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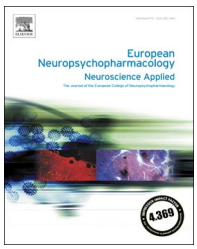

Lower dopamine tone in the striatum is associated with higher body mass index

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Abstract
Existing literature suggests that striatal dopamine (DA) tone may be altered in individuals with higher body mass index (BMI), but evidence accrued so far only offers an incomplete view of their relationship. Here, we characterized striatal DA tone using more comprehensive measures within a larger sample than previously reported. In addition, we explored if there was a relationship between striatal DA tone and disinhibited eating. 60 healthy participants underwent a 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) positron emission tomography (PET) scan. Disinhibited eating was measured with the Three-Factor Eating Questionnaire on a baseline visit. Individual whole-brain PET parameter estimates, namely ^{18}F-DOPA influx rate constant (k_{occ} i.e. DA synthesis capacity), ^{18}F-DA washout rate (k_{loss}) and effective distribution volume ratio (EDVR= k_{occ} / k_{loss}), were derived with a reversible-tracer graphical analysis approach. We then computed parameter estimates for three regions-of-interests (ROIs), namely the ventral striatum, putamen and caudate. Overweight/mildly obese individuals had lowered EDVR than normal weight individuals in all three ROIs. The most prominent of these associations, driven by lowered k_{occ} ($r = -.28$, $p = .035$) and heightened k_{loss} ($r = .48$, $p < .001$), was found in the ventral striatum ($r = -.46$, $p < .001$). Disinhibition was greater in higher-BMI individuals ($r = .31$, $p = .015$), but was unrelated to PET measures and did not explain the relationship between PET measures and BMI. In sum, our findings resonate with the notion that overweight/mildly obese individuals have lower striatal DA tone and suggest new avenues for investigating their underlying mechanisms.

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1. Introduction

Body weight regulation involves an intricate network of dopaminergic processes that control food intake and energy expenditure (Berthoud and Morrison, 2008). Accumulating literature suggests that striatal dopamine (DA) functioning is altered in obesity (Stice et al., 2010), but there are inconsistencies in the literature on how they are altered. A majority of human studies have investigated the relationship between basal striatal DA functioning and BMI using DA D2/3 receptor (DRD2/3) binding potential measures (Dang et al., 2016; Horstmann et al., 2015b). Seminal work by Wang and colleagues suggested that obese individuals had lower striatal DRD2/3 binding potentials than normal weight controls (Wang et al., 2001). This was in keeping with other lines of research which showed that animals with diet-induced obesity have less striatal DRD2 (Johnson and Kenny, 2010). However, this relationship became less clear when further research point to higher striatal DRD2/3 binding potentials in obese individuals than normal weight controls, while others found no differences (Horstmann et al., 2015b). As outlined by Dang and colleagues (Dang et al., 2016), inconsistencies across studies could be due to differences in body-mass index (BMI) ranges and sample sizes tested. Further, DA receptor binding reflects, in part, competition from endogenous DA levels (Laruelle, 2000). This means that higher binding could be interpreted as *reduced* competing endogenous DA levels and/or *increased* receptor availability (Ito et al., 2011). As such, it is difficult to infer whether BMI is related to altered DA levels, DRD2/3 expression or both. Some studies have attempted to address this issue by using PET tracers with higher DA receptor affinities (e.g. [^{18}F]fallypride) such that binding observations are less sensitive to competition from endogenous DA levels (Mukherjee et al., 1995). Although these studies inferred that there is a heightened striatal DRD2/3 availability in higher-BMI individuals (Dang et al., 2016; Dunn et al., 2012; Guo et al., 2014), endogenous DA levels (DA tone) may also be altered in these individuals (Dunn et al., 2012).

Indeed, Horstmann and colleagues proposed that tonic DA levels in the striatum may be associated with BMI in a U-shaped manner (Horstmann et al., 2015b). DA neurones play an unequivocal role in mediating approach behaviour towards rewards. These neurones fire in two distinct modes to release DA in the striatum, namely single spike mode which maintains steady-state extracellular DA levels i.e. tonic DA levels, and burst firing mode which releases DA in transient, massive bursts i.e. phasic DA release (Goto et al., 2007). Tonic DA levels in the striatum reflect a state of equilibrium which is dependent on tonic firing and DA reuptake transporters (Sulzer, 2011). It has been suggested that DA responsivity to reward-related stimuli in the ventral striatum is regulated by tonic DA levels, such that when tonic DA levels are low, amplitudes of phasic DA released upon stimulation are high (Bilder et al., 2004; Floresco et al., 2003; Grace, 1991). Along with this line of argument, Horstmann proposed that overweight/mildly obese individuals have the lowest tonic DA levels relative to normal-weight and severely obese individuals, thus having the highest phasic DA responses to rewards (Horstmann et al., 2015b).

PET tracers used conventionally for measuring presynaptic DA integrity (Doudet et al., 1999) have been used more recently to assess tonic DA levels in the striatum (Schlagenhauf et al., 2013). One such indicator, DA synthesis capacity, is commonly measured as the rate of influx (or uptake) of the PET tracer (e.g. ^{18}F-DOPA, ^{18}FMT) into the striatum (Kumakura and Cumming, 2009). ^{18}F-DOPA uptake has been positively related to post-mortem striatal DA levels (Snow et al., 1993) and reflects net clearance of ^{18}F-DOPA from circulation into brain tissue (Gjedde et al., 1991). So far, two independent ^{18}FMT studies found that DA synthesis capacity in the dorsal striatum (caudate) was lower in overweight/mildly obese than normal weight individuals (Wilcox et al., 2010; Wallace et al., 2014). Although these results resonate well with Horstmann's proposal, there are some open questions to be resolved. The first study did not find an association within the ventral striatum (Wilcox et al., 2010), whereas the second study only focused their investigations on associations within the caudate (Wallace et al., 2014). Given the importance of nucleus accumbens (ventral striatum) in food-seeking behaviour (Balleine, 2005) and its dopaminergic alterations identified so far in association with BMI (Caravaggio et al., 2015b; Dang et al., 2016; Guo et al., 2014), the relationship between BMI and DA tone in the whole striatum warrants further investigation.

Disinhibition, a trait measure that captures habitual susceptibility to overeat in response to external cues, situations or negative emotion (Bond et al., 2001), has been consistently associated with BMI (Bryant et al., 2008). Recently, both BMI and disinhibition have been positively associated with DRD2/3 binding in the dorsolateral striatum (putamen) (Guo et al., 2014), the brain region required for habit formation (Yin and Knowlton, 2006). Higher-BMI individuals have been found to be less sensitive to food reward devaluation, suggesting that they had more habitual tendencies (Horstmann et al., 2015a). Since both enhanced and reduced DA levels have been related to a shift towards habitual control (de Wit et al., 2012; Nelson and Killcross, 2006), we were interested to see whether striatal DA tone might also be related to disinhibited eating.

Along with prior ^{18}FMT findings, we hypothesized that DA tone would be lower in overweight/mildly obese than in normal weight individuals. Using a sample nearly four times larger in size than previously reported, we characterized striatal DA tone comprehensively by using a 4-hour ^{18}F-DOPA protocol to measure ^{18}F-DOPA influx and ^{18}F-DA washout rate. Effective distribution volume ratio (EDVR), which is the ratio of ^{18}F-DOPA influx rate to ^{18}F-DA washout rate, reflects the level of DA available for vesicular storage at *steady-state* (Kumakura and Cumming, 2009). As such, EDVR should be a better reflection of striatal DA tone than ^{18}F-DOPA influx or ^{18}F-DA washout rate alone (Sossi et al., 2001). We hypothesized that both DA synthesis capacity and EDVR would be lowered in overweight/mildly obese than normal weight individuals. In addition, we included ^{18}F-DA washout rate to better understand whether the relationship between BMI and EDVR (if any) was driven by ^{18}F-DOPA influx and/or ^{18}F-DA washout rate. Lastly, we expected higher-BMI individuals to exhibit stronger disinhibition, and explored its relationship with striatal DA tone.

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