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FOOD ADDICTION (A MEULE, SECTION EDITOR)

Lost in Translation? On the Need for Convergence in Animal and Human Studies on the Role of Dopamine in Diet-Induced Obesity

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Abstract

Purpose of Review Animal and human studies suggest that diet-induced obesity and plasticity in the central dopaminergic system are linked. However, it is unclear whether observed changes depend on diet or obesity, and whether they are specific to brain regions and cognitive functions. Here, we focus on neural and cognitive changes in frontostriatal circuits.

Recent Findings Both diet and obesity affect dopaminergic transmission. However, site and direction of effects are inconsistent across species and studies. Non-specific changes are observed spanning all frontostriatal loops, from sensory input to motivated behaviour. Given the impact of peripheral signals on central dopaminergic signalling and the interaction between the frontostriatal loops, modulation of dopamine likely propagates through all loops and, thus, affects behaviour on various levels of complexity.

Summary To improve convergence between animal and human studies on diet-induced obesity, animal studies should include sophisticated cognitive measures and diets resembling human obesogenic diets, and human studies should adopt diet interventions and longitudinal designs.

Keywords Obesity · Dopamine · Diet · Frontostriatal loops

Introduction

Obesity has been associated with prominent changes in dopamine transmission [1–3] and cognitive domains that are crucial for adaptive behaviour, such as motivation, decision-making, reinforcement learning and working memory [4–9]. Importantly, food-related but also general non-food-related cognitive differences have been recently highlighted in obesity [10–16]. However, animal studies contributed to the understanding that obesogenic *diet*, rather than adiposity itself, actually causes observed differences in dopamine transmission [17, 18••, 19–21].

Excellent obesity-related reviews have focused on either DA transmission [22], or cognition with little or no emphasis on the relation with dopamine [7, 11, 15]. Others have argued for dopamine-mediated cognitive changes in obesity [1–3, 8, 9, 23–27] paralleling findings from addiction research, with controversial opinions towards the existence of food addiction [22, 23, 28–31]. Here, we argue for a more detailed assessment on the relationship between dopamine and the variety of possibly dopamine-mediated cognitive changes in obesity.

Some reviews suggested a major role of reward function in obesity, which resonates well with abundant evidence for striatal dopamine alterations in both animals and humans. Others have argued for a deficit that is predominantly mediated by the prefrontal cortex (PFC) (e.g. [10, 32]), which is not well investigated regarding a direct link to the dopaminergic system yet. Both perspectives might mirror different angles of the same changes as dense anatomical connections exist

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between frontal and striatal regions. These connections are organised in functionally relevant *frontostriatal loops* that are strongly modulated by dopamine. This makes it important to examine the cognitive literature in obesity in the light of these frontostriatal loops.

Here, we will address the following open questions: First, do findings from animal and human studies on dopamine changes converge, given the different methodologies available to study the dopaminergic system in these species? Second, does a comprehensive picture emerge regarding major obesity-related cognitive differences and their possible association with frontostriatal loops? Third, can these differences be regarded as global, i.e. affecting several cognitive domains, or are they specific to, e.g. the food context? Fourth, to what extent are *diet*-induced dopamine differences responsible for the observed differences in cognitive domains? And fifth, what are candidate mechanistic links between diet and central dopamine?

In this review, we will summarise recent findings of obesity and diet-related differences in dopamine transmission, in particular in the striatum, from human and animal studies. We will then describe the different frontostriatal loops, followed by an evaluation of obesity-related differences in the sensory input to this circuit. Finally, we will discuss the neurocognitive profile of obesity within the theoretical framework of frontostriatal loops. We will point out major gaps in the literature, as well as challenges that need to be overcome in order to get at the heart of the role of dopamine in diet-induced obesity.

Obesity and Diet-Related Dopamine Differences

In humans, structural changes in the dopamine system can be imaged most directly with positron emission tomography (PET) using radioactively labeled ligands that bind to a specific substrate. Such studies have revealed obesity-related differences, in particular related to D2-receptor (D2R) (Appendix Table 1). D2R binding has been found to correlate positively to BMI in normal-weight to obese individuals in several studies [49, 52, 94], but not in others [57, 59, 71]. In the latter study, dopamine release did correlate positively with BMI in putamen and substantia nigra [59]. Another PET study revealed a positive relationship with BMI in the dorsal and lateral striatum, whereas a negative relationship was observed in the ventral striatum [53]. These, together with other inconsistent results concerning D2R binding in human obesity, have been proposed to reflect a quadratic relationship between severity of obesity and striatal D2R availability, or rather a U-shaped relationship with dopamine tone [2]. The idea of lower tone in overweight to mildly obese individuals is supported by a recent [18F] DOPA PET study [62•]. However, striatal dopamine transporter (DAT) binding as measured with single-photon emission computed tomography (SPECT) did not relate to BMI in a sample of normal-weight to severely obese participants [95], nor to self-reported ad libitum food intake in normal-weight participants [90•]. Importantly, due to the cross-sectional design of most human studies, it is debated whether or not the observed differences in dopamine transmission in humans are cause or consequence of obesity.

Rodent models allow for the investigation of more causal links between obesity and dopamine transmission and have begun to disentangle the effects of an obesogenic diet from adiposity. Short-term and chronic high fat diets (HFDs) as well as diet-induced obesity were shown to reduce D2R-mRNA and protein expression levels ([96–99], but see [100]) (Table 2). An elegant study suggests that diet-induced obesity may be the cause rather than the result of reduced D2R availability [18••]. The authors found decreased striatal D2R binding after a chronic HFD, despite unchanged D2R-mRNA or protein levels, which could be explained by receptor internalisation. D2R binding also did not predict weight gain, nor did deletion of D2Rs in striatal neurons increase risk for obesity. *Overexpression* of striatal D2Rs in development has been shown to causally relate to diet-induced obesity through its effect on energy expenditure and thermogenesis [103]. Effects of sugar on the dopamine system have also been observed, although the findings diverge. One study showed increased D2R-mRNA expression and decreased D2R-protein levels in the nucleus accumbens [104], whereas others found the opposite for the striatum as a whole [100]. This may be due to the specific striatal regions under study or the diet composition (for more details on diet composition and duration, see Appendix Table 2). Moreover, chronic HFD may also lead to reduced D1R-mRNA in the rat striatum ([97, 101], but see [18••, 105]) depending on diet composition [106]. One study showed reduced D1R signalling when a diet high in saturated, but not monounsaturated fats (palm oil vs. olive oil), was administered [101]. Finally, diet-related changes in dopamine synthesis [108], release [59, 102, 105] and uptake (DAT) [98, 99] have been observed.

In sum, excessive weight and chronic exposure to an obesogenic diet has been associated with changes in striatal dopamine transmission in humans and rodents, in particular related to D2Rs. The wide variety of observed diet-induced dopamine changes described above suggests a complex interplay between obesogenic diet and the different parts of the dopamine pathway. Future research is required to get a clearer picture of diet-induced dopamine changes in both obese and non-obese individuals and to unravel the mechanisms through which an obesogenic diet exerts its action on

the dopamine system (see Box 1 for potential mechanistic links). To translate findings from animal studies to human studies, it is crucial to increase convergence between the two fields. First, human studies with dietary interventions and dopamine measurements are needed. Second, diets in animal intervention studies should be more carefully designed in terms of composition and duration to mimic human obesogenic diets. Finally, a recent review emphasises the importance of the element of dietary choice in modelling the characteristics of human diet-induced obesity [109].

Metabolic factors interacting with dopamine

Endogenous homeostatic hormones, nutrients from the bloodstream such as triglycerides and inflammatory factors connect dopamine and obesity. They are related to adipose tissue and obesity and can also affect mesolimbic brain structures and thus dopamine-mediated cognitive function and reward processes. Below, examples are discussed of how insulin, leptin, ghrelin and inflammation factors may interact with dopamine, without aiming to be comprehensive. The reader is referred to recent reviews on nutritional lipids [110, 111], homeostatic and hedonic influencers on diet and obesity [112] and mechanisms of obesity-induced inflammation [113] for further information.

Insulin, Leptin and Ghrelin

In the healthy individual, various hormones are secreted into the bloodstream according to nutrient levels, satiation and nutritional state. Insulin is postprandially released from pancreatic β cells, promotes glucose utilisation and an anabolic metabolism and suppresses appetite centrally. Leptin is synthesised and stored in adipocytes in proportion to fat mass and adipocyte size [114, 115]. In obesity, insulin and leptin are often elevated (e.g. [116]), while (central) sensitivity to them is impaired [115]. Ghrelin, a gastric peptide, promotes food intake, is secreted in the fasting state and suppressed postprandially [117] in proportion to calorie content of the meal [119]. Fasting levels of the active form, acyl ghrelin, are often lower in obesity and eating disorders [118, 119], and levels decrease less after meals [118, 120]. Impaired insulin sensitivity might mediate this effect, independent of BMI [121].

For homeostatic functions, as well as regulation of food intake, the ability of insulin, leptin and ghrelin to cross the blood–brain barrier and bind to hypothalamic receptors is crucial [122]. Also, neurons in dopaminergic areas, e.g. ventral tegmental area (VTA), express receptors for leptin, insulin [123] and ghrelin [117, 124] thereby allowing for modulation of dopamine signalling. For instance, insulin-receptor binding in VTA reduced dopamine release in nucleus accumbens and induced long-term depression of excitatory synapses in rodents [125], which was proposed to explain previous findings of insulin-mediated inhibition of feeding and food seeking. Another link between insulin and dopamine exists in striatal insulin-receptor expressing interneurons that have been shown to modulate dopamine release in response to insulin stimulation [126]. Furthermore, peripheral insulin sensitivity correlated positively with dopamine levels in ventral striatum in human non-obese individuals [48] and, in line with that, negatively with D2R binding in obese participants [116]. Higher D2R binding may in fact reflect reduced dopamine levels. Insulin sensitivity may thus mediate obesity-related alterations in striatal dopamine levels. For a more detailed overview of insulin action in the human brain, see [127].

In addition, leptin can mediate effects of obesity on dopamine transmission (or vice versa). Leptin was found to correlate positively with BMI, as well as with D2R binding in the ventral striatum and caudate nucleus, again interpreted as reduced dopamine levels [116]. Only minutes after administration, leptin attenuated reactivity of VTA neurons to food cues [128]. In addition to a direct influence on the VTA, leptin can affect motivation for feeding via hypothalamic control over VTA [129•]. In contrast to leptin, ghrelin is associated with lower D2R binding in the ventral striatum, caudate nucleus and putamen and, in the fasting state, plays an important role in food reward sensitivity by modulating dopamine tone [116].

Inflammation Factors

Adipose tissue, notably macrophages, can secrete inflammatory cytokines, such as interleukin 6 (IL-6) or tumor necrosis factor alpha (TNF-α) [130]. As a result, chronic low-grade inflammatory state is often observed in obesity. Inflammation can lead to insulin resistance and diabetes [131], as well as dopamine changes, suggesting the possibility of a (causal) connection between inflammation and dopamine changes in obesity.

In humans, several studies investigated the effect of experimentally induced inflammation on striatal brain structures. In healthy participants, a reduction in ventral striatal activity during reward learning was observed following an increase of IL-6 [132, 133]. This led to lower reward and higher punishment sensitivity [133]. Furthermore, experimentally induced transient inflammation (IL-6, IL-8, TNF-α) was shown to enhance methylphenidate-induced dopamine release in the dorsal striatum (i.e. caudate nucleus and putamen) [134]. This supraphysiologic dopamine elevation due to inflammation might lead to reduced inhibitory control resulting in higher responsiveness to potentially addictive stimuli. For an excellent review of the role of dopamine in inflammation effects on motivation and motor function in clinical and non-clinical individuals, see [135].

Inflammation can also be affected by the above-mentioned metabolic factors and, as such, influence dopamine. Dysregulated metabolic factors might therefore sustain the inflammatory state observed in obesity. Leptin is considered a pro-inflammatory cytokine and increases in response to systemic inflammation and TNF-α [115]. Ghrelin has been shown to instead suppress pro-inflammatory cytokines in human monocytes and T cells [136].

Finally, dopamine may also act on metabolic and inflammatory factors, with possibly differential effects depending on receptor types and tissues. Adipocytes express D2Rs, and stimulation with quinpirole (D2R agonist) in rodents elicited increased expression of leptin and IL-6 in these cells [137], which counteracts the effect of dopamine. In a rat study, bromocriptine (D2R agonist) exerted a positive effect on metabolic syndrome parameters [138].

In summary, the relationship between insulin, leptin, ghrelin and dopamine is complex. It strongly depends on caloric state, time-scale (acute vs. chronic) and involves multiple mechanisms rather than one simplistic regulatory circuit. Furthermore, inflammation factors may interact with dopamine, metabolic factors or both.

Frontostriatal Loops

The striatum shares major connections with regions in the frontal cortex that are strongly modulated by dopamine and subserve adaptive behaviour. Across species, frontostriatal connections are organised in anatomically and functionally segregated loops [139–142] (Fig. 1). These loops are often grouped into three functionally relevant categories: (1) the *affective loop* between the ventromedial prefrontal cortex/orbitofrontal cortex (vmPFC/OFC) and nucleus accumbens (NAc) in the ventral striatum is important for motivational control,

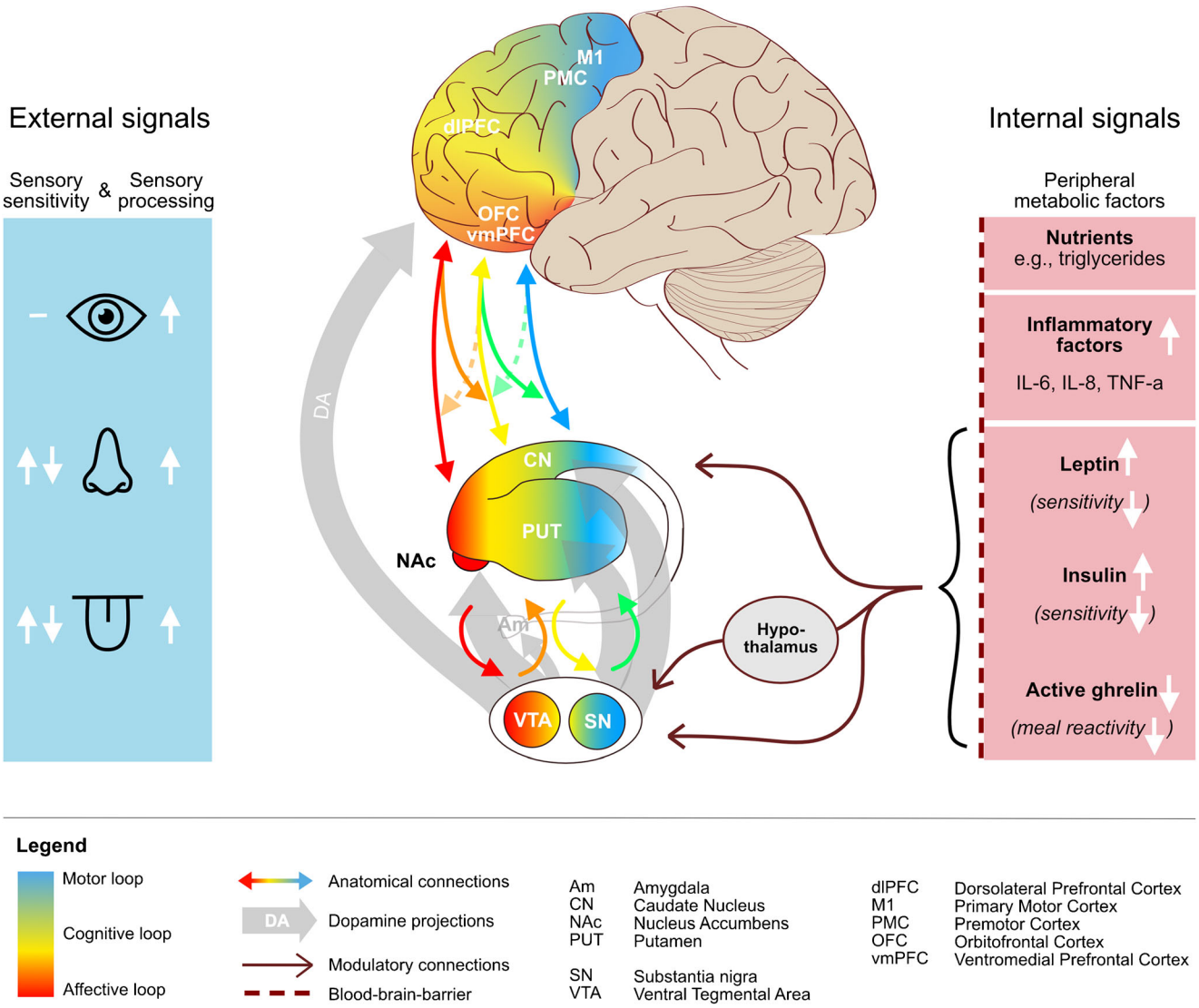

Fig. 1 Schematic overview of the frontostriatal circuit and their relationship with external and internal signals as discussed in the main text. Striato-nigro-striatal connections that can serve as the interface between the loops are also displayed. The affective loop (red) consists of connections between vmPFC/OFC and NAc and is predominantly modulated by dopamine projections from VTA, the cognitive loop (yellow) of connections between dlPFC and CN/aPUT and is modulated by dopamine projections from VTA and SN, and the motor loop of connections between PMC/M1 and pPUT and is predominantly modulated by dopamine projections from SN. The color gradient between the loops reflects the shared connections that enable cross-talk between all loops. Dopamine projections are highlighted by thick grey arrows. External signals that affect the frontostriatal circuit in the context of food include visual, olfactory and gustatory sensory signals (left panel, in blue). Adaptations in sensory sensitivity (left white arrows) and subsequent processing, or cue reactivity (right white arrows), have been associated with obesity. Important internal signals that can affect the circuit include nutrients, inflammatory factors, and hormones such as leptin, insulin and ghrelin (right panel, in red). Adaptations in leptin, insulin and active ghrelin (in fasting state) have been observed in obesity, as well as in central sensitivity to these hormones (white arrows). Leptin, insulin and ghrelin can modulate the frontostriatal circuit through action on receptors in striatum, in VTA directly, or indirectly via hypothalamic control of VTA

(2) the *cognitive loop* between the dorsolateral prefrontal cortex (dlPFC) and caudate nucleus (CN) and anterior putamen (aPUT) in the dorsomedial striatum is important for cognitive control and (3) the *motor loop* between the (pre) motor cortex (PMC/M1) and posterior putamen (pPUT) in the dorsolateral striatum is important for motor control. The loops also share substantial connections to enable information transfer from ventromedial to dorsolateral loops [141–143]. The different striatal regions may, in addition, receive input from prefrontal areas outside of their loop as was recently shown in a primate study [143], enabling cross-talk between all loops.

Dopamine-dependent plasticity is thought to underlie reward-based learning in all loops [141], although dopamine has also been proposed as the interface between the loops through the striato-nigro-striatal connections [142]. As reviewed above, obesity- and diet-related changes in dopamine have been consistently shown in the ventral and dorsal striatum. However, dopamine is suggested to not only modulate learning and motivated behaviour through its effect on striatal output, but also by its effect on input coming from the PFC or sensory regions, as discussed next. Evidence of obesity-related dopamine changes in PFC is scarce, due to difficulty imaging prefrontal dopamine (but see a new PET development by [144, 145•]) and due to the ongoing debate on what are the rodent homologues of the prefrontal cortex [146].

Dopamine Modulation of Sensory Inputs

Dopamine modulates sensory perception and processing [43••, 91, 92]. Since sensory perception, in particular visual, gustatory and olfactory perception, influences when, how much and what we eat [147, 148], dopamine might play a key role in influencing food choice via this route as well.

There is solid evidence that obesity is accompanied with alterations in especially the gustatory and olfactory systems. However, as the results are contradictory, the direction and interpretation of this relationship remains unclear. For instance, some researchers show higher gustatory sensitivity [38, 149]; others lower gustatory sensitivity or no difference in obese when compared to normal-weight individuals [39, 150, 151]. Similarly, it has been shown that obese participants had higher [152] or lower olfactory sensitivity [36, 37].

Of note, the olfactory and dopamine systems are highly interconnected and are therefore of particular interest in the context of eating behaviour and obesity. It has been shown that food odour perception activates dopaminergic brain regions in a human fMRI study [93]. Moreover, dopamine neurons have been detected in the olfactory bulb [153] and a reduction of dopamine neurons induced olfactory impairment in an animal model [154]. Greater availability of DATs in the caudate nucleus and putamen, as measured with SPECT in healthy human individuals, has been associated with higher olfactory performance [92]. Interestingly, one study found evidence of decreased dopamine uptake in the caudate nucleus in Parkinson's disease (PD) patients with and without olfactory impairments [89]. Although PD patients constitute a particular clinical group, the results support the link between dopamine function and olfactory perception.

Beyond affecting perceptual aspects in sensory systems, dopamine modulation of sensory signals may also serve as adjusting the sensory input for the affective frontostriatal loop. As such, dopamine can affect higher-order processing of sensory input, such as hedonic value of, and cue reactivity to visual, gustatory and olfactory input. It has been shown that obese compared to normal-weight individuals perceive food odours as more pleasant [152] and have a higher food cue reactivity in response to food pictures [155] and odours [44]. There is solid evidence that increased physiological (e.g. salivation, skin conductance, neural activation) and craving responses to food-related stimuli are associated with both food consumption and body weight [138]. Such food stimuli also potently activate the brain's reward system, i.e. the striatum and PFC value areas [23, 25, 26, 93].

In conclusion, dopamine can modulate sensory input and the subsequent processing of sensory information. While enhanced reactivity of the limbic system to visual and olfactory food cues, which is likely mediated by dopamine, is quite well established in obesity, general differences in sensory sensitivity require further investigation. Whether a diet high in fat and sugar leads to similar changes through its effects on dopamine, independent of obesity or only as a result of excessive adiposity and the associated metabolic changes (Box 1), is an open question for future investigation.

Neurocognitive Profile of Obesity

Apart from distinct reactions to food and food cues, obesity has been associated with a wide variety of

higher-order neurocognitive differences that crucially rely on dopamine action in all parts of the frontostriatal loops [1, 9] (Table 1). In specific tasks, impairments in executive skills including attention, (working) memory and learning [10–16] are consistently shown in obesity. In addition, reductions in cognitive flexibility [7] and increases in several types of impulsivity [156–159] seem to characterise obesity. Such general cognitive features are likely the roots that feed maladaptive decision-making in a food context.

Food Reward Responses and General Reinforcement Learning

When it comes to reward processing of food and non-food stimuli, brain regions associated with the affective loop, i.e. NAc and mPFC/OFC, are particularly involved [160], and activation patterns in these regions can depend on metabolic state [161]. As discussed above, enhanced reactivity to sensory food cues is typically observed in obesity. In simple reaction tasks where (often hypothetical) food rewards are anticipated, enhanced activation in the affective loop is observed in obesity [70], which may be mediated by decreases in leptin and insulin sensitivity (see also Box 1). When a food reward is received, however, hypoactivation is often reported (e.g. [8, 25]). Interestingly, Kroemer and Small [8] elegantly show how obesity-related hypoactivation of reward regions in response to reward receipt may be explained by impairments in general reinforcement learning, similar as proposed for substance addiction [162].

Reward-related learning within the frontostriatal loops critically relies on dopamine-dependent plasticity [141], which may go beyond *reward* learning and extends to associative learning ([161], preprint). The reinterpretation of the findings in a learning framework supports the idea that obesity is related to general rather than food-specific differences, and dovetails with the widespread role of dopamine in motivation, cognition and behaviour. General reinforcement learning differences in obesity, be it impairments [5, 6, 58, 61, 74] or improvements ([4], Kube et al., under revision), are indeed suggested based on evidence from non-food and food-related reinforcement learning tasks. Difficulties with integrating negative feedback may be central to observed impairments [5, 6, 58], which could result in insensitivity to the negative consequences associated with obesity.

Food-Related Attentional Bias and Craving

What happens once food-related stimuli have been registered and led to initially enhanced responses in terms of activation of affective frontostriatal regions, invoking craving, or attracting attention? In case no food is actually available or you are trying to break a habit of giving into temptations, disengaging your attention or regulation of craving may be necessary. Obese individuals show an enhanced attentional bias to food cues across different experimental paradigms and measures ([6, 58, 61, 74], but see [163]), which may be due to difficulty disengaging from such stimuli. Food attentional bias has been linked to striatal DAT binding, although no relationship was observed between DAT binding and craving or ad libitum food intake [90•]. Furthermore, glucose intake enhanced attentional food bias in obesity [41] and intra-individual variability in a similar bias measure was stronger in obesity [64], supporting the dynamic nature of attentional bias [164•]. Food attentional bias can be attenuated by cognitive factors such as a healthy mindset [87], which emphasises the importance of cross-talk between the frontostriatal loops. Regulation of craving has been associated with differential activation in the putamen and functional connectivity between the putamen and dlPFC [50], also spanning the loops.

Self-Control and Cost–Benefit Decision-Making

What if food *is* available? Then self-control may be needed, which again requires cross-talk between the affective and cognitive loops. Exercising self-control in a food choice task involved dlPFC activity in dieting human participants, which correlated with vmPFC activity [86]. In a similar task, Medic and colleagues [67] found no evidence for a difference in vmPFC activity for overweight to severely obese participants, whereas vmPFC activity did predict subsequent consumption of, particularly, unhealthy foods at a buffet. At the level of the striatum, reduced NAc food cue reactivity was also associated with successful self-control of eating behaviour in daily life in dieting female students, as measured with experience sampling [165]. Experience sampling is a promising method that can be used in obesity research to link neurocognitive findings to maladaptive decisions in daily life. The right food choice always depends on your current state and situation, but also on possibly conflicting internal goals. Decreased goal-directed control of behaviour in a food context has also been associated with obesity [54, 55].

Food often comes at a cost, which requires weighing your options. Obese individuals may be less willing to, first, pay money for plain than highly palatable food items [73]; second, exert effort to obtain food or monetary rewards [66, 166]; and third, wait for a larger reward if a smaller immediate reward is offered simultaneously, as consistently observed in delay discounting tasks ([167–170], but see [51•]). Willingness to exert effort relies on regions in the affective loop and is particularly interesting because of its link to dopamine [171, 172] as well as low-grade systemic inflammation [173], which is highly prevalent in obesity (see Box 1). A recent PET study using a highly specific D2 tracer [51•] together with measures of insulin sensitivity revealed no difference in willingness to wait (nor striatal D2R -binding) in obese relative to non-obese participants. However, greater D2R availability in obese was associated with less willingness to wait and reduced insulin sensitivity. This raises the questions whether and how striatal D2R binding and metabolic factors interact to affect temporal discounting in obesity. In another study, lower willingness to wait (i.e. steeper temporal discounting) was associated with reduced dlPFC–vmPFC connectivity in obesity [169] and may thus rely on cross-talk between the affective and cognitive loop. Interestingly, thinking about how the larger later rewards can be used (i.e. future thinking) has been effective in reducing temporal discounting and food intake in obesity [174–179] and involves cognitive control areas ACC and dlPFC, as well as mPFC–hippocampus interaction [180, 181]. Of note, diet effects have been consistently shown in the hippocampus [11].

Behavioural Control and Action Inhibition

It can also occur that an action has already been initiated upon perceiving a palatable food stimulus. The decision to stop such a response can happen at the level of behavioural control in the cognitive loop, or gating of motor responses. Investigations of response inhibition, tapping into the latter, revealed small obesity-related differences [45]. However, in a resting state fMRI study, disruption was observed in motorcortico-striatal networks in obesity consistent with habit formation theories [182]. More evident results have been observed using the go/no-go task, which indicated impaired performance in obesity [183]. A behavioural intervention that trained no-go responding to high-calorie food cues led to devaluation of those items in normal-weight [184, 185] and in morbidly obese participants [34, 186], as well as impulsive food choices in normal-weight individuals [184, 185]. The authors have proposed that training acts bottom-up by creating associations between no-go food items and stopping responses and reducing valuation of no-go food items (in the affective loop) [187]. A similar mechanism may explain a reduction of food intake in uncontrolled eaters after inhibitory control training [82] and of approach bias to unhealthy food cues in obesity after training automated action tendencies [42, 188].

In sum, obesity-related differences are predominantly observed in the affective and cognitive frontostriatal loops. A simple explanation could be that studies on motor gating or learning are lacking. Many of the neurocognitive constructs investigated in obesity rely on cross-talk between the loops. Studies implementing tasks that specifically investigate the interplay between the different loops may help us further. Also, more convergence in the use of experimental stimuli and task parameters in food-related neuroimaging is needed (as argued by [181]), and there is a need of inclusion of a wider BMI range in obesity studies (see Table 1). However, a more mechanistic explanation is also plausible. That is, the more ventral and medial parts of the frontostriatal circuits may be particularly vulnerable for the effects of diet and adiposity-related metabolic factors in the bloodstream. It is important to better understand the mechanism of the cross-talk between loops. That is, where in the loops can interaction occur (e.g. is the motivational signal from the affective loop to higher-order cognitive loop, or can the cognitive loop affect the state of the affective loop?) and at what point in the process can maladaptive decisions be prevented from being made?

Conclusion

Both diet and obesity affect dopaminergic transmission. However, site and direction of effects are inconsistent across species and studies. Non-specific changes are observed spanning all frontostriatal loops, from sensory input to motivated behaviour. Given the impact of peripheral signals on central dopaminergic signalling and the interaction between the frontostriatal loops, modulation of dopamine likely propagates through all loops and, thus, affects behaviour on various levels of complexity. In line with [112], we

highlight in Box 1 that homeostatic factors have direct access to hedonic systems via dopaminergic modulation, indicating that these can be highly interdependent, going against the historical, dichotomous concept of homeostatic vs. hedonic control over eating behaviour. However, in this review, we mostly focused on the hedonic system. Interactions between the hypothalamus and the frontostriatal circuits require further investigation.

Despite the wealth of literature, it has proven difficult to evaluate the degree of convergence of findings between animal and human studies on the role of dopamine in diet-induced obesity. The main reason is the lack of studies utilising overlapping measures of dopamine and cognition in both species. Human studies are largely observational in nature and lack direct measures of dopaminergic transmission. As such, there is a great need for diet intervention studies, more longitudinal studies [13] and mechanistic studies on the relationship between dopamine and the observed neurocognitive differences, preferably linked to metabolic factors as discussed in Box 1. Further, although some attempts have been made [109], the usage of animal diets that do not closely resemble human obesogenic diets limits comparability of the effects of diet exposure, and higher-order cognition is often not studied in relation to diet-induced dopamine changes.

Due to the narrow scope of the current review, some aspects should be highlighted that were not directly addressed but are likely of high relevance for understanding diet-induced obesity. First, this review dealt with the relationship between diet-induced obesity, cognition and dopamine transmission. Although playing a central role in motivation and cognition, dopamine is not the only neurotransmitter involved. In fact, dopamine interacts closely with other systems such as the opioid, serotonin and noradrenergic system [57, 71, 189, 190]. A relationship to obesity has been demonstrated for all of them. Second, most human research is cross-sectional in nature. In addiction, the existence of subsequent behavioural phases has been proposed, leading from incentive-guided towards compulsive behaviour with accompanying central changes that indicate a transition of changes from ventromedial to dorsolateral frontostriatal loops [191]. Here, we cannot tell whether group differences similarly relate to a transition-in-progress or resemble an endpoint (although a vicious cycle model has been proposed by [11]). We do not even know whether or not overweight people are prone to obesity or represent a special "subpopulation". This transitional aspect could be addressed in animal studies that longitudinally monitor changes following diet exposure or obesity induction. It would also be of interest to take into account the severity of obesity and the individual history of being obese in human studies. Moreover, inconsistent results in the literature could be related to not assessing important latent variables such as the genetic background or possible epigenetic edits induced by lifestyle or family history. Although common variation in dopaminergic genes seems not to have a direct relationship to obesity [24], its relation to cognition is well established. Thus, ignoring this information may lead to either false positives or negatives assigned to the obesity factor.

Finally, an intriguing open question that deserves attention in future research is whether or not the changes that are observed in diet-induced obesity are really maladaptive in nature. Whereas physiological, behavioural and neural differences are often interpreted as maladaptive, it may be that some actually reflect functional adaptations that could be beneficial either at the individual or population level. This would call for a more nuanced interpretation of any obesity-related differences.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Appendix Table I

Table 1 Summary of the human studies addressed in the sections on dopamine manipulation of sensory inputs and neurocognitive adaptations in obesity

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
Bongers et al. [33]	Obesity	OB	185	$M = 38.18$	54/131	18–45	Behavioural (impulsivity, AB for high- and low-caloric foods), questionnaire (impulsivity, trait craving)	–	Only in OB: ↑ impulsivity → ↑AB for high-caloric foods
		NW	134	$M = 22.35$	35/99				
Chen et al. [34]	Obesity	OB	59	$M = 44.49$	14/45	46.1	Behavioural (go/no-go training, evaluation of go/no-go/untrained items)	–	Posttraining: 1. Go items were evaluated more positively than no-go items in both groups 2. Go items were evaluated more positively than untrained items in NW 3. Effects of the training on food evaluation did not differ between the two participant groups
		NW	58	$M = 22.64$	15/43	23.1			
Contreras-Rodríguez et al. [35]	Obesity	OW	42	$M = 30.51$	20/22	18–45	Neuroimaging (fMRI), questionnaire (food craving)	VS, DS, mPFC, PC, SSC	1. OW: ↑ FC between the VS and mPFC and PC and between the DS and the SSC 2. DS FC correlated with food craving and predicted BMI gains
		NW	39	$M = 22.09$	18/21				
Fernández-Aranda et al. [36]	Obesity	NW	36	$M = 22.4 \pm 2.6$	n.a.	37.3 ± 5.9	Sensory (taste and smell assessment with Taste Strips and Sniffin Sticks)	–	Smell capacity impaired in obesity and related to decreased ghrelin levels in obesity, taste function did not differ between groups
		OB	59	$M = 42.7 \pm 6.6$	n.a.	37.5 ± 8.7			
Fernandez-Garcia et al. [37]	Obesity	Low weight	17	$M = 17.91 \pm 0.51$	f	23.1 ± 6.7	Sensory (taste and smell assessment with Taste Strips and Sniffin Sticks)	–	Smell performance correlated negatively with BMI and was negatively related to visceral fat mass
		NW	77	$M = 21.6 \pm 1.7$		27.1 ± 7.3			
		OW	12	$M = 26.8 \pm 0.9$		33.6 ± 8.7			
		OB	28	$M = 35.2 \pm 2.6$		46.4 ± 12.2			
		Morbidly obese	45	$M = 46.3 \pm 5.1$		42.3 ± 10.7			
Hardikar et al. [38]	Obesity	NW	31	$M = 21.8$	17/14	18–35	Sensory (Taste Strips)	–	Obese individuals are more sensitive to sweet and salty taste
		OB	23	$M = 33.8$	11–12				
Hardikar et al. [39]	Obesity	NW	30	$M = 22.13 \pm 1.83$	25/30 (no details for groups)	18–35	Sensory (EEG of taste perception)	–	Taste representations faded earlier in EEG in obese group and exhibited reduced strength
		OB	25	$M = 35.48 \pm 4.53$					
Horst et al. [40]	Obesity	OB	7	26.7–30.6 ($M = 30.4$)	4–3	41–53	Metabolic (glucose; DBS vs. no DBS)	STR	DBS in STR area, which induced dopamine release
		NW	7		4–3	38–49			

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
				22.3–24.7 ($M = 24.0$)					→ ↑ hepatic and peripheral insulin sensitivity
Mason et al. [41]	Obesity	OB NW	18 17	> 30 18.5–25	n.a.	n.a.	Cognitive (WM task to assess food-related AB under fasting and glucose challenge conditions), metabolic (blood glucose and insulin), sensory (taste test), behavioural (food consumption)	–	BMI ↑ → ↑ food AB after glucose ingestion
Mehl et al. [42]	Obesity	OB	30	$M = 35.2$	15/15	18–35	Behavioural (training in AAT)	–	1. Pretraining: OB → ↑ approach tendencies towards food pictures
		NW	30	$M = 21.9$	15/15				2. Posttraining: OB → ↓ approach for unhealthy food 3. Posttraining: NW → ↑ approach tendencies towards healthy food
Pepino et al. [43••]	Obesity	NW OB	19 22	$M = 22.5 \pm 2.4$ $M = 40.3 \pm 5.0$	4/15 3/19	28.3 ± 5.4 31.2 ± 6.3	Neuroimaging (PET), sensory (taste)	–	Sucrose liking decline with aging is associated with reduced striatal D2 receptor binding in normal weight but not obese participants
Proserpio et al. [44]	Obesity	OB	40	$M = 35.1 \pm .8$	f	52.1 ± 2.1	Behavioural (food intake after odour exposure)	–	Ambient odour exposure to a food odour-stimulated appetite for congruent food items in obese women
Voon et al. [45]	Obesity	OB w BED	30	n.a.	m/f	> 18	Behavioural (premature responding task)	–	1. AD and MD subjects and CA users → ↑ premature responding
		OB wo BED	30						2. No differences observed in OB subjects w/ wo BED
		aAD aMD CA healthy	30 23 30 110						3. AD subjects had lower motivation for explicit monetary incentives 4. Motivation Index correlated negatively with alcohol use and BED severity
Voon et al. [46]	Obesity	OB w BED OB wo BED OCD SUD Healthy	31 31 32 53 3:1 matc-hed	n.a.	m/f	> 18	Behavioural (2SRLT measuring model-free vs. model-based learning)	–	Bias towards model-free acquisition (habit) in disorders involving both natural (BED) and artificial (SUD) rewards and OCD

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
Balodis et al. [47]	BMI (groups)	OB NW	19 19	$M = 34.6 \pm 3.5$ $M = 23.3$ 1.1	9–10 9–10	38.3 ± 7.5 34.8 ± 10.7	Neuroimaging (fMRI), cognition (MIDT)	VS, vmPFC	OB > NW ventral striatal and ventromedial prefrontal cortex activity during anticipatory phases
Caravaggio et al. [48]	BMI (continuous)	[11C]-(+)-PHNO [11C]-raclopride Both	26 35 15	18.61–27.77	19–7 21/14 11/14	20–47	Neuroimaging (PET)	VS, CAU, PUT, GP, SN	BMI ↑ → D2R affinity in VS ↑
Coppin et al. [5]	BMI (groups)	OB	26	$M = 36.02 \pm 6.54$	17–9	25.17 ± 4.39	Cognition (working memory, CCPT, PRLT)	–	1. OW/OB < NW (working memory)
		OW	23	$M = 27.63 \pm 1.49$	16–7	24.94 ± 4.55			2. OB > OW/NW paradoxical preferences for negative cues with food rewards, no preference with monetary rewards (CCPT)
		NW	25	$M = 22.43 \pm 1.45$)	16–9	24.25 ± 4.25			3. OB < NW (negative outcome learning PRLT)
Cosgrove et al. [49]	BMI (continuous)	fMRI	29	20.8–36.5	m/f	19–39 $M = 26.9 \pm 5.9$	neuroimaging (fMRI, PET)	DS	1. BMI ↑ → D2R/D3R availability ↑
		PET	12						2. BMI ↑ → BOLD response to food cue ↓
		Both	8						
Dietrich et al. [50]	BMI (continuous)	–	43	19.4–38.8 ($M = 27.5$)	f	21–36	neuroimaging (fMRI), cognitive (admit vs. regulation of food craving)	lPUT, AMG, GP, INS, dlPFC, dmPFC, LG, CAU	1. During regulation BMI correlated with brain activity in the lPUT, AMG and INS in an inverted U-shaped manner 2. FC between PUT and dlPFC correlated positively with BMI 3. FC of AMG with GP and LG was non-linearly (U-shaped) associated with BMI 4. Disinhibition correlated negatively with the strength of FC between AMG and dmPFC and CAU
Eisenstein et al. [51]	BMI (groups)	OB	27	$M = 39.90 \pm 4.76$	4/23	31.5 ± 6.61	Imaging (PET), cognition (DDT, PDT)	STR	1. OB = NW/OW DRD2 binding
		NW/OW	20	$M = 22.42 \pm 2.40$	5/15	28.64 ± 5.28			2. OB = NW/OW reward discounting
Gaiser et al. [52]	BMI (groups)	NW OB	14 14	$M = 22.3$ $M = 35.3$	10/4 10/4	34.9 ± 10.2 37.0 ± 10.1	Neuroimaging (PET)	AMG, CAU, HTH, GP, PUT, SN, VTA, TH, VS	BMI ↑ → D2R/D3R availability ↑
Guo et al. [53]	BMI (groups)	NW/OW	23	$M = 22.4$		18–45	Neuroimaging (PET)		

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
		OB	20	$M = 36.1$	22/21 (in follicular phase of menstrual cycle)			PUT, CAU, NAc	1. BMI ↑ → D2R binding ↑ in DS/LS 2. BMI ↑ → D2R binding ↓ in VS
Horstmann et al. [54]	BMI (continuous)	–	30	19.20–45.06	m	19–30	Cognition (devaluation in free operant task)	–	BMI ↓ behavioural adaptation and response rate after devaluation
Janssen et al. [55]	BMI (continuous)	–	76	19–35	13/63	18–53	Neuroimaging (fMRI), cognitive (food Stroop task), behavioural (ODT measuring goal-directed vs. automatic food choices)	lPFC	1. BMI ↑ → ↓ lPFC responses during food AB 2. BMI ↑ → ↓ goal-directed control following OD
Jonker et al. [56]	BMI (continuous)	–	607	> 18.5	280/327	13–19	Behavioural (AB), questionnaire (reward/punishment sensitivity)	–	No relation of BMI (changes) to AB or reward and punishment sensitivity
Karlsson et al. [57]	BMI (groups)	OB NW	13 14	$M = 41.89$ $M = 22.65$	f	39.08 ± 10.74 44.86 ± 12.88	Neuroimaging (PET)	VS, dorsal CAU, PUT, INS, AMY, TH, OFC, ACC, MCC, PCC	OB > NW → no difference in D2R availability
Kastner et al. [58]	BMI (groups)	OB	24	$M = 35.59 \pm 3.39$	12/12	26.7 ± 3.2 (m); 26.0 ± 4.11 (w)	Cognition (PRLT)	–	OB < NW learning to avoid negative consequences
		NW	24	$M = 22.18 \pm 1.37$	12/12	26.2 ± 5.78 (m); 25.0 ± 4.41 (w)			
Kessler et al. [59]	BMI (continuous)	Baseline (before amphetamine intake)	33	19–35; $M = 24.8$	18/15	18–35; $M = 25.8$	Neuroimaging (PET)	VS, SN, AMY, CAU, PUT	1. No effect of BMI on D2R (trend sign.)
		Follow-up (3 h after amphetamine intake)	16	19–35; $M = 25.2$	8/8	21–32; $M = 24.3$			2. BMI ↑ → DA release ↑ (significant for right putamen and left substantia nigra)
Kube et al. [60]	BMI (groups)	OB	14	$M = 35.2 \pm 4.3$	f	25.4 ± 2.6	Cognition (MIDT, SIDT)	–	1. OB > NW RT social cue vs. monetary cues
		NW	14	$M = 21.1 \pm 1.5$		25.2 ± 3.1			2. OB < NW heart rate response to negative social outcomes if they reported more emotional pain after weight-related teasing
Kube et al. [61]	BMI (groups)	OB NW	19 23	$M = 35.4 \pm 4.5$ $M = 22.4 \pm 1.7$	9/10 12/11	29.5 ± 5.6 30.0 ± 5.0	neuroimaging (fMRI), cognition (PRLT)	mPFC, STR, INS	1. OB < NW correct choices

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									2. OB < NW overall monetary outcome in OB, aberrant medial prefrontal cortex responses to monetary losses 3. OB > NW functional connectivity VS-insula
Lee et al. [62]	BMI (continuous)	–	60	19.2–36.6; $M = 25.2 \pm 3.-33$	49/11	30–40; $M = 36.4 \pm 3.84$	neuroimaging (PET)	VS, PUT, CAU	OW/OB (BMI 25–35) > NW → EDVR ↓ in all ROIs (most prominent in VS) => lower striatal DA tone
Lehner et al. [63]	BMI	NW OW OB	20 17 17	$M = 21.9 \pm 1.6$ $M = 27.3 \pm 1.5$ $M = 36.9 \pm 5.1$	7/13 11/6 6/11	29 ± 9 30 ± 8 33 ± 12	Behavioural (PIT paradigm = instrumental conditioning task, Pavlovian conditioning task, PIT test + eye movements)	–	OW > NW: goal-directed behaviour stronger influenced by food-predicting cues (i.e. stronger PIT effect)
Liu et al. [64]	BMI (groups)	OW/OB	22	$M = 23.90$	f	$M = 19.45$	Behavioural (VDPT: EM and RT measuring food-related AB)	–	1. Variability of AB for food stimuli and variability of RT on filler trials can predict BMI
		NW (RE)	34						2. Controlling for variability of RT on filler trials and mean AB score, larger variability of AB for food stimuli still existed in OB children 3. AB for food stimuli showed no significant correlation with RE
Lopez et al. [65]	Food desire, mood	–	75	n.a.	f	18–23	Neuroimaging (fMRI), cognitive (self-regulatory depletion and food cue reactivity task), questionnaire (eating behaviour, food desire, mood)	IFG	1. Beneficial combination: low desire and positive mood → supported successful self-regulation 2. Autonomous motivation and IFG activity characterised the most successful subgroup of dieters and also predicted greater likelihood of experiencing the beneficial combination
Mata et al. [66]	BMI 3-month weight loss (WL) treatment after completing the EEfRT (for OW and OB only)	NW OW OB	26 26 21	$M = 21.52 \pm 1.96$ $M = 27.41 \pm 1.41$ $M = 33.12 \pm 2.16$	38% m 36% m 14% m	21.69 ± 2.11 21.72 ± 1.7 21.37 ± 1.53	Behavioural (effort expenditure for rewards task (EEfRT))		1. OB > OW: probability of making hard-task choices ↓ 2. OB > OW: willing to expend effort for rewards ↓

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									3. WL completers > WL dropouts → effort for uncertain rewards ↑
Mathar et al. [6]	BMI (groups)	OB	28	$M = 34.1 \pm 2.5$ (w); 34.0 ± 3.1 (m)	13/15	28.3 ± 4.7 (w); 27.2 ± 5.3 (m)	Neuroimaging (fMRI), cognition (WPT)	VS, SMA	OB < NW incorporation of negative PEs into behavioural adaptation; OB < NW functional coupling between ventral striatum and supplementary motor area subsequent to negative PEs
		NW	30	$M = 21.9 \pm 1.9$ (w); 22.3 ± 1.5	15/15	26.6 ± 3.6 (w) 27.2 ± 5.3 (m)			
Medic et al. [67]	BMI (groups)	EW	40	$M = 30.84 \pm 4.82$	23/17	29.78 ± 6.00	Neuroimaging (fMRI), cognition (health and taste value judgments)	vmPFC	↑ Value-based responses in the ventromedial PFC → ↑ subsequent consumption at buffet
		NW	23	$M = 21.88 \pm 1.3$	13/10	29.85 ± 5.75			EW > NW consumption of unhealthy foods in EW, ↑ impulsivity scores → ↑ consumption of unhealthy foods
Meemken et al. [4]	BMI (groups)	OB	30	$M = 36.04 \pm 6.66$ (m), 33.73 ± 4.20 (w)	15/15	25.93 ± 3.85 (m), 27.40 ± 3.72 (w)	Cognition (PRLT active/passive, money/food)	–	OB > NW passive learning; opposite effects of BMI on performance with food vs. money rewards
		OW	28	$M = 26.85 \pm 1.14$ (m), 26.79 ± 0.96 (w)	14/14	27.14 ± 4.35 (m), 26.43 ± 3.03 (w)			
		NW	29	$M = 22.74 \pm 1.72$ (m), 22.83 ± 1.65 (w)	14/15	24.07 ± 3.35 (m) 26.00 ± 3.72 (w)			
Morys et al. [68]	BMI	NW	30	$M = 22.14 \pm 1.81$	15/15	25.83 ± 3.14	Neuroimaging (fMRI)	dlPFC, vmPFC	1. OB > NW: activity in the left ldPFC ↓ during priming with negative gustatory cues towards delayed
		OB	26	$M = 34.32 \pm 3.37$	14/12	27.42 ± 4.16			2. BMI ↑ → modulation of functional connectivity dlPFC–vmPFC by the behavioural priming effect ↓
Mühlberg et al. [69]	BMI	OB	26	30.2–39.8 ($M = 34.3$)	13/13	18–35	Behavioural (food picture rating task, SST measuring inhibitory control), questionnaire (eating behaviour, trait impulsivity)	–	1. f: ↑ liking for low-caloric food items in f (vs. m), ↓ SSRT after high (vs. low) caloric food pictures, ↓

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									SSRT for high-caloric food in f (vs. m) 2. no influence of gender on SSRT outside of the food context 3. SSRTs did not differ between OB and NW across picture categories 4. moderating effect of trait impulsivity on the relationship between BMI and SSRT, specifically in the high-caloric food context ↑ 5. BMI → ↑ SSRT only for participants with low-normal trait impulsivity
		NW	30	18.65–25.3 ($M = 21.83$)	16/14				
Simon et al. [70]	BMI (continuous)	–	24	18.4–40	5/19	24–34	Neuroimaging (fMRI), cognition (MIDT, FIDT)	VS	Anticipatory food reward processing predicted the individual BMI (current and maximum lifetime)
Tuominen et al. [71]	BMI (groups)	OB	25	$M = 41.30 \pm 4.14$	f	41.24 ± 9.17	Neuroimaging (PET)	VS, CAU, PUT	1. NW: μ-opioid-R density → mesolimbic DRD2 density ↑ 2. OB: no correlation = >aberrant dopamine–opiate interaction may underlie altered reward processing
		NW	20	$M = 22.4 \pm 2.62$		42.00 ± 13.20			
Vainik et al. [72]	BMI (continuous)	–	835	n.a.	m/f	22–35	Neuroimaging (MRI), cognitive (various executive- and non-executive-function tasks), genotyping	Fl, PFC, PC, OCL, EC, PHG	1. ↑ BMI → ↓ cortical thickness in rFL and ↑ thickness in the lFL, notably in lPFC 2. ↑ BMI → ↓ thickness and volume in EC-PHG structures and ↑ thickness in PC-OCL structures in → supports the role of visuospatial function in obesity 3. ↑ BMI → ↓ visuospatial function, verbal episodic memory, impulsivity and cognitive flexibility

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									4. Personality–BMI correlations were inconsistent 5. Heritable variance in BMI had genetic correlations 0.25–0.45 with cognitive tests, cortical thickness and regional brain volume
Verdejo-Román et al. [73]	BMI (groups)	OW/OB	39	$M = 30.41 \pm 3.69$	18/21	33.59 ± 6.23	Neuroimaging (fMRI), cognition (food WTPT, MIDT)	frontal, striatal, parietal areas	1. EW < NW functional connectivity during the processing of food rewards in a network involving primarily frontal and striatal areas
		NW	37	$M = 22.28 \pm 1.77$	17/20	33.00 ± 6.53			2. EW > NW functional connectivity during the processing of monetary rewards in a network involving principally frontal and parietal areas 3. EW < NW willingness to pay for plain foods
Zhang et al. [74]	BMI (groups)	OB	33	$M = 38.7 \pm 1.6$ (m), 39.1 ± 1.6 (w)	17/16	32.8 ± 2.4 (m), 33.8 ± 2.7 (w)	Cognition (ARLT money/food)	–	OB (w) < OB (m)/NW (m + w) (food ARLT, acquisition and update)
		NW	34	$M = 23.0 \pm 0.4$ (m), 22.0 ± 0.5 (w)	17/17	30.3 ± 2.4 (m), 31.9 ± 3.2 (w)			
		OB	35	$M = 39.2 \pm 2.3$ (m), 37.0 (1.0) (w)	17/18	32.1 ± 2.5 (m), 32.4 ± 2.4 (w)			
		NW	33	$M = 22.1 \pm 0.5$ (m), 22.2 ± 0.3 (w)	15/18	29.9 ± 2.6 (m), 29.0 ± 1.8 (w)			
Navas et al. [75]	Body fat (continuous)	–	68	Unclear from paper	34/34	16.56 ± 1.35	Neuroimaging (fMRI), cognition (MIDT)	M1, supramarginal gyrus	↑ Body fat levels → ↓ activation of the primary somatosensory cortex (S1) and the supramarginal gyrus during reward feedback
Manasse et al. [76]	Weight loss treatment	ABT	90	$M = 36.50$	17.9% m 82.1% f	51.61	Behavioural (SST measuring inhibitory control, delay discounting task)	–	1. ↓ inhibitory control → ↓ percent weight loss 2. This effect was attenuated by assignment to ABT vs. SBT
		SBT	100	$M = 37.40$		51.67			

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									3. Treatment condition also moderated the impact of delay discounting and food-specific inhibitory control on percent weight loss: ↑ impulsivity → ↑ benefit from ABT
Simon et al. [77]	Weight loss maintenance (groups)	Successful weight loss maintenance	18	$M = 27.3 \pm 5.7$	f	31.5 ± 9.8	Neuroimaging (fMRI), cognition (MIDT, FIDT)	–	1. Successful weight loss maintenance > weight regain satiety-induced attenuation of brain activation during the receipt of a food-related reward
		Weight regain	18	$M = 28.6 \pm 4.9$		37.3 ± 14.4			2. Successful weight loss maintenance → attenuation of active ghrelin levels was related to brain activation in response to food-related reward anticipation during satiety
Van Ens et al. [78]	Hunger, blood glucose, dietary restraint, eating disorder symptoms	–	53	16.8–26.4 ($M = 21.7$)	f	$M = 26$	Behavioural (VDPT: EM and RT measuring food-related AB), metabolic (glucose), questionnaire (hunger, RE, eating disorders)	–	Hunger, blood glucose, RE and eating disorder symptoms were not correlated with food-related AB
Manasse et al. [79]	BED	OW/OB w BED	25	$M = 35.23$	f	$M = 45.06$	Behavioural (SST measuring inhibitory control)	–	1. BED group: ↓ inhibitory control
		OW/OB wo BED	65	$M = 36.72$		$M = 52.40$			2. Deficits did not differ by stimuli type (food vs. non-food)
Franken et al. [80]	Food addiction	FA	34	$M = 22.7$	m/f	$M = 19.9$	Neuroimaging (EEG: ERN and Pe), behavioural (Eriksen flanker task measuring performance monitoring)	–	1. FA → ↓ ERN and Pe waves
		Control	34	$M = 20.7$		$M = 20.8$			2. FA → ↑ errors on the flanker task
Van Dillen et al. [81]	Cognitive load (low vs. high), stimuli (high- vs. low-caloric)	–	29	18.5–25	13/16	$M = 21.03$	Neuroimaging (fMRI), cognitive (digit span task), behavioural (food categorisation task)	dlPFC, NAc	1. Digit span task engaged dlPFC when cognitive load was high
									2. Exposure to high-calorie food pictures → ↑ activation in the NAc, but only when cognitive load was low
									3. Load altered the functional coupling between NAc and right dlPFC during

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									presentation of the high-calorie food pictures
Oomen et al. [82]	Training	Food-specific RIT	21	18.5–30	10/31	18–34	Behavioural (bogus taste test, food cue sensitivity test)	–	1. sRIT → ↓ snack consumption in the bogus taste test
		Unspecific RIT	20						2. sRIT did not improve inhibitory control towards food, nor did it reduce food cue sensitivity
Hare et al. [83]	Health cues	–	33	n.a.	10/23	*M* = 24.8	Neuroimaging (fMRI), behavioural (food choice task)	vmPFC, dlPFC	1. Subjects made healthier choices in the presence of health cues 2. Stimulus value signals in vmPFC were more responsive to the healthiness of foods in the presence of health cues 3. This effect was modulated by activity in the regions of dlPFC
Mehl et al. [84]	Cognitive bias modification	CBM	17	*M* = 36.49	6/11	18–35	Neuroimaging (fMRI), behavioural (AAT)	rAG, ACC, FG	1. Baseline: approach tendencies towards food in all participants
		Sham	16		9/7				2. Avoiding vs. approaching food → ↑ activity in the rAG 3. CBM → ↓ approach bias towards unhealthy food, ↓ activation in the rAG and ↑ activation in the ACC 4. ↑ FC between the rAG and rsFG increased 5. Training-related FC changes of the iFG and bilateral mFG
Gillan et al. [85]	Goal-directed control	–	1961	n.a.	m/f	n.a.	Behavioural (2SRLT measuring model-free vs. model-based learning), questionnaire (OCD symptoms)		Deficits in goal-directed control were most strongly associated with a symptom dimension comprising compulsive behaviour and intrusive thought
Hare et al. [86]	Self-control	Self-controller	19	n.a.	m/f	n.a.	Neuroimaging (fMRI), behavioural (food rating and food choice task)	vmPFC, dlPFC	1. Activity in vmPFC correlated with goal values regardless of the amount of self-control
		Non-self-controller	18						

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
									2. vmPFC incorporated both taste and health in self-controllers, but only taste in non-self-controllers 3. Activity in dlPFC increased when subjects exercised self-control and correlated with activity in vmPFC
Werthmann et al. [87]	Cognitive manipulation	Health mindset	28	*M* = 22.29	f	*M* = 19.33	Behavioural (VDPT: EM and RT measuring food-related AB, RE)	–	1. interaction of mindset and RE on RT bias 2. health mindset (vs. palatability mindset) attenuated attention bias for high-caloric food only in participants with higher RE
		Palatability mindset	32	*M* = 21.72		*M* = 19.94			
Donofry et al. [88]	Cognitive manipulation	Neutral mood	47	*M* = 22.52	f	*M* = 21.57	Behavioural (RT measuring food-related AB)	–	1. No interaction between mood condition and RE 2. Mood had an influence on attention allocation 3. *I*ndividuals in neutral mood condition, but not in negative mood condition, showed AB for food
		Negative mood	49	*M* = 22.54		*M* = 20.76			
Oh et al. [89]	Parkinson disease (PD)	PD with olfactory impairment	50	n.a.	31/29	66.6 ± 7.3	Neuroimaging (PET), sensory (CC-SIT)	CAU, left ant./post. PUT	Reduced dopamine transporter uptake in the PD group with smell impairment when compared to normosmic PD
		PD without olf. impairment	37	n.a.	13/24	66.1 ± 10.5			
Koopman et al. [90]	DAT and SERT binding	–	36	19.6–24.9 (*M* = 22.3)	m	*M* = 22.2	Neuroimaging (SPECT: striatal DAT and diencephalic SERT binding), behavioural (RT measuring food-related AB and impulsivity), questionnaire (craving, emotional eating, hunger)	STR, DE	1. STR, DAT and DE SERT binding negatively correlated with food detection speed, but not with food distraction time, ratings of hunger, craving or impulsivity 2. STR, DAT and DE SERT binding did not correlate with free choice food intake 3. Food detection speed positively correlated with total caloric intake, protein intake, carbohydrate intake and fat intake
Beste et al. [91]	DA manipulation	High dosage	25	n.a.	13/12	*M* = 25.5	Behavioural (moving dots task, perceptual decision-making)	–	Dopamine modulates the efficacy of perceptual decision-making
		Low dosage	25	n.a.	12/13	*M* = 22.9			
Horst et al. [40]	DA	–	10	*M* = 22.0	m	*M* = 23		–	

Table 1 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	BMI* (in kg/m^2)	Gender (male/female)	Age (in years)	Method	Brain regions of interest	Main result
							Metabolic (glucose; DA depletion vs. control)		DA depletion → ↓ peripheral insulin sensitivity
Pak et al. [92]	DA	Healthy participants	181	n.a.	117/64	> 30	Neuroimaging (SPECT), sensory (UPSIT)	CAU, PUT, STR	Olfactory function is positively correlated with the availability of striatal dopamine transporter uptake
Sorokowska et al. [93]	Olfactory processing	Healthy participants	30	$M = 23.94 \pm 2.4$	13/17	22–28	Neuroimaging (fMRI)	ACC, right INS, right PUT	Food odours compared to non-food odours generated activation in dopaminergic regions

This table provides the main properties of the study design (compared factor, groups if applicable, sample size, methods and regions of interest if suitable) as well as sample characteristics (BMI, gender, age) of each study together with a summary of the main results. If the study design contains groups, sample characteristics are given separately for each group unless groups did not differ in a criterion or the variable is only given for the entire sample

2SRLT, 2-step reinforcement learning task; *aAD*, abstinent alcohol dependent; *AAT*, approach-avoidance task; *AB*, attentional bias; *ABT*, acceptance-based behavioural treatment; *ACC*, anterior cingulate cortex; *AG*, angular gyrus; *aMD*, abstinent methamphetamine dependent; *AMG*, amygdala; *ARLT*, appetitive reversal learning task; *BED*, binge-eating disorder; *BMI*, body mass index: *if not stated differently, BMI categories follow WHO guidelines; *BOLD signal*, blood oxygenation level-dependent signal; *CA*, cannabis user; *CAU*, caudate nucleus; *CCPT*, conditioned cue preference test; *CC-SIT*, cross-cultural smell identification test; *DA*, dopamine; *DAT*, dopamine active transporter; *DBS*, deep brain stimulation; *DDT*, delay discounting task; *DE*, diencephalon; *dlPFC,* dorsolateral prefrontal cortex; *dmPFC*, dorsomedial prefrontal cortex; DRDX/DXR: Dopamine receptor X; *DS*, dorsal striatum; *EC*, entorhinal cortex; *EDVR*, effective distribution volume ratio; *EEfRT*, effort expenditure for rewards task; *EEG*, electroencephalography; *EM*, eye movement; *EW*, excess weight; *f*; female; *FA*, food addiction; *FC*, functional connectivity; *FG*, frontal gyrus; *FI*, frontoinsula; *FIDT*, food incentive delay task; *fMRI*, functional magnetic resonance imaging; *GP*, globus pallidus; *HTH*, hypothalamus; *IFG*, inferior frontal gyrus; *INS*, insula; *l*, left; *LG*, lingual gyrus; *m*, male; *M*, mean; *MCC*, medial cingulate cortex; *MIDT*, monetary incentive delay task; *mOFC*, medial orbitofrontal cortex; *mPFC*, medial prefrontal cortex; *n.a.*, not available/applicable; *NAc*, nucleus accumbens; *NW*, 18.5–24.99 kg/m^2; *OB*, > 30 kg/m^2; *OCD*, obsessive–compulsive disorder; *OCL*, occipital lobe; *ODT*, outcome devaluation task; *OW*, 25–29.99 kg/m^2; *PC*, parietal cortex; *PCC*, posterior cingulate cortex; *PDT*, probabilistic discounting task; *PE*, prediction error; *PET*, positron emission tomography; *PHG*, parahippocampal gyrus; *PIT*, Pavlovian to instrumental transfer; *PRLT*, probabilistic reinforcement learning task; *PUT*, putamen; *r*, right; *RE*, restrained eating/eater; *RIT*, response inhibition training; *ROI*, region of interest; *RT*, reaction time; *SBT*, standard behavioural treatment; *SERT*, serotonin transporter; *SIDT*, social incentive delay task; *SMA*, supplementary motor area; *SN*, substantia nigra; *SPECT*, single-photon emission computed tomography; *SSC*, somatosensory cortex; *SSRT*, stop signal reaction time; *SST*, stop signal task; *STR*, striatum; *SUD*, substance use disorder; *TH*, thalamus; *UPSIT*, University of Pennsylvania Smell Identification Test; VDPT, visual dot probe task; *vmPFC*, ventromedial prefrontal cortex; *VS*, ventral striatum; *WL*, weight loss; *WM*, working memory; *WPT*, weather prediction task; *WTPT*, willingness-to-pay task

Appendix Table2

Table 2 Summary of animal studies addressed in the section on obesity and diet-related structural dopamine adaptations

Reference	Compared factor	Groups	Sample size (*N*)	Species	Weight (g)	Gender	Age (in years)	Method	Brain regions of interest	Main result
Barry et al. [99]	Diet (HFD) LFD for 7 days, then HFD for 14 days	Control LFD (10%) HFD (60%)	8 10	Rats	275–300	m	n.a.	Neuroimaging (fMRI, PET)	STR	1. Short-term HFD → D2R availability ↓ 2. Short-term HFD → interactions between elements of the mesolimbic and sensorimotor circuits ↓
Hryhorczuk et al. [101]	Diet (HFD)	Control LFD Monounsaturated HFD (50% olive oil) Saturated HFD (50% palm oil)	36	Rats	250–280	m	n.a.	DA transmission (immunoblotting of TH, DAT, DRD1/2, DARPP-32)	NAc	HFD (saturated fat) > monounsaturated fat → D1R and DARPP-32 expression ↑, DAT ↓
Zhang et al. [97]	Diet (HFD)	Control (10%) +DBS/−DBS HFD (45%) +DBS/−DBS	8–8 8–8	Rats	$M = 422 \pm 4$ before DBS $M = 542 \pm 6$ before DBS	m	6 weeks at start of experiment	DA transmission (DBS in NAc; DA/DOPAC level, mRNA expression of DRD1/2)	NAc	1. DIO → D1R mRNA ↓ 2. NAc-sh DBS → appetite/weight gain ↓ in DIO 3. DIO + DBS → DA levels ↑ 4. DBS in DIO → D2R expression ↑
Ducrocq et al. [102]	Diet (HFD)	Control HFD (45%)	n.a.	Mice	Similar average	m	3 weeks at the start of experiment	DA transmission (extracellular DA) Behaviour (operant conditioning)	NAc	1. Chronic HFD (ad lib. and restricted) → operant responding ↓ 2. Chronic HFD → stimulated DA release ↓
Friend et al. [18••]	Diet (HFD) for 18 weeks	Control (13%) HFD (60%)	8 8	Mice	n.a.	m	3–4 months	DA transmission (transgenic knockout of DRD2; quantification of multiple aspects of dopamine signalling)	STR	1. OB → D2R binding ↓ 2. Genetically removing D2Rs → motor activity ↓ 3. Restoring Gi signalling in the striatum → activity ↑ in non-OB 4. Mice with low D2Rs were less active, but not more vulnerable to diet-induced weight gain
Labouesse et al. [103]	diet (HFD)	Control HFD (60%)	n.a.	Mice	n.a.	m	Adult	DA transmission (transgenic D2 receptor overexpression)	n.a.	D2R overexpression → predisposed for diet-induced obesity
Hakim and Keay [104]	Diet (HSD) HSD for 21 days	Control (water) HSD	11 18	Rats	n.a.	m	Adults (no numbers given)	DA transmission (RNA expression of DRD1/DRD2; western blot of TH/DRD2)	NAc	1. HSD → D1R mRNA expression in left NAc ↑ 2. HSD → D2R mRNA expression ↑, D2R protein expression in right NAc ↓
Adams et al. [96]	Diet (HFSD) 2 weeks diet intervention, then 12 weeks	Control HSD (60%) HFD (60%)	8 8 8	Rats	275–300	m	n.a.	DA transmission (immunoblotting of CREB, DARPP-32, DRD1/2)	CAU, NAc	1. Chronic HFD → D2R expression ↓ in VS 2. No effect for HSD and no effect in DS

Table 2 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	Species	Weight (g)	Gender	Age (in years)	Method	Brain regions of interest	Main result
Robertson and Rasmussen [84]	calorie--restricted diet Diet (HFSD) for 8 weeks	Age 21 days Age 70 days	30 30	Rats	For behavioural testing: *n* = 10 with lowest body weight (standard diet, both age groups) *n* = 10 with highest body weight (cafeteria diet, both age groups)	m	n.a.	DA transmission (D2/D3 blockage with haloperidol), behavioural (delay discounting)	–	1. HFSD → leftward shift in the dose–response curve 2. DRD2/3 blocking unmasked subtle diet-related differences by dose-dependently reducing choice for the larger, later reinforcer
Rospond et al. [100]	Diet (HFSD) HFD/HSD for 5 weeks	Control ad lib. or limited HFD (86.7%) ad lib. or limited HSD (79.6%)	8 8 8	Rats	290–310	m	n.a.	DA transmission (RNA/protein expression of DRD2) Neuroimaging (PET)	DS	ad lib. HSD → D2R protein ↑, D2R mRNA/affinity ↓
Jones et al. [98]	Diet for 25–30 days	Obesogenic diet Restricted diet	n.a.	Rats	n.a.	m	9–12 weeks at start of experiment	DA transmission (DA uptake, DAT surface)	CAU, PUT, NAc, SN, VTA	HSD → DAT and D2R expression ↓ in the CAU/PUT (not in NAc)
Patel et al. [105]	Diet for 21–32 days	Control Food-restricted diet (FR) Obesogenic diet (HFSD)	5 5 5	Rats/mice	456 ± 6 after diet 308 ± 3 after diet 505 ± 15 after diet	m	8–10 weeks	DA transmission (DAT activity) Metabolic factors (insulin)	CAU, PUT, NAc	1. Insulin in controls → dopamine uptake ↑ 2. FR > controls → DA uptake ↓ → effects of insulin on DAT activity amplified by FR but blunted by HFSD
Robinson et al. [106]	Susceptibility to diet induced obesity	Exp 1 (junk food) Exp 2 (chow) Exp 2 (junk food) Exp 3	30 10 13 12	Rats	n.a.	m	70–75 days	Behaviour (wanting, liking)	STR	1. Susceptible > non-susceptible conditioned approach prior to the development of obesity 2. Susceptible > non-susceptible willingness to gain access to a sucrose cue 3. In susceptible rats, ↓ Mu opioid receptor mRNA expression in striatal 'hotspots'; exposure to junk food → cross-sensitisation to

Table 2 (continued)

Reference	Compared factor	Groups	Sample size (*N*)	Species	Weight (g)	Gender	Age (in years)	Method	Brain regions of interest	Main result
										amphetamine-induced locomotion and downregulation of striatal D2R mRNA
Horst et al. [40]	DA	–	9	Mice	n.a.	n.a.	n.a.	metabolic (glucose; optogenetic activation on vs. off)		Optogenetic activation of DA D1 receptor-expressing neurons in the NAcc increased glucose tolerance and insulin sensitivity
Sharpe et al. [107]	optogenetic DA activation	ChR2 exp. group (Exp 1)	8	Rats	n.a.	n.a.	4 months	cognition (conditioned reinforcement learning, sensory preconditioning task, configural learning task)	VTA	DA transients → ↑ (valueless) associative learning
		eYFP control group (Exp 1)	8					DA transmission (optogenetic manipulation)		
		ChR2 exp. group (Exp 2)	14							
		eYFP control group (Exp 2)	14							
		ChR2 exp. group (Exp 3)	6							
		eYFP control group (Exp 3)	6							

This table provides the main properties of the study design (compared factor, groups if applicable, sample size, methods and regions of interest if suitable) as well as sample characteristics (species, BMI, gender, age) of each study together with a summary of the main results. If the study design contains groups, sample characteristics are given separately for each group, unless groups did not differ on a criterion or the variable is only given for the entire sample

ad lib., ad libitum; *CAU*, caudate nucleus; *CREB*, cAMP response element-binding protein; *DA*, dopamine; *DARPP-32*, dopamine- and cAMP-regulated neuronal phosphoprotein; *DAT*, dopamine active transporter; *DBS*, deep brain stimulation; *DIO*, diet-induced obesity; *DOPAC*, 3,4-dihydroxyphenylacetic acid; *DRDX/DXR*, dopamine receptor X; *DS*, dorsal striatum; *Exp*, experiment; *fMRI*, functional magnetic resonance imaging; *HFD*, high fat diet (given in brackets the percentage of calories consumed from fat); *HFSD*, high fat and sugar diet (given in brackets the percentage of calories consumed from sugar/fat); *HSD*, high sugar diet (given in brackets the percentage of calories consumed from sugar); *LFD*, low fat diet (given in brackets the percentage of calories consumed from fat); *m*, male; *M*, mean; *n.a.*, not available/applicable; *n*, sample size; *NAc*, nucleus accumbens; *OB*, obese; *PET*, positron emission tomography; *PUT*, putamen; *sh*, shell; *SN*, substantia nigra; *STR*, striatum; *TH*, tyrosine hydroxylase; *VTA*, ventral tegmental area

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