes their appetite may influence both the strategy they adopt for eating less and the success of that strategy. For example, *belief* in energy balancing, that is, that eating less is physiologically significant, may cause a person to dismiss ever intentionally missing a meal. Furthermore, if they were to miss a meal, their experience would likely be more distressing regarding feelings of deprivation (i.e., 'hunger'), perceived effects on

performance, and elaborated thinking about food [73].<sup>6</sup> In other words, our individual and collective adoption of an energy-balancing narrative makes eating less harder than is necessary – harder, perhaps, than if we were to attribute our appetite to our anticipation of the pleasure of eating (i.e., a 'we-eat-for-pleasure' narrative).

A more subtle approach to eating less is to consume reduced-energy foods, though according to our analysis (Section 6) merely replacing energy-yielding nutrients in a food with non-nutritive bulk, or supplementing it with non- or low-energy fullness-enhancing agents, will devalue the food. An at least partial exception to this is to use low-calorie sweeteners (LCS) to replace sugar in beverages, because the reward value of sweet beverages is determined substantially by our congenital liking for sweetness [75]. Another view, however, is that consumption of LCS in the diet may increase rather than decrease energy intake and body weight (e.g., [76,77,78]). One criticism is that, by confusing the relationship between sweet taste and energy content of food, exposure to LCS weakens the learned control of energy intake [77] (see also [79]), and another is that exposure to LCS increases preference for sweetness and consequently encourages further intake of sweeteners, including sugar [76,78].

Motivated by the uncertainty about the effects of LCS consumption on energy intake and body weight, we recently conducted a systematic review of the full range of evidence on this subject [17]. We found that the evidence clearly favoured the use of LCS in place of sugar. We identified many short-term studies that measured the effect of consuming a fixed amount (preload) of, usually a beverage, on subsequent energy intake in an ad libitum test meal. Although test meal intake was reduced after sugar versus LCS, this only compensated for half of the higher energy content of the comparison sugar-sweetened product. Consequently, consuming LCS resulted in an overall reduction in energy intake. Consistent with this, LCS versus sugar very reliably reduced energy intake and body weight in sustained randomised controlled trials (duration 10 days to 40 months). Importantly, the results of these trials were the same irrespective of blinding of the intervention, that is, whether or not participants were aware they were consuming LCS. Also outcomes were similar for studies in which the test products were added to the diet and those in which the participants were already consuming sugar-sweetened products and the intervention was (partial) replacement of sugar with LCS.

By far the largest prospective cohort study (125,000 participants from three cohorts) found a small significant association in the direction of reduced weight with LCS consumption [80]. Combining this with smaller prospective cohort studies resulted in no overall association between LCS consumption and body weight; however, given the results of the intervention studies, this result is presumably explained by reverse causation and confounding [17].

We also identified a variety of relevant studies on animals (rats and mice). The primary purpose of many of these was to test the safety of LCS, but they also included data on body weight, and other studies included LCS as a control in tests of the effects of sugars on body weight. Out of 68 such studies, the large majority (59) found that LCS reduced or had no effect on weight. By contrast, in 19 out of 22 studies comparing the effects of intermittent exposure to LCS versus glucose, weight increased more in the LCS group. This is the result that has been interpreted in terms of LCS consumption blurring the relationship between the sweetness and the energy content of food [77]. However,

<sup>5</sup> The inverse correlation between missing breakfast and weight is probably explained largely by overweight people trying, in their efforts to eat less, to delay eating for as long as possible in the day [70]. There is also evidence that the negative feedback effect of body fatness on appetite works primarily by delaying meal initiation. Rats placed on an energy dense 'cafeteria diet' increased their energy intake. Over time, however, their degree of overeating declined and their rate of weight gain slowed and eventually plateaued in parallel with control rats (fed a standard lab diet). Decreased meal frequency, rather than a change in meal size, which actually increased somewhat, accounted for the obesity-related decrease in energy intake [9].

<sup>6</sup> An example of the powerful influence of beliefs on the experience of appetite is our recent study in which participants consumed soup from a bowl from which substantial amounts of soup could be added or removed without their knowledge (via a hidden tube attached to the bottom of the bowl) while it was being eaten. Results showed that 2 and 3 h later the experience of hunger/fullness was dominated by the amount of soup participants saw disappear from the bowl rather than the actual amount they consumed [22]. Similarly, merely creating an expectancy that a liquid food would gel in the stomach increased fullness, reduced subsequent eating, and even affected gastro-intestinal hormone release and gastric emptying rate [74].

the relevance of this for human consumption of LCS is doubtful. Sweetness does predict the sugar content of foods when LCS products are excluded [81], but it is less clear that it predicts energy content. In any case, the flexibility afforded by storing sizeable energy reserves makes short-term energy balancing unnecessary (Section 2), so in this respect being able to predict accurately the energy content of food is also unnecessary.<sup>7</sup> Furthermore, even if flavour-nutrient learning did participate significantly in the control of energy (and specifically sugar) intake, and this was disrupted by consumption of LCS, the evidence indicates that for humans this is outweighed by the benefit of energy dilution which is not fully compensated for in subsequent eating.

Overall, the verdict for the effects of consumption of LCS in place of sugar in reducing energy intake and body weight in humans is clear – they are useful on both counts. This depends on sugar intake (mainly in beverages) not suppressing appetite on a kJ for kJ basis. Based on the redundancy of short-term energy balancing, there is no reason that it should, and in fact other carbohydrates [84] and fat [85] appear to be not much different from sugar in this respect, whilst protein and fibre may have a greater than kJ for kJ satiating capacity [56,86].

Finally, it is also important to note that in preload, test-meal studies there was no difference in energy intake after LCS versus either water, unsweetened food, or no preload [17]. Perhaps surprisingly, in sustained intervention studies LCS versus water reduced relative body weight [17]. The latter effect may depend on context, for example switching to water from LCS [87] or switching from sugar to LCS or water [88], but together these results show that LCS consumption does not increase appetite or body weight compared with water. Indeed, it is possible that LCS satisfy rather than increase desire for sweetness, via for example sensory-specific satiety [89].

## 9. Final comments and conclusions

We have not discussed individual differences in susceptibility to overweight and obesity. Genotype, early-life (including in utero) events, and childhood experiences are known to be significant influences in this regard [66], but we humans are much more alike than different in having physiological and anatomical traits that allow us to store energy and nutrients in very considerable excess of immediate needs. Not having to balance short-term energy expenditure with intake gave us more flexibility in balancing the cost of getting and eating food with the value of engaging in other activities, including doing nothing (cf. [90]). As a result, prevalence of obesity is greater in low cost food environments.<sup>8</sup> The effect is not uniform, however; partly due to genotypic variation, but also because there is considerable heterogeneity within such environments, for example in relation to what foods are most readily available or culturally acceptable. Furthermore, the extent to which individuals are equipped and motivated to resist excessive energy intake is also partially environmentally determined (e.g., variation in knowledge about food and nutrition, individual differences in

<sup>7</sup> That is not to say that there are no advantages in learning about the energy content of food, which can assist for example in learning the relative value of foods (energy-rich foods being more valuable), and perhaps in avoiding over-satiation [82,83]. Nonetheless, in humans, at least, food aversion learning is more robust than flavour-nutrient learning [82,83]. This may reflect the relative importance in the past of using our experience to reject something potentially harmful compared with learning to limit energy intake. Paradoxically, in our present food environment, where the food to which we have access is generally safe to eat (i.e., it very rarely makes us acutely ill), the greater priority would seem to be to avoid eating excessively.

<sup>8</sup> Some bird species eat less when food is more abundant, and therefore risk of starvation is low. This allows them to benefit from the reduced risk of predation conferred by their lower body weight (gut content plus fat stores) [91]. Larger animals, however, have proportionally lower energy requirements [92], so the relative cost of increased intake over immediate need at times of food surplus is smaller. Furthermore, release from predation risk may have led to genetic 'drift' that over time has further favoured human fatness [12]. More generally, these effects of scaling underline the need for caution in using studies on smaller animals (e.g., including rats and mice) in our endeavour to understand human appetite control.

valuation of thinness, and stigmatisation versus normalisation of overweight and obesity).

Our main thesis is that human biology neither strongly resists eating in excess of immediate energy requirements nor strongly resists eating less than is required. The latter, though, is denied by beliefs about the discomfort of hunger and adverse effects on performance of even brief fasting. We suggest that updating this narrative to be consistent with biological reality would helpfully inform both personal (i.e., self-directed) efforts to eat less and publically-recommended strategies for healthy weight management.

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## References

- [1] P.J. Rogers, Eating habits and appetite control: a psychobiological perspective, *Proc. Nutr. Soc.* 58 (1999) 59–67.
- [2] D.A. Levitsky, The non-regulation of food intake in humans: hope for reversing the epidemic of obesity, *Physiol. Behav.* 86 (2005) 623–632.
- [3] D.A. Levitsky, C.R. Pacanowski, Free will and the obesity epidemic, *Public Health Nutr.* 15 (2011) 126–141.
- [4] B.J. Rolls, What is the role of portion control in weight management? *Int. J. Obes.* 38 (Supplement 1) (2014) S1–S8.
- [5] J. Fisher, Y. Liu, L.L. Birch, B.J. Rolls, Effects of portion size and energy density on young children's intake at a meal, *Am. J. Clin. Nutr.* 86 (2007) 174–179.
- [6] C.F. Smith, D.A. Williamson, G.A. Bray, D.H. Ryan, Flexible vs. rigid dieting strategies: relationship with adverse behavioural outcomes, *Appetite* 32 (1999) 295–305.
- [7] K.N. Frayn, *Metabolic Regulation: A Human Perspective*, Wiley-Blackwell, Chichester UK, 2010.
- [8] J.C.K. Wells, *The Evolutionary Biology of Human Body Fatness: Thrift and Control*, Cambridge University Press, Cambridge UK, 2010.
- [9] P.J. Rogers, J.E. Blundell, Meal patterns and food selection during the development of obesity in rats fed a cafeteria diet, *Neurosci. Biobehav. Rev.* 8 (1984) 441–453.
- [10] D.J. Mela, P.J. Rogers, *Food, Eating and Obesity: The Psychobiological Basis of Appetite and Weight Control*, Chapman and Hall, London, 1998.
- [11] A.P. Coll, I.S. Farooqi, A. O'Rahilly, The hormonal control of food intake, *Cell* 129 (2007) 251–262.
- [12] J.R. Speakman, A nonadaptive scenario explaining the genetic predisposition to obesity: the "Predation Release" hypothesis, *Cell Metab.* 6 (2007) 5–12.
- [13] A.M. Prentice, A.E. Black, W.A. Coward, T.J. Cole, Energy expenditure in overweight and obese adults in affluent societies: an analysis of 319 doubly-labelled water measurements, *Eur. J. Clin. Nutr.* 50 (1996) 93–97.
- [14] D. Whirtsafter, J.D. Davis, Set points and settling points, and the control of body weight, *Physiol. Behav.* 19 (1977) 75–78.
- [15] J.P.J. Pinel, *Biopsychology*, second ed. Allyn and Bacon, Boston, 1993.
- [16] E. Almiron-Roig, L. Palla, K. Guest, C. Ricchiuti, N. Vint, S.A. Jebb, A. Drewnowski, Factors that determine energy compensation: a systematic review of preload studies, *Nutr. Rev.* 71 (2013) 458–473.
- [17] P.J. Rogers, P.S. Hogenkamp, C. de Graaf, S. Higgs, A. Lluch, et al., Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies, *Int. J. Obes.* 40 (2016) 381–394.
- [18] M.M. Schubert, B. Desbrow, S. Sabapathy, M. Leveritt, Acute exercise and subsequent energy intake. A meta-analysis, *Appetite* 63 (2013) 92–104.
- [19] D. Thivel, J. Aucouturier, É. Doucet, T.J. Saunders, J.-F. Chaput, Daily energy balance in children and adolescents. Does energy expenditure predict subsequent energy intake? *Appetite* 60 (2013) 58–64.
- [20] S. Higgs, J.E. Donohoe, Focussing on food during lunch enhances lunch memory and decreases later snack intake, *Appetite* 57 (2011) 202–206.
- [21] R.E. Oldham-Cooper, C.A. Hardman, C.E. Nicoll, P.J. Rogers, J.M. Brunstrom, Playing a computer game during lunch affects fullness, memory for lunch, and later snack intake, *Am. J. Clin. Nutr.* 93 (2011) 308–313.
- [22] J.M. Brunstrom, J.F. Burn, N.R. Sell, J.M. Collingwood, P.J. Rogers, L.L. Wilkinson, E.C. Hinton, O.M. Maynard, D. Ferriday, Episodic memory and appetite regulation in humans, *PLoS One* 7 (2012), e50707.
- [23] A. Hoyland, L. Dye, C.L. Lawton, A systematic review of the effect of breakfast on the cognitive performance of children and adolescents, *Nutr. Res. Rev.* 22 (2009) 220–223.

- [24] M.W. Green, N.A. Elliman, P.J. Rogers, Lack of short-term fasting on cognitive function, *J. Psychiatr. Res.* 29 (1995) 245–253.
- [25] E.M. Benau, N.C. Orloff, E.A. Janke, L. Serell, C.A. Timko, A systematic review of the effects of experimental fasting on cognition, *Appetite* 77 (2014) 52–61.
- [26] E. Pollitt, R.L. Leibel, D. Greenfield, Brief fasting, stress, and cognition in children, *Am. J. Clin. Nutr.* 34 (1981) 1526–1533.
- [27] P.J. Rogers, D. Ferriday, J.E. Smith, S. Duxbury, S. Richards, J.M. Brunstrom, Inverse dose-response effect of breakfast on psychomotor performance, *Behav. Pharmacol.* 24 e-Supplement A (2013) e48.
- [28] A. Craig, E. Richardson, Effects of experimental and habitual lunch-size on performance, arousal, hunger and mood, *Occup. Environ. Health* 61 (1989) 313–319.
- [29] A. Smith, A. Ralph, G. McNeill, Influence of meal size on post-lunch changes in performance efficiency, mood, and cardiovascular function, *Appetite* 16 (1991) 85–91.
- [30] E.E. Pivonka, K.K. Grunewald, Aspartame- or sugar-sweetened beverages: effects on mood in young women, *J. Am. Diet. Assoc.* 90 (1990) 250–254.
- [31] S.C. Woods, The eating paradox: how we tolerate food, *Psychol. Rev.* 98 (1991) 488–505.
- [32] K.A. Bazar, A.J. Yun, P.Y. Lee, Debunking a myth: neurohormonal and vagal modulation of sleep centers, not redistribution of blood flow, may account for postprandial somnolence, *Med. Hypotheses* 63 (2004) 778–782.
- [33] D.G. Mook, *Motivation: The Organization of Action*, Norton, New York, 1996.
- [34] J.E. Blundell, Perspective on the central control of appetite, *Obesity* 14 (Supplement 4) (2006) 1605–1635.
- [35] M.R. Lowe, M.L. Butryn, Hedonic hunger: a new dimension of appetite? *Physiol. Behav.* 91 (2007) 432–439.
- [36] H. Zheng, N.R. Lenard, A.C. Shin, H.-R. Berthoud, Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals, *Int. J. Obes.* 33 (2009) S8–S13.
- [37] K.C. Berridge, Food reward: brain substrates of wanting and liking, *Neurosci. Biobehav. Rev.* 20 (1996) 1–25.
- [38] S. Assanand, J.P.J. Pinel, D.R. Lehman, Personal theories of hunger and eating, *J. Appl. Soc. Psychol.* 28 (1998) 998–1015.
- [39] P.J. Rogers, C.A. Hardman, Food reward: what it is and how to measure it, *Appetite* 90 (2015) 1–15.
- [40] B.J. Rolls, R.J. Wood, E.T. Rolls, H. Lind, W. Lind, J.G.G. Ledingham, Thirst following water deprivation in humans, *Am. J. Phys.* 239 (1980) R476–R482.
- [41] J.A. Chalela, J.I. Lopez, Medical management of hunger strikers, *Nutr. Clin. Pract.* 28 (2013) 128–135.
- [42] H. Valtin, “Drink at least eight glasses of water a day.” really? Is there scientific evidence for “8 × 8”? *Am. J. Phys.* 283 (2002) R993–R1004.
- [43] P.J. Rogers, N.J. Richardson, N.A. Elliman, Overnight caffeine abstinence and negative reinforcement of preference for caffeine-containing drinks, *Psychopharmacology* 120 (1995) 457–462.
- [44] E.M. Stricker, Biological bases of hunger and satiety: therapeutic implications, *Nutr. Rev.* 42 (1984) 333–340.
- [45] M.K. Zaliyah, D.R. Greenway, N.A. Caffin, B.R. D’Arcy, M.J. Gidley, Application of labelled magnitude satiety scale in a linguistically-diverse population, *Food Qual. Prefer.* 19 (2008) 574–578.
- [46] Y. Izumida, N. Yahagi, Y. Takeuchi, M. Nishi, A. Shikama, et al., Glycogen shortage during fasting triggers liver-brain-adipose neurocircuitry to facilitate fat utilization, *Nat. Commun.* 4 (2013) 2316.
- [47] A. Efeyan, W.C. Comb, D.M. Sabatini, Nutrient-sensing mechanisms and pathways, *Nature* 517 (2015) 302–310.
- [48] P.R. Wiepkema, Positive and negative feedbacks at work during feeding, *Behaviour* 39 (1971) 266–273.
- [49] J.R. Brobeck, Exchange, Control and Regulation, in: J.R. Brobeck, W.S. Yamamoto, J.R. Brobeck (Eds.), *Physiological Controls and Regulation*, W.B. Saunders, Philadelphia 1965, pp. 1–13.
- [50] P. Sterling, Allostasis: a model of predictive regulation, *Physiol. Behav.* 105 (2012) 5–15.
- [51] B.I. Rapoport, Metabolic factors limiting performance in marathon runners, *PLoS Comput. Biol.* 6 (2010), e1000960.
- [52] R.L. Cowin, N.M. Avena, M.M. Boggiano, Feeding and reward: perspectives from three rat models of binge eating, *Physiol. Behav.* 104 (2011) 87–97.
- [53] C.E. Cornell, J. Rodin, H. Weingarten, Stimulus-induced eating when satiated, *Physiol. Behav.* 45 (1989) 695–704.
- [54] H.P. Weingarten, Conditioned cues elicit eating in sated rats: a role for learning in meal initiation, *Science* 220 (1983) 431–433.
- [55] B.J. Rolls, Experimental analyses of the effects of variety in a meal on human feeding, *Am. J. Clin. Nutr.* 42 (1985) 932–939.
- [56] S.H.A. Holt, J.C. Brand Miller, P. Petocz, E. Farmakalidis, A satiety index of common foods, *Eur. J. Clin. Nutr.* 49 (1995) 675–690.
- [57] A. Sclafani, K. Ackroff, The relationship between food reward and satiation revisited, *Physiol. Behav.* 82 (2004) 89–95.
- [58] J.M. Brunstrom, P.J. Rogers, How many calories are on our plate? Expected fullness, not liking, determines meal-size selection, *Obesity* 17 (2009) 1884–1890.
- [59] J.M. Brunstrom, I need to eat otherwise I’ll feel hungry later: Is satiety reinforcing in humans, Paper Presented at the 13th Benjamin Franklin/Lafayette Seminar, Fréjus, France, 2015 (June).
- [60] L.H. Epstein, J.J. Leddy, J.L. Temple, M.S. Faith, Food reinforcement and eating: a multilevel analysis, *Psychol. Bull.* 133 (2007) 884–906.
- [61] M. Stroud, The nutritional demands of very prolonged exercise in man, *Proc. Nutr. Soc.* 57 (1997) 55–61.
- [62] T.F. Heatherton, J. Polivy, C.P. Herman, Dietary restraint: some current findings and speculations, *Psychol. Addict. Behav.* 4 (1990) 100–106.
- [63] N. Jones, P.J. Rogers, Preoccupation and failure: an investigation of cognitive performance deficits in dieters, *Int. J. Eat. Disord.* 33 (2003) 185–192.
- [64] J. Shaw, M. Tiggemann, Dieting and working memory: preoccupying cognitions and the role of the articulatory process, *Br. J. Health Psychol.* 9 (2010) 175–185.
- [65] A. Geliebter, E.K. Yahav, M.E. Gluck, S.A. Hashim, Gastric capacity, test meal intake, and appetitive hormones in binge eating disorder, *Physiol. Behav.* 81 (2004) 735–740.
- [66] A.A. van der Klaauw, I.S. Farooqi, The hunger genes: pathways to obesity, *Cell* 161 (2015) 119–132.
- [67] D.A. Levitsky, C.R. Pacanowski, Effect of skipping breakfast on subsequent energy intake, *Physiol. Behav.* 119 (2013) 9–16.
- [68] <http://www.nhs.uk/Livewell/loseweight/Pages/Healthybreakfasts.aspx> downloaded 5th October 2015.
- [69] A.W. Brown, M.M. Bohan Brown, D.B. Allison, Belief beyond the evidence: using the proposed effect of breakfast on obesity to show 2 practices that distort scientific evidence, *Am. J. Clin. Nutr.* 98 (2013) 1298–1308.
- [70] C.G. Fairburn, *Overcoming Binge Eating*, second ed. Guildford press, New York, 2013.
- [71] M. Moseley, M. Spencer, *The Fast Diet*, Atria, New York, 2012.
- [72] M. Harvie, C. Wright, M. Pegington, D. McMullan, E. Mitchell, et al., The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women, *Br. J. Nutr.* 110 (2013) 1543–1547.
- [73] D.J. Kavanagh, J. Andrade, J. May, Imaginary relish and exquisite torture: the elaborated intrusion theory of desire, *Psychol. Rev.* 112 (2005) 446–467.
- [74] B.A. Cassady, R.V. Conside, R.D. Mattes, Beverage consumption, appetite, and energy intake: what did you expect? *Am. J. Nutr.* 95 (2012) 587–593.
- [75] J.E. Steiner, D. Glaser, M.E. Hawilo, K.C. Berridge, Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates, *Neurosci. Biobehav. Rev.* 25 (2001) 53–74.
- [76] D.S. Ludwig, Artificially sweetened beverages: cause for concern, *J. Am. Med. Assoc.* 302 (2009) 2477–2478.
- [77] S.E. Swithers, A.S. Martin, T.L. Davidson, High-intensity sweeteners and energy balance, *Physiol. Behav.* 100 (2010) 55–62.
- [78] Q. Yang, Gain weight by ‘going diet’? Artificial sweeteners and the neurobiology of sugar cravings, *Yale J. Biol. Med.* 83 (2010) 101–108.
- [79] J.E. Blundell, A.J. Hill, Paradoxical effects of an intense sweetener (aspartame) on appetite, *Lancet* 8489 (1986) 1092–1093.
- [80] A. Pan, V.S. Malik, T. Hao, W.C. Willett, D. Mozaffarian, F.B. Hu, Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies, *Int. J. Obes.* 37 (2013) 1378–1385.
- [81] M.V. van Dongen, M.C. van den Berg, N. Vink, F.J. Kok, C. de Graaf, Taste-nutrient relationships in commonly consumed foods, *Br. J. Nutr.* 108 (2012) 140–147.
- [82] J.M. Brunstrom, Associative learning and the control of human dietary behavior, *Physiol. Behav.* 49 (2007) 268–271.
- [83] M.R. Yeomans, Flavour-nutrient learning in humans. an elusive phenomenon? *Physiol. Behav.* 106 (2012) 345–355.
- [84] L. Te Morenga, S. Mallard, J. Mann, Dietary sugar and body weight: a systematic review and meta-analysis of randomised controlled trials and cohort studies, *BMJ* 346 (2013), e7492.
- [85] L. Hooper, A. Abdelhamid, H.J. Moore, W. Douthwaite, C.M. Skeaff, C.D. Summerbell, Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies, *Br. Med. J.* 345 (2012), e7666.
- [86] A.K. Gosby, A.D. Conigrave, D. Raubenheimer, S.J. Simpson, Protein leverage and energy intake, *Obes. Rev.* 15 (2013) 183–191.
- [87] J.C. Peters, H.R. Wyatt, G.D. Foster, Z. Pan, A.C. Wojtanowski, et al., The effects of water and non-nutritive sweetened beverages on weight loss during a 12-week weight loss treatment program, *Obesity* 22 (2014) 1415–1421.
- [88] D.F. Tate, G. Turner-McGrievy, E. Lyons, J. Stevens, K. Erickson, et al., Replacing caloric beverages with water or diet beverages for weight loss in adults: main results of the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial, *Am. J. Clin. Nutr.* 95 (2012) 555–563.
- [89] M. Hetherington, B.J. Rolls, V.J. Burley, The time course of sensory-specific satiety, *Appetite* 12 (1989) 57–68.
- [90] G. Collier, D.F. Johnson, the paradox of satiation, *Physiol. Behav.* 82 (2004) 149–153.
- [91] R. Macleod, P. Barnett, J.A. Clark, W. Cresswell, Body mass change strategies in blackbirds *Turdus merula*: the starvation-predation risk trade-off, *J. Anim. Ecol.* 74 (2005) 292–302.
- [92] C.R. White, R.S. Seymour, Mammalian basal metabolic rate is proportional to body mass<sup>2/3</sup>, *Proc. Natl. Acad. Sci.* 100 (2003) 4046–4049.