Acta Neuropsychiatrica 2013

DOI: 10.1017/neu.2013.18

ACTA NEUROPSYCHIATRICA

Review Article

Perspective food addiction, caloric restriction, and dopaminergic neurotransmission

Stankowska AUM, Gjedde A. Perspective food addiction, caloric restriction, and dopaminergic neurotransmission.

People attempt to change their lifestyle when obesity impairs their quality of life. The attempts often fail when multiple habits must be changed in unison. Here we explore relations among food addiction, the neurobiology of habits, and caloric restriction, when people seek to return to normal eating behaviour, with particular emphasis on the role of dopaminergic neurotransmission.
Severely obese individuals have specific neurobiological characteristics in common with drug abusers, including low availability of dopamine receptors in the striatum, impaired neuronal responses to dopamine, and reduced activity in prefrontal regions of the cerebral cortex. The neurobiological characteristics suggest that obese people also have a pathological dependence in common with addicts, in the form of food addiction. Malnutrition and dieting both relate to binge eating, possibly as a compensation for a reduced cognitive reward condition. The combination of caloric restriction and food addiction imparts a high risk of relapse as a result of further reduction of dopaminergic neurotransmission and the subsequent loss of reward. As with drugs of abuse, ingestion of large quantities of sugar in circumstances of uncontrolled eating increases dopamine release in the nucleus accumbens. This and other evidence suggests that abuse of food is a habit learned by means of mechanisms centred in the basal ganglia, with an increased risk of relapse in the presence of associative amplifiers. This risk is predicted by the relationship between dopamine receptor availability in the striatum and sensation-seeking in the form of an inverted U, suggested by recent findings, consistent with two opposite states of hypodopaminergic and hyperdopaminergic neuromodulation.

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Keywords: caloric restriction, dopamine, reinforcement, reward, substance-related disorders

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Accepted for publication March 13, 2013

First published online 28 May, 2013

Summations

- With neurobiological similarities among the brain functions of individuals with behaviour suggestive of addiction, obese individuals with reduced reward sensitivity suffer from pathological addiction to food.
- Both undernutrition and dieting are positively correlated with strong craving for food and accompanying overeating, evidently as a compensation for reduced activity of neurobiological reward mechanisms.
- The combination of caloric restriction and food addiction alone has a high risk of continued bouts of overeating as results of the reduced gain from dopaminergic neurotransmission maintained by repeated relapses. The risk can be diminished by lifestyle modifications that at the very least include exercise and counselling or group therapy. The inverted U-shaped model is a measure of the efficiency of a given individual's reward system.

Considerations

- The neurobiological similarities among the brain functions of individuals with behaviour suggestive of addiction suggest but do not prove that obese individuals with reduced reward sensitivity in fact suffer from an addiction.

- The observation that both undernutrition and dieting are positively correlated with a strong craving for food and accompanying overeating is not in and of itself proof of causation, owing to reduced activity of neurobiological reward mechanisms.
- The observation that a combination of caloric restriction and food addiction is associated with a high risk of continued bouts of overeating suggests but does not prove reduced gain from dopaminergic neurotransmission, as maintained by repeated relapses. Hence, it is not known to what extent lifestyle modifications such as exercise and counselling or group therapy are in fact effective, nor to what extent the inverted U-shaped model provides a significant measure of the efficiency of a given individual's reward system.

Introduction

In this perspective, we define caloric restriction as the cessation of systematic overeating and intake of refined sugars and associated high-calorie foods, in the context of a return to normative patterns of food intake. As a lifestyle change, caloric restriction is not a diet, and hence excludes food weighing and consultation of calorie tables but rather an active reliance on individual physiologically regulated feelings of satiety and hunger.

In most Western societies, high food availability makes it unnecessary to be physically active to obtain food. The acquisition and ingestion of food, on the other hand, yields rewards that are thought to be triggered by the release of monoamines, serotonin, norepinephrine, and dopamine (DA), as well as opioids, in keeping with the simple experience that more calories yield more rewards (1,2). Furthermore, the gut peptides, peptide YY, glucagon-like peptide 1, ghrelin, and the metabolism-regulating hormones insulin and leptin are involved in nutritional homeostasis and reward in the central nervous system (3,4). Food-induced reward is omnipresent and marketed. Generally, however, it is also held to be beneficial *per se* to be physically active (5), and the exertion yields a reward state of the brain that is also associated with the release of endorphins and the monoamines (6).

As evolution may favour the physically least-demanding approach to survival (7), people tend not to be more physically active than prescribed by the anticipation of reward. As physical activity is correlated negatively with the occurrence of depression (5,6,8), significant reduction in physical activity therefore may reduce mood and interfere with appreciation of the quality of life, through such physical disorders as impaired bone formation, decreased peristalsis, and increased fat deposits (9) and possibly the mental disorder associated with low levels of happiness because of physical ailments, unless compensated by the rewards gained by excessive feeding.

Reduced enjoyment of life in the presence of highly available food can motivate a search for alternative reward sources on the basis of the satisfaction of a feeding–eating instinct that yields comfort by means of overeating of the fattest and the sweetest foods that offer the most rewards and block the mechanisms generating the low mood (10). A correlation also exists between a genetically impaired reward system and the propensity for addiction (11,12). With the potential for abuse combined with rare physical activity, the most susceptible individuals gain weight and develop obesity with accompanying lifestyle limitations (13) as a result of a process of maladaptive plasticity of functional brain activity.

A physically non-intrusive treatment of food addiction is lifestyle transformation with search for alternative sources of reward (14), constituted in part by fewer calories compared with the former intake, and more frequent exercises. The new lifestyle builds on new habits and the elimination of old habits. We claim that this revision requires rewiring of memory networks in the brain by means of plasticity, which is a time-consuming, unstable, and dopamine release-dependent learning process (15), which regularly succumbs to short or permanent relapses.

Therefore, a better understanding of the neurobiology of habit forming helps the dedicated practitioners maintain the new lifestyle. As DA is associated with both the formation of habits and with reward, it is important to review the interaction between restricted intake of calories and food addiction. This interaction is reviewed in the present perspective, with a particular focus on the role of dopaminergic neurotransmission serving the maladaptive plasticity in the brain of people that are addicted to food. Furthermore, we look for dopaminergic patterns as determinants of obesity, thus excluding important obesity factors, such as social class, environment, genetic constitution, hormonal status, and personality traits. Some treatments are suggested, inspired by the main thesis of this perspective, that is, that obesity is a form of addiction to food motivated by a reward-deficiency trait, and maintained by the consequences of return to reward deficiency upon abstention from food intake.

https://doi.org/10.1017/neu.2013.18 Published online by Cambridge University Press

Addiction and dopamine

The World Health Organization (16) defined a behavioural, cognitive, and physiological state of addiction known as the dependence syndrome, characterised by a strong desire to obtain the abused substance, impaired ability to control its use, and persistent use of the substance, despite harmful consequences, with high priority given to the use of this substance rather than to other activities and responsibilities, increased tolerance, and followed sometimes by a physical withdrawal state upon cessation of use. This state develops after repeated substance use as the manifestation of identifiable neurobiological alterations. Drug abusers in general have low DA D_2 receptor levels in striatum and a low DA release (17), which is linked to the observation that repeated intake of addictive substances such as amphetamine or cocaine significantly downregulates available DA D_2 receptor levels, understandable as a compensation for the high and persistent DA concentration in the synaptic cleft (18). Gjedde et al. (19) showed that healthy Danish men who are more sensation-seeking than other healthy men have significantly fewer available DA receptors in striatum because a greater fraction are occupied by the increased extracellular DA. This greater dopamine in turn is thought to be the result of constant dopaminergic stimulation, yielding the lower binding potential (BP) of the receptors. At the same time, the tissue apparently compensates for the DA receptor occupation by generating additional receptors (Fig. 1).

In rats, sensation-seeking has been associated with the initiation of drug taking rather than with addiction, in contrast to impulsivity, which predicts the development of drug addiction (20). The results of a sibling study suggest that sensation-seeking tends to be an effect of drug use, whereas impulsivity is more likely to be the risk factor for addiction (21). Decreased DA $D_{2/3}$ receptor availability in ventral striatum has been noted in highly impulsive rats compared with non-impulsive rats (22), and Ishibashi et al. (23) recently found a negative correlation between dysfunctional impulsivity and availability of DA D_2 receptors in healthy men.

Individuals with fewer available DA receptors find the effect of methylphenidate more pleasant than do subjects with normal receptor availability who tend to find the effect aversive (24). In this study, the authors suggest that the given dose may have been too high for those with higher DA D_2 levels, and that a smaller dose may have had a more pleasant effect, suggesting that drug abusers in general suffer from lower DA gains in the striatum (17,19,25).

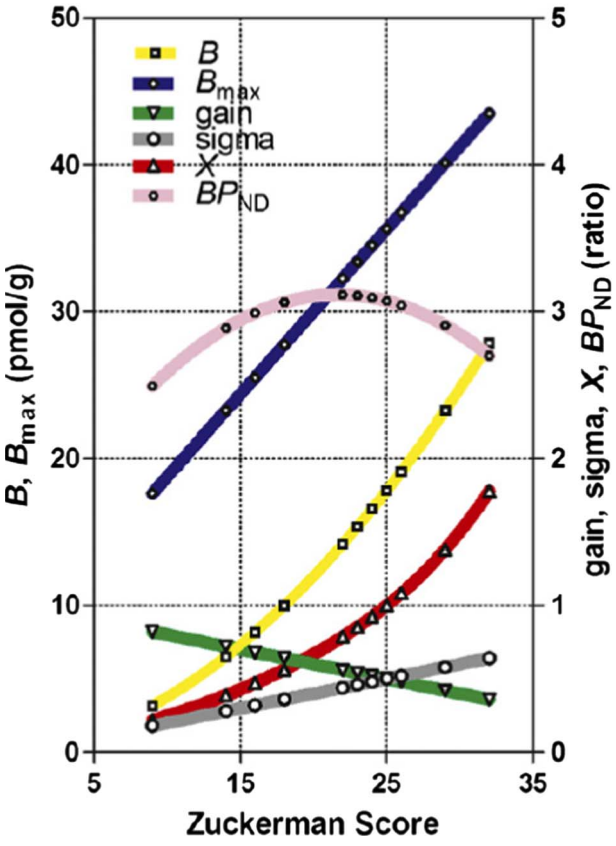

Fig. 1. Dopaminergic neurotransmission in relation to the Zuckerman score found by the Zuckerman questionnaire that reveals how sensation-seeking a person is. Subjects found furthest to the right of the figure are the most sensation-seeking. These individuals also have the largest amount of $D_{2/3}$ receptors (blue line), the largest percentage of occupied receptors (grey line), the smallest neurobiological response to dopamine (green line), and a reduced binding potential of the receptors (pink line). The neurobiology of the individuals with the highest binding potential in the middle is optimal. The figure is taken from Gjedde et al. (19).

Habituation

First-time ingestion of a palatable food is the key to release DA into the nucleus accumbens (NA) and prefrontal cortex (PFC). Repeated ingestion of the same food releases DA into the PFC and into the core of the NA, whereas DA release into the shell of the NA is diminished because of habituation or learning. Addictive substances such as morphine, nicotine, amphetamine, and cocaine are characterised by failure of habituation; instead, they release DA into the shell of the NA upon each exposure, with strengthened learning at each instance (26). Everitt and Robbins describe a possible association between long-term substance abuse and changing response locations in the brain. According to these authors, prefrontal cortical regions are active at the initiation of drug abuse, but the response to drug

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intake eventually and gradually shifts to the striatum, as the response of the PFC declines. The shift of focus in the brain reflects the transition from intake of the drug for enjoyment to the habitual use of the drug. After prolonged drug intake, a further shift takes place, as the response of the dorsal striatum now exceeds the response of the ventral striatum (predominantly NA), which may reflect the compulsive consumption of the drug (27). It is a reasonable interpretation of these transitions that they are initiated by highly active dopaminergic transmission in the shell of the NA, related to abuse of the drug. The shell of the NA affects the core of the NA, which in turn affects the central striatum (mainly nucleus caudatus) with passage to the dorsolateral striatum (mainly putamen) through a dopaminergic pathway (28). However, the authors acknowledge that there are no sharp distinctions among the three stages.

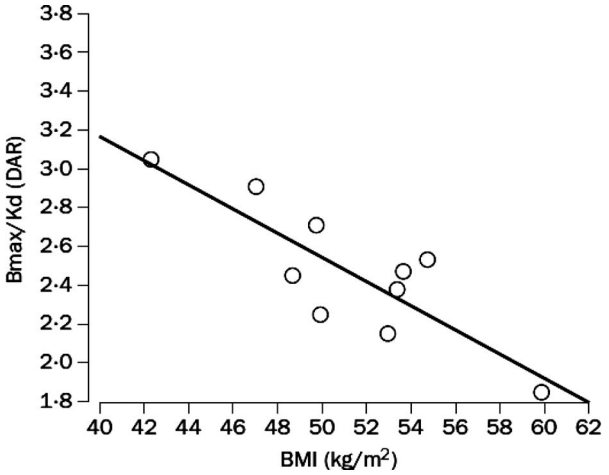

Fig. 2. Linear regression between the dopamine D_2 receptor availability and body mass index (BMI) in severe obese subjects. The figure is taken from Wang et al. (29).

Food addiction

The neurobiological alterations observed in drug abusers, including fewer available DA D_2 receptors, also appear in obese subjects with body mass indices (BMI) above 40 (29), with direct comparison of the two groups (30) showing that greater obesity is associated with lower receptor availability (Fig. 2). Subjects with BMI above 40 also have lower metabolic rates in PFC (17). In a pilot study, the DA D_2 receptor availabilities (BP_{ND}) rose as the BMI fell in four out of five women with gastric bypass surgery (31), whereas another bariatric surgery study gave opposite results (32). A questionnaire examination by Davis and Fox of 369 subjects revealed an inverted U shape of the correlation between BMI and reward sensitivity (Fig. 3) (33), indicating increasing reward sensitivity until a peak at BMI of 30. After the peak, the sensitivity declined with increasing BMI. Recent results also reveal a correlation between binge eating and increased secretion of DA in the striatum (34), as well as weight gain and reduced striatal response to palatable food (35). Haltia et al. (36) found no significant difference in DA receptor BP_{ND} in relevant brain areas at baseline between overweight to mildly obese individuals and individuals with a normal body weight. In this study, the striatal response to i.v. glucose was characterised by increased BP in women but decreased BP in men, regardless of body weight. Davis and Claridge suggest that both anorexic and bulimic patients may be considered as addicts, because their position on the addiction scale according to Eysenck's personality questionnaire resembles those of drug abusers in this study (37).

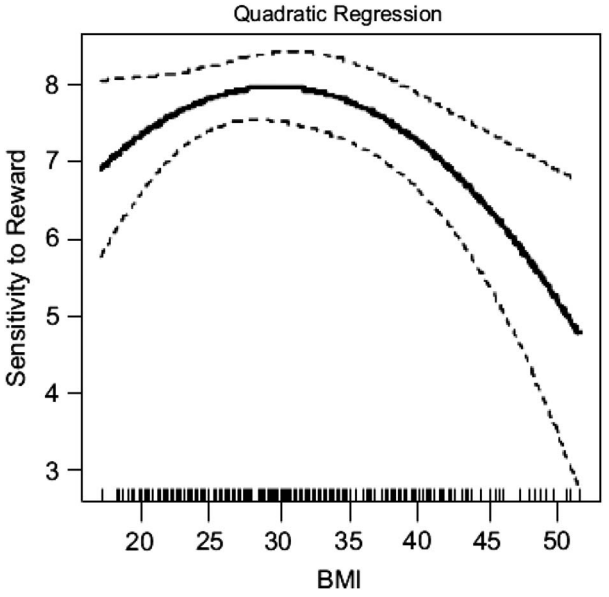

Fig. 3. The correlation between body mass index (BMI) and reward sensitivity, where 95% of the subjects are located within the dotted curves. The figure is taken from a study by Davis and Fox (33).

Bohon et al. found differences in which brain regions were active in emotional eaters versus non-emotional eaters in response to food, both in depressed and normal moods. In addition, the emotional eaters had higher depressive symptoms and a higher expectation that the eating would eliminate the negative affect and alleviate boredom (38). Gearhardt et al. found elevated activity in relevant brain areas during palatable food anticipation in subjects with food addiction versus non-food addicts. Further, decreased activity was seen in left lateral OFC during food intake in the food addiction group versus non-food addicts (39). The food addiction versus non-food addiction groups in this study were assessed with the Yale Food Addiction Scale (YFAS), developed in accordance with the DSM-IV-TR substance dependence criteria

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(40). Finally, there is some evidence that eating disorders, particularly bulimia nervosa (BN), are associated with the use of psychoactive substances (41). Most of these human studies point to the pathological basis of food addiction as a real disorder, although the role of dopaminergic neurotransmission in this context is not clear.

Indeed, several animal studies show that sugar is addictive. Colatuoni et al. found that intermittent excessive sugar consumption leads to opioid dependence in rats (42), in agreement with the review of animal studies by Fullerton et al. (10). The authors hold that ingestion of sugar causes additional reward by opioids, with possible increase of the affinity and number of opioid receptors, which leads to binge eating and obesity. In a review of rat studies, Avena et al. suggest that sugar under some conditions can be addictive, with both neurochemical and behavioural effects (43). In one such study, Rada et al. intermittently fed sucrose and chow to rats for 21 days. The intermittent feeding did not blunt the DA release in the NA shell, in contrast to three groups of rats, one with ad libitum access to sugar and chow, a second group that only tasted sugar twice, and a third group that had intermittent access only to chow (44). These results may indicate a mechanism of reinforced habituation. Avena et al. argue that sugar acts as a substance of abuse when it is consumed in a "binge-like" manner. Furthermore, the authors explain that the daily intermittently sucrose- and chow-fed rats did not gain weight because of compensation for the extra sucrose calories consumed by decreasing their chow intake. Another neurobiological indication of sugar as a drug of abuse is the result of a study on rats by Bello et al., in which 7 days of repeated sugar availability decreased the DA D_2 receptor binding in the striatum (45). In a recent study, rats intermittently fed palatable high-fat sweet pellets developed binge eating and gained significantly more weight than rats with ad libitum access to the same pellets, although no significant withdrawal symptoms were seen between the two groups, apart from the number of times cages were crossed (46), which suggests fat as a possible anxiety reducer. Overall, there is compelling evidence that sugar in the refined form and in relatively large amounts is pathologically addictive in rodents.

Caloric restriction

Pothos et al. found that restricted eating with weight loss in rats lowered the extracellular DA concentration by 20–50% in the NA, but not in the striatum or the PFC. Intake of regular rodent chow in this study resulted in a lower percentage DA release in the 20–30% underweight rats, compared with the control group, whereas amphetamine injection administered locally into the NA caused greater release of DA in the underweight rats than in the control rats. No upregulation of DA receptors compensated for the low levels of DA in the accumbens of the underweight rats (47). Carr and Kim later showed that chronic food restriction raises the reward to substances that bind to DA receptors in rats (48). Thus, the reward threshold is lower in the group with food restriction than in those with ad libitum access to food, and the restricted group appears to achieve a greater gain from DA when release is elicited by psychoactive substances.

With respect to the effects of reduced amounts of calories consumed by humans, Polivy and Herman indicate that restrictive diets provoke binge eating (49). In this review based on both clinical and experimental studies, it is postulated that caloric restriction may lead to eating disorders. Years later, Bulik et al. examined 108 women with BN and concluded that eating disorders mainly but not always occur after dieting (50). In an experiment, 27 obese women were randomly assigned to an exercise group or a caloric restriction group, where participants ate 500 fewer calories every day than usual, or to a control group, for 7 weeks. At weeks 4 and 6, all subjects participated in a laboratory session designed to assess food intake. Results showed that the subjects in the caloric restriction group ate significantly more than the subjects in either the exercise or the control group (51). Ogden described a tendency to all-or-nothing patterns of thoughts of dieting individuals, where even a slight excession of 1 day's quota could lead to binge eating (52). These findings suggest that a diet as a deliberately chosen psychological restriction can cause overeating. Frank et al. found that patients who recovered from anorexia nervosa (AN) had increased $D_{2/3}$ receptor binding in the antero-ventral striatum, compared with control subjects (53). It is not known whether the increase was due to increased density of the DA $D_{2/3}$ receptors, or increased availability caused by reduced intrasynaptic DA, and hence reduced competition with the radioligand.

The inverted U as a model of relations among reward conditions

The graphs of Figs. 2 and 3 are equivalent functions of BMI above the value of 40, implying that the available DA D_2 receptors and reward sensitivity may share a common mechanism in obese individuals, with further reductions of both with further weight gain. This relationship is consistent with trends suggested by Fig. 1, in which the number of available receptors (equivalent with the BP) corresponds to the measure of reward sensitivity shown in

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Fig. 3, both expressing inverted U shapes. Figure 1 also shows that the DA $D_{2/3}$ receptor availability declines as the sensation-seeking propensity grows. When compared with the information shown in Figs. 2 and 3, the relation suggests that overweight individuals become increasingly sensation-seeking as the body weight rises. Together, the three curves work as a model of the efficiency of a given individual's reward system. For example, the undernourished rats from the study of Pothos et al. (47) hold positions at the left of the inverted U shape (Fig. 4), which is consistent with the lower quantities of DA released by the intake of ordinary foods and implies reduced reward sensitivity. The increased DA excretion elicited by the amphetamine administration to the rats suggests that the gain of reward from the DA release, because of a psychoactive substance, is highest at the low BP and low reward sensitivity at the left of the inverted U shape, where the effect on euphoria is greater than at the peak of the inverted U. The feeling of euphoria seems to depend of the rate at which the extracellular DA concentration rises to abnormally high levels from baseline (17). Subjects located to the right of the peak of the inverted U found the effect of psychoactive substances more pleasant than subjects with normal DA receptor levels, presumably because of decreased availability of DA D_2 receptors (Fig. 4) (24), which suggests that the change of extracellular DA concentration is also greater at the low BPs on the right side. Thus, the reward from the DA release by a psychoactive substance seems to be higher at the extremes of the inverted U than at the peak. Another possible explanation holds that both gain and rise of dopamine are greatest at the peak, but the effect is unpleasant to the individual because of its magnitude. It is not directly clear where the former anorexic patients of Frank et al. (53) fit on the inverted U. The increased BP of [^{11}C]raclopride, hypothesised to be due to a reduction of DA release, suggests a shift from the right leg towards the centre of the inverted U, which is not consistent with the low BMI values of these patients. The increased receptor density hypothesis, on the other hand, suggests a shift from the left leg towards the centre, which corresponds to the elevated DA receptor binding as well as their BMI (22 ± 3), presumably as in the case of undernourished rats that resume feeding (Fig. 4).

Frieling et al. showed that patients with AN have hypermethylation of the DA receptor D_2 gene promotor, such that this gene is significantly less transcribed in these patients than in control subjects. Patients with BN, on the other hand, have lower DA receptor D_2 gene transcription than control subjects but higher than in AN patients, albeit not

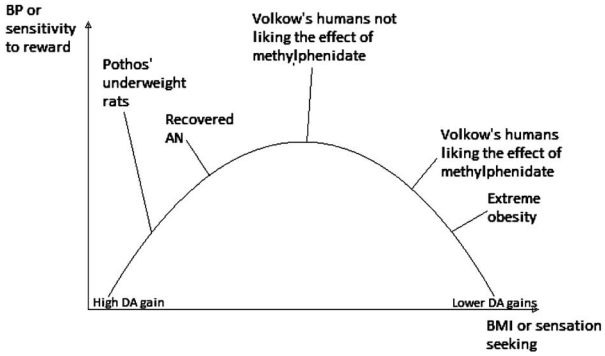

Fig. 4. The inverted U model that unites the three previous figures. Optimal dopaminergic reward occurs at the top in the middle, whereas reward-deficiency syndrome (RDS) is hypothesised associated with the extremities of the inverted U.

significantly (54). In the light of this study, the former AN patients best fit the left side of the inverted U.

Johnson and Kenny found that obese rats addicted to palatable foods have significantly fewer DA D_2 receptors in total compared with normally fed rats (55), but the 'sensation-seeking' propensity of individual rats is not known, of course. This is in contrast to a study of male humans, in which Gjedde et al. (19), on the basis of a mathematical model of the inverted U concept, estimated that more sensation-seeking but otherwise normal men of normal body weight had fewer available DA $D_{2/3}$ receptors but greater total number of DA $D_{2/3}$ receptors. We suggest that the reward-deficiency syndrome (RDS) (12) is linked to the extremities of the inverted U, implying that reward deficiency can arise from an absence of stimuli in the presence of a high gain at the left extremity, as well as from a surfeit of stimulation with low gain at the right extremity.

Discussion

The complexity of obesity

Although it has been shown that foods such as sugar can be addictive, it is noteworthy that sugar addiction in rats does not produce obesity, unless it is mixed with fat. In a recent commentary, obesity was held to be the result of chronic psychosocial stress rather than sugar addiction in humans, as excessive sugar ingestion reduces the intake of other foods (56,57).

The role of addiction in obesity is likely complex. Whereas striatal DA $D_{2/3}$ receptor downregulation is seen in compulsive drug use and in extremely obese people, the changes in dopaminergic neurotransmission in mild to moderate obesity are unclear. In the Wang et al. paper (29), which reports decreased striatal DA $D_{2/3}$ levels in the extremely obese, it is

https://doi.org/10.1017/neu.2013.18 Published online by Cambridge University Press

noteworthy that the least obese subject in the obese group with BMI of 42 had striatal DA $D_{2/3}$ levels actually higher than the mean of the control group. There are little data regarding DA $D_{2/3}$ levels for mildly to moderately obese subjects. Dopaminergic neurotransmission alone most likely may not be able to explain obesity because of its multiple elements. The few studies of extremely obese individuals hardly give us a platform, from which to draw conclusions about the development of food addiction in relation to obesity.

The metabolic regulators insulin, leptin, and ghrelin are linked to the food reward mechanisms, as reviewed by Figlewicz and Sipols who hold that insulin and leptin attenuate the rewards from dopaminergic neurotransmission that are elicited by ghrelin (4). Dunn et al. found that acyl ghrelin levels may be a more important indicator of dopaminergic neurotransmission than BMI (58). Gejl et al. found that glucagon-like peptide-1 alters brain glucose during hyperglycemia (59). These regulatory hormones are central to the understanding of obesity, and further investigations into the links to RDS (12) are mandatory.

Causes of reward deficiency

As the role of dopaminergic neurotransmission in the development of obesity remains unclear, BMI is less appropriate as the abscissa in the inverted U model of Fig. 4. From the study of Davis et al., it seems that approximately only one fourth of obese people, with mean BMI under 40, can be diagnosed as food addicted assessed from the YFAS (60). This is somewhat consistent with the equivocal neurobiology of mild to moderate obesity, although 24.1 percent of the obese subjects in the non-addicted group had binge eating disorder (BED) in this study. Thus, it is likely that BED would qualify as a food addiction disorder on brain scans, at least in rats. To evaluate dopaminergic neurotransmission as a marker of food addiction in humans, subjects would answer an addiction questionnaire such as YFAS or take a personality test, in addition to the brain scans.

In search for the origin of the lower availability of DA receptors in people who are not yet addicted, the contending mechanisms are genetics and epigenetics or environment (12,17). In terms of the epigenetics, it is possible that high levels of sugar consumption in the Western world (61–63) plays an important role (64), considering the finding that ingestion of high quantities of refined sugar may lead to opioid dependence and increased DA release in the NA of rats (44) and in the striatum of obese individuals who suffer from BED (34), although the latter study tested favourite foods rather than sugar. The increased release of DA may accompany the development of RDS, possibly associated with specific abnormalities (12) of the interaction of genotype and environment, making some people more vulnerable to obesity.

Regarding genetics. Stice at al. found that adolescents at high versus low risk of future obesity had higher sensitivity to food reward, indicating that addiction starts as hyperreward that mimics reward deficiency following food/drug induced downgrading (65). Davis et al. (66) found a correlation between BED and a mu-opioid receptor gene. Further, Sinha et al. show a correlation between vulnerability to stress and addiction or relapse (67). However, we cannot exclude an environmental influence in either of these studies.

The relationship between restrictive diets and overeating by patients suffering from BN can be explained in part by a psychological process of all-or-none (52) and in part by consideration of the neurobiological relationship between malnutrition and reduced reward from natural enhancers such as food, at least in rats. It is possible that undernourished rats gain substantial rewards only when they overeat. Some researchers working with rodents utilise the effects of food deprivation in order to rapidly place the rodents in a state of addiction. In humans, it is likely that reduced intake of calories similarly attenuates the biochemical mechanism of reward, which after a while may trigger the irresistible urge to engage in binge eating (49–51). In rodents as well as people, a relation with reward deficiency is a strong possibility. Thus, it is an important question, which is the bigger issue, the sugar or the restriction?

Restoring reward efficiency

As far as we know, there is no evidence of upregulated dopaminergic activity or density of DA $D_{2/3}$ receptors in the accumbens associated with weight loss. In the study by Pothos et al. (47), the absence of compensatory DA D_2 receptor upregulation can be explained by the absence of prior downregulation of receptors, as rats were starved from a baseline of normal bodyweight rather than obesity. The findings of the upregulation associated with bariatric surgery are inconsistent. However, in contrast, we argue that the upregulation is bound to happen when physical withdrawal symptoms last for a limited period of time (5–7 days) after removal of the abused substance (68). Years after the termination of abuse, recovered abusers remain at risk of relapse as a result of the learning imposed by the abuse on basal ganglia mechanisms by means of elevated DA release into the shell of the NA (27,28). In addition the high risk of relapse in recovered addicts suggests that the number of occupied DA

https://doi.org/10.1017/neu.2013.18 Published online by Cambridge University Press

receptors is kept constant by alternative behaviour with dopaminergic effects, if it actually raises DA release as a sufficient substitute for the earlier abuse, even when palatable foods fail to elicit the same quantities of released DA as the erstwhile drugs. At rehabilitation clinics, young drug abusers significantly gain weight during the stay. One partial explanation of the weight gain is the satisfaction of reward needs with food (69). Another reason for the weight gain may be the use of psychotropic medication (70). Third, the association of prolonged drug abuse with low body weight may result in a significant weight gain upon return to normal life. The positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies on humans reviewed by Volkow et al. (71) confirm that the number of available DA receptors remains low in the striatum, even after prolonged drug freedom.

Overall, it is a clue to the hypothetical condition when an obese individual, with a presumed addiction to rewards from food and an established attenuation of gain from dopaminergic neurotransmission, lowers the turnover of DA by avoiding both refined sugar and periods of overeating, immediately senses the lack of dopaminergically generated reward, as predicted by the hypothesis. Therefore, it is reasonable to conclude that sufficiently strong effects of caloric restriction alone, in severely obese individuals but possibly also in people of normal weight, may lead to compensatory behaviours such as overeating. This inference is made with the caveat that neurobiological and psychological differences may exist between, on one hand, the individuals with eating disorders and, on the other hand, people who just happen to be overweight, as well as the differences that exist between rats and humans. Because recent studies are lacking, we do consider the correlation to be insufficiently supported by evidence, but as a hypothesis it is indeed ready for further investigation. It is supported by the results of the meta-analysis offered by Fabricatore et al. (14), who focus on the relation between weight loss and the change in depressive symptoms and conclude that supervised exercise is positively related to changes in symptoms of depression among participants engaged in lifestyle modification programs.

The obese individuals, with whom this perspective is concerned, appear to occupy positions to the right of the centre of the inverted U curve of the relation of sensitivity to reward vs BMI (Fig. 4). The position implies a trait of high sensation-seeking propensity, manifested as an irresistible urge to overeat. The overeating of refined sugar and high-calorie foods keep these individuals at the right of centre of this curve, as the binges and the overeating keep the DA receptors relatively more occupied than at the centre of the curve. The vicious circle can only be broken by blocking the excessive food intake, seen from a neurobiological point of view. We predict that initially this may be difficult because everyday life may be less rewarding because of the low gain from dopaminergic neurotransmission at the right extremity of the inverted U, consistent with the low availability of the DA D_2 receptors, but perhaps also because of low mood inhibition by serotonin, a neuromodulator normally released by carbohydrate ingestion, ultimately accompanied by the downregulation of serotonin receptors (18).

Deficits of serotonin have been linked to low mood disorders and depression, induced by dieting (15), although Fabricatore et al. (14) find that weight loss associated with lifestyle modification lowers the symptoms of depression, and Meule et al. (72) find that rigid control of eating behaviour is correlated with food craving, compared with a more flexible control of eating behaviour. Thus, Hagan et al. (73) suggest that decline of mood in relation to dieting is associated with actual starvation. From the Minnesota starvation experiment, this correlation appears clear (74). However, we hypothesise that, with time, as the individuals in question move to the left towards the peak of the inverted U with the accompanying rise of BP and available DA receptors, they find it increasingly easy to maintain a normal eating habit. For this progression to proceed in the healthiest and fastest way possible, DA-releasing stimulants, including opioid-releasing substances, must be avoided, because the stimulants maintain the low receptor availability and low gain from dopaminergic neurotransmission. Of course, it is important to provide the body with sufficient nutrients to avoid craving, and to enjoy food of good quality. The limitations imposed by a change of lifestyle may be suitable only to people who are sufficiently motivated by surplus energy.

In review, Blum et al. recommend that individuals with signs of RDS to be treated with selected amino acids such as D-phenylalanine, L-phenylalanine, L-glutamine, L-tyrosine, and L-5-hydroxytryptophan, and with chromium salts, which are held to stimulate mechanisms that mimic the brain reward cascade and induce physiological release of serotonin and DA without side effects (75). Several studies are cited as evidence of effects of the recommended treatment with a list of the alleged function of each amino acid (76). The intended goal of the supplementation is release of DA in physiologically moderate amounts. A similar effect may be achieved by other more alternative activities thought to abate the sensation of reward deficiency, such as exercise, yoga, or meditation (77), which are all associated with claims of reward. Exercise is already a staple element of the Western wellness lifestyle, and release

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of DA as a result of exercise in the best of cases may contribute to the acquisition of healthier habits.

Habituation and associative amplifiers

Although the deficient effects of DA and serotonin may make it difficult to break a habit of overeating in the short term, as long as other concurrent abuse is avoided, actual habituation of overeating is a potential obstacle in the longer term that may trigger overeating behaviour in the presence of associative amplifiers (27). Possible individual triggers to pathological overeating may be stress or feelings of loneliness or inadequacy (78), acting as associative amplifiers. Group therapy may be of value, rendering patients aware of the presence of individual associative amplifiers and psychosocial stress, as well as cognitive and dialectic behaviour therapies, which have been shown to be effective in eating disorders (79,80).

Individuals with a desire for lifestyle change, as well as substance abusers, may benefit from more studies of the possible forms of optimisation of DA release and reversal of receptor upregulation, accompanied by studies of the induction of reward sensations by physiological means.

Acknowledgement

The authors gratefully acknowledge the support from The University of Copenhagen.

References

1. Hoebel BG, Hernandez L, Schwartz DH, Mark GP, Hunter GA. Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior – theoretical and clinical implications. Ann N Y Acad Sci 1989; **575**:171–193.
2. Kelley AE, Baldo BA, Pratt WE. A proposed hypothalamic-thalamic-striatal axis for the integration of energy balance, arousal, and food reward. J Comp Neurol 2005;**493**:72–85.
3. De Silva A, Salem V, Long CJ et al. 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 2011;**14**:700–706.
4. Figlewicz DP, Sipols AJ. Energy regulatory signals and food reward. Pharmacol Biochem Behav 2010;**97**:15–24.
5. Erikssen G. Physical fitness and changes in mortality – the survival of the fittest. Sports Med 2001;**31**:571–576.
6. Rot M, Collins KA, Fitterling HL. Physical exercise and depression. Mt Sinai J Med 2009;**76**:204–214.
7. Platek SM, Keenan JP, Shackleford TK. Evolutionary Cognitive Neuroscience. London: The MIT press, 2007.
8. Helmich I, Latini A, Sigwalt A et al. Neurobiological alterations induced by exercise and their impact on depressive disorders [corrected]. [Erratum appears in Clin Pract Epidemiol Ment Health. 2010;7:106]. Clinical Practice & Epidemiology in Mental Health [Electronic Resource]: CP & EMH;6:115–25.
9. Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ. Modern Nutrition in Health and Disease. Baltimore: Lippincott Williams & Wilkins, 2006.
10. Fullerton DT, Getto CJ, Swift WJ, Carlson IH. Sugar, opioids and binge eating. Brain Res Bull 1985;**14**:673–680.
11. Cohen MX, Young J, Baek JM, Kessler C, Ranganath C. Individual differences in extraversion and dopamine genetics predict neural reward responses. Cogn Brain Res 2005;**25**:851–861.
12. Blum K, Sheridan PJ, Wood RC et al. The D-2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996;**89**:396–400.
13. McInnis KJ. Diet, exercise, and the challenge of combating obesity in primary care. J Cardiovas Nurs 2003;**18**:93–100; quiz 101-2.
14. Fabricatore AN, Wadden TA, Higginbotham AJ et al. Intentional weight loss and changes in symptoms of depression: a systematic review and meta-analysis. Int J Obes 2011;**35**:1363–1376.
15. Bear MF, Connors BW, Paradiso MA. Neuroscience: Exploring the Brain, 3rd edition. Baltimore: Lippincott Williams and Wilkins, 2006.
16. World Health Organization. http://www.dimdi.de/static/en/klassi/icd/icd10/onlinewho/index.htm
17. Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction – results of imaging studies and treatment implications. Arch Neurol 2007;**64**: 1575–1579.
18. Seger D. Cocaine, metamfetamine, and MDMA abuse: the role and clinical importance of neuroadaptation. Clin Toxicol 2010;**48**:695–708.
19. Gjedde A, Kumakura Y, Cumming P, Linnet J, Moller A. Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. Proc Nat Acad Sci U S A 2010;**107**:3870–3875.
20. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. Science 2008;**320**:1352–1355.
21. Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW. Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. Biol Psychiatry 2010;**68**:770–773.
22. Dalley JW, Fryer TD, Brichard L et al. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 2007;**315**:1267–1270.
23. Ishibashi K, Robertson C, Brown A et al. Differential roles of dopamine D1- and D2-like receptors in impulsivity: a preliminary PET study. J Cereb Blood Flow Metab 2012;**32**:S82–S83.
24. Volkow ND, Wang GJ, Fowler JS et al. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D-2 receptor levels. Am J Psychiatry 1999; **156**:1440–1443.
25. Martinez D, Gil R, Slifstein M et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biol Psychiatry 2005;**58**:779–786.
26. Di Chiara G, Bassareo V. Reward system and addiction: what dopamine does and doesn't do. Curr Opin Pharmacol 2007;**7**:69–76.

https://doi.org/10.1017/neu.2013.18 Published online by Cambridge University Press

27. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addition: from actions to habits to compulsion. Nat Neurosci 2006;**9**:979–979.
28. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci 2000;**20**:2369–2382.
29. Wang GJ, Volkow ND, Logan J et al. Brain dopamine and obesity. Lancet 2001;**357**:354–357.
30. Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J Addic Dis 2004;**23**:39–53.
31. Steele KE, Prokopowicz GP, Schweitzer MA et al. Alterations of central dopamine receptors before and after gastric bypass surgery. Obes Surg 2010;**20**:369–374.
32. Dunn JP, Cowan RL, Volkow ND et al. Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings. Brain Res 2010;**1350**:123–130.
33. Davis C, Fox J. Sensitivity to reward and body mass index (BMI): evidence for a non-linear relationship. Appetite 2008;**50**:43–49.
34. Wang GJ, Geliebter A, Volkow ND et al. Enhanced striatal dopamine release during food stimulation in binge eating disorder. Obesity 2011;**19**:1601–1608.
35. Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. J Neurosci 2010;**30**:13105–13109.
36. Haltia LT, Rinne JO, Merisaari H et al. Effects of intravenous glucose on dopaminergic function in the human brain in vivo. Synapse 2007;**61**:748–756.
37. Davis C, Claridge G. The eating disorders as addiction: a psychobiological perspective. Addict Behav 1998;**23**: 463–475.
38. Bohon C, Stice E, Spoor S. Female emotional eaters show abnormalities in consummatory and anticipatory food reward: a functional magnetic resonance imaging study. Int J Eat Disord 2009;**42**:210–221.
39. Gearhardt AN, Yokum S, Orr PT et al. Neural correlates of food addiction. Arch Gen Psychiatry 2011;**68**:808–816.
40. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. Appetite 2009;**52**:430–436.
41. Corcos M, Nezelof S, Speranza M et al. Psychoactive substance consumption in eating disorders. Eat Behav 2001;**2**:27–38.
42. Colantuoni C, Rada P, McCarthy J et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes Res 2002;**10**:478–488.
43. Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 2008;**32**:20–39.
44. Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience 2005;**134**:737–744.
45. Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum. Neuroreport 2002;**13**:1575–1578.
46. Bocarsly ME, Berner LA, Hoebel BG, Avena NM. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: implications for nutrient-specific food addiction behaviors. Physiol Behav 2011;**104**:865–872.
47. Pothos EN, Creese I, Hoebel BG. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. J Neurosci 1995;**15**:6640–6650.
48. Carr KD, Kim GY, de Vaca SC. Rewarding and locomotor-activating effects of direct dopamine receptor agonists are augmented by chronic food restriction in rats. Psychopharmacology 2001;**154**:420–428.
49. Polivy J, Herman CP. Dieting and binging – a causal analysis. Am Psychol 1985;**40**:193–201.
50. Bulik CM, Sullivan PF, Carter FA, Joyce PR. Initial manifestations of disordered eating behavior: dieting versus binging. Int J Eat Disord 1997;**22**:195–201.
51. Wardle J, Beales S. Control and loss of control over eating: an experimental investigation. J Abnorm Psychol 1988;**97**: 35–40.
52. Ogden J. The Psychology of Eating – From Healthy to Disordered Behaviour. Blackwell Publishing, 2003.
53. Frank GK, Bailer UF, Henry SE et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and C-11 raclopride. Biol Psychiatry 2005;**58**:908–912.
54. Frieling H, Römer KD, Scholz S et al. Epigenetic dysregulation of dopaminergic genes in eating disorders. Int J Eat Disord 2010;**43**:577–583.
55. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 2010;**13**:635–641.
56. Peters A. Does sugar addiction really cause obesity? Front Neuroenergetics 2012;**3**.
57. Peters A, Kubera B, Hubold C, Langemann D. The selfish brain: stress and eating behavior. Front Neurosci 2011;**5**.
58. Dunn JP, Kessler RM, Feurer ID et al. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. Diabetes Care 2012;**35**:1105–1111.
59. Gejl M, Egefjord L, Lerche S et al. Glucagon-like peptide-1 decreases intracerebral glucose content by activating hexokinase and changing glucose clearance during hyperglycemia. J Cereb Blood Flow Metab 2012;**32**: 2146–2152.
60. Davis C, Curtis C, Levitan RD et al. Evidence that 'food addiction' is a valid phenotype of obesity. Appetite 2011; **57**:711–717.
61. Langlois K, Garriguet D. Sugar consumption among Canadians of all ages. Health Rep 2011;**22**:23–27.
62. Wang YC, Bleich SN, Gortmaker SL. Increasing caloric contribution from sugar-sweetened beverages and 100% fruit juices among US children and adolescents, 1988–2004. Pediatrics 2008;**121**:E1604–E1614.
63. Thornley S, Stewart A, Marshall R, Jackson R. Per capita sugar consumption is associated with severe childhood asthma: an ecological study of 53 countries. Prim Care Respir J 2011;**20**:75–78.
64. Hodgkins C, Frost-Pineda K, Gold MS. Weight gain during substance abuse treatment. J Addict Dis 2007;**26**:41–50.
65. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci 2011;**31**: 4360–4366.

https://doi.org/10.1017/neu.2013.18 Published online by Cambridge University Press

66. Davis CA, Levitan RD, Reid C et al. Dopamine for "Wanting" and Opioids for "Liking": a comparison of obese adults with and without binge eating. Obesity 2009;**17**:1220–1225.
67. Sinha R, Fox HC, Hong KIA et al. Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. Arch Gen Psychiatry 2011;**68**:942–952.
68. Miller NS, Gold MS. Management of withdrawal syndromes and relapse prevention in drug and alcohol dependence. Am Fam Physician 1998;**58**:139–146.
69. Hodgkins CC, Jacobs WS, Gold MS. Weight gain after adolescent drug addiction treatment and supervised abstinence. Psychiatr Ann 2003;**33**:112–116.
70. McCloughen A, Foster K. Weight gain associated with taking psychotropic medication: an integrative review. Int J Ment Health Nurs 2011;**20**:202–222.
71. Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 2004; **47**:3–13.
72. Meule A, Westenhöfer J, Kübler A. Food cravings mediate the relationship between rigid, but not flexible control of eating behavior and dieting success. Appetite 2011;**57**: 582–584.
73. Hagan MM, Tomaka J, Moss DE. Relation of dieting in college and high school students to symptoms associated with semi-starvation. J Health Psychol 2000;**5**:7–15.
74. Keys A. Experimental human starvation – general and metabolic results of a loss of one 4th the body weight in 6 months. Federation Proceedings 1946;**5**:55–55.
75. Blum K, Chen ALC, Chen TJH et al. Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary. Theor Biol Med Model 2008;**5**.
76. Blum K, Chen TJH, Chen ALC et al. Dopamine D2 receptor Taq A1 allele predicts treatment compliance of LG839 in a subset analysis of pilot study in the Netherlands. Gene Ther Mol Biol 2008;**12**:129–140.
77. Kjaer TW, Bertelsen C, Piccini P et al. Increased dopamine tone during meditation-induced change of consciousness. Cogn Brain Res 2002;**13**:255–259.
78. Heatherton TF, Baumeister RF. Binge eating as escape from self-awareness. Psychol Bull 1991;**110**:86–108.
79. Wisniewski L, Kelly E. The application of dialectical behavior therapy to the treatment of eating disorders. Cogn Behav Prac 2003;**10**:131–138.
80. Iacovino JM, Gredysa DM, Altman M, Wilfley DE. Psychological treatments for binge eating disorder. Curr Psychiatry Rep 2012;**14**:432–446.

https://doi.org/10.1017/neu.2013.18 Published online by Cambridge University Press