

## Atlas of type 2 dopamine receptors in the human brain: Age and sex dependent variability in a large PET cohort

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### ABSTRACT

**Background:** The dopamine system contributes to a multitude of functions ranging from reward and motivation to learning and movement control, making it a key component in goal-directed behavior. Altered dopaminergic function is observed in neurological and psychiatric conditions. Numerous factors have been proposed to influence dopamine function, but due to small sample sizes and heterogeneous data analysis methods in previous studies their specific and joint contributions remain unresolved.

**Methods:** In this cross-sectional register-based study we investigated how age, sex, body mass index (BMI), as well as cerebral hemisphere and regional volume influence striatal type 2 dopamine receptor (D<sub>2</sub>R) availability in the human brain. We analyzed a large historical dataset (n=156, 120 males and 36 females) of [11C]raclopride PET scans performed between 2004 and 2018.

**Results:** Striatal D<sub>2</sub>R availability decreased through age for both sexes (2-5 % in striatal ROIs per 10 years) and was higher in females versus males throughout age (7-8% in putamen). BMI and striatal D<sub>2</sub>R availability were weakly associated. There was no consistent lateralization of striatal D<sub>2</sub>R. The observed effects were independent of regional volumes. These results were validated using two different spatial normalization methods, and the age and sex effects also replicated in an independent sample (n=135).

**Conclusions:** D<sub>2</sub>R availability is dependent on age and sex, which may contribute to the vulnerability of neurological and psychiatric conditions involving altering D<sub>2</sub>R expression.

### 1. Introduction

Dopaminergic function regulates emotion, cognition and learning as well as motor functions (Beaulieu et al., 2015, Jackson and Westlind-Danielsson, 1994), making the dopamine system a key component for goal-directed behavior (Calabresi et al., 2007, Juárez Olguín et al., 2016, Roitman et al., 2004). Aberrant dopaminergic function is observed in various neurological and psychiatric conditions, such as Parkinson's disease, schizophrenia, drug abuse, obesity and depression (Bonci and Hopf, 2005, Leggio et al., 2016, Maia and Frank, 2011). Dopamine receptors are divided into type 1 (D<sub>1</sub>R including types D<sub>1</sub> and D<sub>5</sub>) and type

2 (D<sub>2</sub>R including types D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>) receptor families (Beaulieu and Gainetdinov, 2011, Jackson and Westlind-Danielsson, 1994). Particularly the D<sub>2</sub>R which is abundantly expressed in the striatum (De Keyser et al., 1988, Usiello et al., 2000) is centrally involved in the pathophysiology of neuropsychiatric conditions (Leggio et al., 2016).

Patients with schizophrenia show striatal hyperactivity of dopaminergic function (Breier et al., 1997) and elevated in vivo D<sub>2</sub>R density (Laruelle, 1998, Wong et al., 1986), yet it remains unresolved how the disorder itself (e.g. illness duration) and exposure to antipsychotic medication link to these observations (Guma et al., 2018). D<sub>2</sub>Rs also mediate anxious symptomology (Zarrindast and Khakpai, 2015,

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Nummenmaa et al., 2020) and elevated D<sub>2</sub>R expression is observed in motivational disturbance (Simpson et al., 2014) and possibly in depression, although the elevated D<sub>2</sub>R has been shown particularly in medicated (D'haenen and Bossuyt, 1994) rather than unmedicated depression (Hirvonen et al., 2008), possibly reflecting antidepressant treatment (Hirvonen et al., 2008). Conversely, Parkinson's disease is associated with lowered D<sub>2</sub>R expression (Leggio et al., 2016), at least after the early disorder stage when increase of D<sub>2</sub>Rs may occur as a compensation to nerve terminal loss or medical treatment (Kaasinen et al., 2021, Seeman and Niznik, 1990). In addition to this neurodegenerative disease (Leggio et al., 2016, Elbaz et al., 2016), drug abuse is also associated with striatal D<sub>2</sub>R loss, and the lower D<sub>2</sub>R density may constitute a vulnerability factor for drug abuse (Volkow et al., 2003, Volkow et al., 2009).

To understand dopaminergic dysfunction and related pathophysiology, factors contributing to dopamine function in the healthy population need to be identified. Small-scale PET studies suggest that subject demographics, such as age (Antonini et al., 1993, Kim et al., 2011, Dang et al., 2016), sex (Pohjalainen et al., 1998, Fazio et al., 2017) and body mass index (BMI) (Dang et al., 2016, Wang et al., 2001, but see Karlsson et al., 2015) might affect the D<sub>2</sub>R availability in striatum. However, there has been increasing concern over the lack of replicability of neuroimaging findings (Poldrack et al., 2017). Insufficient statistical power (Poldrack et al., 2017, Button et al., 2013), variable methods for analyzing data (Simmons et al., 2011), as well as failure to appropriately control for multiple comparisons (Eklund et al., 2016) have been proposed as main sources of the poor replicability.

Because PET imaging is expensive, data pooling has recently emerged as an effective way of increasing sample sizes and consequently providing more accurate statistical estimates (Kantonen et al., 2020). Additionally, Bayesian hierarchical modeling has been proposed to facilitate reproducible science by limiting the “researcher degrees of freedom” in the analysis phase (Lindquist and Gelman, 2009) and by removing the need for arbitrary multiple comparison correction methods (Gelman et al., 2012). The primary aim of this study was to address the effects of age, sex, BMI, and hemisphere on D<sub>2</sub>R availability using a well-powered dataset of historical scans. Using hierarchical Bayesian modeling, we were able to address the potential hierarchical nature of the effects and differences arising from different PET scanners. We analyzed a large dataset of 156 historical controls scanned with [11C]raclopride, a selective D<sub>2</sub>R antagonist. We also replicated the results in an independent sample of 135 subjects. Our secondary goal was development of age and sex-specific atlases of D<sub>2</sub>R availability in the brain that would be released to the neuroimaging community via NeuroVault (<https://neurovault.org>; <https://identifiers.org/neurovault.collection:12099>).

## 2. Methods and materials

### 2.1. Subjects

The data were 156 baseline [11C]raclopride scans of healthy control subjects (sex 120 males and 36 females; age 19-71 years, BMI range 18-38, no information about the menstrual cycle) scanned at Turku PET Centre between 2004 and 2018. Detailed sample information is shown in Table 1 (see also Table S6 for exclusion criteria). Studies were included in the analysis if they were baseline scans with injected dose > 100 megabecquerel (MBq) to avoid low signal-noise ratio (SNR) (see Table S7 for radiochemical details) and the magnetic resonance (MR) scan and basic demographic and anthropometric information (height, weight) was available. If multiple baseline scans were acquired for an individual, chronologically first scan was included in the analysis. The data were compiled across 5 different PET scanners (see Supplementary Material section Scanner Considerations for detailed information). Finnish legislation does not require ethical approval for register-based studies.

**Table 1**

Characteristics of the sample. SD= standard deviation.

	Males (n= 120)			Females (n= 36)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	25	5	19-56	37	14	20-71
Height (cm)	181	7	167-199	166	7	151-190
Weight (kg)	79	12	58-130	61	8	47-85
BMI (kg/m <sup>2</sup> )	24	3	19-38	22	3	18-33

### 2.2. PET data acquisition and image processing

Antagonist radioligand [11C]raclopride binds to D<sub>2</sub>Rs (Farde et al., 1985, Farde et al., 1989, Mishra et al., 2018), allowing reliable quantification of striatal and thalamic D<sub>2</sub>R availability (Mishra et al., 2018, Hirvonen et al., 2003, Ginovart, 2005, Cárdenas et al., 2004, Innis et al., 2007, Alakurtti et al., 2015). However, the reliability of thalamic measures using [11C]raclopride is not as robust as in the striatum (Freiburghaus et al., 2021), and its binding in extrastriatal regions, such as the cerebral cortex, is unspecific (Hirvonen et al., 2003, Freiburghaus et al., 2021, Svensson et al., 2019, but see Alakurtti et al., 2015, Papenberg et al., 2019). In this study, we included the following four regions of interest (ROIs): striatal nucleus accumbens (accumbens), caudate nucleus (caudate), putamen, as well as thalamus close by the striatal ROIs. The PET data was acquired using five different scanners (Scanner Considerations including Table S1 in SM).

Preprocessing and kinetic modeling were done using Magia toolbox (Karjalainen et al., 2020). Preprocessing consisted of framewise realignment and co-registration of the PET and MR images. Tracer binding was quantified using the outcome measure binding potential (BP<sub>ND</sub>), which is the ratio of specific binding to non-displaceable binding in tissue (Innis et al., 2007). BP<sub>ND</sub> was estimated using a simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) with cerebellar gray matter as the reference region (Hall et al., 1996). Acquisition length was harmonized by including first 52 minutes from each scan. Previous studies have shown that 52 minutes provides sufficient reproducibility and reliability for modeling striatal [11C]raclopride binding with SRTM (Hirvonen et al., 2003). We thus used this cut-off for all the studies as it allowed us to apply it as a standard way to calculate the BP<sub>ND</sub> estimates for the dataset while harmonizing the scan times across protocols.

Individual frames were first realigned to account for between-frame movements. The first frame was omitted because it did not contain sufficient signal for every subject. T1-weighted MR images were processed using FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>). The MR images were then co-registered with the PET data for region of interest extraction.

### 2.3. Statistical modeling

Statistical modeling was carried out in (R Core Team, 2021) using brms (Bürkner, 2017, Bürkner, 2018) that applies the Markov-Chain Monte Carlo sampling tools of (Stan Development Team, 2020). The analysis script is available in Supplementary code.

#### 2.3.1. Primary analysis

We first standardized the continuous variables and log-transformed binding potential estimates because according to posterior predictive checks (Gabry et al., 2019, Gelman et al., 2013), log-transformation of non-negative dependent variable enhances model fit, as it makes the model multiplicative instead of additive that is not optimal when limited to positive values (Gelman and Hill, 2006). We also confirmed that the age and BMI effects on logarithmic BP<sub>ND</sub> are well approximated by a linear function in each ROI (Linearity Assessment of the Age and BMI effects in SM). For the sake of conciseness, we simply refer to the linear effects on a logarithmic scale as linear. We used Bayesian hierarchical regression to model the data. Because ROI-wise effects were partially

pooled across ROIs, this essentially removes the need to correct for multiple comparisons induced by investigating multiple ROIs (Neath et al., 2018).

We estimated one primary model for assessing the main effects of age, sex and BMI on  $BP_{ND}$ . The effects were calculated separately for the left and right hemisphere. We also investigated the main effect of cerebral hemisphere (i.e. lateralization) on  $BP_{ND}$  separately for males and females, as our initial modeling showed sex-differences in lateralization and as previous research has pointed to greater lateralization in the male versus female brain (Bakan and Putnam, 1974, Toga and Thompson, 2003, Wager et al., 2003). Toward the end of the age range, the relative number of males decreased, as did the overall number of observations. Although this might have masked the interaction effect of age and sex, there was no clear evidence for sex-specific age-effect (Fig. S8), prompting us to calculate the age effect together for males and females with maximal statistical power. To estimate the effects of age, sex, BMI and hemisphere, we used regionally varying random slopes. Subjects, scanners, and ROIs were all modeled as varying (random) intercepts. We included a varying intercept for the combination of scanners and ROIs, to allow for regionally varying scanner effects (Scanner Considerations in SM). For the residual variances, we applied the same grouping structure, except for subject (no individual differences expected). Additional modeling information is presented in SM (Sampling Settings and Convergence Estimates).

### 2.3.2. Sensitivity analysis and replication in an independent sample

The large number of young male subjects resulted in an imbalanced sex ratio, especially after the age of 40. Hence, we repeated the primary model with a balanced subset of the data ( $n = 140$ , see Tables S4 and S6), including the data of subjects aged 40 and under. We also checked whether adjusting for inter-individual differences in regional volumes of the ROIs changed the results or had main effects on  $D_2R$  binding (See SM file).

Differences between the scanner characteristics, such as spatial resolution and sensitivity, may have influenced our results (Table S1). Hence, we took the multiple scanners into account by adjusting for the scanner in the statistical modeling. This allowed us to calculate the main effects of age, sex, BMI, hemisphere, and regional volume while allowing  $BP_{ND}$  to vary by scanner. Additionally, we conducted supplementary statistics where we assessed the associations of age and sex with  $BP_{ND}$  (including correlations and unpaired t-tests, see Scanner Considerations in SM) in scanner-specific subsets of the primary dataset. The results highlight that using historical datasets pooling observations across scanners and holding imbalance (different age ratio of the sexes), modeling the variables in the same model, including scanner-specific effects, is advantageous, as it can detect and account for this kind of variability in the effects.

Our independent secondary sample of 135 scans (104 males, mean age 33 years, Tables S5 and S6) was not included in the primary analysis due to missing MR images or anthropometric measurements (weight, height) from these subjects. In a secondary analysis, we maximized statistical power by applying template-based normalization method to the whole available sample (primary and secondary). We first validated the normalization and ROI extraction protocol without the MR images by conducting a within-subject comparison of the  $BP_{ND}$  estimates produced by the two normalization methods for the subjects that both normalization methods could be applied (MR image available,  $n = 189$ , Table S6). The analysis showed that both methods yield comparable  $BP_{ND}$  estimates (Pearson's product-moment correlation coefficients 0.97-0.99). Then, we replicated the statistical analysis of the global effects of age and sex on the  $D_2R$   $BP_{ND}$  (using template-based normalization method) using the secondary sample with no available MRI image. Finally, we also tested the effects of injected mass on the regional  $BP_{ND}$  estimates and found only weak evidence for a negative association between injected mass and  $BP_{ND}$  (see Injected mass in SM). See SM for more detailed information about the samples (Tables S5 and S6), validation and

replication (Validation of an alternative approach for defining ROIs and reference regions, Injected mass).

## 3. Results

The [ $^{11}C$ ]raclopride binding was highest in striatum and practically nonexistent in the neocortex (Fig. 1). The  $BP_{ND}$  in the ROIs varies from below 1 to above 5, being lowest in thalamus and highest in putamen (Fig. 2). Please see Fig. S14 for the correlation of the  $BP_{ND}$  estimates between the ROIs and age and sex specific  $D_2R$  atlas images in NeuroVault (<https://neurovault.org>; <https://identifiers.org/neurovault.collection:12099>).

### 3.1. Age and sex

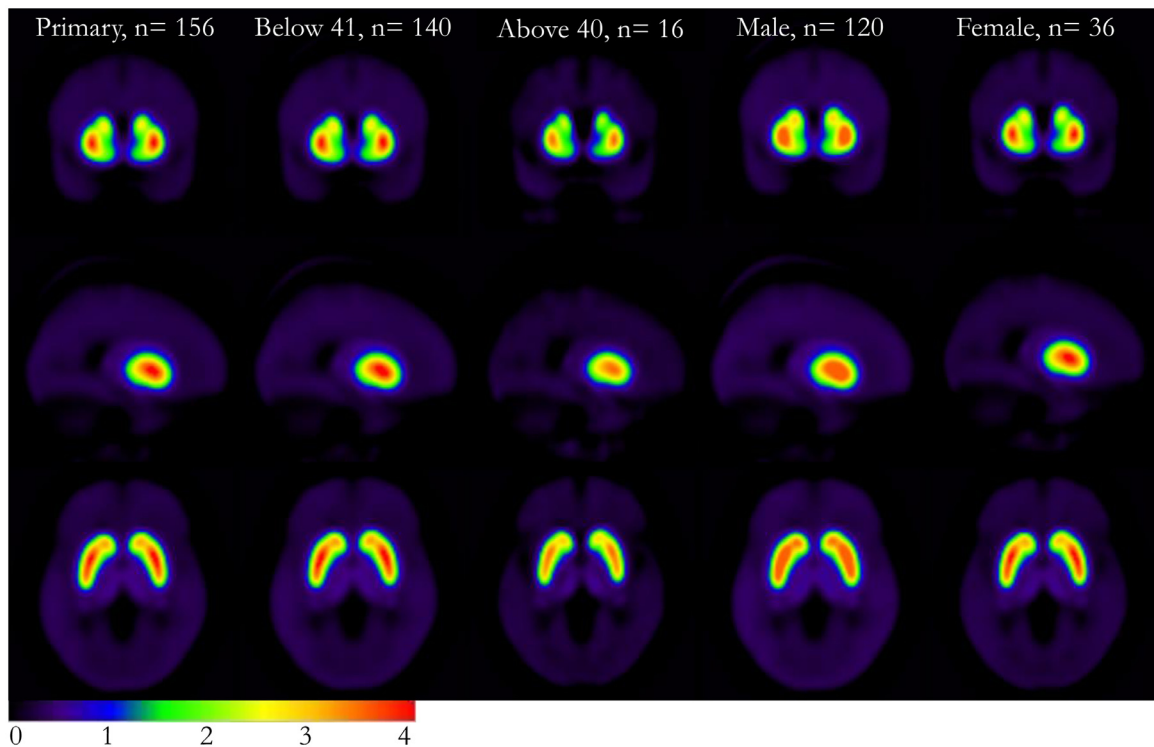
There was a consistent age-related decline in striatal  $D_2R$  binding (Fig. 3, 4). This applied particularly to the age-range from early 20s to 60s for which we had sufficient data. In putamen and caudate, 10 years of ageing (one SD) decreased the binding approximately 5%. In accumbens, the approximate decrease was 2-3% per SD. Only in thalamus, the 95% posterior uncertainty interval overlapped with zero, suggesting uncertainty in the effects. These effects were similar in both hemispheres. The further assessment supported the linearity of the age effect (Linearity Assessment of the Age and BMI effects in SM) and that the effect remains clear even when adjusting for regional volumes (Fig. S9).

The data did not support an interactive effect of age and sex on  $D_2R$  binding (Fig. S8), instead suggesting that the age-related decline is similar for both sexes. However, the data revealed that females had on average approximately 7-8% higher  $D_2R$  binding than males bilaterally in putamen (Fig. 4).  $BP_{ND}$  tended to be higher in females versus males also in the other ROIs, although the 95% posterior uncertainty intervals overlapped with zero.

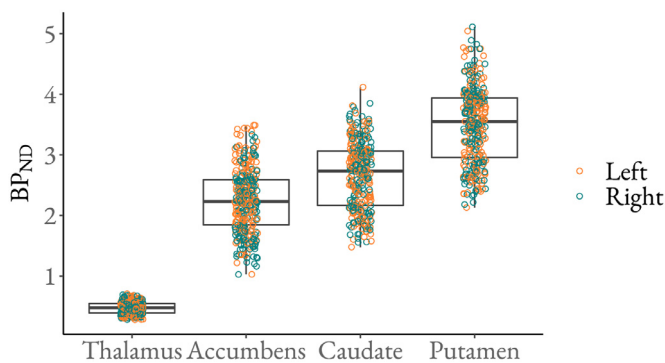
The effect of sex was in general similar in both hemispheres, suggesting higher binding in females than males. Only in the accumbens, the effect of sex appeared to be hemisphere-specific (Fig. 4). Left accumbens was the only region where the binding in males was similar as in females. After adjusting for regional volumes (Fig. S9), the sex-specific lateralization effects became weaker, and the model suggested only slightly higher binding in females versus males across both hemispheres. However, the posterior uncertainty intervals were wide in both conditions (Fig. 4 and S9), reflecting uncertainty in the effects, and only in putamen the intervals did not cross zero. As there was overlap in the posterior uncertainty intervals, these results do not clearly support lateralization of the sex effect even in accumbens. Adjusting for regional volumes did not change the overall effects of sex. After the adjustment for regional volumes, however, the 95% posterior uncertainty interval of right accumbens and right caudate no longer overlapped with zero, suggesting that the difference between males and females was more profound (8% in accumbens and 6% in caudate) when adjusting for regional volumes (Fig. S9).

### 3.2. Body mass index

We found no clear evidence for the effect of BMI in the  $D_2R$  availability. However, the weak effect suggested an increase in  $BP_{ND}$  as a function of BMI across the whole range (18-38) (Fig. 4). In the right thalamus, the posterior 95% uncertainty interval did not overlap with zero with an estimation of an approximate 3% increase in  $D_2R$  binding for the increase of one SD (3 units) in BMI. In other ROIs, particularly in putamen, the majority of the posterior uncertainty intervals were above zero, also supporting the positive effect. Further assessment supported the linearity of the effects (Linearity Assessment of the Age and BMI effects in SM). Adjusting for regional volumes did not change the overall results of BMI (Fig. S9).



**Fig. 1.** Mean [11C]raclopride  $BP_{ND}$  (original scale from 0 to 4, MNI coordinates  $x=26, y=6, z=0$ ) in the primary sample, as well as its subsamples (subjects below 41 and above 40 years of age, males and females).



**Fig. 2.** Regional [11C]raclopride  $BP_{ND}$  (original scale). The figure shows medians (middle line), 25% (lower hinge) and 75% (upper hinge) quantiles, min value (lower whisker) and max value (upper whisker), as well as the data points for the  $D_2R$   $BP_{ND}$ .

### 3.3. Lateralization

According to our data, lateralization was more prominent in males than in females. This was particularly prominent in accumbens, where males had higher left-hemispheric binding, as the posterior mean and the relatively narrow posterior uncertainty interval clearly parted from zero. The binding was approximately 9% higher in left versus right accumbens. For males, the data supported lateralization in all ROIs, although the direction was not coherent between the closely located ROIs (modeling results in Fig. 5). The binding was increased in left versus right putamen, and right versus left thalamus and caudate. These effects were however smaller and the posterior uncertainty intervals overlapped zero. In females, no clear lateralization effects were found (Fig. 5). The uncertainty intervals for females were wider than for males, as we had less data for females than males. Although the posterior uncer-

tainty interval overlapped with zero, there was some support for higher binding in right versus left caudate, in line with the data from male subjects.

### 3.4. Replication analysis

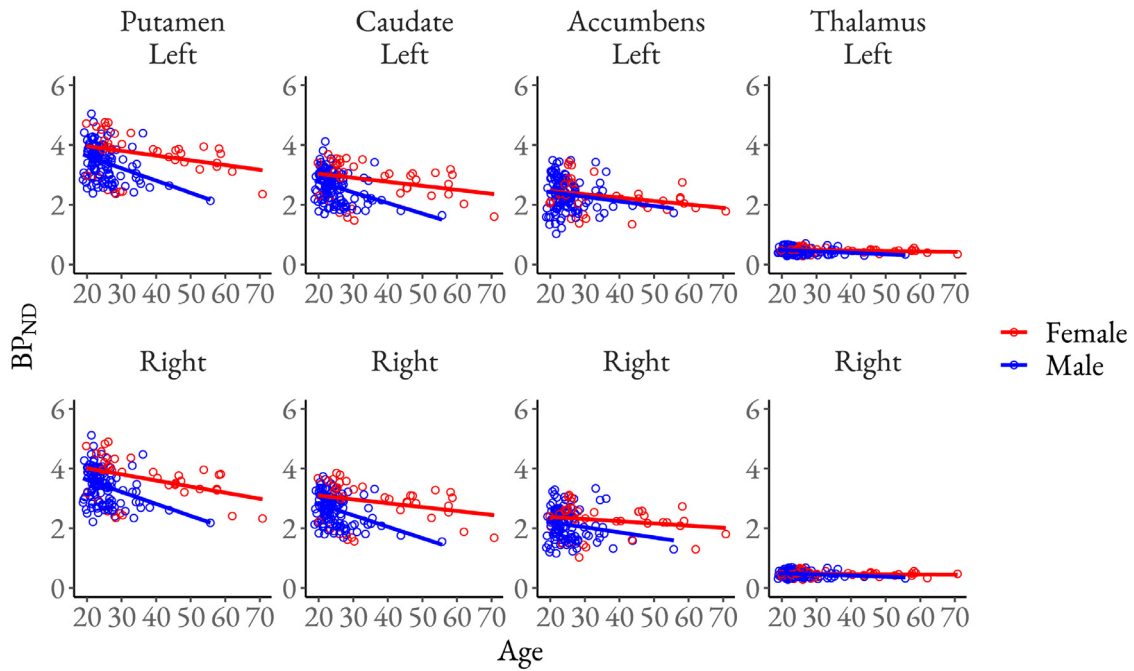
The regional effects of age and sex were replicated in the secondary sample ( $n=135$ , see Tables S5 and S6) that was spatially normalized with an alternative method that does not require MR image, as many subjects were lacking it (please see the detailed description of the secondary sample in SM). BMI could not be included in the analysis due to missing anthropometric measurements (weight, height) for some of the subjects.

## 4. Discussion

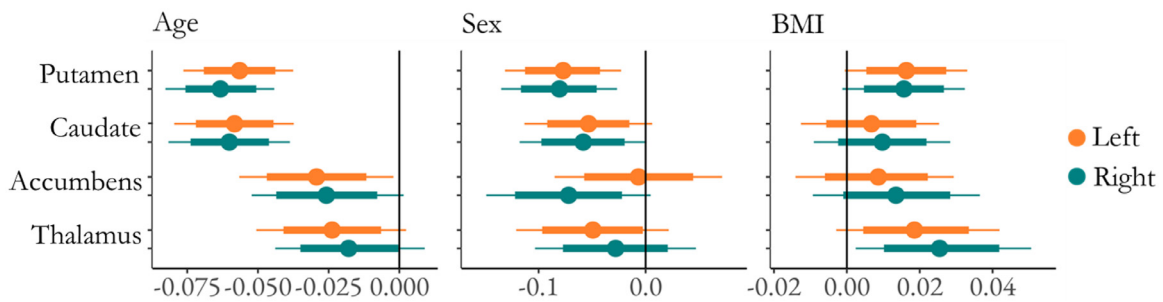
Our main findings were that i) there is a steady decline in  $D_2R$  availability as a function of ageing and ii) females have higher  $D_2R$  availability than males irrespective of age (at least from 20 to 60 years of age for which we had sufficient data). Additionally, higher BMI might be associated with increased  $D_2R$  availability, as we found a weak positive effect of BMI. The effects of lateralization did not show clear consistence. Adjusting for volumes of the ROIs did not change the overall results, suggesting that among healthy adults, the striatal effects of age and sex on the  $D_2R$  availability are global and independent from the regional volumes.

### 4.1. Effects of age & sex

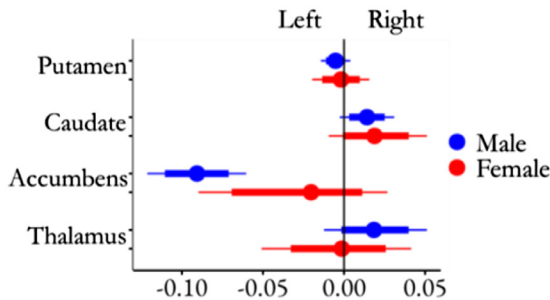
Our data showed a clear age-dependent decline in the striatal  $BP_{ND}$ , supporting decrease through age in  $D_2Rs$  (Volkow et al., 2000, Mukherjee et al., 2002), starting from early adulthood. Compared to previous smaller studies (Antonini et al., 1993, Kim et al., 2011, Pohjalainen et al., 1998, Rinne et al., 1993), our large-scale sample allowed a reliable assessment of this effect across a wide age range.



**Fig. 3.** Left and right hemisphere D<sub>2</sub>R BP<sub>ND</sub> (original scale) as a function of age (original scale) in each ROI. The Fig. shows the original BP<sub>ND</sub> estimates (points) and regression lines separately for males and females (lines).



**Fig. 4.** The effects of age (standardized), sex (male-female) and BMI (standardized) on striatal and thalamic D<sub>2</sub>R BP<sub>ND</sub> (logarithmic) separately for left and right hemisphere. The Fig. shows medians (circles), 80% (thick line) and 95% (thin line) posterior uncertainty intervals of the regression coefficients on a logarithmic scale.



**Fig. 5.** The effect of hemisphere (estimate for right-left) on striatal and thalamic D<sub>2</sub>R BP<sub>ND</sub> (logarithmic) separately for males and females. The figure shows medians (circles), 80% (thick line) and 95% (thin line) posterior uncertainty intervals of the regression coefficients on a logarithmic scale.

Dopamine receptor loss starts already in early twenties and continues steadily throughout ageing, while previously the decline has suggested to slow down with age (Antonini et al., 1993, Kim et al., 2011, Ichise et al., 1998). The observed receptor decline changes the properties of dopamine neurotransmission (Nagatsu, 2000), of which disturbance

relates to several cognitive and motor symptoms (Leggio et al., 2016). The etiology of Parkinson’s disease differs from mere age-related neurodegeneration (Kish et al., 1992) and does not appear as accelerated ageing of the dopaminergic function (Kaasinen et al., 2015). The decline in dopamine neurotransmitter (Kish et al., 1992, Haaxma et al., 2007), receptors and transporters (DATs) (Karrer et al., 2017, van Dyck et al., 1995, Kaasinen et al., 2015, Volkow et al., 1996), emerging through age, could however contribute to both the mild cognitive decline and motor deficiency commonly observed among the elderly (Peters, 2006, Royall et al., 2002), as well as the more severe forms of neurodegeneration, such as Parkinsonism (Leggio et al., 2016).

According to our data, the D<sub>2</sub>R availability declines in both sexes. This is in line with previous studies that have detected the age-related decline in dopamine receptors (Volkow et al., 2000) and transporters (Volkow et al., 1996). However, our data also showed that the average D<sub>2</sub>R level remains higher in females throughout the studied age range. This contrasts with prior studies that have reported sex-dependent decline in dopamine function (Wong et al., 1988), with males showing steeper reduction in receptors (Pohjalainen et al., 1998) particularly in young adulthood (Wong Dean et al., 1984), and presynaptic dopamine synthesis (Laakso et al., 2002).

Our data shows that although the decline in the available D<sub>2</sub>R is not sex dependent, the overall D<sub>2</sub>R level is, consistently higher in

females from early adulthood to at least the age 60. However, with the current dataset overrepresenting young adults (particularly males), the associations of ageing and sex on D<sub>2</sub>R availability are more reliable in the subjects aged 40 and below than in the primary dataset with the wider age range. Sex differences have previously been observed in D<sub>2</sub>R affinity (lower in women) but not density, pointing to higher dopamine concentration in women (Pohjalainen et al., 1998). One study with [18F]Fluorodopa also showed greater striatal presynaptic dopamine synthesis capacity in females versus males (Laakso et al., 2002).

Sex differences in the dopamine system may contribute to vulnerability for neuropsychiatric disorders (Pohjalainen et al., 1998, Laakso et al., 2002). Accordingly, females (who have higher D<sub>2</sub>R binding) might be predisposed to pathology associated with elevated D<sub>2</sub>R availability, such as mood disorders (Loke et al., 2015, but also consider Hirvonen et al., 2008), schizophrenia, and psychoses (Wong et al., 1986, Wong et al., 1997, but see also Farde et al., 1987, Farde et al., 1990). Conversely, lower D<sub>2</sub>R level in males may predispose them to Parkinson's disease (Loke et al., 2015) that involves receptor loss (Kaasinen et al., 2021, Leggio et al., 2016) and is approximately 1.5 more common in males versus females (Elbaz et al., 2016). This may also explain males' higher prevalence of addictions, such as alcoholism (Kalaydjian et al., 2009, Volkow et al., 1996), substance use disorders (James et al., 2018), drug abuse (Becker and Hu, 2008, Volkow et al., 2009), as well as mood-related impulsivity (Clark et al., 2012) which are associated with lower D<sub>2</sub>R availability.

Finally, low striatal D<sub>2</sub>R density has also been associated with A1 allele of the D<sub>2</sub>R gene (Pohjalainen et al., 1998) that possibly links to alcoholism (Blum et al., 1990). As the deficiency in dopaminergic function does not only increase impulsive behavior toward the object of addiction but also disturbs saliency attribution of other objects (Volkow et al., 2009), altered dopaminergic function may well constitute a significant vulnerability endophenotype for addictive behaviors. Finally, sex-differences in the dopamine system have been observed not only in the striatal (Pohjalainen et al., 1998) and cortical (Kaasinen et al., 2001) D<sub>2</sub>Rs but also in DATs (Kaasinen et al., 2015, Varrone et al., 2013) and presynaptic dopamine synthesis capacity (Laakso et al., 2002). In addition, sex-specific hormones and genes play a role in the dopaminergic function and neuropsychiatric well-being (Loke et al., 2015, Haaxma et al., 2007). Hence, the sex-differences in the D<sub>2</sub>R level may reflect broader dopaminergic, as well as dopamine related hormonal and genetic differences between sexes, and those differences may together contribute to sex-dependent prevalence of neuropsychiatric disorders.

#### 4.2. Effect of BMI

BMI was only weakly associated with higher D<sub>2</sub>R availability, mainly in putamen and thalamus. Although the modeling showed uncertainty in the BMI effect, the effect was systematically positive in each ROI. As most subjects had BMI in the range of 18-30, the effects are uncertain beyond this point, thus being uninformative regarding the most seriously obese phenotypes. Previous *in vivo* imaging studies have yielded mixed results on the association between BMI and dopamine system suggesting i) diminished D<sub>2</sub>R availability in obesity (Wang et al., 2001, van de Giessen et al., 2014), ii) positive association after the age of 30 (Dang et al., 2016), and iii) no association between D<sub>2</sub>R availability and obesity with no effects of surgical weight loss on D<sub>2</sub>R availability (Karlsson et al., 2015, Karlsson et al., 2016). Previously, decreased dopamine function (van de Giessen et al., 2014), TaqA1 variant of D<sub>2</sub>R gene (Carpenter et al., 2013, Chen et al., 2012, Stice et al., 2008) and diminished incentive to physical exercise (high energy expenditure) (Beeler et al., 2016) has been linked to obesity. As dopamine contributes to food-related hedonia (Bray and Tartaglia, 2000), the decreased dopaminergic function could limit the rewarding effect of food-intake compensated by compulsive overeating (van de Giessen et al.,

2014, Johnson and Kenny, 2010, Volkow et al., 2011), and amplify the saliency of food while the inhibitory control weakens (Volkow et al., 2011). Decreased dopamine function is supported by studies showing declined D<sub>2</sub>R in obesity both in humans (de Weijer et al., 2011, Wang et al., 2001, van de Giessen et al., 2014, Volkow et al., 2008) and in animals (Johnson and Kenny, 2010). However, in some studies these findings have not replicated, as the association between BMI and D<sub>2</sub>R was observed either positive and dependent on age (Dang et al., 2016) or nonexistent (Eisenstein et al., 2013, Karlsson et al., 2015, Karlsson et al., 2016). Some studies also point towards a curvilinear relationship between BMI and D<sub>2</sub>R, such that the association is positive up to a certain BMI level after which the relation turns negative (Cosgrove et al., 2015). The contribution of D<sub>2</sub>R genotype to obesity neither replicated in a large sample (Hardman et al., 2014). The present large-scale study suggests that the age-adjusted association of BMI and D<sub>2</sub>R availability is positive and linear, at least up to BMI of 30. It is thus possible that the effect is reversed beyond that point, but the current dataset does not have sufficient data for higher BMIs thus precluding such modeling that would be of great interest to confirm our finding. Overall, even though the estimates have some degree of uncertainty, we found no evidence for a negative relationship between BMI and striatal D<sub>2</sub>R availability.

#### 4.3. Lateralization of D<sub>2</sub>Rs

Lateralization effects, strongest in nucleus accumbens (right > left), were subtle with stronger hemispheric asymmetry of D<sub>2</sub>R availability in males than in females. Our finding of greater hemispheric asymmetry of males versus females may have resulted from better statistical power in the male sample and overall, the lateralization of D<sub>2</sub>Rs remains uncertain (Hietala et al., 1994). However, some studies have found lateralization (left > right) of striatal D<sub>2</sub>R on preadolescent (Andersen and Teicher, 2000) and adult (Schneider et al., 1982) male rats. In humans, meta-analyses suggest that emotion-related brain activity is more lateralized in males than females (Wager et al., 2003). Although the direction of this lateralization is region-specific, it is consistently greater for men (Wager et al., 2003), similarly as in our data. Accordingly, sex differences in lateralized emotional processing in the brain may link with D<sub>2</sub>R expression, but this issue needs to be addressed in future studies. Finally, hemispheric asymmetry might relate to reward experiences involving dopaminergic function. Self-administered cocaine exposure evokes D<sub>2</sub>R lateralization (left > right) in male monkeys (Czoty et al., 2007). In humans, evocative stimuli also elicit left lateralized brain activation, and in cocaine users (14 males, 3 females) it is particularly the cocaine-related cues that precede such activation (Garavan et al., 2000). As cerebral lateralization and addictive behavior may both be more common in males, the interplay between these factors should be investigated in more detail.

#### 4.4. Limitations

The data were acquired using five different scanners. Although we adjusted for the differences between the scanners in statistical modeling, this may have introduced noise in the data. The predictor variables were not optimally balanced, with relatively high sex-ratio (120 males and 36 females) and different age ranges across sexes. We also did not have complete documentation about the reconstruction algorithms that have been used for all the studies, thus these could not be taken into account. While the reconstruction algorithms are stable for a particular scanner in our site, it is possible that several different reconstruction algorithms have been used for some of the scanners. Our statistical model was however flexible with respect to such variation, as the residual variances were allowed to vary by scanner.

In addition to age, sex and BMI, previous studies have revealed that genetic polymorphisms, such as A1 allele (Pohjalainen et al., 1998) and C957T (Hirvonen et al., 2009), as well as other genetic and environmental factors that were not considered here may explain some of the indi-

vidual differences in D<sub>2</sub>R availability (Jönsson et al., 1999). We used [11C]raclopride and BP<sub>ND</sub> to measure striatal D<sub>2</sub>R availability. BP<sub>ND</sub> being a product of receptor density and affinity (Mintun et al., 1984) of unoccupied receptors (Cumming et al., 2002), the level of binding reflects i) the D<sub>2</sub>R density, ii) the D<sub>2</sub>R affinity and ii) the D<sub>2</sub>R occupancy by endogenous dopamine (Ginovart, 2005, Innis et al., 2007, Volkow et al., 2009, Laruelle, 2000). Hence, using only one baseline image per subject we could not analyze receptor density and affinity separately (Slifstein and Laruelle, 2001). However, as the binding affinity between dopamine and D<sub>2</sub>R is assumed constant (Endres et al., 1997), as the endogenous dopamine does not override D<sub>2</sub>R antagonists (e.g. [11C]raclopride) as effectively as agonists (Cumming et al., 2002) and as we used baseline scans including no interventions boosting dopamine firing (Weinstein et al., 2018), we expect the BP<sub>ND</sub> to dominantly measure the D<sub>2</sub>R density.

#### 4.5. Conclusions

Striatal D<sub>2</sub>R availability decreases globally through age for both sexes. Females show on average 5-10% higher D<sub>2</sub>R availability than males. High BMI was associated with increased D<sub>2</sub>R availability, although this effect was only weak. D<sub>2</sub>R availability was more lateralized in males than in females, but the lateralization effects were overall subtle. Importantly, we confirmed that the template-based normalization method allows for accurate global ROI-level modeling of the PET data when deformation-field-based spatial normalization method is not possible due to missing MR image. In sum, D<sub>2</sub>R availability is dependent on subject demographics, particularly on age and sex. These effects may contribute to age and sex dependent prevalence in neurological and psychiatric conditions involving altered D<sub>2</sub>R expression.

#### Credit authorship contribution statement

**Tuulia Malén:** Visualization, Validation, Formal analysis, Data curation, Project administration, Writing – original draft, Writing – review & editing. **Tomi Karjalainen:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Project administration, Visualization, Supervision, Validation, Formal analysis. **Janne Isojärvi:** Software, Data curation, Writing – review & editing. **Aki Vehtari:** Methodology, Formal analysis, Writing – review & editing. **Paul-Christian Bürkner:** Methodology, Formal analysis, Writing – review & editing. **Vesa Putkinen:** Data curation, Writing – review & editing, Visualization. **Valteri Kaasinen:** Investigation, Writing – review & editing. **Jarmo Hietala:** Investigation, Resources, Writing – review & editing. **Pirjo Nuutila:** Investigation, Resources, Writing – review & editing. **Juha Rinne:** Investigation, Resources, Writing – review & editing. **Lauri Nummenmaa:** Conceptualization, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Funding acquisition.

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#### Disclosures

Authors have nothing to disclose.

#### Supplementary materials

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