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Keywords

Dopamine; obesity; PET; reward sensitivity

Summary

Alterations in the dopaminergic system have been implicated in both animal and human obesity. However, to date, a comprehensive model on the nature and functional relevance of this relationship is missing. In particular, human data remain equivocal in that seemingly inconsistent reports exist of positive, negative or even no relationships between dopamine D2/D3 receptor availability in the striatum and measures of obesity. Further, data on receptor availability have been commonly interpreted as reflecting receptor density, despite the possibility of an alternative interpretation, namely alterations in the basal levels of endogenous dopaminergic tone. Here, we provide a unifying framework that is able to explain the seemingly contradictory findings and offer an alternative and novel perspective on existing data. In particular, we suggest (i) a quadratic relationship between alterations in the dopaminergic system and degree of obesity, and (ii) that the observed alterations are driven by shifts in the balance between general dopaminergic tone and phasic dopaminergic signalling. The proposed model consistently integrates human data on molecular and behavioural characteristics of overweight and obesity. Further, the model provides a mechanistic framework accounting not only for the consistent observation of altered (food) reward–responsivity but also for the differences in reinforcement learning, decision-making behaviour and cognitive performance associated with measures of obesity.

Introduction

Obesity is associated with prominent alterations in the dopaminergic system in both animals and humans [1]. However, human data remain equivocal in that seemingly inconsistent reports exist of positive, negative or even no relationships between dopamine D2/D3 receptor availability in the striatum and measures of obesity. Further, data on receptor availability have been commonly interpreted as reflecting D2/D3 receptor density, despite the possibility of an alternative interpretation, namely alterations in the basal levels of endogenous dopaminergic tone. Here, upon reviewing the existing data, we provide a unifying framework that is able to (i) explain the seemingly contradictory findings and (ii) offer an alternative perspective on the existing data. The main question posed by this review is thus the following: can the assumption of a quadratic relationship between dopaminergic tone and degree of obesity reconcile the conflicting results on postsynaptic dopaminergic signalling in human obesity?
**Dopamine signalling**

**Phasic and tonic dopamine signalling**

The dopaminergic system is composed of three main pathways in the brain (for an overview, see Fig. 1). Dopaminergic input arises from neurons in the substantia nigra pars compacta (SNpc) and the ventral tegmental area (VTA), both located in the midbrain. The nigrostriatal pathway (Fig. 1, 1) delivers dopaminergic input from the SNpc to the dorsal striatum. This pathway has mostly been associated with motor control and the formation of automatic stimulus–response links such as habits. Secondly, information within the mesolimbic pathway (Fig. 1, 2) travels from the VTA to the nucleus accumbens (NAcc) in the ventral striatum from where it is relayed to the limbic system, i.e. the amygdala, hippocampus and prefrontal cortex (PFC). Finally, the mesocortical pathway (Fig. 1, 3) provides direct dopaminergic input from the VTA to the frontal cortex.

![Figure 1. Schematic overview on the three main dopaminergic pathways in the human brain.](image)

**Figure 2.** Overview on central dopaminergic metabolism (simplified). DOPA, dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; VMA, vanillylmandelic acid.
Dopamine (DA) in the central nervous system (CNS) acts as both neurotransmitter and neuromodulator. These functions differ with respect to their time scale of action, local distribution of DA and their effects in the CNS.

Phasic DA release, in keeping with DA’s function as neurotransmitter, is fast (with a millisecond precision), is dependent upon DA neuron burst firing, acts almost exclusively on postsynaptic cells and is quickly removed from the synaptic cleft, apparently without diffusion into the adjacent space. Phasic burst spiking activity depends upon glutamatergic excitatory synaptic input [2]. In contrast, background tonic DA release, reflecting DA’s role as a neuromodulator, is independent of DA neuron burst firing, is not limited to the synapse and acts on a longer time scale of minutes to hours. Normally, tonic DA release is under potent GABAergic inhibition [2, 3], and spontaneous tonic spiking activity of VTA neuron populations determines the concentration of tonic extracellular DA [2].

Phasic DA release is triggered by behaviourally relevant stimuli, thereby serving as a learning and eventually prediction signal [4-6]. However, the intensity of phasic DA response can be
modulated by tonic DA release through an effect on extracellular DA levels [7]. Tonic DA activity has been demonstrated to be a potent inhibitor of phasic signals due to activation of release-regulating presynaptic autoreceptors [8-11]. Exogenous DA has been experimentally shown to hyperpolarize and eventually silence isolated dopaminergic neurons [12]. Importantly, tonic DA release at physiological levels may define the background level of DA receptor stimulation and availability at both the levels of autoreceptors and postsynaptic receptors [7]. Importantly, extrasynaptic tonic DA levels have been shown to exhibit slow but substantial alterations in response to drugs or stress [13]. Therefore, homeostatic processes induced by altered DA tone may contribute to a modulation of phasic DA responsivity.

Alterations in the balance between tonic and phasic DA signalling have been described during adolescence and in psychiatric diseases such as schizophrenia and depression [7]. Adolescence is accompanied by increases in incentive–reward motivation, potentially mediated by an altered interplay between tonic and phasic modes of DA transmission [14]. In schizophrenia, abnormally large responses to phasic DA release are suggested to be induced by a reduced overall DA tone [7, 15], caused by a reduction of excitatory afferent input from hippocampus and PFC to the ventral striatum [2]. Here, we hypothesize that the opposite may be true for severe obesity, namely that abnormally small responses in phasic DA release might be paralleled by an overall increased DA tone.

**Dopaminergic signalling and subjective reward**

With the introduction of optogenetic techniques, it is feasible to manipulate the firing properties of DA neurons, and hence the tonic and phasic release of DA, in a highly controlled fashion in freely behaving animals. Phasic, unlike tonic, light-activated stimulation of VTA DA neurons results in a transient release of DA in the ventral striatum in vivo. Animals develop a preference for a chamber associated with phasic DA neuron stimulation over a chamber associated with tonic DA neuron stimulation [16], which is illustrative of the rewarding properties of phasic DA release. Similarly, phasic stimulation of VTA DA neurons was shown to positively reinforce actions associated with delivery of food. Interestingly, such actions were not reinforced in the absence of food delivery [17]. These results suggest that phasic stimulation of DA neurons modulates reward-related learning and can specifically impact on food-seeking behaviour. While phasic firing of DA neurons thus may signal the arrival of reward, tonic firing of the same neurons is thought to subserve motivational states [18]. For example, in DA transporter knock-down mice, chronically elevated extracellular DA facilitates ‘wanting’ and learning of an incentive motivation task for a sweet reward [19], whereas the general ‘liking’ of food reinforcers seems to be mostly unaffected by changes in DA tone [20]. Thus, individuals with increased dopaminergic tone might attribute higher incentive salience to rewarding stimuli.
Further, it has been shown for drugs of abuse that the subjective perception of reward depends upon the ability to induce a fast and steep increase in phasic striatal DA release [21]. Drugs that are more potent in this regard are classified as being more addictive. Further, the kinetics of the drug determine the intake frequency: drugs with a slower clearance are consumed less frequently compared with drugs that are cleared faster [22]. The obese state is accompanied by a reduced phasic DA release in the striatum in response to pharmacological [23] or glucose challenge [24], and unexpected taste rewards [25], an effect that may depend upon dietary fat content [26]. Importantly, the observation of reduced phasic DA release indicates less subjective reward in obese subjects. From this, the ‘reward-deficiency hypothesis’ for obesity has been derived, stating that obese subjects overeat to compensate for a reduced feeling of subjective reward from food [27], caused by attenuated phasic dopaminergic signalling.

**Obesity and the dopaminergic system**

The following paragraphs will review and interpret existing human data, analysing obesity-associated differences in essential factors controlling dopaminergic tone and phasic dopaminergic responses.

Phasic dopaminergic transmission and basal dopaminergic tone depend upon various factors such as DA synthesis capacity, stipulated by levels of DA precursors, the density and availability of DA receptors, the activity and level of dopamine transporter (DAT), which defines the rate of DA removal from the synaptic cleft in the striatum, and enzymes involved in the synthesis (tyrosine hydroxylase) and degradation of DA in prefrontal areas, such as catechol-O-methyl transferase and monoamine oxidase. In humans, some of these components can be measured either indirectly by molecular neuroimaging or by determining the level of the metabolites of DA in the cerebrospinal fluid (CSF), blood or urine.

Several alterations within the dopaminergic system have been observed in overweight and obese subjects. Most prominent are reports on altered striatal D2/D3 receptor availability and functional differences in the striatum, e.g. DA release. However, some studies have also addressed a differential level in DA metabolites.
Catecholamine metabolites (homovanillic acid, vanillylmandelic acid, 3-methoxy-4-hydroxyphenylglycol, dihydroxyphenylacetic acid)

Adult obese subjects have been reported to have higher levels of homovanillic acid (HVA) in the CSF [28]. HVA measured in the CSF, blood or urine is DA's main catabolite and is suggested to reflect the central dopaminergic turnover and tone [29], while peripherally measured DA is unlikely to reflect the centrally synthesized DA because DA itself cannot cross the blood–brain barrier. Central DA is synthesized from dihydroxyphenylalanine (DOPA) and is further metabolized to noradrenaline and adrenaline (see Fig. 2). Its degradation leads to the catabolites dihydroxyphenylacetic acid (DOPAC) and eventually HVA. Degradation of noradrenaline leads to 3-methoxy-4-hydroxyphenylglycol (MHPG) and vanillylmandelic acid (VMA), and the degradation of adrenaline to VMA. These catabolites can be measured peripherally, i.e. directly in the blood or after clearance by the kidneys in the urine.

Further, obese children show significantly increased urinary levels of HVA and MHPG compared with normal controls and a nominally increased secretion of DOPAC [30]. This indicates that obesity might be paralleled by increases in tonic DA as a result of increased synthesis or turnover.

In contrast, malnourished individuals with anorexia nervosa show reduced levels of HVA in the CSF, an effect that even persists after recovery [31]. Taken together, these results indicate that weight status in general might be associated with altered dopaminergic tone in the CNS. Interestingly, patients suffering from Prader–Willi syndrome, a rare genetic disorder that is linked to severe hyperphagia, also show increased levels of HVA in the CSF independent of body mass index (BMI) [32]. This finding supports the notion that dopaminergic tone might be associated with characteristics of eating behaviour, or dietary content, rather than weight status per se.

Dopamine release, dopamine reuptake and dopaminergic tone via dopamine transporter

Rodent studies suggest that there might be an increase in striatal extracellular DA following prolonged high fat intake or diet-induced obesity (DIO) [26, 33]. This has been ascribed in part to a reduced rate of DA reuptake in the striatum, as has been demonstrated in non-obese animals that have been fed a high-fat diet (HFD) for 6 weeks when compared to animals receiving a low-fat diet [26]. Reduced uptake is thought to be mediated by either disturbed trafficking or post-translational modifications of the DAT protein in non-obese HFD rats [26], or its reduced
production in DIO rats [33]. In humans, however, there seems to be no reliable association between obesity and DAT availability [34, 35].

**D1, D2/D3 receptors**

While human studies on the relationship between D1 receptors and obesity are missing so far, several studies have addressed the relationship between D2/D3 receptor availability and obesity. However, studies investigating the binding potential (BP) of D2/D3 receptors provide seemingly contradictory results. Wang et al. and de Weijer et al. both found lower striatal availability of D2/D3 receptors in obese subjects using [11C]raclopride with positron emission tomography (PET) and [123I]IBZM with single photon emission computed tomography (SPECT), respectively [36, 37]. In contrast, Guo et al. found that BP in caudate and putamen is actually higher in subjects with obesity when using [18F]fallypride, while there was no difference in the NAcc [38]. Dunn and colleagues also used [18F]fallypride to determine D2/D3-receptor BP in lean and obese women [39]. Their study also revealed higher BP in the caudate for obese women compared with their lean counterparts. Two studies reported no difference in BP between lean and obese subjects [40, 41]. Karlsson and colleagues also used [11C]raclopride, while Eisenstein and colleagues used [11C]NMB, a D2-receptor-specific compound that cannot be replaced by endogenous DA [40].

Interestingly, Guo and colleagues reported an association of BP and characteristics of eating behaviour, namely ‘opportunistic eating’, even when controlling for BMI. They identified positive associations with ‘opportunistic eating’ in dorsal and lateral striatum and a negative association in the ventromedial striatum [38]. This supports the notion of a relationship between BP and eating behaviour rather than BMI alone. Further, women who recovered from anorexia nervosa had a significantly increased BP using [11C]raclopride in the antero-ventral striatum compared with control women without a history of anorexia [42]. As [11C]raclopride competes with endogenous DA, this result is suggestive of lower dopaminergic tone in formerly anorectic women. Further, this finding fits well with the observation of lower levels of dopamine's main catabolite HVA in women who recovered from anorexia nervosa compared with control women [31].

**Can the results be ascribed to receptor density or dopaminergic tone?**

Importantly, depending upon the tracer used, BP does not directly reflect the density of DA receptors but rather is a measure of receptor availability. The number of available, i.e. free, receptors depends upon the total number of receptors and their rate of occupancy. Hence, under the assumption of a relatively constant receptor density with an altered dopaminergic tone, in some cases a lower BP can be observed as receptors are competed for by endogenous dopamine.
For example, this was shown in the dorsal striatum in a study of lean individuals treated with [11C]raclopride and scanned before and after a meal [43].

All studies that report a difference in BP used compounds that are not specific for D2-receptors but bind also to D3-receptors, and, importantly, can be displaced by endogenous DA (see Table 1 for details). One study that showed no differences in BP used a D2-specific tracer, which in addition cannot be competed for by endogenous dopamine. Taken together, these results leave open two alternative ways of interpreting the data: either the observed effects can be driven by alterations in D3-receptor availability, or by an altered level of endogenous DA in obese subjects. Due to the comparably low expression levels of D3Rs when compared to D2Rs [44], it seems unlikely that the effect would be mainly driven by altered D3R density. Dunn and colleagues discussed the possibility of altered endogenous DA levels in obese subjects when interpreting their data. Their study is the only one that exclusively measured subjects in the early evening (starting at 18:30) after an 8.5-h fast. Interestingly, obese subjects had lower levels of ghrelin compared with lean subjects directly prior to the scanning session. This is important because BP correlated negatively with ghrelin levels. Ghrelin has been shown to increase VTA DA neuron firing and tonic (but not phasic) accumbal DA release, i.e. extracellular DA levels [45-47]. Therefore, the difference between lean and obese groups in the study of Dunn and colleagues could have been induced by a differential physiological reaction in terms of ghrelin-mediated DA release to the 8.5-h fasting period directly before scanning. In the remainder of the studies, nutritional status and scan condition with respect to time of day are heterogeneous between studies and even study groups (see Table 1). As nutritional status may influence D2R availability due to dopamine release, the discussion of a potential impact of variance in this variable on the seemingly conflicting results on the association between D2R availability and overweight or obesity is difficult.
Table 1. Study and participant characteristics of human studies comparing striatal binding potential (BP) between lean and obese groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Wang et al. [36]</th>
<th>de Weijer et al. [37]</th>
<th>Dunn et al. [39]</th>
<th>Guo et al. [38]</th>
<th>Karlsson et al. [41]</th>
<th>Eisenstein et al. [40]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI lean</strong></td>
<td>24.7 (2.6)</td>
<td>21.7 (2.1)</td>
<td>23 (2)</td>
<td>22.4 (21.3–23.49) CI</td>
<td>22.65 (2.94) ns</td>
<td>22.6 (2.2)</td>
</tr>
<tr>
<td></td>
<td>21–28</td>
<td>19.5–27.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI obese</strong></td>
<td>51.2 (4.8)</td>
<td>46.8 (6.5)</td>
<td>40 (5)</td>
<td>36.1 (33.96–38.3) CI</td>
<td>41.89 (3.88)</td>
<td>40.3 (4.9)</td>
</tr>
<tr>
<td></td>
<td>42–60</td>
<td>38.7–61.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age lean</strong></td>
<td>37.5 (5.9)</td>
<td>28 (10.4)</td>
<td>40 (9)</td>
<td>28 (25.1–30.4) CI</td>
<td>44.86 (12.88)</td>
<td>29.7 (5.6)</td>
</tr>
<tr>
<td></td>
<td>25–45</td>
<td>20–60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age obese</strong></td>
<td>38.9 (7.3)</td>
<td>37.8 (7)</td>
<td>40 (8)</td>
<td>35 (31.9–38.8) CI</td>
<td>39.08 (10.74)</td>
<td>32.5 (5.9)</td>
</tr>
<tr>
<td></td>
<td>26–54</td>
<td>26–49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity lean</strong></td>
<td>ns</td>
<td>ns</td>
<td>1/7/0</td>
<td>ns</td>
<td>ns</td>
<td>1/14/0</td>
</tr>
<tr>
<td>(black/white/Hispanic)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity obese</strong></td>
<td>ns</td>
<td>ns</td>
<td>5/9/0</td>
<td>ns</td>
<td>ns</td>
<td>6/8/1</td>
</tr>
<tr>
<td>(black/white/Hispanic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Males/females lean</strong></td>
<td>7/3</td>
<td>0/15</td>
<td>0/8</td>
<td>12/11</td>
<td>0/14</td>
<td>4/11</td>
</tr>
<tr>
<td><strong>Males/females obese</strong></td>
<td>5/5</td>
<td>0/15</td>
<td>0/14</td>
<td>10/10</td>
<td>0/13</td>
<td>3/12</td>
</tr>
<tr>
<td><strong>Scan condition lean</strong></td>
<td>About 11:00 am after overnight fast</td>
<td>At various times of day</td>
<td>6:30 pm after 8.5 h fasting, standard BF and meal before 10:00 am</td>
<td>Morning after standard BF</td>
<td>Not specified, after 2 h fasting</td>
<td>Not influential</td>
</tr>
</tbody>
</table>
Scan condition
obese

<table>
<thead>
<tr>
<th>Time</th>
<th>Condition</th>
<th>BMI, body mass index; BF, breakfast; CI, confidence interval; ns, not specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>About 11:00 am after overnight fast</td>
<td>Lower D2/D3 BP in obese subjects</td>
<td>Taken together, altered dopaminergic tone seems to be a plausible explanation of the observed effects. However, an influence of differences in D2/D3 receptor density cannot be excluded.</td>
</tr>
<tr>
<td>After overnight fast in the morning</td>
<td>Lower D2/D3 BP in obese subjects</td>
<td></td>
</tr>
<tr>
<td>6:30 pm after 8.5 h fasting, standard BF and meal before 10:00 am</td>
<td>Higher D2/D3 BP in obese subjects</td>
<td></td>
</tr>
<tr>
<td>Morning after standard BF</td>
<td>Higher D2/D3 BP in obese subjects</td>
<td></td>
</tr>
<tr>
<td>Not specified, after 2 h fasting</td>
<td>No differences in D2/D3 BP</td>
<td></td>
</tr>
<tr>
<td>Not influentia</td>
<td>No differences in D2 BP</td>
<td></td>
</tr>
</tbody>
</table>

**Main finding**

- Lower D2/D3 BP in obese subjects
- Higher D2/D3 BP in obese subjects
- No differences in D2/D3 BP

**Is dopaminergic tone dependent upon the level of obesity?**

Comparing the BMI range of the obese groups across all studies reveals profound differences between studies. Mean BMI of the obese group in the studies of Wang and colleagues and De Weijer and colleagues was higher than in the studies of Dunn et al., Eisenstein et al., Karlsson et al. and Guo et al. (for study characteristics, see Table 1). To test the hypothesis that BMI might influence BP in the overweight to obese range of body weight, potentially induced by alterations in DA tone, the relative difference in BP between lean and obese groups for all studies reported above was plotted against the relative difference in BMI between lean and obese controls for each study. A linear association would indicate a dependency between dopaminergic tone and grade of obesity. As shown in Fig. 3, indeed, there was a linear relationship, starting with higher levels of availability (interpreted as lower DA tone) in the moderately obese range and then quickly transitioning into profound reductions in availability (interpreted as higher DA tone) in the morbidly obese range.

The assumption of a linear relationship between markers of human obesity and dopaminergic tone is further supported by correlational analyses performed within the obese group in the study of Wang and colleagues [36]. They observed a significant negative relationship between BMI and BP in severely obese subjects but not in the group of lean subjects (Fig. 4b). Conversely, Cosgrove et al. recently observed a positive relationship between BP and BMI in a group of normal weight to moderately obese subjects [48] (Fig. 4a; BMI 21.5–36.5 kg m−2). Taken together, these data point to a non-linear quadratic relationship between BP and BMI with higher
BP in the lower ranges of obesity and lower BP with more severe obesity. The observations of Kessler and colleagues corroborate our interpretation of the data: while they observed small negative relationships between BP and BMI in mildly obese subjects, they found a strong positive association between BMI and DA release in the striatum and SN [49]. This observation would be in line with a BMI-dependent decrease of tonic DA that boosts phasic DA signalling in the mildly obese range.

Figure 4. Different linear relationships between body mass index (BMI) and dopamine receptor availability. (a) Positive association between receptor availability and BMI in moderately obese subjects from the study of Cosgrove et al. [48]. (b) Negative association between receptor availability (Bmax/Kd) and BMI in severely obese subjects from the study of Wang et al. [36].

The proposed quadratic changes in DA tone that takes place with the progression of obesity from none, to mild, to severe is potentially paralleled by changes in other BMI-dependent tonic signalling molecules such as insulin and leptin. For example, the adipokine leptin circulates in proportion to adiposity and inhibits VTA DA neurons and DA release [50, 51]. Therefore, a higher BMI could be associated with higher levels of leptin and decreased tonic DA until a ‘break-point’ is reached when leptin resistance develops and progressively worsens, resulting in an escalation in DA tone. However, Guo and colleagues [38] argued that endogenous DA occupies only about 10% of DA receptors, thus alterations in endogenous DA may not fully explain the observed changes in DA receptor availability associated with overweight and obesity which are bigger in magnitude. Further, as opposing relationships between DA receptor availability in different parts of the striatum have been reported [38], the seemingly contradictory observations in the studies reviewed earlier might in part also be ascribed to variance in region of interest (ROI) selection across studies and averaging over the whole striatum.
In summary, differences in tonic endogenous DA levels between lean and obese subjects could be the main driver of group differences in studies using tracers that can be displaced by endogenous DA. Furthermore, a quadratic relationship between DA tone and degree of obesity is able to reconcile the seemingly conflicting results.

If there is indeed an increase in tonic DA signalling in morbid obesity, would this result in the recruitment of extra-synaptic DA receptors? It appears at least from a recent PET study on humans that [11C]raclopride binds to an appreciable level of extra-synaptic D2Rs [52]. This raises the tantalizing possibility that the findings from Wang et al. are a result of decreased occupancy of extra-synaptic D2Rs as a consequence of increased tonic DA signalling.

**Human model and implications**

**Suggested human model**

Our main hypothesis is that overweight/mild obesity and severe obesity are associated with different states of dopaminergic tone: overweight may be paralleled by a reduction in dopaminergic tone and associated exaggerated phasic DA responses in the striatum. On the contrary, severe obesity may be characterized by an increased dopaminergic tone with associated blunted striatal DA burst firing. Importantly, these two states would lead to differential predictions regarding reward sensitivity and cognitive functioning. As we built our model on data exclusively obtained in the striatum, it is likewise possible that alterations in DA tone are restricted to the striatum or also pertain to other structures with dopaminergic input, e.g. the PFC.

**Reward sensitivity and dopamine tone**

An inverted u-shape has been proposed for the relationship between the sensitivity and responsiveness to reward and markers of obesity [53, 54]. This is consistent with parallel associations between tonic DA levels and degree of obesity, if the reference BP in lean subjects is additionally taken into account (Fig. 5). Higher reward sensitivity in the overweight/mildly obese state would thus be associated with lower DA tone and higher phasic DA responses. On the contrary, higher tonic DA level with higher BMI would thus be associated with lower reward sensitivity, induced by a down-regulation of phasic DA responses.
Figure 5. Inverted U-shaped relationships in reward sensitivity and dopaminergic tone. Davis and Fox (a) as well as Dietrich, Federbusch and colleagues (b) reported a quadratic relationship between different measures of reward sensitivity and body mass index (BMI). The characteristics of this relationship match the here-proposed quadratic relationship between dopamine tone and BMI (c). Control: reference binding potential (BP) of lean groups. Light grey dot: study of Eisenstein and colleagues, who used a tracer that is not displaceable by endogenous dopamine. Labels refer to first author and year of publication of the respective study.

Differential impact of tonic and phasic dopaminergic signals on reinforcement learning

Reinforcement learning depends upon both positive and negative learning signals, the so-called prediction errors (PEs): positive PEs, i.e. when an outcome is better than expected, are paralleled by an increase in phasic DA levels. Negative PEs, i.e. signalling that an outcome is worse than expected and behaviour should subsequently be adapted, are paralleled by a dip in tonic dopaminergic firing rate [5]. Recently, it has been shown in healthy, normal-weight volunteers that learning from negative outcomes is associated in an inverted u-shaped manner with D2/D3 receptor availability in the striatum [55]. As variation in D2/D3 receptor density is likely to be limited in healthy volunteers, availability may likewise have been dependent upon dopaminergic tone in this study. Thus, one might hypothesize that obesity-associated alterations in dopaminergic tone should be also paralleled by specific alterations in learning from positive and negative feedback with increasing degree of obesity. Indeed, this has been observed in different paradigms: Mathar and colleagues observed in moderately obese subjects a specific impairment in learning from negative PEs in a probabilistic classification paradigm while learning from positive PEs was unaffected (D Mathar, J Neumann, A Villringer A, A Horstmann, unpublished data). This impairment was paralleled by differences in functional connectivity between the ventral striatum and premotor and motor cortices. In line, Coppin and colleagues observed deficits in negative but not positive outcome learning when comparing moderately obese subjects to normal-weight control subjects [56].
**Cognition and dopamine**

Dopaminergic tone is important not only for reward and learning but also for performance in several cognitive domains, most prominently in tasks requiring working memory [57]. The influence of dopaminergic transmission on performance has been shown to be variable and is probably domain-specific. Early work has indicated an ‘inverted u-shaped’ function for working memory, i.e. that either too much or too little dopaminergic transmission in the PFC impaired working memory performance in rats [58]. Obesity has been associated with impairments in working memory [59, 60], although findings remain equivocal [60]. Interestingly, Coppin and colleagues [56] reported impairments in both overweight and obese subjects compared with normal-weight controls with a nominally more pronounced effect in overweight (mean BMI 27.6 kg/m2) compared with mildly obese (mean BMI 36 kg/m2) subjects. These data might hint at a dynamic and quadratic relationship between degree of obesity and performance on a working memory task, possibly mediated by parallel changes in DA tone. Because of the inverted u-shaped function for DA tone and working memory performance, both lower and higher DA tone would result in impairments in working memory.

Recent work proposes several other dependencies between dopaminergic tone and performance in different cognitive domains [61]. For example, dopaminergic tone in the PFC has been suggested to be associated with cognitive flexibility [61]: a low tone is suggested to underpin heightened flexibility, while a high tone mediates lowered behavioural flexibility. Hence, following from our proposed model, behaviour in overweight and mild obesity should be characterized by increased flexibility, while severe obesity should be paralleled by a certain rigidity of behaviour. Indeed, in a lever-pressing task conducted on severely obese rats with restricted access to a palatable food, behavioural rigidity was induced and alleviated when a DA receptor antagonist was administered into the striatum [62]. Further, increasing levels of obesity were associated with heightened habitual responding in a classical sensory devaluation task in obese men [63]. Although it has been proposed that striatal and PFC DA tone are related in a reciprocal manner under normal conditions [64], this might no longer be the case in obesity. Thus, the balance between striatal and PFC signalling might be disturbed by a general increase in DA tone.

**Conclusion**

The assumption of non-linear changes in the general DA tone over the spectrum of overweight and obesity leads to the hypothesis that feedback-dependent behaviour, i.e. reactions to reward and punishment, as well as different domains of cognition may be differentially affected in different stages of developing obesity. Further, alterations of dopaminergic tone with increasing states of obesity might be regarded as disturbances of dopaminergic regulation rather than
deficits in DA transmission, comparable to conditions such as schizophrenia or affective disorders [13]. Overweight and mild obesity may be paralleled by a reduction in dopaminergic tone and associated exaggerated phasic DA responses in the striatum. Severe obesity, in contrast, may be characterized by an overall increased dopaminergic tone with associated blunted striatal DA burst firing. This should be taken into account when designing pharmacological therapies in obesity, e.g. targeting the dopaminergic system. Further, looking for quadratic associations in samples spanning mild to severely obese subjects might reveal compatible patterns in cognition. The failure to do so might have contributed to the lack of homogeneous associations between performance in several cognitive domains and obesity [60].

**Conflict of interest statement**

No conflict of interest was declared.

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