Neurobiological aspects of obesity: dopamine, serotonin, and imaging
van de Giessen, E.M.

Citation for published version (APA):

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NO ASSOCIATION BETWEEN STRIATAL DOPAMINE TRANSPORTER BINDING AND BODY MASS INDEX: A MULTI-CENTER EUROPEAN STUDY IN HEALTHY VOLUNTEERS

Elsmarieke van de Giessen
Swen Hesse
Matthan W.A. Caan
Franziska Zientek
John C. Dickson
Livia Tossici-Bolt
Terez Sera
Susanne Asenbaum
Renaud Guignard
Umit O. Akdemir
Gitte M. Knudsen

Flavio Nobili
Marco Pagani
Thierry Vander Borght
Koen Van Laere
Andrea Varrone
Klaus Tatsch
Jan Booij
Osama Sabri

Neurolmage, in press.
ABSTRACT
Introduction: Dopamine is one among several neurotransmitters that regulate food intake and overeating. Thus, it has been linked to the pathophysiology of obesity and high body mass index (BMI). Striatal dopamine D_2 receptor (DRD2) availability is lower in obesity and there are indications that striatal dopamine transporter (DAT) availability is also decreased. In this study, we tested whether BMI and striatal DAT availability are associated.

Methods: The study included 127 healthy individuals from a large European multi-centre database. They had a BMI range of 18.2 – 41.1 kg/m^2 and were scanned using \[^{[123]}\text{I}\]FP-CIT SPECT imaging. Scans were analyzed with both region-of-interest and voxel-based analysis to determine the binding potential for DAT availability in the caudate nucleus and putamen. A direct relation between BMI and DAT availability was assessed and groups with high and low BMI were compared for DAT availability.

Results: No association between BMI and striatal DAT availability was found.

Conclusion: The lack of an association between BMI and striatal DAT availability suggests that the regulation of striatal synaptic dopamine levels by DAT plays no or a limited role in the pathophysiology of overweight and obesity.
INTRODUCTION

Overweight and obesity are an increasing health problem worldwide and are defined as a body mass index (BMI) of 25-30 and >30 kg/m², respectively. Overeating of highly palatable and caloric foods is thought to play a major role in the overweight and obesity epidemic (1). There is a large body of evidence that suggests that dopamine is one of the neurotransmitters that is involved in the regulation of food intake and overeating (2). Food is able to induce a dopamine release in the nucleus accumbens in animals (3) and in the striatum in humans (4). The ability of food to increase dopamine is by some thought to be crucial for its rewarding and reinforcing effects. Changes in the mesolimbic dopaminergic reward system might therefore result in overeating (5). It has indeed been consistently demonstrated that striatal dopamine D₂ receptor (DRD2) levels are decreased in obese subjects (6;7) and that BMI correlates negatively with DRD2 availability (6). Functional MRI studies with food-related stimuli also show that the brain activity in the striatal subregions caudate nucleus and putamen is altered in obesity (8-10) and that this is dependent on DRD2 genotype (8).

Brain synaptic dopamine levels are regulated by the dopamine transporter (DAT), which controls the dopamine level by driving synaptic dopamine back into the pre-synaptic neuron. Influencing brain dopamine levels affects food intake. For example, drugs that increase dopamine levels by inhibiting DAT, such as methylphenidate, have an anorexigenic effect. Animal studies demonstrate that diet-induced obese rodents on a high-fat diet show a significant decrease in DAT density on the cell surface in the striatum (11;12) or in gene and mRNA expression (13;14), which is possibly mediated via impairment of a central kinase (Akt) that is involved in insulin signaling (11). In healthy humans, a negative correlation between striatal DAT availability and BMI has been reported (15). This association was not replicated in a monozygotic twin study, where the lean siblings did not differ in striatal DAT availability from their twin siblings with higher BMI (16). A role for the DAT in obesity and BMI is thus not yet conclusively demonstrated. This knowledge is important, though, for our understanding of the (dys)function of the dopaminergic system in overweight and obesity.

Therefore, the objective of this study is to test for an association between striatal DAT availability and BMI in a large sample of healthy subjects with a large BMI range. Based on the data of the previous animal and human studies, we hypothesize that they are negatively correlated. A European database of [¹²³I]FP-CIT SPECT scans of healthy controls provides a unique opportunity to test this hypothesis.

METHODS

Subjects

The subjects were healthy volunteers who participated in the ENC-DAT project, i.e. the European Database of [¹²³I]FP-CIT (DATSCAN) SPECT scans of healthy controls (17). This is a collaborative effort by 13 European institutions in 10 European countries. Inclusion criteria were: 1. age between 20 and 90 years, 2. Unified Parkinson’s Disease Rating Scale (UPDRS) score of 0 when < 60 years or ≤ 5 when ≥ 60 years, 3. Symptom Checklist-90-R (SCL-90-R) score < 63 to ensure minimal psychological problems, 4. Beck Depression Inventory (BDI) score < 9, 5. no evidence for cognitive impairment as assessed with the Mini-mental state examination (MMSE; score ≥ 28), 6. for females
negative urine based pregnancy test or hormonal contraceptive method or intra-uterine device (IUD) or postmenopausal state (last menstruation ≥12 months, age > 60), and 7. negative urine based screening test for drug abuse. Exclusion criteria were: 1. history or evidence of neurological or psychiatric disease, 2. history or evidence of major systemic disease that contraindicates radiopharmaceutical administration and/or interferes with subject’s compliance during the study, 3. thyroid disease, 4. aberrant MRI scan, diffuse or confluent white matter hyperintensities in T2-weighted images, corresponding to a white matter lesion (WML), age-related white matter changes (ARWMC) scale score > 0 when < 60 years or > 2 when ≥ 60 years (18), 5. hypertension that was not controlled with diet or with monotherapy, 6. history of parkinsonism in first-degree relative (sibling, parent, or children), 7. pregnant or lactating female, 8. medication affecting DAT binding or potentially interfering with the dopaminergic system, 9. body temperature ≥ 38.5°C on SPECT scanning day, and 10. contraindications for MRI examination.

All subjects were seen by a neurologist and received a general physical examination, including weight and height measurement for BMI calculation. The protocol was approved by the Medical Ethical Committees of all participating centres and all subjects provided written informed consent.

SPECT and MRI acquisition
Each subject underwent one SPECT session, prior to which they received thyroid blockade. SPECT scans were performed with the radioligand [123I]FP-CIT (DaTSCAN; GE Healthcare, Eindhoven, the Netherlands), which has a high affinity for the DAT. A total dose of approximately 185 MBq (specific activity > 185 MBq/nmol; radiochemical purity >95%) was given as an intravenous bolus. The SPECT cameras that were used were dual- or triple-headed cameras: Amsterdam – E.CAM (Siemens), Ankara – Infinia (GE Healthcare), Copenhagen – Irix (Philips), Genoa – Millennium VG (GE), Leipzig – Symbia (Siemens), Leuven – E.CAM (Siemens), London – Infinia (GE), Munich – Symbia (Siemens), Nice – Prism 3000 (Picker), Southampton – Nuclie x-Ring/4HR (Mediso), Stockholm – Trionix (Trionix), Vienna – Irix (Philips), Yvoir - Trionix (Trionix). The main technical data of all the SPECT systems used in this study have been reported by Tossici-Bolt (19). The scans were acquired at 3 hours post-injection, except in Amsterdam, Leipzig, and Yvoir, where they were acquired at 4 hours post-injection due to acquisition of another scan at 3 hours on a different type of camera, e.g. brain-dedicated system. At both time points the specific-to-nonspecific striatal [123I]FP-CIT binding ratio (SBR) is stable (20). Scan parameters were standardized for the participating centres and are shown in table 2 of Dickson et al. (17).

For anatomical reference and exclusion of significant structural pathologies (see above), each subject was scanned with MRI (at least 1.5 T) and T1 (SPRG or MPRAGE) and T2 sequences were acquired.

Data analysis
A single core lab reconstructed the SPECT data on a Hermes workstation (Hermes Medical Systems, Stockholm) using iterative reconstruction with 10 iterations and 10 subsets (12 iterations and 8 subsets for 128 project studies), with calculated attenuation correction and scatter correction using the triple-energy window method (21). Post reconstruction filtering was applied using a Butterworth filter (0.5 cm⁻¹, power 10), and the resultant in-plane matrix size was 128 x 128 with a pixel size < 3mm.
2.3.1 Region-of-interest analysis
For region-of-interest (ROI) analysis, the SPECT data were transferred to a HERMES workstation and manually coregistered with the T1 MRI scans by using the HERMES MultiModality software according a previously described procedure (22;23). In a first step, the individual MRI scan was reoriented towards the anterior commissure – posterior commissure line based on a normal standardized MRI. Second, the individual SPECT data were co-registered onto the realigned individual MRI in all three (x, y, z) planes and, third, the atlas-based predefined ROI templates in the normal standardized MRI atlas were adjusted to the individual anatomy. The uptake in each ROI (highest mean count density in adjacent slices comprising the entire brain structure, i.e. the DAT-rich striatal subregions head of the caudate nucleus and the putamen) was determined. The occipital cortex was used as the region for non-specific binding to calculate the SBR for the left and right head of the caudate nucleus and left and right putamen by (mean counts in ROI – mean counts in occipital cortex)/mean counts in occipital cortex (24). To reduce intersite variation, a correction factor was applied to the SBRs using the site-specific calibration values for attenuation and scatter corrected (ACSC) data, which were determined in a previous phantom study (see Table 2 in (19)).

2.3.2 Voxel-based analysis
To explore the potential association between BMI and striatal DAT availability in more detail, we performed a voxel-based analysis in SPM8 running on Matlab 7.5 for Windows (MathWorks, Natick, MA). First, a mean scan was generated in the realignment module of SPM8. Next, the individual scans were coregistered to the mean scan by rigid followed by non-linear affine registration in the coregistration and normalisation module of SPM8. The individual scans were smoothed at a full-width half maximum of 10 mm. Next, individual SBR maps were created by extracting the uptake in the occipital cortex for each scan and calculating the SBR for the full brain by (activity per voxel – activity in occipital cortex)/activity in occipital cortex. To reduce intersite variation, a correction factor was applied to the SBR maps using the site-specific calibration values for attenuation and scatter corrected (ACSC) data, which were determined in a previous phantom study (see Table 2 in (19)). The ROI for the occipital cortex was drawn manually on the mean scan using itk-SNAP software (version 2.1, PICSL, University of Pennsylvania).

Figure 1. Striatum mask. Mean [123I]FP-CIT SPECT scan with striatum mask for voxel-based analysis.
In SPM8, a regression analysis was performed with the SBR maps as dependent variable, BMI as independent variable and age, gender and scan time (3 or 4 hours post-injection) as covariates. Comparison of images between groups (BMI ≤ 25 versus BMI > 25 and BMI ≤ 25 versus BMI > 30) was done by ANCOVA with SBR maps as dependent variable, BMI group as independent variable and age, gender, scan time, and site as covariates. All analyses were confined to the striatum using explicit masking with a striatum ROI drawn on the mean scan using intensity thresholding in itk-SNAP (figure 1). P-values <0.05, FWE-corrected, were considered significant.

2.3.3 Statistical analysis

PASW/SPSS 18.0.2 was used for statistical analysis on SBR and BMI data. To test for an association between SBR and BMI, we used a regression analysis with SBR for each ROI as dependent variable, BMI as independent variable and age, gender, scan time (3 hours or 4 hours post-injection), and site as covariates, which were entered simultaneously. Age and gender were introduced as covariates, because they can affect striatal DAT availability (25;26). In addition, we tested whether subjects with BMI ≤ 25 versus BMI > 25 and BMI ≤ 25 versus BMI > 30 would differ in DAT availability using an ANCOVA with SBR for each ROI as dependent variable, BMI group as independent variable and age, gender, scan time, and site as covariates. P-values <0.05 were considered significant.

RESULTS

The final sample consisted of 123 subjects with a mean age of 52.3 ± 18.3 years and mean BMI of 25.2 ± 3.8 kg/m² (for subject characteristics, see table 1). The total ENC-DAT sample consists of 146 scans, however, six scans from Amsterdam, one scan from Leuven, twelve scans from Nice and four scans from Vienna were not included in the final sample due to inferior image quality, a lack of scatter windows, truncation of data (i.e. not entire striatum or occipital cortex were scanned), or missing calibration value.

ROI analysis

The regression analyses showed a significant effect in both the caudate nucleus (F = 3.44, p = 0.006) and putamen (F = 2.63, p = 0.027), which was based on an age effect (i.e. lower DAT availability at higher age; caudate nucleus: p = 0.004; putamen: p = 0.007), a gender effect (i.e. higher DAT availability in women; p = 0.033) and site effect (p = 0.044) in the caudate nucleus, but not on BMI (caudate: p = 0.159, putamen: p = 0.187, figure 2), or scan time (caudate: p = 0.780, putamen: p = 0.930). Gender (p = 0.102) and site (p = 0.074) were not significant predictors in the putamen either.

When comparing the BMI ≤ 25 group with BMI > 25 group, we found no group difference in DAT availability in neither the caudate nucleus (BMI ≤ 25: SBR (mean ± standard deviation) = 4.4 ± 1.2, BMI > 25: SBR = 4.3 ± 0.9, p = 0.789) nor the putamen (BMI ≤ 25: SBR = 4.3 ± 1.2, BMI > 25: SBR = 4.2 ± 0.9, p = 0.564), although the model showed again an age effect (caudate: p = 0.009, putamen: p = 0.012), but no significant effect of gender (caudate nucleus: p = 0.052, putamen: p = 0.131) or scan time (caudate nucleus: p = 0.704, putamen: p = 0.890). In the caudate nucleus, there was a significant, but small site effect (caudate: p = 0.043), but this was not significant in the putamen (p = 0.074).

Also, the BMI ≤ 25 versus BMI ≥ 30 analysis did not show a group effect (caudate nucleus: BMI ≤ 25: SBR = 4.4 ± 1.2, BMI ≥ 30: SBR = 4.6 ± 1.2, p = 0.519, putamen: BMI ≤ 25: SBR = 4.3 ± 1.2, BMI ≥ 30: SBR = 4.3 ± 1.2, p = 0.519).
Table 1. Subject characteristics

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Number of subjects</td>
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</tr>
<tr>
<td>Male/female</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Mean ± SD</td>
<td>52.1 ± 18.1</td>
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<td>Range</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Mean ± SD</td>
<td>25.3 ± 3.8</td>
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<tr>
<td>Subjects with BMI 25-30</td>
<td>48</td>
</tr>
<tr>
<td>Subjects with BMI ≥ 30</td>
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</tr>
<tr>
<td>SBR (mean ± SD; ROI analysis)</td>
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<tr>
<td>Caudate nucleus</td>
<td>4.4 ± 1.1</td>
</tr>
<tr>
<td>Putamen</td>
<td>4.2 ± 1.1</td>
</tr>
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SD = standard deviation, SBR = striatal binding ratio, BMI = body mass index, ROI = region of interest.

Figure 2. Striatal dopamine transporter (DAT) availability and body mass index (BMI). Displayed are the raw data for the striatal binding ratio (SBR) and BMI for the caudate nucleus (A) and putamen (B) with regression line and 95% confidence interval. There is no significant association between SBR and BMI, neither for the caudate nucleus ($r = 0.130, p = 0.159$) nor for the putamen ($r = 0.122, p = 0.187$).

30: SBR = 4.3 ± 0.9, $p = 0.677$), but only an age effect (caudate nucleus: $p = 0.034$, putamen: $p = 0.028$) and a gender effect in the caudate nucleus ($p = 0.031$), although not significant in the putamen: ($p = 0.064$). There were no scan time (caudate nucleus: $p = 0.958$, putamen: $p = 0.979$) or site effects (caudate: $p = 0.286$, putamen: $p = 0.425$).

Voxel-based analysis

The voxel based analysis showed no significant association in the striatum between DAT availability and BMI, neither was there an association with gender, scan time, and site. Age correlated negatively with striatal DAT availability in three clusters located in the left and right striatum (figure 3B; sizes: 351, 2, and 2 voxels; FWE-corrected $p$-values: <0.001, 0.041 and 0.041, respectively).
A group comparison between subjects with BMI ≤ 25 and subjects with BMI > 25 also showed no group difference, but only an age effect with two significant clusters at similar locations as in the previous analysis (sizes: 216 and 2, FWE-corrected p-value: <0.001 and 0.037, respectively). Comparable results were found for the group comparison between subjects with BMI ≤ 25 and subjects with BMI ≥ 30. Again there was no group difference and only one cluster indicating an age effect (size: 147 voxels, FWE-corrected p-value: <0.001). There were also no significant associations between DAT availability and BMI, gender, scan time or site when the threshold was set to p<0.001, uncorrected.

DISCUSSION

The results of this study do not show an association between BMI and striatal DAT availability. We found a robust association between striatal DAT availability and age, which is consistent with previous findings (25-28). Thus, the results do not confirm our hypothesis. Whereas the finding of lower striatal DRD2 availability in obesity could be replicated (6;7), we cannot replicate the negative correlation between BMI and DAT availability by Chen et al. (15). Our results are in line though with the twin study of Koskela et al., who also found no association...
between striatal DAT availability and BMI (16). This suggests that the DAT availability is not lower at a high BMI, while the DRD2 availability is.

The two major differences between this study and the one of Chen et al. (15) are the different subject sample and the use of a different tracer. Chen et al. included 50 healthy subjects with a BMI range of 18.7 - 30.6 and a mean BMI of 23.0. The sample in the present study is more than twice as large and covers a broader range in BMI, in particular in the higher range. The fact that we also do not find group differences between overweight (BMI > 25) or obese (BMI > 30) subjects compared to normal weight subjects supports the notion that people with a high BMI do not have lower striatal DAT availability.

The tracer that was used in this study for measurement of striatal DAT availability, [123I]FP-CIT, has some advantages over [99mTc]TRODAT-1, which was used by Chen et al. (15). For example, the specific to non-specific binding is much higher for [123I]FP-CIT and the time window, in which the tracer is in pseudo-equilibrium, is very short for [99mTc]-TRODAT-1 (and much longer for [123I]FP-CIT), which affects the image quality. [123I]FP-CIT is better comparable to, but more selective for DAT than [123I]-nor-β-CIT, which was used by Koskela et al. (16). They also did not show a relation between BMI and striatal DAT availability when comparing siblings with higher BMI (mean BMI: 26.8) with their twin siblings with lower BMI (mean BMI: 24.5) in a monozygotic twin study. The tracer use might thus be one of the reasons for the different finding by Chen et al. (15). It is worth to note that the significance thresholding in the present study was similar to the that used in the ROI analysis of the study of Chen and co-workers (15).

The role of dopamine in food intake regulation and obesity has been convincingly shown (5). The results of this study only suggest that the regulation of striatal synaptic dopamine levels by DAT may be not the major component of the dopaminergic system that is related to high BMI. It is more likely related to changes at the post-synaptic DRD2 levels, although a role for dopamine synthesis also cannot be excluded. The lower level of available DRD2 in the striatum in obesity results in a reduced signal transduction. It seems that this is not compensated by an increase of synaptic dopamine levels through a downregulation in DAT availability at high BMI.

It is interesting that overeating behavior and obesity have been compared to substance abuse with regard to pathophysiologic mechanisms (29). Both disorders show symptoms of craving and compulsive behavior. Like in obesity, lower striatal DRD2 availability has also been found in abusers of different types of substances, including cocaine, methamphetamine, alcohol, and heroin (30). The addiction literature shows inconclusive results on striatal DAT levels in drug abusers, but in general these studies rather suggest decreased levels of DAT in drugs users: lower DAT levels for methamphetamine (31;32), alcohol (33), and nicotine users (34;35), and no change or an increase in DAT levels for users of cocaine (36;37). However, lower DAT in drug users may also be related to dopaminergic neurotoxicity. This may be particularly true for methamphetamine use, although repeated administration of dexamphetamine may also lead to loss of FP-CIT binding to striatal dopamine transporters due to dopaminergic toxicity (38;39). For substance abuse, the evidence for lower striatal DRD2 availability is however much stronger than for lower striatal DAT availability. This might be similar to what we see in obesity or at high BMI.

The available studies on DAT genotype and BMI or obesity do not support a role for the DAT gene in obesity or food intake (40;41). A polymorphism in DAT genotype is known to influence striatal DAT availability (42;43). Only one small association study reports that this
polymorphism would be a risk factor for obesity in African-American smokers but not in Caucasians (44). However, this has never been replicated and in a large sample (n=1150) from the general female population Need et al. showed that there was no association between the DAT polymorphism and obesity (40). This is contrary to the role of DRD2 genotype. The Taq1A allele is reported as a risk factor for obesity (45;46) (although not consistently (47)), a risk factor for greater food reinforcement and food intake (41) and it influences striatal brain activity on food stimuli (8). In addition, this allele has been associated with a lower striatal DRD2 availability (48). This fits the finding of lower striatal DRD2 availability in obesity (6;7). So, whereas DRD2 genotype and striatal DRD2 are both related to obesity, this does not seem the case for both DAT genotype and striatal DAT availability.

Based on our data, we cannot yet fully exclude that high BMI and striatal DAT availability are related. The number of morbidly obese subjects is very limited in the present study. The difference in striatal DRD2 availability between obese and normal-weight subjects was primarily shown in subject samples largely consisting of morbidly obese subjects. Thus, it could still be that the DAT availability is affected in the people with the highest BMIs, which have overeaten more intensively.

Furthermore, it is possible that there might be a small effect that we were not able to detect in this sample. The present study was sensitive enough though to replicate previous findings of a gender effect on striatal DAT availability (26;49;50), whereas others could not replicate this effect (25;51;52). However, the available animal studies show that a high-fat diet for obesity induction can lead to lower striatal DAT availability and gene expression (11-14), although one animal study shows that this effect only occurs in obesity-resistant mice on a high-fat diet and not in the obesity-prone mice on the same high-fat diet (53). Unfortunately, we do not have data on eating behavior of the subjects to correlate to striatal DAT availability. A study on striatal DAT availability in morbidly obese subjects compared to age and gender matched controls, which also assesses eating pattern, could be an important addition to the available studies so far.

As the sample of this study is a European sample, which is recruited and scanned in different centers, it has been inevitable that scan conditions were not exactly the same for all scans. For example, different SPECT cameras were used. This is also reflected in a site effect in some analyses on the caudate nucleus. To reduce variation, all participating centers have done a great effort to equalize conditions (17). All scans have been quality checked, post-processed and reconstructed by one core lab (17) and have been corrected to reduce inter-site variation based on independently obtained calibration values in a phantom study (19). In addition, site has been added as a covariate in the analyses to correct for any effects. Thus, we are convinced that the multi-center aspect of the study has not substantially affected the final outcome and conclusions of the study. At the same time, the cooperation between the different centers has created the opportunity to scan a large sample of subjects.

As the multi-center aspect, there are some other limitations to the study. First of all, the use of BMI has some disadvantages. It is a commonly used measure to study overweight and obesity, which enhances the comparability with other studies. However, it is limited by the fact that it is not directly related to body fat mass and might not be equally meaningful at different ages. Other measures such as waist-hip ratio or percentage fat mass might be more relevant in relation to overweight or obesity. Therefore, it would be interesting to assess associations between these measures and striatal DAT availability, as well.
Secondly, there are other factors that possibly influence striatal DAT availability and which are not taken into account in the present study. Preclinical data support circadian variability in DAT levels and suggested that insulin signalling may regulate DAT expression (11;54). Consequently, these two factors may also influence striatal DAT availability in-vivo in humans, as well. In this study, all subjects were imaged in the fed state and most of them were imaged in the afternoon. Insulin levels were not measured. However, a previous study did not show a correlation between DAT binding and glucose and HbA1c concentrations in humans (15). Also, to the best of our knowledge no DAT imaging studies have been performed in humans that examined whether there is a circadian variability in DAT binding. This may be of interest to examine in future studies.

A point that is not directly a limitation to the study is the use of strict exclusion criteria (including neurological examination and MRI scan for brain abnormalities) to ensure the homogeneity of the subject sample and inclusion of only healthy subjects. This reduces the influence of confounding factors, but might impede the extrapolation of the results to overweight or obese subjects with comorbidities, such as type 2 diabetes mellitus.

At last, it is worth to mention that the practical implication of the results of this study is that when referred for a diagnostic [123I]FP-CIT scan, the patient’s body weight need not be considered when comparing to a normal database.

In conclusion, we have shown that there is no association between BMI and striatal DAT availability. This suggests that the regulation of striatal synaptic dopamine levels by DAT plays only a limited role in the pathophysiology of overweight and obesity. Since previous studies consistently showed that the striatal DRD2 availability is lower in obesity, the DRD2 availability seems to be of more importance. This reduced signal transduction capacity at high BMI is probably not compensated by increasing synaptic dopamine levels by lower DAT availability.

ACKNOWLEDGEMENTS

The participating centres thank GE and the German Parkinson Association for their financial contribution to this study, ABX-CRO for managing the network activities and the Executive Committee of the EANM for establishing the EANM Research Ltd. (EARL) as an administrative framework for this project. The authors also thank the personnel from each Nuclear Medicine Centre responsible for the quality controls and acquisition of the SPECT data.

CONFLICT OF INTEREST

Swen Hesse has received travel grants and honoraria from GE Healthcare, Jan Booij is consultant at GE Healthcare and Osama Sabri has received project funding from GE Healthcare. The other authors have no conflicts of interest to disclose.
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