

## 70th Anniversary Conference on ‘Body weight regulation – food, gut and brain signalling’

### Symposium III: Brain signalling and onwards communications

#### Food-induced brain responses and eating behaviour

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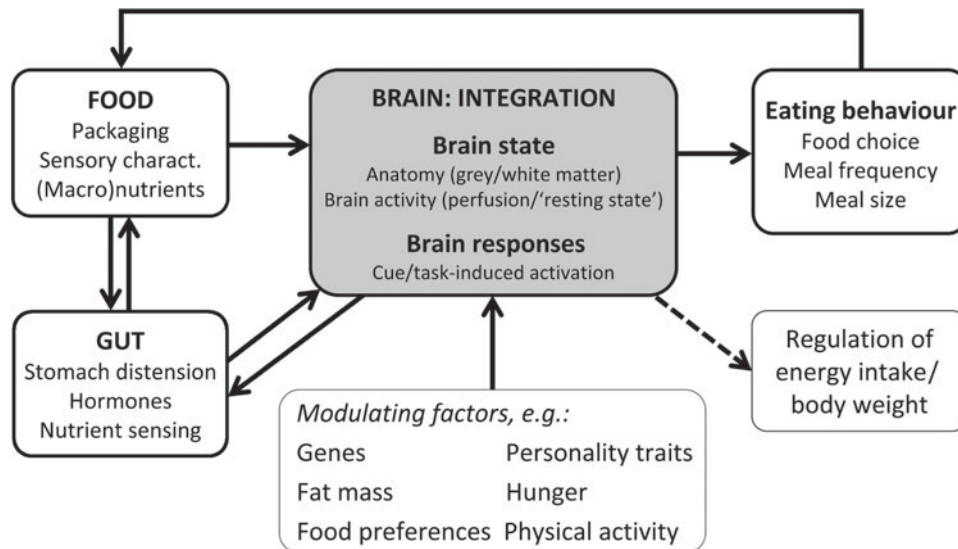
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The brain governs food intake behaviour by integrating many different internal and external state and trait-related signals. Understanding how the decisions to start and to stop eating are made is crucial to our understanding of (maladaptive patterns of) eating behaviour. Here, we aim to (1) review the current state of the field of ‘nutritional neuroscience’ with a focus on the interplay between food-induced brain responses and eating behaviour and (2) highlight research needs and techniques that could be used to address these. The brain responses associated with sensory stimulation (sight, olfaction and taste), gastric distension, gut hormone administration and food consumption are the subject of increasing investigation. Nevertheless, only few studies have examined relations between brain responses and eating behaviour. However, the neural circuits underlying eating behaviour are to a large extent generic, including reward, self-control, learning and decision-making circuitry. These limbic and prefrontal circuits interact with the hypothalamus, a key homeostatic area. Target areas for further elucidating the regulation of food intake are: (eating) habit and food preference formation and modification, the neural correlates of self-control, nutrient sensing and dietary learning, and the regulation of body adiposity. Moreover, to foster significant progress, data from multiple studies need to be integrated. This requires standardisation of (neuroimaging) measures, data sharing and the application and development of existing advanced analysis and modelling techniques to nutritional neuroscience data. In the next 20 years, nutritional neuroscience will have to prove its potential for providing insights that can be used to tackle detrimental eating behaviour.

#### Functional MRI: Eating behaviour: Peptide hormones: Personality characteristics

Food is required for survival and therefore is a primary reward. Abundance of food has become a greater problem than food shortage: the number of overweight and obese people exceeds that of those suffering from under-nutrition<sup>(1)</sup>. Obesity is driven by rapid changes in our food environment<sup>(2,3)</sup> which promote overeating. Such eating behaviour is maladaptive in the longer term. This review addresses the interactions between foods, the gut and the brain, which give rise to eating behaviour (Fig. 1). With ‘eating behaviour’ we refer to food choice, meal frequency

and meal size (where a ‘meal’ includes eating occasions such as eating a snack food or drinking something energetic). Eating behaviour is determined by eating decisions, namely what to eat, when to start and when to stop eating. These decisions are taken in the brain, which integrates a multitude of neural and hormonal signals reflecting internal state and the environment. They determine diet nutrient composition, eating frequency and portion size, i.e., a person’s diet. Understanding how eating decisions come about is crucial for understanding maladaptive patterns of



**Fig. 1.** Schematic representation of food–gut–brain interactions in relation to eating behaviour together with modulators of brain structure and function. Note that both brain state and brain responses can be affected by trait as well as state factors. Sensory charact., Sensory characteristics.

eating behaviour and improvement of their prevention and remediation. Note that eating decisions are usually not made (entirely) consciously, nor are they necessarily the result of ‘free will’ (see<sup>(4)</sup>).

Relatively recently, neuroimaging techniques such as positron-emission tomography and MRI have enabled studying the brain *in vivo*. The beauty of MRI is its versatility: many different types of measurements can be obtained with the same machine. In brain research, the most commonly used types of MRI scans are: anatomical scans, showing e.g. grey and white matter; functional (f) MRI scans, either obtained during a task such as looking at food images or during ‘rest’ (resting state fMRI, see<sup>(5)</sup>), or perfusion scans, which use arterial spin labelling techniques to obtain a semi-quantitative measure of cerebral blood flow; and diffusion-tensor imaging scans, which yield images of the white matter tracts. The most widely used fMRI technique is blood-oxygen level dependent fMRI<sup>(6)</sup>. This form of fMRI exploits the fact that at a site of increased neuronal firing (brain activation), increased local blood flow leads to a decreased concentration of deoxygenated Hb. This in turn attenuates the local distortion of the magnetic field by deoxygenated Hb, which is paramagnetic, and leads to a small increase in the fMRI signal (about 0.5–4%). Only a small percentage of all fMRI studies involve food-induced brain responses; however, a great deal of neuroscientific work has addressed brain systems intimately involved in, or relevant for, eating behaviour. This includes the neurophysiology and functional neuroanatomy of e.g. sensory perception, reward, emotion and decision-making.

Neuroimaging techniques can be used to measure (changes in) brain state (anatomy, resting state) as well as food cue-induced brain responses. These brain characteristics are affected by multiple trait as well as state factors, such as sex, age and BMI, which in turn modulate eating

behaviour (Fig. 1). Understanding how eating behaviour is produced requires the integration of neuroimaging data with physiological, psychological and behavioural measures. In particular, linking brain measures to eating behaviour is necessary to be able to interpret neuroimaging findings and assess their real life relevance. Later, we will review the human neuroimaging literature on the interactions between food, gut, brain and eating behaviour and highlight research needs and techniques that could be used to foster progress.

### Food–brain interaction

All senses are involved in the perception of foods and the regulation of food intake. Food perception induces innate and learned autonomic anticipatory physiological responses, which are referred to as cephalic phase responses (for reviews see<sup>(7,8)</sup>). In addition to cephalic phase responses, the sensory perception of a food before and during consumption induces numerous brain responses governing food choice and food intake behaviour. Eventually, this results in meal termination and possibly satiety. Of course, once ingestion has started, gastrointestinal neural and hormonal signals also start to contribute. Summaries and detail on the basic processing of food stimuli in the brain can be found in several reviews and meta-analyses addressing visual food stimuli (food images)<sup>(9)</sup>, odour<sup>(10)</sup>, taste<sup>(11,12)</sup> and flavour (taste, odour and somatosensory stimulation)<sup>(13,14)</sup>.

A well-known phenomenon driven by cephalic stimulation is sensory-specific satiety<sup>(15)</sup>. Sensory-specific satiety has been demonstrated in the human orbitofrontal cortex for *ad libitum* consumption<sup>(16,17)</sup>. However, further investigation is needed in order to disentangle liking and wanting effects (see e.g.<sup>(18)</sup>), and assess correlations with eating

behaviour (rather than subjective ratings) when there is no *ad libitum* consumption. Under such conditions it has proven hard to observe sensory-specific satiety effects in the brain<sup>(19)</sup>.

fMRI studies have shown that anticipation of consumption (food reward) and subsequent consumption (reward receipt) recruit partially different brain areas<sup>(20–23)</sup>. The distinction between reward anticipation and reward receipt processing in the brain is particularly relevant for a deeper understanding of aberrant responses to food cues since these could be driven by abnormalities in either one of these processes. For example, neuroimaging studies have shown not only diminished striatal responsivity to reward receipt in obese subjects<sup>(24,25)</sup> but also hyper-responsivity to both anticipation and consumption of palatable food in somatosensory, gustatory and reward valuation regions<sup>(26)</sup>. Interestingly, a recent study found that the association between brain reward responsivity to imagined consumption and weight gain is modulated by genotype<sup>(27)</sup>.

There can be strong cognitive effects, so-called top-down effects, on food perception and eating behaviour, and this is also studied with functional neuroimaging. A growing number of studies has addressed effects of (selective) attention to specific product characteristics, such as taste and healthiness<sup>(28,29)</sup>. Other studies involve neuroimaging of the effects of product appearance or product labels<sup>(26,30)</sup>. These topics are addressed further under section ‘Cognitive effects’.

### Gut–brain interaction

The brain receives input from the viscera, including the gastrointestinal tract, and adipose tissue by way of multiple neural and hormonal signals. Most neural information is transmitted by the afferent part of the vagus nerve, which projects to the brain stem where vagal input from each visceral organ is directed to particular subnuclei of the nucleus of the solitary tract as well as integrated with input from other brain regions which regulate autonomic functions and homeostasis<sup>(31,32)</sup>. In addition, many gut peptides and other hormones such as leptin act on vagal afferents, brainstem nuclei and higher brain regions, in particular the hypothalamus, exerting both acute and long-term effects on the regulation of food intake and body weight<sup>(33,34)</sup>. Later, work on the relations between stomach distension and hormones and the human brain is reviewed (for detailed reviews of the latter, see<sup>(35,36)</sup>).

### Stomach distension

An important determinant of meal termination and satiety is stomach distension by the volume (and weight) of food<sup>(37,38)</sup>. To date, surprisingly little studies have investigated the neural correlates of non-painful stomach distension. In neuroimaging studies in which the stomach was distended with a gastric balloon, activation was observed in the brainstem, insula, amygdala, posterior insula, left inferior frontal gyrus and anterior cingulate cortex<sup>(39,40)</sup>. Moreover, the response in the left amygdala and insula correlated negatively with changes in fullness and positively

with changes in plasma ghrelin<sup>(40)</sup>. In addition, Wang *et al.*<sup>(40)</sup> found that subjects with a higher BMI had a diminished responsivity to stomach distension in the right amygdala and insula. They interpret this as a greater insensitivity to stomach fullness. However, it is hard to rule out differences in stomach volume, which would affect the degree of stretch induced in the stomach wall. Also, a recent animal study has suggested that effects of food-like stomach distension on brain activity may in part be attributable to concomitant transient increases in blood pressure<sup>(41)</sup>. Future studies should ideally combine fMRI measures of brain activation with MRI measures of gastric volume and data on gastric pressure and stomach emptying, in the case of gastric loads (see e.g.<sup>(42)</sup>).

### Hormones

For studying hormone–brain interaction, there are several options that are only beginning to be explored. The first is to assess which brain areas respond to a particular hormone by infusing it intravenously and assessing effects on baseline brain activity as well as on task-induced activation, e.g., tasting, smelling, or looking at foods. The same can be done by correlating such brain responses to baseline serum concentrations of hormones or to hormone responses induced by a nutrient load. Such experiments have been done for Peptide YY<sup>(43)</sup>, cholecystokinin<sup>(44,45)</sup>, insulin<sup>(46–48)</sup>, glucagon-like peptide 1<sup>(49)</sup>, ghrelin<sup>(50,51)</sup> and leptin<sup>(52–54)</sup>. Most of these studies do not link brain (and hormone) responses to actual eating behaviour and this constitutes an important research gap that needs to be addressed if we are to understand the complex interaction between the gut and the brain in relation to (aberrant) eating behaviour. Similarly, the neural effects of ‘anti-obesity’ drugs can and should be assessed not only in animals<sup>(55)</sup> but as far as possible also in human subjects (see e.g.<sup>(56)</sup>).

### Modulating factors

Evidently, there are many, often interrelated, factors which affect the brain response to food cues and ensuing eating behaviour (Fig. 1). Very basic ones are age, sex, BMI and internal state (hunger/satiety). Both age and sex affect brain structure and function, as well as eating behaviour. More specifically, there are many studies showing sex effects on the responses to food, e.g.<sup>(57–61)</sup>, and interactions between sex and internal state<sup>(58,61)</sup>. Of course, internal state modulates the (brain) response to food, see e.g.<sup>(9,18,62,63)</sup>, as well as ‘resting’ brain activity (brain perfusion)<sup>(64,65)</sup>.

Many functional studies have shown differences between lean and obese subjects (e.g.<sup>(24–26)</sup>) or correlations between brain responses and BMI (e.g.<sup>(40,66)</sup>). In addition, studies looking at grey and white matter volumes (voxel-based morphometry studies) have reported effects of BMI<sup>(67–70)</sup>. For example, in obese adults, lower grey matter density was found in brain areas involved in taste perception, reward and behavioural control<sup>(69)</sup>. Moreover, several studies have linked brain morphology, in particular

impairments in the orbitofrontal cortex, with cognitive performance and eating behaviour<sup>(71,72)</sup>. To a large extent, it remains to be determined in how far structural and functional differences between lean and obese subjects are cause or effect, and in how far they are reversible. For example, one study demonstrated that brain measures show partial structural recovery with weight loss<sup>(73)</sup>; however, a functional study has suggested that aberrant responses to food cues persist after weight loss<sup>(74)</sup>. In line with this, hormone levels continue to deviate in post-obese subjects up to 1 year after weight loss<sup>(75)</sup>.

#### *Genetic effects*

Although functional neuroimaging appears to be a powerful tool to investigate the relations between genes, the brain and behaviour, and many polymorphisms have been implicated in obesity, only few neuroimaging studies have addressed specific polymorphisms implicated in body weight control<sup>(25,27)</sup> (both on dopamine receptor polymorphisms). A primary reason for this may be that it is hard to obtain enough suitable subjects. An indirect way of selecting for a particular genotype (usually involving multiple genes) may be to select extreme phenotypes<sup>(76)</sup>. This is in fact what one does, albeit in a crude way, by selecting on extreme BMI. Thus, it may be worthwhile to select on more specific or additional (endo)phenotypic characteristics, such as personality characteristics or measures of eating behaviour. For example, it was shown that cholecystokinin and leptin (receptor) polymorphisms are associated with meal size and snacking frequency<sup>(77)</sup>, which makes these behavioural measures potential selection criteria for a genotype associated with 'overeating'.

#### *Personality characteristics*

Evidence is mounting that variation in brain responses can be explained by differences in personality characteristics<sup>(78,79)</sup>. Nevertheless, in spite of neural differences the observed behaviour can be the same<sup>(19,79)</sup>. For example, Diekhof *et al.*<sup>(79)</sup> found that the same behavioural performance was subserved by different neural responses in highly impulsive and highly controlled individuals during a task in which subjects were required to decline immediate rewards.

There are several personality characteristics relevant for eating behaviour. These include reward sensitivity, impulsivity and inhibitory potential. How such personality characteristics affect food-induced brain responses has hardly been investigated (one exception is<sup>(80)</sup> on reward sensitivity). All of them have a bearing on self-regulation capacity and specifically on the ability to resist immediate reward in favour of a longer-term benefit, i.e., on the ability to delay gratification. The neural correlates of self-control, in particular in the food domain, have only been started to be addressed recently<sup>(81,82)</sup> and the brain mechanisms underlying conscious as well as unconscious self-control and inter-individual differences therein need to be explored in more detail. This constitutes an important research area since knowledge on these mechanisms, in particular those underlying effortless self-control<sup>(83)</sup>, could

be used to develop more effective ways of improving self-control so as to empower individuals to make healthier food choices.

#### *Cognitive effects*

Numerous studies show that food characteristics, such as appearance, packaging characteristics (e.g. labelling) and price, can strongly affect expectations, sensory perception and (eating) behaviour (e.g.<sup>(30,84,85)</sup>). Not surprisingly, this is also apparent in the brain. For example, changing the price label of a wine alters perceived pleasantness as well as taste activation in the medial orbitofrontal cortex<sup>(30)</sup>. The nature and extent of such cognitive effects may depend on subject characteristics such as BMI or dietary restraint. For example, a low-fat label increased snack intake more in overweight than in lean subjects<sup>(85)</sup>. Product features affecting perceived healthiness and thereby eating behaviour are of great interest because of their bearing on healthier eating patterns. Nevertheless, such features have only begun to be investigated explicitly on the brain level<sup>(26,28,81)</sup>.

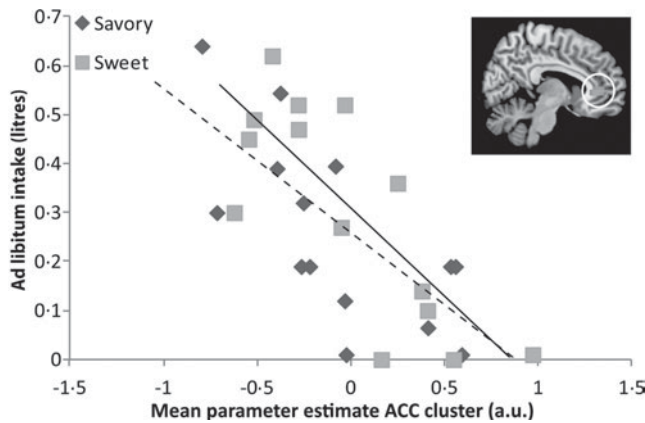
Another type of cognitive effect is that of (selective) attention (and distraction) on food-induced brain responses and eating behaviour. Many fMRI studies have shown that selective attention increases brain activation in specific areas for taste<sup>(86–88)</sup>, odour<sup>(88,89)</sup> and food images<sup>(60,66)</sup>. So far, attention effects on brain responses remain to be correlated with eating behaviour (but see e.g.<sup>(66)</sup> on BMI), although evidence from non-imaging studies suggests that such correlations should exist. At the same time, these findings underscore that task design and task instruction can have strong attention-related effects on fMRI results (see also<sup>(90)</sup>).

#### **Do brain measures predict eating behaviour?**

Neuroimaging studies in which brain responses are correlated with eating behaviour are fairly scarce. Apart from the fact that such correlations may be beyond the scope of the study and increase study complexity, there are several interrelated factors that hamper their study. A principal one is sample size: behavioural studies tend to require more subjects than brain studies and scaling up a brain study can be costly. Furthermore, not only may behavioural measures show considerable variability, the same is true for imaging measures, which makes their combination prone to low statistical power. This can be ameliorated by stringent selection criteria, good fMRI task design and use of dedicated scan sequences. Note, however, that accurate power calculations in fMRI are far from straightforward, among others because many factors are in play, pertaining to hardware specifications, the scan sequence used, experimental design and subject characteristics.

#### *Food choice*

Of the eating behaviours defined earlier, food choice, although perhaps not entirely realistic in an MRI environment (or any other laboratory environment), is relatively easy to investigate provided that visual stimuli are used.



**Fig. 2.** Example of a correlation between food-induced brain responses and eating behaviour. The scattergram shows the association between taste-induced brain responses in the anterior cingulate after a 350-ml juice preload and subsequent *ad libitum* juice intake. Sweet: fruit juice (solid line),  $r$  0.78; Savoury: tomato juice (dashed line),  $r$  0.70. Adapted version of a figure from<sup>(18)</sup>.

Basically, there are three types of choice paradigms that have been employed in the food domain: choice (yes/no) for single food items<sup>(28,81,91)</sup>, forced choice from two options<sup>(92)</sup> (using liquids), and choice from a set of options (a menu)<sup>(93,94)</sup>. In addition to the relatively small number of studies specifically addressing food choices there is much brain research on decision making and the trade-off between different rewards and types of reward (see e.g.<sup>(95)</sup>). In decision neuroscience, the idea that there is a common currency in the brain for different types of reward has received much empirical support<sup>(95)</sup>; however, there is evidence that in addition to common areas reflecting stimulus reward value (ventromedial prefrontal cortex and striatum), there are specific brain areas involved in encoding the reward value of primary (food: hypothalamus) and secondary (money: posterior cingulate) rewards<sup>(96)</sup>.

#### Meal onset

Meal onset is hard to measure in an fMRI paradigm, thus, to our knowledge there are no studies addressing this. There is a fair amount of work though on anticipation and subsequent consumption of foods, as mentioned earlier.

#### Food intake

To date, only a few studies with different types of stimuli have correlated brain responses with subsequent food intake<sup>(18,43,91)</sup>. An example is shown in Fig. 2. It seems logical that it is harder to predict intake from anticipatory responses, e.g., responses to food images than from consummatory responses (i.e., tasting, such as in<sup>(18)</sup>, Fig. 2). In any case, such studies should be replicated and extended in order to establish whether there are neural markers for general and food-specific appetite. Note that single meals are fairly irrelevant for long-term weight and health outcomes<sup>(97,98)</sup>. Therefore, such laboratory studies need to be complemented with data on actual dietary behaviour. Indeed, it is of great interest to find neural markers for

dietary behaviour. Recent studies indicate that this is feasible on the level of BMI: brain reactivity to high-energy foods was found to predict 3-month and 9-month outcome in a weight-loss programme<sup>(99)</sup> and less activation in prefrontal areas during a monetary delayed discounting task predicted a greater rate of weight gain over the next 1–3 years<sup>(82)</sup>. This shows the potential of neuroimaging measures for subject profiling. The next step would be to use this information to improve preventive strategies or treatment.

#### Better value for research money

Ultimately, one wants to be able to model eating behaviour of an individual in specific contexts, i.e., be able to predict behaviour resulting from the integration of a great array of input signals with a particular set of state and trait characteristics in a brain model. Such a model system would enable improved design of prevention strategies, interventions and treatment of maladaptive patterns of eating behaviour. This requires combining data from multiple studies, which is something that can increase the scientific yield from research in general and neuroimaging studies in particular. For this one needs the following.

#### Standardisation of measures

In order to facilitate pooling of data, meta-analysis and reduced variability between studies, standardisation of measures is required. Specifically, one could agree on a basic set of measures that is acquired from every subject. In addition, one can then add custom measures tuned to the specific experiment at hand. Basic measures could be, e.g., relevant subject characteristics, beyond already common ones such as sex, age, and BMI. Furthermore, for neuroimaging experiments standardisation of data acquisition, pre-processing and analysis would help to increase consistency<sup>(100)</sup>. In addition, it would be helpful if the same (validated) fMRI tasks or the same food stimuli were used for measuring responses to food stimuli or other relevant brain responses such as those related to reward sensitivity or impulsivity. A long-standing example is the International Affective Picture System, a database of >700 pictures<sup>(101,102)</sup>. Similarly, we are striving to set up a food picture database.

#### Data sharing

Existing datasets can be exploited further by pooling them, such that variation attributable to measures of interest can be separated from noise and variance resulting from differences in methodology and factors of no interest. The value of a database, whether it contains brain scans or other data, depends on the associated meta-data, such as relevant subject characteristics. Some types of MRI data are easier to share than others; it is relatively easy to share resting state and anatomical data, and this is already fairly well established. The idea to share neuroimaging data (and link databases) is already more than 10 years old<sup>(103,104)</sup>. Nowadays, there are more and more data sharing initiatives and databases are growing week by week. Examples are

the International Neuroimaging Data-Sharing Initiative 1000 Functional Connectomes Project (holding resting state data), Open Access Series of Imaging Studies (holding structural MRI data). Proponents of data sharing have demonstrated the benefits<sup>(5,105)</sup> and there is growing interest in data sharing in the neuroimaging community. Concurrently, tools for data sharing and management such as COINS (Collaborative Informatics and Neuroimaging Suite)<sup>(106)</sup> and XNAT (Extensible Neuroimaging Archive Toolkit)<sup>(107)</sup> are under intense development. Unfortunately, for nutritional neuroscientists, these databases are unlikely to contain food-specific meta-data, although they will contain meta-data relevant for food scientists and neuroscientists alike, such as age and sex.

#### *Application and development of (meta)analysis and modelling techniques*

Many, if not all, of the meta-analysis and modelling techniques employed or to be employed to neuroimaging and food science data build on existing algorithms or techniques used in other fields. Several techniques of interest are as follows.

*Activation-likelihood estimation meta-analysis.* Activation-likelihood estimation (ALE) meta-analysis is a technique used to assess common ground between neuroimaging studies on the same task, process or anatomic region. It is a so-called voxel-based meta-analysis technique that determines concurrence in reported peak coordinates between studies<sup>(108,109)</sup>. It is considered to be much more accurate than previous methods, such as counting anatomical labels. However, the concurrence measure (ALE-value) is based on peak proximity and does not take statistical significance of the reported peak voxel into account (e.g., the Z-score) and/or size of the cluster of significant voxels surrounding the peak voxel, or the number of contributing studies. Unfortunately, many ALE meta-analyses fail to report the number of studies/foci contributing to significant clusters. This makes it harder to assess the generalisability of reported clusters, e.g. as in<sup>(12)</sup>. When more studies contribute to an ALE-cluster, more credible or at least generic it is. We addressed this limitation in a meta-analysis of the brain response to food pictures<sup>(9)</sup>, by ranking clusters on the number of contributing studies. Surprisingly, few clusters (only four) survived a criterion of >33% contributing studies. We anticipate that ALE-meta-analysis will be further developed in the near future so as to overcome its current limitations.

*Multivariate pattern analysis.* Classic neuroimaging analysis is ‘mass univariate’: every voxel is tested separately, creating the need to correct for multiple comparisons (there are approximately 25,000 brain voxels in a brain sampled in 4 × 4 × 4 mm voxels). In the 2000s, neuroscientists began to employ multivariate classification algorithms to fMRI data<sup>(110–112)</sup>. The main characteristic of multivariate pattern analysis (MVPA) is that patterns of activation are analysed instead of single-voxel responses. More specifically, a mathematical model that incorporates the associations between voxel values is used to differentiate between conditions. Several algorithms can be used

as the basis of such a model, e.g., support vector machines or simple linear regression. After training the model with a subset of the data, the model can be used to predict responses in other trials. MVPA has been used for ‘brain reading’ or decoding of patterns of activation, such as predicting what a person is looking at from the pattern of activation in the visual cortex<sup>(110,111)</sup>. Another application is the attempt to try and predict subsequent (choice) behaviour from fMRI data obtained during exposure to certain cues<sup>(113)</sup>, i.e., choice prediction as is commonly done in neuromarketing<sup>(114)</sup>. As far as we know, only one study applied MVPA to food choices, so as to predict choice from brain responses to viewing products differing in packaging characteristics<sup>(115)</sup>. However, the use of MVPA will undoubtedly continue to grow, in particular because MVPA analysis tools have become much more accessible.

*Bayesian network modelling.* Bayesian network modelling is a modelling technique complementary to classical statistical analysis. A Bayesian network is a probabilistic graphical model, also referred to as a ‘belief network’ or a ‘causal probabilistic network’. Expert knowledge can be used to create network structure and, subsequently, data can be used to calculate the parameters describing the strength of the relations between network nodes. Bayesian networks can learn by the addition of new data. Moreover, by changing specific parameters in the network possible outcomes can be assessed. Alternatively, based on new data the most likely outcomes can be inferred<sup>(116)</sup>. Despite a wide application of Bayesian networks in other fields<sup>(117)</sup>, the application to food science is new. A layman’s introduction to Bayesian networks and an outline of potential applications in the food domain have been provided recently by Phan *et al.*<sup>(118)</sup>. Particularly interesting is the potential to be able to assess product characteristics such as pleasantness, while manipulating other characteristics such as taste or odour intensity or physical product characteristics affecting such characteristics. For example, Phan *et al.* demonstrated how a combined network model of two different studies measuring determinants of the *ad libitum* intake of a tomato soup can provide additional insights into the process of satiation<sup>(119)</sup>. However, as they indicate there are still significant methodological obstacles that need to be addressed, in particular to facilitate the combination of data from different studies into one model. Ideally, studies should be designed with the integration of data already in mind, i.e., within the broader scope of a wider encompassing model. This will involve obtaining information beyond the scope of single studies, such that the same measures are available from all studies whose data are to be merged, i.e., standardisation. If this is not done, systematic missing data in the combined database will lead to unreliable parameter estimation<sup>(119)</sup>.

The incorporation of neuroimaging data seems to be quite a step further, although at present it would seem feasible to employ summary measures of imaging data, e.g. responses in a particular region of interest the brain in a Bayesian network model, in addition to or instead of e.g. subjective ratings. The next step would be to incorporate spatial and/or temporal patterns of brain activation,

perhaps by using classifier algorithms or independent component analysis to summarise subject's brain responses.

### Future directions

To progress more efficiently in food research in general, and neuroimaging in particular, needs standardisation of measurements, data sharing (neuroimaging data+meta-data), and the application and further development of analysis and modelling techniques to exploit large heterogeneous datasets. While single studies are certainly necessary, data sharing holds great promise for elucidating the effects of multiple factors on eating behaviour. The integration of a wide array of data, ranging from genetic and hormone data to psychological characterisations is needed to be able to assess the effects of manipulations aimed at e.g. changing eating behaviour within a complex of myriad interactions. A first step in this direction would be to create a test battery for profiling individuals so as to steer personalised interventions aimed at changing eating habits.

As yet ill-explored neuroscience research topics that hold great potential for enabling healthier patterns of eating behaviour are (eating) habit and food preference formation, (eating) habit modification, and the neural mechanisms underlying self-control (in particular delayed gratification). Related relevant research topics that have received relatively little or no attention in human nutritional neuroscience are nutrient sensing, dietary learning and the regulation of body adiposity (see<sup>(120)</sup>). In the next 20 years, nutritional neuroscience will have to prove its potential for providing insights that can be used to tackle detrimental eating behaviour.

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### References

1. Reworking the Global Food System (2011). World Disasters Report 2011 – Focus on Hunger and Malnutrition. International Federation of Red Cross and Red Crescent Societies, pp. 10–35.
2. Eaton SB & Eaton SB, III (2000) Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr* **39**, 67–70.
3. Speakman JR (2004) Obesity: the integrated roles of environment and genetics. *J Nutr* **134**, 8 Suppl., 2090S–2105S.
4. Levitsky DA & Pacanowski CR (2012) Free will and the obesity epidemic. *Public Health Nutr* **15**, 126–141.
5. Biswal BB (2012) Resting state fMRI: a personal history. *Neuroimage* **62**, 638–644.
6. Smith K (2012) Brain imaging: fMRI 2.0. *Nature* **484**, 24–26.
7. Zafra MA, Molina F & Puerto A (2006) The neural/cephalic phase reflexes in the physiology of nutrition. *Neurosci Biobehav Rev* **30**, 1032–1044.
8. Smeets PA, Erkner A & De Graaf C (2010) Cephalic phase responses and appetite. *Nutr Rev* **68**, 643–655.
9. van der Laan LN, de Ridder DT, Viergever MA *et al.* (2010) The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. *Neuroimage* **55**, 296–303.
10. Wilson DA & Sullivan RM (2011) Cortical processing of odor objects. *Neuron* **72**, 506–519.
11. Small DM (2006) Central gustatory processing in humans. *Adv Otorhinolaryngol* **63**, 191–220.
12. Veldhuizen MG, Albrecht J, Zelano C *et al.* (2011) Identification of human gustatory cortex by activation likelihood estimation. *Hum Brain Mapp* **32**, 2256–2266.
13. Lundstrom JN, Boesveldt S & Albrecht J (2011) Central processing of the chemical senses: an overview. *ACS Chem Neurosci* **2**, 5–16.
14. Small DM (2012) Flavor is in the brain. *Physiol Behav* (In Press).
15. Rolls BJ, Rolls ET, Rowe EA *et al.* (1981) Sensory specific satiety in man. *Physiol Behav* **27**, 137–142.
16. O'Doherty J, Rolls ET, Francis S *et al.* (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. *Neuroreport* **11**, 893–897.
17. Ringelbach ML, O'Doherty J, Rolls ET *et al.* (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb Cortex* **13**, 1064–1071.
18. Spetter MS, de GC, Viergever MA *et al.* (2012) Anterior cingulate taste activation predicts *ad libitum* intake of sweet and savory drinks in healthy, normal-weight men. *J Nutr* **142**, 795–802.
19. Smeets PA, Weijzen P, de GC *et al.* (2011) Consumption of caloric and non-caloric versions of a soft drink differentially affects brain activation during tasting. *Neuroimage* **54**, 1367–1374.
20. Bohon C, Stice E & Spoor S (2009) Female emotional eaters show abnormalities in consummatory and anticipatory food reward: a functional magnetic resonance imaging study. *Int J Eat Disord* **42**, 210–221.
21. Small DM, Veldhuizen MG, Felsted J *et al.* (2008) Separable substrates for anticipatory and consummatory food chemosensation. *Neuron* **57**, 786–797.
22. O'Doherty JP, Deichmann R, Critchley HD *et al.* (2002) Neural responses during anticipation of a primary taste reward. *Neuron* **33**, 815–826.
23. O'Doherty JP (2004) Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol* **14**, 769–776.
24. Wang GJ, Volkow ND, Logan J *et al.* (2001) Brain dopamine and obesity. *Lancet* **357**, 354–357.
25. 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.
26. Ng J, Stice E, Yokum S *et al.* (2011) An fMRI study of obesity, food reward, and perceived caloric density. Does a low-fat label make food less appealing? *Appetite* **57**, 65–72.
27. Stice E, Yokum S, Bohon C *et al.* (2010). Reward circuitry responsiveness to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. *Neuroimage* **50**, 1618–1625.

28. 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.
29. Grabenhorst F, Rolls ET & Bilderbeck A (2008) How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. *Cereb Cortex* **18**, 1549–1559.
30. Plassmann H, O'Doherty J, Shiv B *et al.* (2008) Marketing actions can modulate neural representations of experienced pleasantness. *Proc Natl Acad Sci USA* **105**, 1050–1054.
31. Travagli RA, Hermann GE, Browning KN *et al.* (2006) Brainstem circuits regulating gastric function. *Annu Rev Physiol* **68**, 279–305.
32. Browning KN & Travagli RA (2011) Plasticity of vagal brainstem circuits in the control of gastrointestinal function. *Auton Neurosci* **161**, 6–13.
33. Schwartz MW (2006) Central nervous system regulation of food intake. *Obesity (Silver Spring)* **14**, Suppl. 1, 1S–8S.
34. Berthoud HR (2002) Multiple neural systems controlling food intake and body weight. *Neurosci Biobehav Rev* **26**, 393–428.
35. Gibson CD, Carnell S, Ochner CN *et al.* (2010) Neuroimaging, gut peptides and obesity: novel studies of the neurobiology of appetite. *J Neuroendocrinol* **22**, 833–845.
36. Schloegl H, Percik R, Horstmann A *et al.* (2011) Peptide hormones regulating appetite-focus on neuroimaging studies in humans. *Diabetes Metab Res Rev* **27**, 104–112.
37. Rolls BJ & Roe LS (2002) Effect of the volume of liquid food infused intragastrically on satiety in women. *Physiol Behav* **76**, 623–631.
38. Powley TL & Phillips RJ (2004) Gastric satiation is volumetric, intestinal satiation is nutritive. *Physiol Behav* **82**, 69–74.
39. Stephan E, Pardo JV, Faris PL *et al.* (2003) Functional neuroimaging of gastric distention. *J Gastrointest Surg* **7**, 740–749.
40. Wang GJ, Tomasi D, Backus W *et al.* (2008) Gastric distention activates satiety circuitry in the human brain. *Neuroimage* **39**, 1824–1831.
41. Min DK, Tuor UI & Chelikani PK (2011) Gastric distention induced functional magnetic resonance signal changes in the rodent brain. *Neuroscience* **179**, 151–158.
42. Kwiatek MA, Menne D, Steingoetter A *et al.* (2009) Effect of meal volume and calorie load on postprandial gastric function and emptying: studies under physiological conditions by combined fiber-optic pressure measurement and MRI. *Am J Physiol Gastrointest Liver Physiol* **297**, G894–G901.
43. Batterham RL, ffytche DH, Rosenthal JM *et al.* (2007) PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature* **450**, 106–109.
44. Dockray GJ (2012) Cholecystokinin. *Curr Opin Endocrinol Diabetes Obes* **19**, 8–12.
45. Lassman DJ, McKie S, Gregory LJ *et al.* (2010) Defining the role of cholecystokinin in the lipid-induced human brain activation matrix. *Gastroenterology* **138**, 1514–1524.
46. Guthoff M, Grichisch Y, Canova C *et al.* (2010) Insulin modulates food-related activity in the central nervous system. *J Clin Endocrinol Metab* **95**, 748–755.
47. Kroemer NB, Krebs L, Kobiella A *et al.* (2012) (Still) longing for food: Insulin reactivity modulates response to food pictures. *Hum Brain Mapp* (In the Press).
48. Wallner-Liebmann S, Koschutnig K, Reishofer G *et al.* (2010) Insulin and hippocampus activation in response to images of high-calorie food in normal weight and obese adolescents. *Obesity (Silver Spring)* **18**, 1552–1557.
49. De Silva A, Salem V, Long CJ *et al.* (2011) The gut hormones PYY 3–36 and GLP-1 7–36 amide reduce food intake and modulate brain activity in appetite centers in humans. *Cell Metab* **14**, 700–706.
50. Malik S, McGlone F, Bedrossian D *et al.* (2008) Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab* **7**, 400–409.
51. Jones RB, McKie S, Astbury N *et al.* (2012) Functional neuroimaging demonstrates that ghrelin inhibits the central nervous system response to ingested lipid. *Gut* (In the Press).
52. Frank S, Heni M, Moss A *et al.* (2011) Leptin therapy in a congenital leptin-deficient patient leads to acute and long-term changes in homeostatic, reward, and food-related brain areas. *J Clin Endocrinol Metab* **96**, E1283–E1287.
53. Farooqi IS, Bullmore E, Keogh J *et al.* (2007) Leptin regulates striatal regions and human eating behavior. *Science* **317**, 1355.
54. Rosenbaum M, Sy M, Pavlovich K *et al.* (2008) Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest* **118**, 2583–2591.
55. Adan RA, Vanderschuren LJ & Fleur EI (2008) Anti-obesity drugs and neural circuits of feeding. *Trends Pharmacol Sci* **29**, 208–217.
56. Fletcher PC, Napolitano A, Skeggs A *et al.* (2010) Distinct modulatory effects of satiety and sibutramine on brain responses to food images in humans: a double dissociation across hypothalamus, amygdala, and ventral striatum. *J Neurosci* **30**, 14346–14355.
57. Frank TC, Kim GL, Krzemien A *et al.* (2010) Effect of menstrual cycle phase on corticolimbic brain activation by visual food cues. *Brain Res* **1363**, 81–92.
58. Frank S, Laharnar N, Kullmann S *et al.* (2010) Processing of food pictures: influence of hunger, gender and calorie content. *Brain Res* **1350**, 159–166.
59. Smeets PA, de Graaf C, Stafleu A *et al.* (2006) Effect of satiety on brain activation during chocolate tasting in men and women. *Am J Clin Nutr* **83**, 1297–1305.
60. Siep N, Roefs A, Roebroek A *et al.* (2009) Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behav Brain Res* **198**, 149–158.
61. Uher R, Treasure J, Heining M *et al.* (2006) Cerebral processing of food-related stimuli: effects of fasting and gender. *Behav Brain Res* **169**, 111–119.
62. Haase L, Cerf-Ducastel B & Murphy C (2009) Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety. *Neuroimage* **44**, 1008–1021.
63. Bragulat V, Dziedzic M, Bruno C *et al.* (2010) Food-related odor probes of brain reward circuits during hunger: a pilot FMRI study. *Obesity (Silver Spring)* **18**, 1566–1571.
64. Tataranni PA, Gautier JF, Chen K *et al.* (1999) Neuroanatomical correlates of hunger and satiety in humans using positron emission tomography. *Proc Natl Acad Sci USA* **96**, 4569–4574.
65. Small DM, Zatorre RJ, Dagher A *et al.* (2001) Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain* **124**, 1720–1733.
66. Yokum S, Ng J & Stice E (2011) Attentional bias to food images associated with elevated weight and future weight



- gain: an fMRI study. *Obesity (Silver Spring)* **19**, 1775–1783.
67. Raji CA, Ho AJ, Parikshak NN *et al.* (2010) Brain structure and obesity. *Hum Brain Mapp* **31**, 353–364.
  68. Ho AJ, Raji CA, Becker JT *et al.* (2011) The effects of physical activity, education, and body mass index on the aging brain. *Hum Brain Mapp* **32**, 1371–1382.
  69. Pannacciulli N, Del PA, Chen K *et al.* (2006) Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage* **31**, 1419–1425.
  70. Walther K, Birdsill AC, Glisky EL *et al.* (2010) Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp* **31**, 1052–1064.
  71. Cohen JI, Yates KF, Duong M *et al.* (2011) Obesity, orbitofrontal structure and function are associated with food choice: a cross-sectional study. *BMJ Open* **1**, e000175.
  72. Maayan L, Hoogendoorn C, Sweat V *et al.* (2011) Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity (Silver Spring)* **19**, 1382–1387.
  73. Haltia LT, Viljanen A, Parkkola R *et al.* (2007) Brain white matter expansion in human obesity and the recovering effect of dieting. *J Clin Endocrinol Metab* **92**, 3278–3284.
  74. DelParigi A, Chen K, Salbe AD *et al.* (2004) Persistence of abnormal neural responses to a meal in postobese individuals. *Int J Obes Relat Metab Disord* **28**, 370–377.
  75. Sumithran P, Prendergast LA, Delbridge E *et al.* (2011) Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* **365**, 1597–1604.
  76. Nebert DW (2000) Extreme discordant phenotype methodology: an intuitive approach to clinical pharmacogenetics. *Eur J Pharmacol* **410**, 107–120.
  77. De Krom M, van der Schouw YT, Hendriks J *et al.* (2007) Common genetic variations in CCK, leptin, and leptin receptor genes are associated with specific human eating patterns. *Diabetes* **56**, 276–280.
  78. Miller MB, Donovan CL, Bennett CM *et al.* (2012) Individual differences in cognitive style and strategy predict similarities in the patterns of brain activity between individuals. *Neuroimage* **59**, 83–93.
  79. Diekhof EK, Nerenberg L, Falkai P *et al.* (2011) Impulsive personality and the ability to resist immediate reward: An fMRI study examining interindividual differences in the neural mechanisms underlying self-control. *Hum Brain Mapp* (In the Press).
  80. Beaver JD, Lawrence AD, van DJ *et al.* (2006) Individual differences in reward drive predict neural responses to images of food. *J Neurosci* **26**, 5160–5166.
  81. Hare TA, Camerer CF & Rangel A (2009) Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* **324**, 646–648.
  82. Kishinevsky FI, Cox JE, Murdaugh DL *et al.* (2012) fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite* **58**, 582–592.
  83. Fujita K (2011) On conceptualizing self-control as more than the effortful inhibition of impulses. *Pers Soc Psychol Rev* **15**, 352–366.
  84. Provencher V, Polivy J & Herman CP (2009) Perceived healthiness of food. If it's healthy, you can eat more! *Appetite* **52**, 340–344.
  85. Wansink B & Chandon P (2006) Can 'low-fat. nutrition labels lead to obesity? *J Mark Res* **43**, 605–617.
  86. Veldhuizen MG, Bender G, Constable RT *et al.* (2007) Trying to detect taste in a tasteless solution: modulation of early gustatory cortex by attention to taste. *Chem Senses* **32**, 569–581.
  87. Grabenhorst F & Rolls ET (2008) Selective attention to affective value alters how the brain processes taste stimuli. *Eur J Neurosci* **27**, 723–729.
  88. Veldhuizen MG & Small DM (2011) Modality-specific neural effects of selective attention to taste and odor. *Chem Senses* **36**, 747–760.
  89. Rolls ET, Grabenhorst F, Margot C *et al.* (2008) Selective attention to affective value alters how the brain processes olfactory stimuli. *J Cogn Neurosci* **20**, 1818–1826.
  90. Bender G, Veldhuizen MG, Meltzer JA *et al.* (2009) Neural correlates of evaluative compared with passive tasting. *Eur J Neurosci* **30**, 327–338.
  91. Born JM, Lemmens SG, Martens MJ *et al.* (2011) Differences between liking and wanting signals in the human brain and relations with cognitive dietary restraint and body mass index. *Am J Clin Nutr* **94**, 392–403.
  92. McClure SM, Ericson KM, Laibson DI *et al.* (2007) Time discounting for primary rewards. *J Neurosci* **27**, 5796–5804.
  93. Born JM, Lemmens SG, Rutters F *et al.* (2010) Acute stress and food-related reward activation in the brain during food choice during eating in the absence of hunger. *Int J Obes (Lond)* **34**, 172–181.
  94. Piech RM, Lewis J, Parkinson CH *et al.* (2010) Neural correlates of affective influence on choice. *Brain Cogn* **72**, 282–288.
  95. Peters J & Buchel C (2010) Neural representations of subjective reward value. *Behav Brain Res* **213**, 135–141.
  96. Levy DJ & Glimcher PW (2011) Comparing apples and oranges: using reward-specific and reward-general subjective value representation in the brain. *J Neurosci* **31**, 14693–14707.
  97. Booth DA & Nouwen A (2010) Satiety. No way to slim. *Appetite* **55**, 718–721.
  98. Smeets PA & van der Laan LN (2011) Satiety. not the problem, nor a solution. Comment on 'Satiety. No way to slim'. *Appetite* **57**, 772–773.
  99. Murdaugh DL, Cox JE, Cook EW, III *et al.* (2012) fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage* **59**, 2709–2721.
  100. Bennett CM & Miller MB (2010) How reliable are the results from functional magnetic resonance imaging? *Ann N Y Acad Sci* **1191**, 133–155.
  101. Lang PJ, Greenwald MK, Bradley MM *et al.* (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology* **30**, 261–273.
  102. Lang PJ, Bradley MM & Cuthbert BN (1999) *International Affective Picture System (IAPS): Technical Manual and Affective ratings*. Gainesville, FL: The Center for Research in Psychophysiology, University of Florida.
  103. Roland P, Svensson G, Lindeberg T *et al.* (2001) A database generator for human brain imaging. *Trends Neurosci* **24**, 562–564.
  104. Amari S, Beltrame F, Bjaalie JG *et al.* (2002) Neuroinformatics: the integration of shared databases and tools towards integrative neuroscience. *J Integr Neurosci* **1**, 117–128.
  105. Van Horn JD & Ishai A (2007). Mapping the human brain: new insights from fMRI data sharing. *Neuroinformatics* **5**, 146–153.
  106. Scott A, Courtney W, Wood D *et al.* (2011) COINS: an innovative informatics and neuroimaging tool suite built for large heterogeneous datasets. *Front Neuroinform* **5**, 33.
  107. Marcus DS, Olsen TR, Ramaratnam M *et al.* (2007) The extensible neuroimaging archive toolkit: an informatics

- platform for managing, exploring, and sharing neuroimaging data. *Neuroinformatics* **5**, 11–34.
108. Turkeltaub PE, Eden GF, Jones KM *et al.* (2002) Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* **16**, 765–780.
  109. Eickhoff SB, Laird AR, Grefkes C *et al.* (2009) Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp* **30**, 2907–2926.
  110. Haxby JV, Gobbini MI, Furey ML *et al.* (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* **293**, 2425–2430.
  111. Cox DD & Savoy RL (2003) Functional magnetic resonance imaging (fMRI) “brain reading”: detecting and classifying distributed patterns of fMRI activity in human visual cortex. *Neuroimage* **19**, 261–270.
  112. Mourao-Miranda J, Bokde AL, Born C *et al.* (2005) Classifying brain states and determining the discriminating activation patterns: support vector machine on functional MRI data. *Neuroimage* **28**, 980–995.
  113. Tusche A, Bode S & Haynes JD (2010) Neural responses to unattended products predict later consumer choices. *J Neurosci* **30**, 8024–8031.
  114. Ariely D & Berns GS (2010) Neuromarketing: the hope and hype of neuroimaging in business. *Nat Rev Neurosci* **11**, 284–292.
  115. van der Laan LN, de Ridder DT, Viergever MA *et al.* (2012) Appearance matters: Neural correlates of food choice and packaging aesthetics. *PLoS One* **7**, e41738. doi:10.1371/journal.pone.0041738.
  116. Hoffer EP, Feldman MJ, Kim RJ *et al.* (2005) DXplain: Patterns of Use of a Mature Expert System. *AMIA Annu Symp Proc* 321–325.
  117. Bayesian Networks (2008) *A Practical Guide to Applications*. New York: John Wiley & Sons Ltd.
  118. Phan VA, Garczarek U, Dekker M *et al.* (2010) Bayesian networks for food science: theoretical background and potential applications. In *Consumer-driven Innovation in Food and Personal Care Products*, pp. 488–513. [SR Jaeger, HJ MacFie, editors]. Cambridge: Woodhead Publishing Limited.
  119. Phan VA, Ramaekers MG, Bolhuis DP *et al.* (2012) On the use of Bayesian networks to combine raw data from related studies on sensory satiation. *Food Quality and Preference* **26**, 119–127.
  120. Speakman JR, Levitsky DA, Allison DB *et al.* (2011) Set points, settling points and some alternative models: theoretical options to understand how genes and environments combine to regulate body adiposity. *Dis Model Mech* **4**, 733–745.