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Abstract

Health 'nudge' interventions to steer people into healthier lifestyles are increasingly applied by governments worldwide, and it is natural to look to such approaches to improve health by altering what people choose to eat. However, to produce policy recommendations that are likely to be effective, we need to be able to make valid predictions about the consequences of proposed interventions, and for this, we need a better understanding of the *determinants of food choice*. These determinants include dietary components (e.g. highly palatable foods and alcohol), but also diverse cultural and social pressures, cognitive-affective factors (perceived stress, health attitude, anxiety and depression), and familial, genetic and epigenetic influences on personality characteristics. In addition, our choices are influenced by an array of physiological mechanisms, including signals to the brain from the gastrointestinal tract and adipose tissue which affect not only our hunger and satiety but also our motivation to eat particular nutrients, and the reward we experience from eating. Thus, to develop the evidence base necessary for effective policies, we need to build bridges across different levels of knowledge and understanding. This requires *experimental models* that can fill in the gaps in our understanding that are needed to inform policy, *translational models* that connect mechanistic understanding from laboratory studies to the real life human condition, and *formal models* that encapsulate scientific knowledge from diverse disciplines, and which embed understanding in a way that enables policy-relevant predictions to be made. Here we review recent developments in these areas.

Introduction

Health nudge interventions to steer people into healthier lifestyles are increasingly applied by governments worldwide (1,2). 'Nudges' are approaches to law and policy that maintain freedom of choice, but which steer people in certain directions (3); they consist of small yet relevant behavioural stimuli such as simplification of information and choices, framing and priming of messages, feedback to one's behaviour, defaults and reminders and similar behavioural cues. Much of the health burden is caused by modifiable behaviours such as smoking, unhealthy food consumption, and sedentary lifestyles, but neither decades of health information and education, nor isolated attempts of hard regulation (such as fat taxes or sugar taxes in some countries), nor voluntary self-regulation of industry have markedly promoted healthier lifestyles or have helped to stop the rise of non-communicable diseases. At the same time, there is increasing evidence that the purposeful design of the living and consumption environments – the "choice architecture" – is key to changing nutritional and activity patterns (4) and to maintaining healthier lifestyles once adopted. There is mounting evidence for the usefulness of World Health Organization's (WHO) motto: "make the healthier choice the easy choice", through easier access, availability, priming and framing (5). More than 150 governments now use behavioral science, with an emphasis on nudges (6,7). In these countries, "nudging for health" is regarded as an attractive option to make health policies more effective and efficient; a recent poll in six European countries found that health nudges are overwhelmingly "approved" by the people (8). This is the backcloth against which we set out to test nudging tools that might be useful add-ons to traditional health policies.

However, to produce policy recommendations that are likely to be effective, we need to be able to make valid, non-trivial predictions about the consequences of particular behaviors and interventions. For this, we need a better understanding of the *determinants of food choice*. These determinants include dietary components (e.g. highly palatable foods and alcohol), but also diverse cultural and social pressures, cognitive-affective factors (perceived stress, health attitude, anxiety and depression), and familial, genetic and epigenetic influences on personality characteristics. Our choices are influenced by how foods are marketed and labelled, and by economic factors, and they reflect both habits and goals, moderated, albeit imperfectly, by an individual understanding of what constitutes 'healthy eating'. In addition, our choices are influenced by an array of physiological mechanisms, including signals to the brain from the gastrointestinal tract and adipose tissue which affect not only our hunger and satiety but also our motivation to eat particular nutrients, and the reward we experience from eating.

To develop the evidence base necessary for effective policies, we need to build bridges across different levels of knowledge and understanding. This requires *experimental models* that can fill in the gaps in our understanding that are needed to inform policy, *translational models* that connect mechanistic understanding from laboratory studies to the real life human condition, and *formal models* that encapsulate scientific knowledge from diverse disciplines, and which embed understanding in a way that enables policy-relevant predictions to be made.

State-of-the-art

Although it seems self-evident that changes in body weight reflect the choices an individual makes about what food to eat, about how much to eat and about how much to exercise, the long-term balance between energy intake and energy output is mainly determined by interacting physiological systems. Since the discovery of leptin in 1994 and of ghrelin in 1999, we have gained a partial mechanistic understanding of how homeostatic and hedonic influences are coded and how they impact on eating behavior, and we have an emerging understanding of the mechanisms by which particular food constituents influence hunger and satiety. The strong evolutionary conservation of these mechanisms has meant that knowledge from animal models translates well into understanding of human physiology and behavior: for example, mutations in genes that affect signalling in these pathways have very similar effects in rodents and humans.

Animal studies and human genetics studies have also framed the contributions of genetic and epigenetic influences on body weight. Body weight in people is estimated (from twin studies) to be ~80% heritable (9) but an extensive search for the genes responsible has (so far) revealed associations that account for only about 20% of the inter-individual variation (10). This has focussed attention on *other* heritable mechanisms, and particularly on the consequences of events in uterine and early post-natal life. Notably, stress and impaired nutrition during gestation and in early post-natal life are now known to have lifelong 'programming' effects on physiology and metabolism.

Against this background of genetics and nurture, an individual's knowledge, preferences and behaviors, lifestyle and eating habits are all shaped by their environment. In our everyday consumption, we are far from "rational" agents; we do not use only evidence-based information when deciding which foods to buy, but are influenced the wider information environment which is shaped by cultural factors, including advertising and other media, and we are strongly influenced by earlier decisions and habits, even if these have not proven to be optimal.

Habits are preferences shaped by past choices. If dietary choices follow habitual patterns, then we need to understand how these arise. Children often have a say in what they eat (at school they often choose what to eat at lunch), but they may be unable to correctly assess the costs and benefits of different options. In that context, *imitative* or *impulsive* behavior may dominate, making them vulnerable to peer pressure and the supply of food in their direct environment. Once habits are in place, they shape preferences and future choices. The habitual pattern of behavior has specific implications for policy interventions: effective interventions must be continued for long enough to affect preferences in the longer run.

Emotional and environmental cues also have a large role. We are influenced by how product information is presented – even whether the name "sounds" healthy. At the point of purchase, a number of *decision heuristics* and *biases* undermine rational decision behavior. The *anchor effect* leads us to

overvalue the information we obtained first; the *source effect* draws greater attention to the source of information and leads to assumptions about its credibility that may be false; and *herd behavior* makes us adopt products that others are purchasing. Furthermore, we are poor at estimating probabilities and objective risks - we overestimate our capacity for self-control, and underestimate the health risks associated with the choices we make. On the other hand, we cheat in our mental book-keeping - "*Today I ate too much, but I'll just eat less tomorrow*" (3). We tend to select current enjoyment (*ice cream now*) over conditions we wish for later (*slim and fit*), which behavioral economists explain in terms of the *temporal discounting* of future conditions (11).

The ***decision-making situation*** itself has a large effect, as demonstrated in human ecology models. The *triple A factors* (affordability, availability, and accessibility) have a major impact on decisions (12), and help to explain the "attitude–behavior gap." (13). Marketers have long understood that how a product is positioned in the the store (e.g. as a "stopper" at eye level) has a major impact. The same is true for the perception of rapid availability ("ready-to-eat" dishes) and the brand's potential of reward. In fact, most preferences appear to be less stable than postulated in neo-classical models; many are first formed at the place where the decision is made. This is why behavioral economists speak of *constructive preferences*.

Decision heuristics **and** ***biases*** apply in situations involving uncertainty, which is true of most real decision-making. In our everyday consumption we are far from "rational" (in the sense of following our best intentions). During the search phase of the consumption process, we only perceive selective product characteristics, and because of our *limited processing capacities*, we restrict our search criteria to just a few (more precisely: to "seven plus or minus two"). The presence of many alternatives is likelier to confuse us than to generate optimal decisions (*choice overload* or *hyperchoice*). Another key finding from behavioral economics is the power of *default options*, such as the standard menu in a cafeteria. People generally follow the default option, even when given an opt-out. This finding is robust in diverse decision areas as organ donation, purchase of organic apples and the use of green electricity, and across a wide range of methods (experiments, questionnaires, secondary evaluations). For this reason, a number of incentive systems have been developed based upon "hard" and "soft" defaults. (e.g. 14).

Hedonic processes and reward are important drivers for our decisions and are strong enough to overrule homeostatic needs. Food selection and intake in humans is largely driven by an interaction of homeostatic control and reward signals. These interaction involves a complex involvement of higher cognitive functions including memory, learning and evaluation of different options.

In summary, we need to understand exactly what conscious and unconscious factors bias our choices and subvert our best intentions. We need to understand how our complex homeostatic and higher cortical processes support healthy eating, and how these mechanisms come to be undermined. Our policies on healthy eating must be framed in this setting if they are to be effective. It is also crucial to

know what real individual responses to policy instruments and actions can be expected, and to customize our "policy toolbox" accordingly.

The *evidence-based policy approach,* currently pursued at all policy levels, is based upon empirical data and valid models of behavior and effect (15). It relies on learning policy cycles of "test-learn-adapt-share" that tests policies in pilot applications and assesses their efficacy and cost-benefits before they are rolled out (16). The most important policy measures are those that rely on *optimized information* (i.e. not more information, but more useful and intuitively understandable information). For an integrated, policy-focussed understanding of food choices, we need to optimize information in four key areas: early life experiences; environmental factors and impulsive choice behaviour; emotions and decision making; and how choices change with age.

Early life experiences

Early life programming can influence stress responses, food choice and weight gain into adult life. The consequences of early life events for cardiovascular and weight-related morbidity have been studied in most detail in the Dutch famine birth cohort, and are associated with changes in the methylation of certain genes in people conceived during the Hunger Winter of 1944-5 (17). However, even modest differences in food intake or food choices in early life can have lifelong repercussions, and the metabolic status of the mother during gestation influences the brain dynamics of the fetus (18). Obesity is most prevalent in lower socio-economic groups, and this is likely to reflect genetics (assortative mating), epigenetics and environmental factors. The environmental factors include a childhood diet of abundant energy-dense foods (19).

Worryingly, obesity has been rising among European children, and it disproportionately affects those in low socio-economic groups. However, we don't know the mechanistic link between stress and/or poor nutrition in early life and obesity in adult life, and in particular, we don't know whether this is mediated by programming effects on the reward systems that affect food choice in adult life. Understanding this is critical, for not only are children in low socio-economic groups most affected by obesity, but they are also particularly resistant to "healthy food" campaigns. In 2004, one London borough, Greenwich, after a healthy food campaign, introduced changes in the meals offered in primary schools - shifting from low-budget processed meals towards healthier options. The effect on educational outcomes was analysed using a *difference in differences* approach, comparing educational outcomes before and after the reform, using the neighbouring Local Education Authorities as a control group. Outcomes improved in English and Science, and authorized absences - linked to illness and health - fell by 14% (20). However, the children that benefited least were those from the lowest socio economic groups – those most in need of support.

As well as poor nutrition, stress in early life is a concern, because it can have *programming effects* that heighten responsiveness to stress in adult life, contributing further to weight gain (21). Stress is a

feature of modern life, particularly in the workplace. Some people eat less and lose weight when stressed, but most eat more: one large study over 19 years in more than 10,000 participants (22) found that employees experiencing chronic work stress had a 50% increased risk of developing central adiposity. How stress impacts on appetite and weight gain has been extensively studied in rodent models, which appear to mimic the human situation well. In rodents, whereas acute stress is anorexigenic, chronic stress can lead to weight gain (23). Chronic stress is related to chronic stimulation of the hypothalamo-pituitary adrenal (HPA) axis, comprising neuroendocrine neurons in the paraventricular nucleus of the hypothalamus that regulate the secretion of adenocorticotrophic hormone from the anterior pituitary gland, which in turn regulates glucocorticoid secretion from the adrenal gland. The hypersecretion of glucocorticoids (cortisol in man, corticosterone in rodents) is implicated in obesity at several levels. Intake of high energy foods suppresses the hyperactivity of the HPA axis, leading to what has been called "comfort eating". The underlying mechanisms are well established: glucocorticoids stimulate behaviors mediated by the dopamine "reward" pathway, resulting in increased appetite for palatable foods (24); stress also releases endogenous opioids, which reinforce palatable food consumption and promote 'non-homeostatic' eating. Conversely, comfort food ingestion *decreases* HPA axis activity (25); thus if stress becomes chronic, then eating patterns become a 'coping' strategy**.** Beyond stress, which affects most of the population at some time, about 7% of the European population suffers from depression every year. A common symptom is an alteration in food intake, and this can result in a vicious circle of weight gain and depression (26).

While we know that early life experience has a major impact upon health throughout life, little is known about how stress, poor nutrition and metabolic challenges like gestational diabetes in early life influences later food selection and valuation, and this is key to defining the timing and nature of policy interventions.

Environmental factors, food reward and impulsive choice behavior

Many aspects of modern diet may contribute to the obesity epidemic, including the composition and palatability of modern food, its availability and affordability, how it is marketed, the modern environment, contemporary food culture, and gene-environment interactions. These all impact on the *reward component* of eating that is key to *impulsive choice behavior* – the behavior that governs momentary choices to eat high or low energy foods. The motivation to eat competes with other motivations via a highly conserved neural circuitry – *the reward circuitry*. One key part of this circuitry is the *nucleus accumbens*, which integrates homeostatic, hedonic, and cognitive aspects of food intake (27,28), and an important element of this circuit is the neurotransmitter dopamine. The nucleus accumbens receives a dense dopamine input from the ventral tegmental area. This does not code 'reward' in the sense of subjective pleasure; rather, it mediates incentive salience ('attractiveness') and motivational properties of positive stimuli and events (29). The dopamine system is regulated by cues that

signal the availability of rewards as well as actual reward: dopamine neurons fire in a way that reflects the reward value, and the dopamine that is released in the striatum has a key role in habit formation, while that released in the orbitofrontal cortex is involved in decision-making.

Human brain imaging studies using *positron emission tomography* (PET) and *functional magnetic resonance imaging* (fMRI) confirm that these mechanisms function similarly in humans as in rodents. Thus the CNS response to palatable foods differs from that to bland foods, and responses of subjects that crave palatable foods differ from those who do not. Importantly, cravings for palatable food activate similar brain regions and involve the same chemical messengers in humans as in rats. In the striatum, the availability of dopamine D2 receptors is reduced in severely obese subjects (30), and people who show blunted striatal activation during food intake are at greater risk of obesity, particularly those with compromised dopamine signalling (31).

Mammals pursue behavior that is likely to yield them the greatest reward *at that time*; when fat stores are high, the rewarding power of food is less, and they are more motivated to pursue other rewards. Thus *hedonic* and *homeostatic* mechanisms interact, and this takes place at defined brain sites. Importantly, endocrine signals such as ghrelin, insulin and leptin are not merely regulators of energy homeostasis, but also influence the reward circuitry to increase the incentive value of food (32-34) and impulsive choice behaviour (35). The consequences are striking – the one intervention of consistent effectiveness for weight loss in the morbidly obese is bariatric surgery, and this works not by restricting intake or absorption, but by reducing the incentives to eat via changes in the endocrine signalling to the brain (36,37). This shows that morbid obesity is resistant to interventions because of a pathological dysfunction of gut-brain signalling, and is important for policy:"blame and shame" strategies that deny the underlying pathology are destined to be ineffective and may be counterproductive by promoting "comfort eating". It is also important because these endocrine signals vary with time of day and according to the timing of meals. This opens a window of opportunity by which changing meal patterns – *when* we eat rather than *how much* –can influence both how we utilise the energy intake and our appetite.

Emotions and decision-making

Eating is triggered by many factors, including the sight, smell and memory of food, and the anticipation of food is associated with activation of well-defined regions of the hypothalamus (38). The sensory characteristics of food (taste, odors and texture) are also important in food choice, and these can be well studied by fMRI (39). Visual attention can be rapidly cued by food items – particularly items with high calorific content, and attentional responding to these is magnified in overweight individuals, suggesting that heightened attention to high-caloric food cues promotes greater intake. Animal studies also indicate a major role for learning; associations are formed between the sensory characteristics of a food and its post-ingestive effects. Over time, these associations generate flavour preferences, and may also control meal size.

The sight of appetizing food modulates brain activity in consistent ways: recent meta-analyses (40,41) found that viewing food items enhances activation both in visually-related brain regions and in regions associated with reward (orbitofrontal cortex, parahippocampal gyrus and the insula) in both adults and children. Visually-driven responses to food are linked to increased connectivity between the ventral striatum, the amygdala and anterior cingulate in individuals at risk of obesity, hence differences in interactions within the appetitive network may determine risk of obesity**.** Obese participants show greater visually-driven responses to food in reward-sensitive brain regions and, for obese individuals, greater responsiveness in these regions before weight-loss treatment predicts treatment outcome. Poor weight loss is also predicted by pre-treatment levels of activity to food stimuli in brain areas associated with visual attention and memory, consistent with the attentional effects of food being a predictor of weight loss success (42).

However, we have a poor understanding of how *valuation and selection* of food are encoded neuronally. The orbitofrontal cortex, dorsolateral prefrontal cortex and ventral striatum are all implicated in food valuation and choice, but we only have limited knowledge of what neuronal mechanisms are subserved by these structures. If we are to use the results of functional neuroimaging studies to inform policies that promote healthier food choices, we need a better understanding of how health interventions impact on the brain mechanisms that control food selection and valuation. Specifically we need to address how molecular and cellular events, initiated by the exposure to food, translate into changes at the neuronal circuit level, and how these translate to food decisions.

Physiological mechanisms of appetite control

In all mammals, appetite and energy expenditure are regulated by conserved neuronal circuitry using common messengers. Ghrelin, secreted from the empty stomach, reaches high levels after a fast, and activates neurons in the arcuate nucleus of the hypothalamus that make a potent orexigen, neuropeptide Y (NPY). Leptin, secreted by adipocytes, reports on the body's fat reserves; it inhibits NPY neurons, while activating others that express anorexigenic factors – notably neurons that express pro-opiomelanocortin (POMC). POMC neurons and NPY neurons are reciprocally linked, and which population is dominant determines how much (on average) an animal will eat. As an animal eats, neural and endocrine signals from the gut report on the volume ingested and on its composition – including its complement of fat, carbohydrates and protein. These signals, relayed by "satiety" centres of the caudal brainstem, converge on the ghrelin-and leptin sensing circuits of the mediobasal hypothalamus (43). These in turn project to other limbic sites, including the paraventricular nucleus; which is the primary regulator of the sympathetic nervous system, and which also regulates the HPA axis. These pathways are powerful moderators of energy intake. Despite huge variations in day-by-day food intake, in the long term, the body weight of most individuals is remarkably stable. However, "crash dieting" is an example

of an intervention that reduces body weight in the short term, but as a result of the disruption of normal homeostatic mechanisms it has counterproductive effects in the long term.

It seems that dietary decisions can be regulated by circulating metabolic hormones, including those that signal to brain areas involved in food intake and appetitive behaviors. One prominent example is ghrelin, an orexigenic hormone that increases anticipatory (44) and motivated behavior for food, notably for fat (45) and sugar (46). Ghrelin enhances the reward value of foods and hence increases their consumption (32). Recently, ghrelin has been shown to guide dietary choice, but not entirely as expected for a reward-promoting hormone. In rats offered a free choice of lard (100% fat), sucrose and chow over 2 weeks, that had increased their lard consumption, ghrelin administration changed food choice and they started to consume chow. Interestingly, these effects of ghrelin diverge from those of fasting, after which the consumption of energy dense foods is prioritised (47). The VTA to Nacc pathways appears to be engaged by ghrelin to bring about changes in food choice (47) and reward-linked behavior (48). Several other gut- and fat-derived hormones also impact on food reward circuitry. Leptin, for instance, affects food reward encoding at the level of ventral tegmental area dopamine neurons (49).

While morbid obesity is characterised by dysfunctional gut-brain signalling, a key stage in the progression to obesity is the development of leptin resistance (insensitivity to the effects of leptin that would normally suppress appetite). As a consequence of this, dietary restriction has limited effect on obesity; long term compliance is poor, and those who lose weight are likely to swiftly regain it and may even overshoot after the end of a diet. Normally, eating is most rewarding when there is energy deficiency, and least in an energy-replete state, but leptin resistance develops in both the appetite circuitry and in the reward circuitry, so food remains rewarding despite a state of energy excess. Imaging studies have confirmed the impact of hormones in the recruitment of both hypothalamic and reward circuits. For example, when subjects are infused with PYY (a postprandial gut-derived satiety factor) the changes in activity in the caudolateral orbital frontal cortex predict feeding, whereas when levels of PYY are low, hypothalamic activation predicts food intake (50). Insulin, which is released in the periphery after food ingestion is also a potent modulator of brain activity in cortical and subcortical structures. In recent years it has become clear that just as peripheral insulin resistance develops in association with obesity, so does insulin resistance in the brain (51).

Thus, paradoxically, one of the strongest predictors of weight gain is weight loss dieting. One of the biggest studies to demonstrate this was *The Growing Up Today Study* (GUTS), a prospective study of >16,000 adolescents (52). At the 3 year follow-up, adolescents that were frequent or infrequent dieters had gained significantly *more* weight than non-dieters. The study controlled for body mass index (BMI), age, physical development, physical activity, caloric intake and height change over the period. The longest study that demonstrates this is Project EAT (Eating and Activity in Teens and Young Adults), a population-based study of middle and high school students (53). This study, which controlled for socioeconomic status and initial BMI, again showed that the strongest predictors of weight gain were

dieting and unhealthy weight control behaviors. The behaviors associated with the largest increases in BMI over a 10 year period were skipping meals, eating very little, using food substitutes and taking "diet pills".

This raises the concern that emphasising the health risks of obesity may lead people into behaviors that exacerbate the problem. This worry is compounded when one looks at the media response in the UK to recent publicity, where concerns about the effects of excessive *weight gain* in pregnancy were translated as concern about *obesity* in pregnancy. These are very different; while excessive weight gain in pregnancy is detrimental, so is weight loss – even from a condition of obesity. Physiologically, dietary restriction during pregnancy can lead to starvation of the fetus, as homeostatic mechanisms defend maternal body weight at the expense of the fetus. Thus, how advice related to healthy eating and lifestyles is formulated and disseminated needs careful attention. There has been little work on food choice in children, and this is important to explore because of the weaker self-control capacity of children, which is coupled to the maturation of their prefrontal cortex [54]. This has a bearing on in-store marketing (and legislation on that) and the development of interventions aimed at preventing childhood obesity.

The neuroimaging of food choice

Human associational and behavioral studies have many potential confounding factors, so interpreting them depends on inferences from our mechanistic understanding of the neurobiology of appetite. However, there is a "disconnect" between our mechanistic understanding and our "softer" knowledge of individual consumer behavior, which makes these inferences incomplete and unsafe. We need to create bridges in our understanding, enabling us to integrate behavioral and observational studies with neurobiological studies in a way that can be used to educate stakeholders and inform policy.

Human neuroimaging is an emerging technology that can be used to define the neural circuits involved in food valuation and selection. Food decision-making has been studied surprisingly little; most neuroimaging studies use passive viewing paradigms in which participants are exposed to food, i.e. they study food cue reactivity rather than the ensuing decision-making processes. Combining different imaging techniques can optimize the temporal and spatial description of the neuronal circuits underlying food valuation and selection during hunger and satiety. Recent developments in fMRI include a) combining diffusion tensor imaging with resting state analysis to determine network structures and changes during different physiological states; b) high-resolution anatomical MRI to improve investigation of hypothalamic and midbrain responses and c) arterial spin labelling techniques to establish a quantitative neural activity measure of hunger and satiety. In addition, developments in magnetoencephalography and electroencephalography include: a) extraction of resting state dynamics with high temporal resolution and combination with diffusion tensor imaging and b) application of Bayesian- based source localization methods to define the temporal and spatial network involved in food selection. Most fMRI studies that link a given brain circuit with cues associated with food (such as an

image of a food item) or with the choice for a particular food are based on *correlations* between an event and a recorded brain activity. To determine *causality*, we need to be able to *change* brain activity and determine its impact on behavior. In humans, defined neuronal structures can be manipulated using transcranial magnetic stimulation) or direct current stimulation to either facilitate or attenuate cerebral activity.

Along with the rise in the number of neuroimaging studies there have been many neuroimaging data-sharing initiatives, and several databases contain resting fMRI data and anatomical MRI data from thousands of individuals. For functional imaging data, things are more complicated but there are notable efforts of sharing complete fMRI datasets (openfmri.org), unthresholded statistical maps (neurovault.org) and coordinate-based data synthesis (neurosynth.org). However, the value of such databases depends on the available metadata, and existing databases lack most or all of the meta-data necessary for research on the determinants of food choice, such as weight [54], restraint eating status [55] and personality characteristics [56].

For policies to be built on a robust evidence base, it is essential that the evidence is developed in a way that facilitates valid meta-analysis. There is great variability in neuroimaging results, and this is especially true for fMRI tasks involving complex stimuli, such as food stimuli (40, 41). Bennett & Miller (57) showed that the reproducibility of fMRI results was only 50%, even for the same task and stimuli in the same group of participants. This was confirmed in the food domain in a meta-analysis, where the brain areas most consistently activated by looking at food versus non-food pictures where only reported in less than 50% of the studies included (40,41). Reproducibility can be improved by standardizing measures, but currently, there are no standardized fMRI protocols for assessing food responsivity and food choice for different food categories. To filter out effects due to subject characteristics rather than methodological difference, standardization of instruments and measures is crucial for data sharing and pooling across studies (58). Recently, researchers have begun to share (standardized) food images for use in experimental paradigms (e.g. 59,60) and tools for standardized collection of food-related subject characteristics (61).

To connect data from human imaging studies with neurophysiological data from rats, we must improve and adapt high-field rodent fMRI technology in a setting that allows to map involvement of neural circuits in food valuation and selection. Small rodent resting state and pharmacological fMRI is an emerging technology that before now has not been applied to address how brain activity changes upon food restriction and food anticipation. Thus it is not known, for example, how brain activity is changed upon food restriction in rodents and how gut peptides like leptin and ghrelin affect functional connectivity between brain regions. Small rodent fMRI bridges the gap between neuronal activity at the cellular level with fMRI measures in humans, making it possible to connect molecular and cellular data with fMRI measures.

Novel technologies to understand the brain mechanisms underlying food choice

There is a poor understanding of what underlies the responses quantified in neuroimaging studies. By combining *in vivo* electrophysiology with optogenetics or pharmacogenetics, it is now possible to record from and interfere with defined neurons involved in food valuation and choice, and this is a key to unravelling what underlies responses recorded by neuroimaging. Optogenetics is a novel technology that takes advantage of genes that encode channels that are light sensitive. Once introduced into neurons, these neurons are either activated or inhibited by shining light upon them. These light-activated channels can be expressed conditionally in specific neurons. This requires that these neurons express the cre recombinase enzyme. Targeting cre for instance to tyrosine hydroxylase (TH: the rate limiting enzyme for dopamine production) neurons such as in (germline) TH-cre rats, allows these light-sensitive channels to be expressed only on midbrain dopamine neurons. To achieve this, light-sensitive channels are cloned into a recombinant AAV vector such that only upon expression of cre, the channels are expressed in dopamine neurons (62,63). This makes it possible to activate very precise populations of neurons in rodents, and to compare observations with brain responses observed by neuroimaging. Similarly, specific subpopulations of dopamine neurons can be targeted with viruses to express novel receptors that are not endogenously present; these neurons can then be specifically activated (or inhibited) by systemically applied drugs that act specifically on those novel, introduced receptors (e.g. 64).

How the life-long learning process contributes to food selection and valuation

The sensory characteristics of food are important in food choice, but learning also has a major role (65). Associations are formed between the sensory characteristics of a food (the conditioned stimulus [CS] and its post-ingestive effects (the unconditioned stimulus [US]). Over time, these 'flavour-nutrient' associations generate flavour preferences and they also control meal size. In humans, fundamental questions remain about the nature of the unconditioned stimulus and how this is combined with sensory signalling from the tongue to the brain.

In adult humans, flavour-nutrient learning is notoriously difficult to observe under controlled laboratory conditions. By contrast, in non-human animals this form of learning is extremely reliable. Several examples of flavour-nutrient learning have been reported in children, and it is possible that this is because most dietary learning occurs in early life. By adulthood, we have encountered so many foods and flavours that our capacity to learn new associations might be saturated (a form of 'latent inhibition'). If so, then this reinforces the importance of childhood as a critical period during which our dietary behaviours are established. A further consideration is the complexity of the modern Western dietary environment. Unlike our pre-agricultural ancestors many humans are now exposed to a much wider range of foods, including foods that are available in numerous different brands and varieties. This may also limit our opportunity to learn about individual foods, which has the potential to promote overconsumption (66).

Learned beliefs impact our dietary choices directly. Typically, we decide how much we are going to eat *before* a meal begins (67). These decisions are often motivated by a concern to avoid hunger between meals, and the learned 'expected satiety' of individual foods is important in this. Calorie-for-calorie low energy-dense foods tend to have greater expected satiety, and foods with this characteristic are often selected to avoid hunger between meals. Increasingly, portions are also determined by external agents such as restaurants or retailers, and concern has been raised about the size of these portions. Recently, it has become clear that larger portions not only increase our food intake but also affect choice. This is because larger portions are likely to satisfy our appetite between meals and, in the absence of concerns about satiety, decisions tend to be motivated primarily by palatability.

A further possibility is that satiation (fullness at the end of a meal) or the absence of hunger between meals is itself valued (68). The results of human appetite studies suggest that both oral and gastric stimulation are needed for optimal satiety (69-71). However, the underlying process also involves integration of explicit 'knowledge' about the food and amount that has been consumed (72,73). Consistent with this proposition, several studies show that satiety and satiation are reduced when eating occurs in the presence of cognitive distraction (74). Eating 'attentively' appears to have the opposite effect (75), and food properties like viscosity can increase perceived fullness for otherwise similar foods [76]. Despite its importance, the process by which interoceptive signals are integrated remains unclear. This merits attention because some studies indicate that individual differences in interoceptive awareness are a predictor of adiposity in humans (77).

How physiological, psychological, and emotional factors predispose people to unhealthy eating

One key question in the effects of sensory, nutrient and satiety contributions to reward is whether the initial response to certain stimuli remains in place after repeated exposure. Is the response to a low-calorie beverage with artificial sweeteners the same after repeated exposure, or do people slowly learn that "diet" product contain less calories? For this case, in which there is no deprivation, it is quite hard to demonstrate such dietary learning [78] although there is some evidence for detection of calories in the mouth [79,80]. Another important consideration is whether it makes a difference whether one goes from, for example, 200 → 50 kcal, or from 150 → 0 kcal. In both cases, there is a reduction of 150 kcal, but in the case of 200 → 50 kcal, there is still energy left in the stimulus, whereas in the case of 150 → 0 kcal, there is no energy left. It has been argued that the absence of any calories will lead to a lower reward value after repeated exposure. Conversely, most 'light'products still contain energy, albeit less than their regular counterparts, with soft drinks as a notable exception.

In both humans and rodents, the motivation to choose one food over another is driven by the emotional, hedonic, and metabolic properties of the foods. The dopamine system is critically involved in this decision-making, and is essential for associating rewards with environmental stimuli that predict these rewards. Activity of this system is affected by both metabolic information and emotional and

cognitive information. The hypothalamus, amygdala and medial prefrontal cortex play important roles in, respectively, feeding behavior, emotional processing, and decision-making. Manipulation of the dopamine system can be achieved by nutritional interventions and reduction of dopamine levels in lean and obese subjects leads to decreased activity in the reward system (81).

It is common for individuals to speak about eating 'comfort food' to 'raise their spirits'. There is also evidence from behavioral science that incidental emotions can affect food choices. Sadness leads to greater willingness to pay for unnecessary consumer goods (82,83) and increased consumption of unhealthy food items (84). Despite these and related behavioral findings, the biological mechanisms linking affective states to food choices are unknown. Recent work has begun to investigate the underlying neural mechanisms of dietary choice in humans using neuroimaging and brain stimulation techniques together with validated choice paradigms and behavioural trait measures (e.g. 84-88).

A natural assumption would be that the physiological and psychological reactions to an affective state would act in unison, using the same neural pathways to influence food choices. However, Maier *et al.* (24) have recently shown using fMRI that experiencing an acute stressor leads to changes in two separate and dissociable neural pathways: one associated with the physiological reaction to stress, and the other with the conscious perception of being stressed. The physiological response was measured by sampling salivary cortisol, the psychological experience was recorded using a visual analog scale on which participants indicated how they felt right after the stress induction. Cortisol was associated with signals about the reward value of food: individuals with a higher cortisol response showed a higher representation of taste in the ventral striatum (VS) and amygdala, and amplified signalling between VS/amygdala and the ventromedial prefrontal cortex (vmPFC) when a tastier food was chosen. Yet the subjective perception of being stressed did not correlate with the strength of this connection. Instead, the perceived stress level (but in turn not the cortisol reaction) was associated with the connectivity strength between left dorsolateral prefrontal cortex (dlPFC) and the vmPFC: the more stressed participants had felt, the weaker was the connectivity between these two regions when self-control was needed to overcome taste temptations in order to choose the healthier food. A series of studies have demonstrated that connectivity between dlPFC and vmPFC relates to the degree to which individuals use self-control in dietary choice (89-92). This connection in the prefrontal cortex may server to maintain a goal context that promotes focusing on long-term outcomes such as future health, whereas sensory and motivational signalling from subcortical areas may promote information about more immediate choice outcomes. Thus, self-control in dietary choice may depend on a balance of signalling and information exchange in value computation networks, and disruptions to this balance during highly affective states may lead to impaired self-control.

Modeling the interactions between physiological, psychological and emotional factors related to feeding behaviour

Finally, an ultimate ambition must be to generate *formal models* that encapsulate scientific knowledge from diverse disciplines, and which embed understanding in a way that enables policy-relevant predictions to be made. Modelling is a natural way of working together to provide added value – it expresses intrinsically the need to make links between levels of understanding. Most importantly, it takes seriously the issue of how to generate policy guidelines that have a robust scientific basis, by providing a common framework of understanding across disciplines. A model which can reproduce observed behaviour can be extended to test and inform choice of interventions.

Modelling provides a logically coherent framework for a multi-level analysis of food choice behavior, integrating measures of the neural components of the appetitive network with 'whole-system' output (behavioural experiments) in a framework consistent with the neuroendocrine mechanisms that underlie homeostatic and hedonic mechanisms, and providing a test-bed for studies of behavioural interventions. The first phase in modelling is a *scheme* that embodies constructs that explain behaviour by describing a causal chain of events. A *computational model* expresses these in mathematical terms, usually as differential equations. Typically such differential equations are a) coupled (expressing interdependence between factors) and b) non-linear (expressing complex dependencies between variables). To be useful, a model must be developed at a level of detail that is appropriate for a) the data it is informed by, and b) the type of prediction that it is called upon to make. It must be complex enough to satisfy the former but be simple enough to satisfy the latter – making models over-complex is counterproductive, as such models are not predictive (93).

For example, oxytocin neurons are well established as playing an important role in satiety (94,95) and, according to recent studies, in food choice (96,97). These neurons respond to signals from the gut that control meal size, and how these neurons respond to some of these appetite-related stimuli has been analysed at the single-cell level. Their behavior can be captured in detail by biophysical (Hodgkin-Huxley style) models, that can then be well approximated by simpler integrate-and fire models that capture the essential behavior while being better suited for modelling networks of neurons (98). Decision making at the level of the neuron networks that oxytocin engages can be well-modelled by biologically realistic "winner-takes-all" networks, which provide predictive models of how continuous variables lead to categorical decision making, and such network models can be fit to human brain imaging data by "mean field approximation" (99). Such models can link brain imaging data with experimental behavioural data in a predictive way, as in the 'spiking search over time & space model' that has been developed to analyse attentional processes (100). Relatively simple mathematical models can capture important features of value-based decisions well, and in a similar way for food-based decisions as for social decisions, indicating that there is a common computational framework by which different types of value-based decisions are made (101). At a high level, the aim must be to generate agent-based models that describe by a set of explicit rules all the factors that influence food choice, validating each of the rules by a mechanistic understanding of the neurobiological and physiological mechanisms that implement these

rules. It is a long goal, but working towards it provides a unified framework for multi-disciplinary research.

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Authorship

All authors participated in writing this review

References

1. Halpern D for VicHealth (2016) *Behavioural Insights and Healthier Lives.* Victorian Health Promotion Foundation, Melbourne.
2. Matjasko JL, Cawley J, Baker-Goering MM *et al.* (2016) Applying behavioral economics to public health policy: illustrative examples and promising directions. *Am J Preventive Med* **50**, S13–S19.
3. Sunstein CS & Thaler RH (2008) *Nudge: Improving Decisions About Health, Wealth, and Happiness* (Yale University Press) New Haven and London. 312p.
4. Bucher T, Collins C, Rollo ME *et al.* (2016) Nudging consumers towards healthier choices: a systematic review of positional influences on food choice. *Br J Nutr* **115**, 2252–2263.
5. Wilson AL, Buckley E, Buckley JD *et al.* (2016) Nudging healthier food and beverage choices through salience and priming. Evidence from a systematic review. *Food Quality and Preference*, doi: http://dx.doi.org/10.1016/j.foodqual.2016.02.009.
6. Ly K & Soman D (2013) *Nudging Around the World* (Research Report Series). Retrieved from the Rotman School of Management, University of Toronto: http://inside.rotman.utoronto.ca/behaviouraleconomicsinaction/files/2013/12/Nudging-Around-The-World_Sep2013.pdf.
7. Sunstein CR (2016b) The council of psychological advisers. *Ann Rev Psychol* **67**, 713-737.
8. Reisch LA & Sunstein CR (2016) Do Europeans like nudges? *J Judgment Decision Making* **11**, 310-325.
9. Wardle J, Carnell S, Haworth CM *et al.* (2008) Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr* **87**, 398-404.

10. Locke AE, Kahali B, Berndt SI *et al.* (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197-206.
11. Benabou R & Tirole J (2005) Incentives and prosocial behavior. *Am Economic Rev* **96**, 1652-1678.
12. Maas J, de Ridder DT, de Vet E *et al.* (2012) Do distant foods decrease intake? The effect of food accessibility on consumption**.** *Psychol Health* **27** Suppl 2:59-73.
13. Reisch LA & Gwozdz W (2013) Smart defaults and soft nudges. How insights from behavioral economics can inform effective nutrition policy. In: Karen Brunsø & Joachim Scholderer (Eds.). "*Marketing, food, and the consumer. Festschrift in Honour of Klaus Grunert.*" pp. 189-200. New Jersey: Pearson Publisher.
14. Sunstein CR & Reisch LA (2014) Automatically green: behavioral economics and environmental protection. *Harvard Environmental Law Rev* **38**, 127-158.
15. Bogenschneider K & Corbett TJ (2010) "*Evidence-based policymaking: Insights from policy-minded researchers and research-minded policymakers*." Routledge 368p.
16. Joint Research Center of the EC (2016). Behavioural insights applied to policy. *European Report Brussels*: JRC:
17. Tobi EW, Goeman JJ, Monajemi R *et al.* (2014) DNA methylation signatures link prenatal famine exposure to growth and metabolism. *Nat Commun* **5**, 5592.
18. Linder K, Schleger F, Kiefer-Schmidt I *et al.* (2015) Gestational diabetes impairs human fetal postprandial brain activity. *J Clin Endocrinol Metab* **100**, 4029-4036.
19. Wang Y & Lim H (2012) The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. *Int Rev Psychiatry* **24**, 176-188.
20. Belot M & James J (2011) Healthy school meals and educational outcomes. *J Health Econ* **30**, 489-504.
21. Brunton PJ. (2015) Programming the brain and behaviour by early-life stress: a focus on neuroactive steroids. *J Neuroendocrinol* **27**, 468-480.
22. Brunner EJ, Chandola T & Marmot MG (2007) Prospective effect of job strain on general and central obesity in the Whitehall II study. *Am J Epidemiol* **165**, 828-837.
23. Rabasa C & Dickson SL (2016) Impact of stress on metabolism and energy balance *Curr Opin Behavl Sci* **9**, 71–77.
24. Maier SU, Makwana AB & Hare TA (2015). Acute stress impairs self-control in goal-directed choice by altering multiple functional connections within the brain's decision circuits. *Neuron* **87**, 621-631.
25. Dallman MF, Pecoraro N, Akana SF *et al.* (2003) Chronic stress and obesity: a new view of "comfort food." *Proc Natl Acad Ssi USA* **100**, 11696-11701.
26. Stunkard AJ, Faith MS & Allison KC (2003) Depression and obesity. *Biol Psychiatry* **54**, 330-337.
27. Kelley AE, Baldo BA, Pratt WE *et al.* (2005) Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. *Physiol Behav* **86**, 773-795.

28.Adan RA, Vanderschuren LJ & la Fleur SE (2008) Anti-obesity drugs and neural circuits of feeding. *Trends Pharmacol Sci* **29**, 208-217.

29.Berridge KC (2007) The debate over dopamine's role in reward. *Psychopharmacology* **191**, 391-431.

30.Benton D & Young HA (2016) A meta-analysis of the relationship between brain dopamine receptors and obesity: a matter of changes in behavior rather than food addiction? *Int J Obes (Lond)* **40**, S12-21.

31.Stice E, Spoor S, Bohon C *et al.* (2008) Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. *Science* **322**, 449-452.

32.Egecioglu E, Jerlhag E, Salomé N *et al.* (2010) Ghrelin increases intake of rewarding food in rodents. *Addict Biol* **15**, 304-311.

33.Figlewicz DP, MacDonald Naleid A & Sipols AJ (2007) Modulation of food reward by adiposity signals. *Physiol Behav* **91,** 473-478.

34.Kullmann S, Heni M, Veit R *et al.* (2015) Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes Care* **38**, 1044-1050.

35.Anderberg RH, Hansson C, Fenander M *et al.* (2016) The stomach-derived hormone ghrelin increases impulsive behavior. *Neuropsychopharmacology* **41**, 1199-1209.

36.Leng G (2014) Gut instinct: body weight homeostasis in health and obesity. *Exp Physiol* **99**, 1101-1103.

37.Frank GK, Oberndorfer TA, Simmons AN et al. (2008) Sucrose activates human taste pathways differently from artificial sweetener**.** *Neuroimage* **39**, 1559-1569.

38.Johnstone LE, Fong TM & Leng G. (2006) Neuronal activation in the hypothalamus and brainstem during feeding in rats *Cell Metab* **4**, 313-321.

39.Lundström JN, Boesveldt S & Albrecht J (2011) Central processing of the chemical senses: an overview. *ACS Chem Neurosci* **2**, 5-16.

40.van Meer F, van der Laan LN, Adan RA *et al.* (2015) What you see is what you eat: an ALE meta-analysis of the neural correlates of food viewing in children and adolescents. *Neuroimage* **104**, 35-43.

41.Van der Laan LN, de Ridder DT, Viergever MA *et al.* (2011) The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues *NeuroImage* **55**, 296-303.

42.Hege MA, Stingl KT, Ketterer C *et al.* (2013) Working memory-related brain activity is associated with outcome of lifestyle intervention. *Obesity (Silver Spring)* **21**, 2488-2494.

43.Murphy KG & Bloom SR (2006) Gut hormones and the regulation of energy homeostasis. *Nature* **444**, 854-859.

44.Verhagen LA, Egecioglu E, Luijendijk MC *et al.* (2011) Acute and chronic suppression of the central ghrelin signaling system reveals a role in food anticipatory activity. *Eur Neuropsychopharmacol* **21**:384-392.

45.Perello M & Dickson SL (2015) Ghrelin signalling on food reward: a salient link between the gut and the mesolimbic system. *J Neuroendocrinol* **27**, 424-434.

46.Skibicka KP, Hansson C, Alvarez-Crespo M *et al.* (2011) Ghrelin directly targets the ventral tegmental area to increase food motivation. *Neuroscience* **180**, 129-137.

47.Schéle E, Bake T, Rabasa C *et al.* (2016) Centrally administered ghrelin acutely influences food choice in rodents. *PLoS ONE* **11**(2):e0149456.

48.Skibicka KP, Shirazi RH, Rabasa-Papio C *et al.* (2013) Divergent circuitry underlying food reward and intake effects of ghrelin: dopaminergic VTA-accumbens projection mediates ghrelin's effect on food reward but not food intake. *Neuropharmacology* **73**, 274-283.

49.van der Plasse G, van Zessen R, Luijendijk MC *et al.* (2015) Modulation of cue-induced firing of ventral tegmental area dopamine neurons by leptin and ghrelin. *Int J Obes (Lond)* **39**, 1742-1749.

50.50 Batterham RL, ffytche DH, Rosenthal JM *et al* (2007) PYY modulation of cortical and hypothalamic brain areas predicts feeding behavior in humans. *Nature* **450**, 106-109.

51.Kullmann S, Heni M, Hallschmid M *et al.* (2016) Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. *Physiol Rev* **96**, 1169-1209.

52.Field AE, Austin SB, Taylor CB *et al.* (2003) Relation between dieting and weight change among preadolescents and adolescents. *Pediatrics* **112**, 900-906.

53.Neumark-Sztainer D, Wall M, Story M *et al.* 2012; Dieting and unhealthy weight control behaviors during adolescence: associations with 10-year changes in body mass index. *J Adolescent Health* **50**, 80-86.

54.van Meer F, Charbonnier L & Smeets PA (2016) Food decision-making: effects of weight status and age. *Curr Diab Rep* **16**, 84.

55.van der Laan LN, Charbonnier L, Griffioen-Roose S *et al.* (2016) Supersize my brain: A cross-sectional voxel-based morphometry study on the association between self-reported dietary restraint and regional grey matter volumes. *Biol Psychol* **117**, 108-116.

56.van der Laan LN & Smeets PA. (2015) You are what you eat: a neuroscience perspective on consumers' personality characteristics as determinants of eating behavior. *Curr Op Food Sci* **3**, 11-18.

57.Bennett CM & Miller MB (2010) How reliable are the results from functional magnetic resonance imaging*? Ann NY Acad. Sci* **1191**, 133-155.

58.Smeets PA, Charbonnier L, van Meer F*et al.* (2012) Food-induced brain responses and eating behavior. *Proc Nutr Soc* **71**, 511-520.

59.Charbonnier L, van Meer F, van der Laan LN *et al.* (2016) Standardized food images: A photographing protocol and image database. *Appetite* **96**, 166-173.

60.Blechert J, Meule A, Busch NA *et al.* (2014) Food-pics: an image database for experimental research on eating and appetite. *Front Psychol* **5**, 617.

61.http://nutritionalneuroscience.eu/resources/forc-toolbox. Nutritional neuroscience laboratory.

62.Witten IB, Steinberg EE, Lee SY *et al.* (2011) Recombinase-driver rat lines: tools, techniques, and optogenetic application to dopamine-mediated reinforcement. *Neuron* **72**, 721-733.

63.de Backer, MW, Garner KM, Luijendijk MC *et al.* (2011) Recombinant adeno-associated viral vectors. *Methods Mol Biol* **789**, 357-376.

64. Boender AJ, de Jong JW, Boekhoudt L et al. (2014) Combined use of the canine adenovirus-2 and DREADD-technology to activate specific neural pathways in vivo. *PLoS ONE* **9**(4):e95392.

65.Brunstrom JM (2007) Associative learning and the control of human dietary behavior. *Appetite* **49**, 268-271.

66.Hardman CA, Ferriday D, Kyle L *et al.* (2015) So many brands and varieties to choose from: does this compromise the control of food intake in humans? *Plos ONE* **10**(4):e0125869.

67.Fay SH, Ferriday D, Hinton EC *et al.* (2011) What determines real-world meal size? Evidence for pre-meal planning. *Appetite* **56**, 284-289.

68.Brunstrom JM & Shakeshaft NG (2009) Measuring affective (liking) and non-affective (expected satiety) determinants of portion size and food reward. *Appetite* **52**, 108-114.

69.Wijlens AG, Erkner A, Alexander E *et al.* (2012) Effects of oral and gastric stimulation on appetite and energy intake. *Obesity (Silver Spring)* **20**, 2226-2232.

70.Spetter MS, Mars M, Viergever MA *et al.* (2014) Taste matters - effects of bypassing oral stimulation on hormone and appetite responses. *Physiol Behav* **137**, 9-17.

71.Spetter MS, de Graaf C, Mars M *et al.* (2014) The sum of its parts--effects of gastric distention, nutrient content and sensory stimulation on brain activation. *PLoS ONE* **9**(3):e90872.

72.Brunstrom JM, Burn JF, Sell, NR *et al.* (2012) Episodic memory and appetite regulation in humans. *PLoS ONE* **7(**12), e50707.

73.Cassady BA, Considine RV & Mattes RD (2012) Beverage consumption, appetite, and energy intake: what did you expect? *Am J Clin Nutr* **95**, 587-593.

74.Brunstrom JM & Mitchell GL (2006) Effects of distraction on the development of satiety. *Br J Nutr* **96**, 761-769.

75.Higgs S & Donohoe JE (2011) Focusing on food during lunch enhances lunch memory and decreases later snack intake. *Appetite* **57**, 202-206.

76.Camps G, Mars M, de Graaf C *et al.* (2016) Empty calories and phantom fullness: a randomized trial studying the relative effects of energy density and viscosity on gastric emptying determined by MRI and satiety. *Am J Clin Nutr* **104**, 73-80.

77.Herbert BM, Blechert J, Hautzinger M *et al.* (2013) Intuitive eating is associated with interoceptive sensitivity. Effects on body mass index. *Appetite* **70**, 22-30.

78.Griffioen-Roose S, Smeets PA, Weijzen PL *et al.* (2013) Effect of replacing sugar with non-caloric sweeteners in beverages on the reward value after repeated exposure. *PLoS One* **8**(11):e81924.

79.Smeets PA, Weijzen P, de Graaf C *et al.* (2011) Consumption of caloric and non-caloric versions of a soft drink differentially affects brain activation during tasting. *Neuroimage* **54**, 1367-1374.

80.van Rijn I, de Graaf C & Smeets PA (2015) Tasting calories differentially affects brain activation during hunger and satiety. *Behav Brain Res* **279**, 139-147.

81. Frank S, Veit R, Sauer H *et al.* (2016) Dopamine depletion reduces food-related reward activity independent of BMI. *Neuropsychopharmacology* **41**, 1551-1559.

82.Lerner JS, Small DA & Loewenstein G (2004). Heart strings and purse strings: Carry-over effects of emotions on economic transactions. *Psychol Sci* **15**, 337-341.

83.Cryder CE, Lerner JS, Gross JJ *et al.* (2008). Misery is not miserly: Sad and self-focused individuals spend more. *Psychol Sci* **19**, 525-530.

84.Garg N, Wansink B & Inman JJ (2007) The influence of incidental affect on consumers' food intake. *J Marketing* **71**, 194-206.

85.Pogoda L, Holzer M, Mormann F *et al.* (2016) Multivariate representation of food preferences in the human brain. *Brain Cogn* pii: S0278-2626(15)30047-6.

86.Val-Laillet D, Aarts E, Weber B *et al.* (2015) Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *NeuroImage* **8,** 1-31.

87.van der Laan LN, de Ridder DT, Viergever MA *et al.* (2014) Activation in inhibitory brain regions during food choice correlates with temptation strength and self-regulatory success in weight-concerned women. *Front Neurosci* **8**, 308.

88.van der Laan LN, Barendse ME, Viergever MA *et al.* (2016) Subtypes of trait impulsivity differentially correlate with neural responses to food choices. *Behav Brain Res* **296,** 442-450.

89.Hare TA, Camerer CF & Rangel A (2009) Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* **324**, 646-648.

90.Hare TA, Malmaud J & Rangel A (2011) Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. *J Neurosci* **31**, 11077-11087.

91.Harris A, Hare T & Rangel A (2013) Temporally dissociable mechanisms of self-control: early attentional filtering versus late value modulation. *J Neurosci* **33**, 18917–18931.

92.Lim SL, Cherry JBC, Davis AM *et al. (*2016) The child brain computes and utilizes internalized maternal choices. *Nature Comm* **7,** 1700.

93.Leng G & MacGregor DJ (2008) Mathematical modelling in neuroendocrinology. *J Neuroendocrinol* **20**, 713-718.

94.Leng G, Onaka T, Caquineau C *et al.* (2008) Oxytocin and appetite. *Prog Brain Res* **170**, 137-151.

95.Blevins JE & Ho JM (2013) Role of oxytocin signaling in the regulation of body weight. *Rev Endocr Metab Disord* 14, 311-329.

96.Olszewski PK, Klockars A & Levine AS. (2016) Oxytocin: a conditional anorexigen whose effects on appetite depend on the physiological, behavioural and social contexts. *J Neuroendocrinol* **28**,

97. Olszewski PK, Klockars A, Olszewska AM *et al.* (2010) Molecular, immunohistochemical, and pharmacological evidence of oxytocin's role as inhibitor of carbohydrate but not fat intake. *Endocrinology* **151**, 4736-4744.

98. Maícas Royo J, Brown CH, Leng G *et al.* (2016) Oxytocin neurones: intrinsic mechanisms governing the regularity of spiking activity. *J Neuroendocrinol* **28**,

99. Deco G, Jirsa VK, Robinson PA *et al.* (2008) The dynamic brain: from spiking neurons to neural masses and cortical fields. *PLoS Comput Biol* **4**:e1000092.

100. Mavritsaki E, Allen HA & Humphreys GW (2010) Decomposing the neural mechanisms of visual search through model-based analysis of fMRI: top-down excitation, active ignoring and the use of saliency by the right TPJ. *Neuroimage* **52**, 934-946.

101. Krajbich I, Hare T, Bartling B *et al.* (2015) A common mechanism underlying food choice and social decisions. *PLoS Comput Biol.* **11**(10):e1004371.