Chapter

12

Basic Human Behaviours

Eating and Addiction

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12.1 Background

In 2016, 1.9 billion or 39% of all adults were overweight, and of these over 650 million were obese. The worldwide prevalence of obesity nearly tripled between 1975 and 2016. There are huge associated medical and socio-economic costs, including diabetes mellitus, cardiovascular disease, certain cancers and psychiatric morbidity. Prevalence rates of 29% obesity in UK adults have a consequent annual cost to the NHS of over £6 billion per year[1] and to the wider economy £27 billion per year. In people living with serious mental illness, rates of obesity are far higher (40%). Obesity is a major contributor to the mortality gap of 15–20 years observed in this population.

Arguably, the most important challenge in treating obesity *on an individual level* is not alleviating hunger or increasing satiation but finding a solution for the human association of food with positive affect and reward. The neural networks controlling our experience of reward and goal-directed behaviour are potently and primarily stimulated by food and especially high-energy-density food. Drugs commonly associated with addiction also happen to exert a rewarding effect on these same neural networks. This is thought to be through the firing of dopamine neurons in the ventral tegmental area, resulting in the release of dopamine into the nucleus accumbens and effects on the mesolimbic pathway, as well as the interaction of these on mu-opioid receptor pathways and areas of the brain associated with learnt behaviour.

In this chapter, we review the evidence for the effect of food on these pathways in the brain and the common neurobiological mechanisms that overlap food and drug addiction, and how this knowledge is informing different treatments for obesity or eating disorders.

The concept of food addiction is a much contested and debated subject. Although the idea has existed in scientific literature since 1956, there is no agreed definition or even agreement that it exists as a pattern of behaviour or that certain elements of food, such as sugar, fat or calories, have an inherently addictive quality. The DSM-5 (the tool recommended by the American Psychiatric Association for diagnosing mental illness) is the first version to include, under substance use disorders, a behavioural addiction, specifically gambling disorder. Internet gaming disorder and food addiction seem likely to follow, but at the moment these are indicated as areas for further research.

12.2 Measurement of Food Hedonics and Reward

Individual reactivity to palatable food is measured in several ways. For instance, the appeal and palatability of food can be measured by asking people to fill in a visual analogue scale or by using food preference or food choice paradigms.[2] Dietary records and questionnaires give information about food choice and actual dietary behaviour but suffer from the vagaries of being subjective in nature, and therefore subject to distortion by observation and underreporting.[3] This appears to be particularly true in the case of people living with obesity.[4] More objective measures of individual reward responsiveness towards palatable food are progressive ratio tasks (which measure how hard a participant is willing to work to obtain a food reward)[5] and implicit measures of attentional bias to food or food cues such as eye movement,[6] Stroop tests[7] and reaction times when rating food cues.[8]

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12.3 Functional MRI (fMRI)

Neuroimaging of food reward pathways offers the additional advantage over these methods of providing objective information about the biological underpinnings on a neural level of behaviour and cognition. Functional magnetic resonance imaging (fMRI) has been used for decades to investigate addiction neurocircuitry and is also used to investigate particularly non-homeostatic control of appetite (or food reward pathways) in the brain.[9]

fMRI measures blood oxygen level–dependent (BOLD) changes in contrast to map neural activity. The difference in magnetic properties of oxygen-rich (oxygenated) and oxygen-depleted (de-oxygenated) blood is exploited by fMRI. A strong magnetic field (B_0) aligns hydrogen nuclei in the brain, and another (the gradient field or radio field) is applied at 90 degrees at regular intervals to move the nuclei in its path to a higher magnetisation level. When the gradient field is removed, the nuclei move back to their original state, and the energy emitted is measured with a coil and converted into images. In anatomical MRI, different tissues can be identified and localised according to the energy they emit, a function of how long their nuclei take to return to baseline. The strength of the signal obtained depends primarily on the proton density of the particular tissue.

In fMRI, the principles of MRI are used to assess changes in blood flow to brain regions that are active, as a marker of neural activity. Increased metabolic activity within an active neurons results in localised increased oxygenated blood to that area, as a result of local vasodilatation increasing cerebral blood flow. The oxygenated non-paramagnetic haemoglobin displaces magnetically active deoxygenated haemoglobin. In areas where more oxygenated blood flows, less interference of the gradient field signal will be registered by the coil, leading to an increase in signal and, therefore, in visible contrast. This is assumed to be an indirect measure of increased neuronal activity in that area and can be linked to a specific trigger event or stimulus being tested. This is termed the *hemodynamic response function* (HRF).

By mapping the hemodynamic response in time against a task undertaken whilst in the scanner, changes in **contrast** during that time period give an indication of how brain activation changes during the task. Since fMRI is only able to measure **changes in** and not a **quantifiable** measurement, a baseline condition is important as a reference point.

The brain is divided into hundreds of thousands of voxels, each assigned signal intensity. Statistical analysis of each voxel or cluster of voxels can ascertain whether the signal intensity in that particular voxel or cluster of voxels is greater than the signal intensity in another part the brain, in response to a particular stimulus. A statistical threshold can then be applied to either the whole brain or to predefined regions of interest (ROI). In analysing 100,000 units of brain (or voxels) at the same time in whole-brain analysis, the problem of multiple comparisons is evident. Even small structures such as the amygdala contain around 50 voxels. This can be corrected for in several ways. For instance, the overall statistical threshold can be raised (e.g. using $P < 0.001$ as a threshold instead of $P < 0.05$) or Bonferroni correction can be made. Further methods include using FDR (false discovery rate) or FEW (family-wise error) corrections for multiple comparisons, using Bayesian cluster statistics. ROI analysis has a greater chance of finding statistically significant results but runs the risk of missing activated areas of the brain that were not included in the original hypothesis. Scans can be performed either when the subject is not doing anything in particular (at rest) or during a specific task.

Rest scans are used to analyse functional connectivity between different brain regions, assuming that distinct neural networks function in a coordinated brain response and that these are altered in various conditions or states. Rest scans are also used for pharmacological fMRI studies in which continuous resting fMRI is measured before and after administration of a drug or hormone.[10–12]

In task-related studies, subjects are asked to complete a task whilst in the scanner. For example, a common approach in appetite studies is for subjects to be presented with images, smells or tastes of food (with further subdivision into high-calorie or low-calorie food, and anticipation or actual receipt of a food) or non-food items. A subtraction analysis is performed to see whether the difference in regional brain activation is altered in different states (e.g. those living with obesity and those with a normal weight) between viewing images of food vs. non-food or high-calorie vs. low-calorie food. Different physiological states (e.g. fasted vs. fed, before vs. after bariatric

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surgery, drug/hormone vs. placebo) can also be examined with similar paradigms.

12.4 Positron Emission Tomography

Another popular imaging technique is positron emission tomography (PET). PET involves detecting changes in neuronal activity from a baseline state by measuring degeneration of an unstable nucleus radioactive tracer injected intravenously. The decaying nucleus emits a positron which collides with surrounding tissue electron to emit a ray which is recorded using detectors around the head. Since the half-life of decay is known, within-subject differences can be quantified between states. The temporal resolution can be accurate, but spatially, the signal can be up to 6 mm from actual neuronal activity. These differences in the indirect measure of neuronal activity are then mapped onto standard-space structural MRI maps, and statistical parametric maps of the average activation across subjects can be created.

PET can measure differences in state but cannot measure task-related activity. By varying the tracer, different neuronal populations can be targeted, offering the advantage of obtaining information about neuronal metabolism (e.g. ^{15}O-water for the measurement of regional cerebral blood flow (rCBF) related to neuronal activity; ^{18}F-fluorodeoxyglucose (FDG) for the measurement of cerebral glucose uptake) and neurotransmitters (e.g. dopamine (DRD2/3), MOR or uptake of precursors, e.g. L-DOPA). Neurotransmitter function can be deduced by receptor binding which depends on the specificity of the ligand, receptor availability and neurotransmitter release (e.g. dynamic changes in dopamine release induced by amphetamine or drug challenges).[13] PET scanning has been used more frequently than fMRI for neuroimaging of particularly dopamine pathways in the brain in examining drug addiction. Comparisons are made between people living with addiction in various phases of the addiction cycle and healthy volunteers.

The advantages of fMRI compared with PET is its ability to acquire task-related information non-invasively (i.e. without radionucleotide injections as in PET) and its superior spatial and temporal resolution over PET, although temporal resolution is dependent on blood flow changes and therefore lags the task by some seconds. fMRI's limitations are due to factors which limit the interpretation of data obtained. These are influenced by the choice of experimental design and how fastidiously the paradigm is carried out. Unwanted signal (noise) from various sources, including from the scanner itself, inhomogeneities in the magnetic field strength, head movement, physiological changes in blood flow independent of the task, neuronal activity not related to the task, and various other sources corrupt the data obtained. Experimental designs, therefore, need to minimise noise as far as possible.

12.5 Voxel-Based Morphology and Diffusion Tensor Imaging

Voxel-based morphology (VBM) and diffusion tensor imaging (DTI) are other neuroimaging techniques sometimes used to analyse reward pathways in the brain. Both measure structural differences between groups – VBM malignly grey brain matter density, and DTI the white integrity of white matter in the brain.[14]

12.6 Appetite Regulation in the Brain

Appetite regulatory systems are often divided into homeostatic and non-homeostatic (or hedonic) control systems, although the divide can be artificial, since these are interlinked. Homeostatic control refers to the control of food intake and meal termination in response to physiological hunger and satiety signalling. These are largely controlled by anorexigenic (e.g. ghrelin) and orexigenic (e.g. PYY, GLP-1, CCK, oxyntomodulin) hormones as well as vagal afferent responses to gastric distension, the effects of insulin and glucose, and, in the longer term, adipokines such as leptin.[15, 16] The main gateway for these mechanisms within the central nervous system is the hypothalamus.[17, 18]

Non-homeostatic mechanisms include various individual and environmental factors that govern the intake of food in addition to physiological hunger. These are primarily the individual hedonic and emotional reactions to food governed by brain reward systems, including dopaminergic and opioid corticolimbic pathways as well as prefrontal decision-making areas and memory systems.[19]

There is increasing recognition that there are societal and environmental factors within developed and, increasingly, in developing countries which encourage epidemic proportions of obesity. Highly palatable

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highly calorific food is cheaply and easily accessible, and a high social value is placed on immediate personal gratification and reward. Furthermore, an evolutionary legacy of defence of a higher rather than a lower body weight, to favour survival in periods of cyclical starvation and plenty, makes humans ill-suited for an 'obesogenic' environment of continuous plenty. Homeostatic and non-homeostatic systems most likely function in synergy with cross-modulation between systems taking place, particularly during periods of food deprivation. However, in an 'obesogenic' environment, the influence of palatable food cues on brain food reward systems may override homeostatic satiety signals and/or exaggerate hunger signals, contributing to weight gain and hindering weight loss during attempted reduced caloric intake.[20]

12.7 Food Reward and Executive Control Systems in the Brain

The hedonic appeal of substance is used to describe how rewarding the expectation of or actual receipt of a particular substance is perceived to be. For instance, palatable or high-calorie foods are usually perceived to be more hedonically appealing and are consumed more than bland or unappetising foods.[21] The concept of hedonic reward encompasses the hedonic appeal but also integrates the influence of learning and memory on behaviour that is cue-elicited. In situations where hedonic appeal is high, approach and consummatory behaviour is elicited, at the expense of other ongoing behaviour. Intake of the substance induces subjective feelings of pleasure, which in turn has a positively reinforcing effect on the behaviour.

This pattern of behaviour is thought to be mediated by reward and cognitive control systems in the brain, as well as dopamine, opioid and other neuroreceptor pathways (5HT, noradrenaline, endocannabinoid).[22–24]

In addictive behaviour, three behavioural phases of an addiction cycle are observed. During the binge/intoxication phase, consuming a substance induces pleasure and hedonic reward. In the withdrawal/negative affect stage, the end of the binge brings negative feelings and often negative consequences to the behaviour. During the preoccupation phase, subjective feelings of compulsion or craving and the anticipation of reward drives the of seeking out the addictive substance or food.

Different structures in the brain are thought to play a role in these different stages cycle, and similarities exist in the neuroimaging findings to support these across people living with drug addiction and people living with obesity. Dopamine pathways in particular are thought to play an important role in the processing of reward, and primarily food reward, in the binge/intoxication phase.[25–28] Reward from natural (e.g. food and sex) and non-natural (e.g. drugs of addiction, which supplant natural rewards in valence and have no beneficial evolutionary purpose) sources both lead to increased dopamine release in the nucleus accumbens the ventral striatum. This is an important site for processing pleasure from reward and crucially involved in the pathology of addiction, particularly to certain drugs considered stimulants, such as nicotine, cocaine and methamphetamine.

12.8 Structural Brain Changes in Obesity

12.8.1 Grey Matter Density and Volume

In general, most studies utilising VBM show an apparent negative association of increased BMI with grey matter density/volume in various areas of the brain associated with the processing of reward, although results are inconsistent. However, caution should be exercised in interpreting the results, since age may play an important role in the interaction of BMI and grey matter volume. For instance, in adolescents, obesity has been associated with lower total grey matter volume[29] and lower grey matter volume in the OFC,[30] and in adults <70 years old, frontal and striatal regions as well the gustatory cortex and amygdala again emerged as holding differences between obese and normal-weight people, although the direction of the association is inconsistent between studies.[31–33] In older adults (>70 years), however, obesity appears to be associated more clearly with reduced grey matter volume in frontal, striatal (putamen),[34] peri-hippocampal,[34] gustatory cortex[35] and amygdala[36] regions. However, this apparent association may be confounded by the effect of age, as there may be an interaction with BMI and age on reducing grey matter volume. In addition, not all studies included age as a covariate in their analyses.[34, 36, 37] There may also be other confounders affecting these results, since many of these studies were originally investigating the effect of dementia on grey and white

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matter volume, and this may have a further interaction with BMI. As Driscoll and colleagues point out, the effect of BMI or obesity may be overestimated in studies of grey matter volume which include older adults, even if non-demented at the time, since a subset of these will go on to develop dementia, and subclinical brain volume effects may already be present.[38] In their study of patients with average age of 69 years, they found an association of age with reduced grey matter volumes over 1 year in frontal, cingulate and hippocampal areas. Midlife obesity emerged as a modifier of brain atrophy associated with dementia, but not in non-demented subjects. Therefore, excluding patients who went on to develop dementia abolished the association with reduced grey matter volume in these areas.

Gender,[31, 33, 39] hypertension[35] or other metabolic diseases in cross-sectional are further confounders which are not always taken into account or corrected for.

12.8.2 White Matter Structure

There have been a few studies examining white matter microstructural integrity using DTI in obesity. All studies thus far have found evidence of reduced structural integrity of white matter with increased body weight. Whereas FA appears to be consistently negatively correlated with BMI, mean diffusivity results are not so straightforward. Mean diffusivity is not easy to interpret, since it represents the average resistance to water flow in all directions within a voxel. Additionally, both intra- and extra-cellular diffusion is represented, further complicating matters. However, it is generally accepted that increased diffusivity is usually the result of loss of cell membrane integrity resulting in increased displacement of water molecules. Chronic inflammation and disease lead to increased mean diffusivity. On the other hand, acute injury, such as ischaemia, results initially in reduced mean diffusivity, followed by gradual increases. BMI negatively correlates with FA and mean diffusivity overall[39] and in specific areas associated with reward processing.[40, 41]

Several studies have shown and association of obesity with increased white matter volume using VBM, in striatal (caudate, putamen),[29, 42, 43] parahippocampal and temporal regions.[42] Haltia and colleagues also found that dieting reduced white matter volume in the above areas in obese patients.[42]

Together results from these two different approaches suggest that white matter is affected by obesity (or increasing BMI) in such a way as to increase volume and reduce tract integrity in specific areas, although the mechanism for this is not known.

Altered functional connectivity between reward areas has also been seen in obesity both at rest[44–46] and when viewing food pictures.[46–48]

12.8.3 Functional Reward Pathways in the Brain

Dopamine pathways appear to be particularly important in processing the hedonic appeal rather than appetitive drive for food, for example preference for sugary food as opposed to hunger for any type of food.[49, 50]

Using PET with (^{11}C) raclopride and FDG, Volkow has showed reductions in striatal D2 receptors in people living with drug addiction associated with decreased metabolism in the prefrontal areas. Dopamine projections run from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens, and to the dorsal striatum where consolidation of the efficient actions to obtain reward occur (e.g. learned behaviour, formation of habits, stimulus response).[25, 51, 52] However, despite Volkow demonstrating a reduction in striatal DRD2 availability correlated to increasing BMI, a review of all studies of dopamine receptor availability in people living with obesity found no evidence for reduced DRD2 receptor availability in people living with obesity.[53] One explanation is that only at higher BMI values is the DRD2 receptor availability effect observed; Volkow's study found that only at a BMI of over 50 was the effect observed.[54] It may also be that it is that the behavioural phenotype of binge eating or food addiction which aligns more with the dopamine hypofunction theory, and that DRD2 reduced availability mandates the risk for compulsive behaviour rather than obesity per se.

The aspect of loss of control over the binge behaviour is thought to be driven by diminished function in executive control centers which modulate behaviour. Dopamine pathways are implicated here too, as reduced striatal dopamine signalling to these areas from the top down is observed both in drug addiction and in some studies of people living with obesity. This has been evidenced in PET studies by reduced glucose

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metabolism in executive control areas in these conditions.[55]

The VTA also projects to the amygdala (governing emotional responses), the hippocampus (memory formation), the OFC (which encodes the predicted reward value of a cue) and dorsolateral-prefrontal cortex (where reward representations are consolidated and suppression of maladaptive responses or initiation of behaviour to obtain a desired goal takes place), and where the withdrawal or negative affect stage of the addiction cycle is most likely processed.

The preoccupation/anticipation stage of addictive behaviour engages the prefrontal cortex, hippocampus and insula. When a stimulus is as rewarding as expected, tonic dopamine release occurs in the nucleus accumbens. Dopamine is fired in phasic bursts when reward exceeds expectation. If the reward does not reach the expected levels of pleasure, there are pauses in dopamine release. Unpredictable or unexpected rewards have a more reinforcing effect than predictable rewards. In addiction states, dopamine is released *regardless* of actual reward but in keeping with the *expectation* of reward. Memory and learning play a role in this, since gains are remembered and losses forgotten.[25, 56, 57] Bello and colleagues in their review of the role of dopamine in binge eating suggest that sustained stimulation of the dopamine systems by bingeing, promoted by pre-existing conditions (genetic traits (D2 receptor polymorphisms), dietary restraint, stress, etc.), results in progressive impairments of dopamine signalling[58] which perpetuate the behaviour.

In addition to dopamine pathways and acting synergistically with them, opioid pathways have also been shown to be important in the processing of reward valence. Mu opioid receptors (MORs) are largely distributed within brain regions mediating food intake and reward, including nucleus accumbens and amygdala. nimal studies have shown that MOR activation in VTA enhances hedonic reaction to sweet and fatty foods,[59–62] and opioid agonists and antagonists injected into VTA respectively increase or decrease food intake.[63–66] In humans, opioid antagonists have shown mixed results: some show reduced food intake,[67] reduced palatability of sugary foods[68–71] and reduced bingeing,[72, 73] whereas others have shown no reduction in bingeing.[74–78]

Gene expression studies in animals support the role of MOR in food hedonics,[79–82] but there is considerable variation in specific hypothalamic and striatal region peptide expression following high-fat food intake, which appears to be modulated by duration of food intake. People living with obesity have significantly lower MOR availability than control subjects in brain regions relevant for reward processing, including ventral striatum, insula and thalamus. Moreover, in these areas, BMI correlates negatively with MOR availability. Striatal MOR availability is negatively associated with self-reported food addiction and restrained eating patterns.[53]

It is generally accepted that dissociation exists between the hedonic preference for food 'liking' and the reinforcing value of food 'wanting'. These appear to be independently affected by homeostatic systems, so that in some studies hunger appears to increase 'wanting' but not necessarily 'liking'.[83] In addition, the interaction between homeostatic and hedonic systems in their control of energy intake does not appear to be symmetrical. For example, increased palatability of food reduces hunger at a slower rate and brings earlier satiety and a quicker return of hunger, whereas decreased hunger does not necessarily reduce the perceived palatability of food, and increased hunger does increase palatability.[84]

fMRI studies that use visual food cues (food pictures) when subjects are hungry elicit activation of brain food reward regions known to be involved in the expectancy, appraisal and receipt of reward, including the striatal nucleus accumbens (nucleus accumbens) and caudate nucleus (key to dopaminergic reward conditioning and learning, motivation and expectancy), amygdala (emotional responses to rewarding stimuli), anterior insula (integrating gustatory and other sensory information) and orbitofrontal cortex (OFC) (reward value appraisal, cognitive control and attention).[9, 19, 85]

In people of normal weight, being fasted and therefore hungry elicits increased activation to food cues in these areas compared to being fed. High-calorie or palatable food pictures elicit more activation than low-calorie or unappetising food pictures. There is also an interaction between the two conditions such that fasting biases food reward responses towards high-calorie foods.[86–96] The inference that can be drawn from this, which is frequently cited to support regular meal intake, is that if one skips meals and is hungry, the brain is effectively on 'high alert' for high-calorie food options, and it stands to reason that food choices in this state may not be as sensible as when satiated.

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12.9 Binge Eating and Food Addiction

The DSM-5 is the first DSM version to include binge eating disorder (BED). Criteria for diagnosis include eating an amount of food larger than most people would eat in a discrete period with associated loss of control overeating. This emphasis on escalated use and loss of control is similarly portrayed in the DSM-5 criteria for substance misuse disorder (where the additional symptom of craving was added in this latest version).

However, although BED and food addiction may be more closely aligned, there are still limitations in this model. For instance, the loss of control needs to be associated with discrete episodes of overeating whereas a more common pattern of eating throughout the day (termed *loss of control eating* or *grazing*) is a frequent phenotype observed in people living with obesity and appears to be a more reliable predictor of response to weight loss treatments.[97] Studies by Gearhardt and colleagues indicate that less than half of individuals who meet criteria for BED also meet criteria for food addiction using the Yale Food Addiction Scale, but that individuals who do meet criteria for both appear to have worsened pathology.[98, 99] Binge eating disorder is associated with overweight and obesity but occurs in only 25–30% of patients seeking bariatric surgery.[100–102]

The behavioural and neuroimaging presentation of binge eating disorder does, however, align more easily with the three-stage behavioural model of addiction than the more heterogenous condition of obesity does.

The binge/intoxication stage of addiction involves the reward neurotransmitters of dopamine and opioid peptides in the nucleus accumbens (NAc) and dorsal striatum. Barbano and colleagues have shown that the endogenous opioid systems are associated with the pleasure of food reward and have a synergistic effect with dopaminergic pathways to promote food intake. Furthermore, a PET study showed that food presentation, smell and taste was associated with greater increases in dopamine in striatal areas in obese people with BED compared to those without BED, and correlated with binge eating scores.[103] In animal models, a chronic deprivation model to elicit bingeing is used. Using this model, the opioid pathways are implicated and MOR antagonists suppress food bingeing in a number of studies.[102]

When palatable foods are forbidden for a period, this leads to bingeing specifically on that palatable food and hypophagia of less appealing food.[104] Using this model, a MOR antagonist decreased binge behaviour (for the preferred diet of chocolate-flavoured high sucrose) but also increased food intake of the less preferred diet (i.e. chow). Using the same model, a specific MOR antagonist (GSK1521498) and naltrexone reduced the propensity to seek (both before and after food ingestion), and binge eat, palatable chow. However only GSK1521498 reduced the impact of high hedonic value on ingestion of chocolate, suggesting that the MOR pathway has a specific role to play in conditioned salience in binge eating.[105]

Furthermore, direct stimulation of MORs with MOR agonists such as morphine or DAMGO ([D-Ala^2, N-Me-Phe^4,Gly^5-ol^5]-enkephalin) within the nucleus accumbens of rats preferentially increases intake of energy-rich foods such as fat and sucrose, as well as tasty non-caloric foods such as saccharin and salt,[64, 102] and increases or amplifies positive affective reactions (i.e. liking reactions) to sucrose taste.[106, 107]

The preoccupation/anticipation stage engages the prefrontal cortex, hippocampus and insula, and fMRI studies in both obese and lean binge eaters show increased activation in frontal pre-central area of the brain[108] and the OFC[109] in response to binge food cues. A VBM study of women in their 20s found increased OFC volume in patients with BED compared to normal controls. No correction was made for BMI, however, so that the higher BMI in the BED group may have been a confounder.[110] Lesion studies suggest that frontal lobe damage may increase eating in response to seeing food, and lead to hyperphagia and obesity.[111]

A difference noted between drug addiction and food addiction is the change seen in the somatosensory cortex. People living with obesity who have low striatal DRD2 availability also have augmented glucose metabolism in the post-central gyrus in the left and right parietal cortex.[112] These areas of somatosensory cortex are associated with perception of taste, suggesting that this group also had a greater sensitivity to taste. Coupled with a reduced DRD2 signal or, in other words, an attenuated reward response to food, higher sensitivity to food's palatability could contribute towards overeating in food addiction.

12.10 Emotional Eating

Emotional eating, or eating in response to emotional cues (such as sadness, anxiety or anger), also known

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as comfort eating, is associated with depression and a need to escape negative affect. Although emotional eating can refer to eating in response to positive emotions, the most common precipitant is negative emotions, particularly in women. In most studies, emotional eating as measured by the DEBQ emotional eating scale is positively associated with BMI.[113] There are also cross-correlations and interactions between dietary restraint, external eating, disinhibition and emotional eating. For example, women who scored highly on TFEQ restraint and disinhibition scores were more likely to eat in response to negative affect, whereas women who scored highly on disinhibition but low on restraint were more likely to overeat in response to positive affect.[114] Emotional eaters and restrained eaters are more likely to eat high-calorie or sweet foods in response to stress.[115, 116] Emotional eating may also be influenced by the type of stressor, such that ego-threat is likely to increase emotional eating whereas a cognitively demanding task does not.[117]

Neuroimaging studies have demonstrated an interaction of emotional eating and neural activation to food. Dysfunction in the central noradrenaline systems appear to be linked to emotional eating, modulated by mood disorders and stress responses, which include taking addictive drugs or overeating. However, the expression of this differs between obesity and drug addiction. For example, using PET, Ding and colleagues have shown that people with cocaine dependence have significant upregulation of noradrenaline receptors in the thalamus,[118] whereas Li and colleagues found that people living with obesity had decreased noradrenaline receptors in the same areas.[119] However, for obese individuals with higher emotional eating scores on the DEBQ, scores correlated with lower noradrenaline receptor availability in the locus coeruleus and higher noradrenaline receptor availability in the left thalamus.[120] The serotonin system, also implicated in the interaction between mood an stress reactions, has been comparatively less studied with respect to obesity. 5-HT_{2A}R availability has been positively correlated to BMI in food reward areas of the brain, while 5-HTT availability has been found to be negatively correlated to BMI, and no correlations were found to alcohol and drug consumption.[121, 122]

In a study of 12 normal-weight individuals, negative emotional state (induced by sad music and faces) was attenuated by intragastric infusion of fatty acids, with corresponding reduction in fMRI BOLD activation in medulla/pons, midbrain, hypothalamus, thalamus, putamen, cerebellum, hippocampus and cingulated cortex, but not the insula or amygdala.[123] In another study, healthy-weight women who scored in the highest quartile on the DEBQ emotional eating scale (emotional eaters) were more likely to experience negative affect compared to women who scored in the lowest quartile (non-emotional eaters), when listening to slow sad music.[124] They also had greater activation in the caudate and pallidum in response to milkshake receipt and greater activation in response to anticipation of milkshake receipt in the parahippocampal gyrus and ACC, compared to non-emotional eaters, suggesting greater food reward sensitivity.

12.11 Impulsivity and Inhibitory Control

The issue of overlap between the reward system and inhibitory control system in food intake can lead to some confusion in interpreting study results. It is likely that these systems function in synergy to coordinate behavioural approach or inhibition towards food, and may be activated in both. For instance, frontal lobe regions, including superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, medial PFC, DLPFC, VLPFC and OFC, all have been consistently implicated in response inhibition,[125–129] whereas the OFC has also been implicated in evaluation of food reward.[130] Poor response inhibition (impulsivity) has been implicated in the development of obesity[131, 132] and poor weight loss during dieting,[133–135] whereas engagement of areas of inhibitory control in response to food cues may ensure successful weight maintenance.[136] Better impulse control has been associated with stronger functional connectivity between VMPFC and DLPFC at rest, which predicted greater weight loss during dieting in obese subjects.[135]

People living with obesity show different activation compared to lean people during tasks designed to elicit self-control or response inhibition. In a task requiring subjects to reduce their craving whilst viewing food pictures, women with obesity showed more activation of the DLPFC compared to lean women when attempting to reduce compared to increase their craving,[137] suggesting increased recruitment of this area was required to achieve the same reduction in appetite. On the other hand, when asked

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to increase their craving (compared to passively viewing or decreasing craving), obese women showed less activation in the insula and dorsal striatum compared to lean women.[137] In another study of normal-weight and overweight young women, using a food-specific response inhibition task, those with a higher BMI responded more quickly but less accurately, particularly to high-calorie food cues.[138] They also had less activation during response inhibition in the frontal lobes, including superior frontal gyrus, middle frontal gyrus, VLPFC, medial PFC and OFC, and increased activation in right temporal operculum extending to frontal operculum and insula.

12.12 Genetic Obesity

Studies of patients with rare genetic obesity syndromes have revealed both structural and functional brain characteristics in neuroimaging studies which may contribute to abnormal eating behaviour. Prader-Willi syndrome (PWS) is a genetic obesity syndrome associated with neuroendocrine abnormalities, learning disability and behavioural problems with marked hyperphagia developing in childhood, due to loss of expression of paternally expressed imprinted genes on chromosome 15 (15q11–13), leading to early-onset morbid obesity.[94] Patients with PWS have increased activation to food pictures compared to healthy controls following a preload in the prefrontal region,[139] OFC, amygdala, insula, hippocampus and parahippocampal areas.[140, 141] Delay in response to glucose ingestion in reward areas of the brain (prefrontal cortex and insula),[142] cerebellar hypoplasia,[143] abnormal cortical structure[144] and pituitary abnormalities[145] has also been demonstrated.

Genetically leptin-deficient individuals also develop early-onset obesity. They have increased neural reactivity to food in the nucleus accumbens, caudate, putamen and globus pallidus[146] with less suppression in these areas after eating than controls,[147] which was reversed by leptin administration.[147] Leptin administration also reduces BOLD activation to food pictures in the insula and parietal and temporal cortex and increases activation in the prefrontal cortex.[146, 148] However, monogenic disorders leading to obesity, such as leptin deficiency (as well as melanocortin 4 receptor (*MC4R*), pro-opiomelanocortin (*POMC*) and prohormone convertase 1 (*PCSK1*)), are rare and probably account for less than 5% of obesity.

The genetic influence on obesity is therefore mostly polygenic, and although this may contribute between 45% and 85% of the heritability in BMI, the effect size is likely to be small. The FTO (fat mass and obesity-associated gene) allele, one of the most established common gene variants, results only in approximately 0.4 kg/m^2 increase in BMI. The mechanism for the effect of individual genetics on weight is thought to be mostly through increased appetite and eating behaviour.[149] Various studies have therefore attempted to link emerging evidence of obesity-associated gene variants, particularly those involved in dopamine pathways, with alterations in the neural circuitry underlying the response to food from an emotional or reward perspective.

A 2015 review of neurogenetic and neuroimaging evidence for dopaminergic contributions to obesity found evidence of a relationship between obesity and polymorphisms in dopamine receptors type 2, 3 and 4 (DRD2, DRD3 and DRD4) as well as the dopamine transporter (DAT1) and genes for enzymes associated with dopamine degradation: catechol-o-methyltransferase (COMT) and monoamine oxidase isomers A and B.[150] The Taq1A A1 allele of the DRD2 gene has been associated not only with alcoholism, drug abuse, smoking and compulsive gambling but also with obesity.[151] Carriers of Taq1A A1 allele have increased impulsivity[152] and increased body weight.[153] Behavioural studies have shown that especially in people living with obesity, those who have the allele will work harder in a food reward task for food than those without the allele.[154] In addition, healthy-weight individuals with the Taq1A A1 allele have reduced dopamine D2 receptors[155] and lower glucose uptake on FDG PET in prefrontal and striatal (caudate, putamen and nucleus accumbens) areas,[156] in keeping with the reward deficiency theory of obesity. Furthermore, two fMRI studies of healthy-weight participants have shown that those with the Taq1A A1 allele have attenuated activation of the reward circuitry (OFC and prefrontal areas/ thalamus, midbrain) in response to appetising food,[157–159] and that attenuation of BOLD activation in the putamen and OFC by the Taq1A A1 predicted the risk of future weight gain.[158] The same genotype appears to moderate the relationship between parental control and emotional eating, so that possession of the allele increased emotional eating in relation to high parental psychological control.[160]

Individuals positive for the obesity risk FTO allele have reduced brain volume[161, 162] and, in one recent

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study, reduced BOLD in response to food-related images within the hypothalamus, left ventral tegmental area/substantia nigra (VTA/SN), left posterior insula, left globus pallidus, left thalamus and left hippocampus.[163]

12.13 Comparison between People Living with Obesity and Normal-Weight People

Based on the behavioural studies which tend to indicate that obese have increased reward responsivity to food and reduced ability to control their response to food stimuli, one might expect neuroimaging studies of obese compared to lean individuals to find increased neural activation to food cues in many areas of the brain associated with modulating dopamine release (VTA, nucleus accumbens, caudate, putamen), reward or saliency interpretation (OFC, ACC), integration of sensory information relating to food (insula, primary gustatory cortex), motivation or drive to seek reward (OFC), emotional response and regulation (amygdala), learning and conditioning (hippocampus) and potentially less activation for inhibitory control areas (DLPFC).[164] In fact, results from studies examining this are surprisingly inconsistent with this hypothesis.[85]

This may be largely due to the fact that obesity is a heterogeneous condition, and although most studies use BMI as a marker of obesity, a raised BMI may be the end result of a combination of any number of etiological pathways and influences, all of which may differentially affect or be affected by the neurological response to food.[20] In other words, although obesity is largely the end product of eating in excess of an individual's energy requirements, eating behaviour itself is complex. The interplay of individual psychological, genetic and metabolic factors with an obesogenic environment affects how an individual's brain reacts to the sight, smell or taste of food, on a conscious and subconscious level, governing eating behaviour in different situations. For instance, individual personality traits (such as impulsivity and reward responsivity), different cognitive styles (such as rigid dietary restraint or self-control) and behaviour indicative of possible underlying deficits in affect regulation (such as emotional eating, binge eating and disinhibition) may all be expressed to varying degrees in the obese population and may also increase with BMI. Each of these will have their own, possibly diverse effect on the reward response to food cues as well as cognitive and executive control network functioning in response to food cues.[165] A better understanding the effects of how these factors affect neural reactivity to food in different parts of the brain, linking this to observed eating behaviour and BMI, could significantly improve our interpretation and analysis of data from neuroimaging studies.[166]

Variability across study paradigms and the fact that subject numbers are often limited by technical difficulties in this population,[167] as well as the expense of neuroimaging food studies, causes significant problems for using fMRI in a population with the level of heterogeneity that occurs in obesity. Furthermore, very large subjects may not be able to fit into conventional scanners, so that studies generally do not include subject with a BMI of more than 50 kg/m^2, potentially excluding patients where large effect sizes might have been found.

The variability across studies also limits the degree to which meta-analyses can be used. One meta-analysis was only able to include 7 of the more than 40 studies carried out in this area.[168] Of the 126 subjects included in the 7 studies examining whole-brain response to food images, obese in comparison to healthy-weight subjects had increased activation in the left dorsomedial prefrontal cortex, right parahippocampal gyrus, right precentral gyrus and right ACC, and reduced activation in the left DLPFC and left insula.

12.14 Correlation with Weight Loss in People Living with Obesity

One of the most valuable contributions of fMRI has been the ability to examine and predict individual treatment responses to a number of interventions in conditions where the brain's response underpins successful treatment. fMRI alongside genomic profiling promises to be able to offer a future of personalised medicine interventions.

Several studies have shown that certain neuroimaging characteristics can be correlated with weight loss and with sustained weight loss after weight loss interventions, including bariatric surgery. Summarised, these indicate that reduced activation to food in food reward pathways follows successful weight loss[87] and more activation to food pictures in areas which have also been implicated in conscious control of food

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intake and dietary restraint.[169] Similarly, PET studies have shown reduced rCBF in the OFC and increased rCBF in the DLPFC in response to satiation with a liquid meal after a 36-hour fast in people who had successfully lost weight.[170, 171] These results suggest that successful dieters may have preferential engagement of areas of inhibitory control (DLPFC) in response to food cues that may ensure successful weight maintenance,[137] as well as reduction in the salience attributed to food (processed in the OFC). These changes were reversible by administration of leptin in some but not all areas.[172]

Studies examining the most successful treatment for obesity, bariatric surgery, have demonstrated that the success of gastric bypass surgery appears at least in part due its ability to influence hedonic food responses in obese people.[173, 174] Longitudinal neuroimaging studies are supportive of this possible mechanism,[175–177] and the underlying mechanism for this may well be gut hormone changes, particularly after gastric bypass surgery.

For example, in one study of 14 patients pre- and 1 month post-surgery there was a reduction in neural response to food pictures in the lentiform nucleus, putamen and frontal gyri (DLPFC). A greater reduction in the desire to eat following exposure to high-calorie food cues compared to low-calorie food cues and 'liking' of high-calorie foods compared to low-calorie foods was seen after RYGB compared to before, mirrored in brain activation patterns.[177] Another longer longitudinal study showed decreased activity in the NAc, caudate, pallidum and amygdala during a task designed to elicit the desire for palatable food 12 months after surgery. Dorsolateral and dorsomedial prefrontal cortex activity (governing regulation), on the other hand, increased. NAc activity accounted for 54% of the explained variance in weight loss at 12 months.[178] Another study found that people living with obesity and not trying to lose weight did not have a decline in BOLD response to high-calorie food in the VTA, but that people following bariatric surgery did.[179] When compared to people who had lost weight through dieting alone, hungry diet weight loss participants had increased activation in the medial PFC and precuneus following weight loss, while bariatric patients had decreased activation in the medial PFC and precuneus,[180] suggesting that changes in the hedonic response to food brought about by bariatric surgery are not due to weight loss.

Several key peptides have been implicated in regulating food intake, and in many cases their action in homeostatic appetite centres have been well researched. Increasingly their effect on non-homeostatic reward systems regulating food intake has generated interest, particularly as it is known that bariatric surgery, and particularly gastric bypass surgery, potently modulates these.

Ghrelin receptors are located in the VTA, and ghrelin acts within the dopaminergic system to increase reward to natural and non-natural rewards.[181] Studies have shown that ghrelin mimics the effect of fasting, leading to increased reward response to food pictures in the OFC, amygdala, caudate, VTA, hippocampus and insula.[96, 182] Recent evidence has also pointed to a significant role of orexin, not only in feeding behaviour dysregulation but also recruitment of the orexin neuronal circuit by drugs of abuse, again pointing to an overlap of reward processes even in the hormonal system.[183]

Leptin administration into the VTA reduces food intake, reduces the work rats will do to obtain a rewarding food in a progressive ratio task[184] and causes rats to no longer prefer an area they have been trained to associate with palatable food.[185] This effect is not seen in rats fed a high-fat diet, suggesting that leptin resistance seen in obesity and applicable to homeostatic appetite centres may apply to reward circuitry in the brain too.

Leptin-deficient humans have increased neural reactivity to food in the nucleus accumbens, caudate, putamen and globus pallidus[146] with less suppression in these areas after eating than controls.[147] This is reversed by leptin administration.[147] Leptin administration in these patients also reduces BOLD activation to food pictures in the insula, parietal and temporal cortex and increases activation in the prefrontal cortex.[146, 148] Leptin administration to obese patients who have lost weight has also been shown to reverse some of the changes in BOLD activation to food pictures seen with weight loss.[172]

Insulin also normally reduces appetite centrally in hypothalamic centres and affects dopamine release in the rat striatum. At low concentrations, insulin increases dopamine release but inhibits it at higher concentrations.[186] As with leptin, central administration of insulin can reduce sucrose intake in rats[187] and increases preference to a place associated with food reward.[188]

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However, as with leptin, insulin resistance seen peripherally in obesity may also be present in the brain and may alter reward processing. For instance, exposure to a high-energy diet increases sucrose self-administration and prevents the ability of centrally administered insulin to reduce sucrose intake.[187, 189] In humans, insulin resistance is associated with attenuated striatal and prefrontal brain glucose metabolism following insulin infusion.[190] Altered resting-state functional connectivity in the OFC and putamen is influenced by insulin resistance.[45] Moreover, although intranasal insulin augments post-prandial satiety and reduces food intake in normal-weight individuals, this effect is not observed in obese individuals.[191, 192]

Evidence of the role of PYY and GLP-1 in the success of RYGB for weight loss has provided renewed support for investigation of the mediation of these hormones on the gut–brain axis controlling food intake. However, it has become increasingly apparent that these and other hormones may act not only on homeostatic hypothalamic appetite centres but also non-homeostatic systems which control ingestive behaviour, as is evidenced by both animal and human studies.[193]

People given a PYY infusion compared to saline showed activation of the parabrachial nucleus, the VTA, limbic regions, the ventral striatum and certain frontal cortical regions as assessed by BOLD imaging.[10] The substantia nigra, parabrachial nucleus and hypothalamic BOLD response correlated with PYY levels, whereas and OFC activation predicted food intake and correlated negatively with hedonic ratings of food when PYY was given.[10]

GLP-1 receptors have been identified in the nucleus accumbens and VTA, and activation of these receptors with GLP-1 agonists intracerebral infusions increased c-fos expression in the nucleus accumbens, decreased intake of especially highly palatable foods and reduced body weight in rats.[194, 195] Moreover, blockade of these in the VTA and nucleus accumbens core resulted in a significant increase in food intake. Food reward behaviour is also reduced in rats by administration of a GLP-1 agonist, as rats no longer prefer an environment previously paired to chocolate pellets. The peripheral administration of a GLP-1 agonist also decreased motivated behaviour for sucrose in a progressive ratio task.[196, 197]

A combination of PYY and GLP-1 infusion reduced average BOLD activation to food pictures in combined reward regions (amygdala, caudate, insula, nucleus accumbens, OFC and putamen) compared to saline and to GLP-1 infusion alone.[198]

Geliebter's group compared bariatric surgery patients before and 4 months after surgery with low-calorie dieters and no intervention group using an fMRI paradigm of high-calorie vs. low-calorie food cues. The surgery group had exaggerated GLP-1 responses to food after surgery and had increased dorsolateral prefrontal cortex (DLPFC) and decreased parahippocampal/fusiform gyrus activation in response to high-calorie food pictures, suggesting greater cognitive dietary inhibition and decreased rewarding effects from food. Postprandial increases in GLP-1 concentrations correlated with postsurgical decreases in brain activity in the inferior temporal gyrus and the right middle occipital gyrus in addition to increases in the right medial prefrontal gyrus/paracingulate for high-calorie food, suggesting involvement of these attention and inhibitory regions in satiety signalling post surgery.

Other studies have found that changes in fasting ghrelin correlated positively with changes in VTA signal and DLPFC activation in bariatric surgery patients.[179]

Taken together, the neurobiological correlates of reductions in hedonic food reward and increases in regulatory control after bariatric surgery have been consistently demonstrated and appear to be mediated by shifts in appetitive hormones after bariatric surgery, which have been shown to act in the DLPFC and parahippocampal/fusiform gyrus areas of the brain.

PET studies of changes in dopamine receptor availability after bariatric surgery, on the other hand, have produced conflicting results. Since D2/3 receptor availability is reduced with increasing obesity, and assuming that this is due to down-regulation of receptors from resistance, then it is hypothesised that this should be corrected by weight loss. In a small study of five obese women who underwent RYGB in their 30s, ^{11}C-raclopride (antagonist radioligand of D2 and D3 receptors) PET studies were carried out 6 weeks pre- and postoperatively. The analysis was limited to striatum (anterior and posterior putamen, and anterior and posterior caudate) and found the predicted increases in D2/D3 receptor binding after RYGB.[199] By contrast, a study of five women in their 40s with similar mean BMI to previous study, pre- and 7 (6–11) weeks post-RYGB and VSG, using PET ^{18}F-Fallypride, to measure D2 receptor availability, found

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decreased D2 receptor availability after surgery in the substantia nigra, caudate, putamen, ventral striatum, hypothalamus, medial thalamus and amygdala.[200]

12.15 Summary

Akin to other addictive behaviours, alterations in dopaminergic and opioid pathways involved in the expectancy, appraisal and receipt of food reward appear to be important in the development and maintenance of obesity. Several components of the reward system, including the striatal nucleus accumbens and caudate nucleus (key to dopaminergic reward conditioning, expectancy and motivation), amygdala (emotional responses to rewarding stimuli), anterior insula (integrating gustatory and other sensory information) and OFC (reward value appraisal, cognitive control and attention), have been implicated. Activation in these areas when exposed to food cues not only predicts food consumption and choice, and prospective weight gain, but may be altered in obesity, predict the success of weight loss strategies, changes with successful weight loss, including surgical treatments, and is altered in specific eating behaviour psychopathology such as dietary restraint, dietary disinhibition, binge eating and hyperphagia in genetic obesity. Interestingly, modulation of activation of these reward systems both at rest and in response to food stimuli by gut hormones has been described, and surgical, rather than psychological, interventions for obesity have proven to be the most effective tool that we have to treat obesity.[14, 15] On the other hand, if anatomical manipulations of the gut powerfully alter the hedonic evaluation of food, then the gut–brain axis may prove to be the most important target for the development of future treatments of obesity.

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