Alterations in type 2 dopamine receptors across neuropsychiatric conditions: A large-scale PET cohort

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Highlights

We compared human striatal and thalamic type 2 dopamine receptor (D_2R) availability between healthy controls, and subjects with Parkinson's disease (PD), antipsychotic-naïve schizophrenia, severe violent behavior, pathological gambling, depression, and overweight.

We present the mean brain maps of group specific D_2R availabilities in NeuroVault (https://neurovault.org; https://identifiers.org/neurovault.collection:12799).

Dopamine type 2 receptor availability is lowered in PD in caudate nucleus, nucleus accumbens and thalamus.

Antipsychotic-naïve schizophrenia, severe violent behavior, and depression were associated with decreased connectivity between the striatal and thalamic D_2R availability.

Altered regional D_2R availability in the striatum and thalamus is linked with motor disorders, while lowered regional connectivity in D_2R might relate to affective disturbance.

Abstract

Aberrant dopaminergic function is linked with motor, psychotic, and affective symptoms, but studies have typically compared a single patient group with healthy controls. Here, we investigated the variation in striatal (caudate nucleus, nucleus accumbens, and putamen) and thalamic type 2 dopamine receptor (D_2R) availability using [11C]raclopride positron emission tomography (PET) data from a large sample of 437 humans including healthy controls and subjects with Parkinson's disease (PD), antipsychotic-naïve schizophrenia, severe violent behavior, pathological gambling, depression, and overweight. We analyzed regional group differences in D_2R availability using Bayesian mixed effects modeling. Subjects with PD showed clearest decline in D_2R availability. Healthy controls and patients with PD showed high interregional correlation of D_2R availability, while this pattern was weaker in schizophrenia, severe violent behavior, and depression. Subjects with pathological gambling or overweight did not show clear changes in either the regional receptor availability or the interregional correlation. We conclude that the dopaminergic changes in neuropsychiatric conditions might not only affect the overall receptor availability but also the connectivity between the regions. The region-specific receptor availability more profoundly links to the motor symptoms, while the between-region connectivity might be disrupted in affective symptoms.

Introduction

Neurotransmitter dopamine is centrally involved in motor, motivational and emotional processes (Beaulieu, Espinoza, & Gainetdinov, 2015). The four major dopaminergic pathways are i) nigrostriatal pathway running from substantia nigra to the dorsal striatum (i.e. caudate nucleus and putamen), ii) mesolimbic pathway from ventral tegmental area (VTA) to the ventral striatum (i.e. nucleus accumbens), iii) mesocortical pathway from VTA to prefrontal and cingulate cortex, and iv) tuberoinfundibular pathway from hypothalamus to pituitary gland (Harsing Jr, 2008; Purves et al., 2018). The nigrostriatal pathway is critically involved in motor function and Parkinson's disease (PD) (Meltzer & Stahl, 1976), while the mesolimbic pathway (also known as the reward pathway) contributes to motivation (Merims & Giladi, 2008; Purves et al., 2018). Particularly, the striatal type 2 dopamine receptor (D_2R) has been linked with a variety of neuropsychiatric symptoms (De Keyser et al., 1988; Leggio, Bucolo, Platania, Salomone, & Drago, 2016; Usiello et al., 2000).

Lowered dopamine transmission in the nigrostriatal pathway is associated with motor symptoms (e.g. rigidity, and bradykinesia) in PD (Leggio et al., 2016), while hyperactivity of the dopamine neurons in the mesolimbic track might promote psychotic symptoms in schizophrenia (Meltzer & Stahl, 1976; but see also Stahl, 2018). Antipsychotic-naïve schizophrenia patients with first-episode psychosis show lowered availability of thalamic D_2Rs (Plavén-Sigray et al., 2022), possibly also linked to elevated presynaptic dopamine release, observed at least in the closely located striatum (Howes et al., 2012). However, while increased presynaptic dopamine synthesis and release is characteristic for schizophrenia, only some patients have altered postsynaptic D_2R, pointing towards subtypes of schizophrenia (Brugger et al., 2020).

Dopamine also contributes to impulsive behavior, such as aggressive outbursts and drug abuse (Schmidt, Schmidt, & Reith, 2005; Schultz, 1998; Seo, Patrick, & Kennealy, 2008; Volkow, Fowler, Wang, & Swanson, 2004). Mesolimbic dopamine pathway and upregulated striatal dopamine function is critical for aggressive behavior (Schmidt et al., 2005). Hyperactive striatal dopaminergic function is also consistently linked with acute effects of drug abuse in addicted subjects, who overall show diminished dopamine and D_2Rs in the striatum (Volkow et al., 2004). Baseline downregulation of dopamine in addictions might associate with their commonly comorbid affective symptoms (Marshall & Farrell, 2007), such as anhedonia (lack of pleasure) and dysphoria (dissatisfaction), that are coherently connected to diminished mesocorticolimbic dopamine (Bressan & Crippa, 2005). Overall, affective symptoms are involved in numerous neurological and psychiatric conditions, including PD, schizophrenia and depression (Bressan & Crippa, 2005; Knable et al., 1997).

Finally, drugs that enhance striatal dopaminergic neurotransmission effectively treat motor symptoms (Poewe & Mahlknecht, 2020) but can also induce psychotic symptoms, impulsivity, and addictive behavior (e.g. gambling and overeating) (Meltzer & Stahl, 1976; Merims & Giladi, 2008; Witjas et al., 2005). Conversely, neuroleptics, pharmacological treatments that inhibit the striatal dopaminergic function by blocking the D_2Rs, reduce psychotic symptoms (Bressan & Crippa, 2005; Kapur & Mamo, 2003) and aggressive behavior (Schmidt et al., 2005), but induce Parkinsonian-like side effects, such as rigidity and bradykinesia (Harsing Jr, 2008; Jackson & Westlind-Danielsson, 1994; Shiraiwa, Tamaoka, & Ohkoshi, 2018; Stahl, 2018) and anhedonia (Bressan & Crippa, 2005). Particularly the antipsychotics that affect the nigrostriatal track in addition to the mesolimbic track might be the ones with motor side-effects (Jackson & Westlind-Danielsson, 1994), further supporting the centrality of the nigrostriatal track in motor functions.

Taken together, existing data suggest that elevated striatal dopamine activity contributes to psychotic symptoms, impulsivity, aggressive outbursts, and acute effects of reward (namely intense hedonia / pleasure), while lowered dopamine activity relates to disturbed motor functions, and blunted affect (e.g., anhedonia, diminished reward experiences). Because several neuropsychiatric conditions share symptoms

(Knable et al., 1997; Seo et al., 2008), perturbations in the dopamine system might link to specific neuropsychiatric symptoms regardless of the diagnosis. To resolve these links between the pathologies with shared dopamine-regulated symptoms of voluntary movement, motivation, and affect, it is crucial to study them together. Only this allows unravelling whether differential patterns of dopaminergic dysfunctions underlie different neuropsychiatric conditions.

Here we investigated the differences in the striatal (caudate nucleus, nucleus accumbens, and putamen), and thalamic D_2R availability in a large (n= 437) historical sample of subjects using positron emission tomography (PET) data with radioligand [11C]raclopride acquired in resting baseline state. The dopaminergic function includes tonic and phasic dopamine firing (Grace, 2016). Because our data pertain to baseline, resting state scans, these data reflect predominantly tonic rather than phasic dopaminergic function. Our sample included healthy controls, and subjects with PD, antipsychotic-naïve schizophrenia, severe violent behavior (violence), pathological gambling (gambling), depression, and overweight. We also analyzed between-region "connectivity" (correlation) of the D_2R availability in each group and assessed the effects of age and sex on D_2R availability in i) the healthy subjects and ii) the other six groups (i.e. groups of interest) together.

Aims and Methods

Data

Basic subject information is shown in **Table 1**. This retrospective register-based study includes 437 subjects (294 males, 143 females), including healthy controls (n= 239), and subjects with PD (n= 60), schizophrenia (n= 7), severe violent behavior, i.e. prison sentence for violence (n= 10), pathological gambling (n= 12), depression (n= 12), and obesity/overweight (n= 97) who had undergone [11C]raclopride PET scan. The age range of the subjects was 19-82 years. The data were retrieved from the Turku PET Centre Aivo database (https://aivo.utu.fi/), including data of imaging studies conducted at the site. The images were acquired between the years 1989 and 2019 with six different PET scanners (GE Advance, HR+, HRRT, GE Advance VCT PET/CT, GE Advance 690 PET/CT, Ecat 931). The scanners are described in detail in our previous work (Malén et al., 2022).

We retrieved the following subject information at the time of each PET scan: subject age, sex, body mass index (BMI, available for 67% of the subjects) and group, as well as the injected dose and the PET scanner used to acquire the imaging data. Although we do not have detailed medication information for all the subjects, the exclusion criteria for the original research projects where that the subjects were drawn from contained medication affecting the central nervous system. The schizophrenia group was antipsychotic-naïve, and the depression group drug-free (mainly drug-naïve subjects with moderate depressive episode). The PD sample contained both unmedicated and medicated patients and given the mean disease duration of 10 years (median= 9 years, range from 0 to 29 years, see supplementary **Figure S1**), most of the patients were probably medicated at the time of imaging. The scans were, however, performed after a short washout period (subjects were withdrawn from medication at least from the night before the scan). We set the BMI cutoff between healthy control and overweight groups to 25 (Engin, 2017). The BMI range of the remaining subjects (including subjects with PD, schizophrenia, severe violent behavior, pathological gambling, and depression) was 19-49 (regards 67% of the total sample for who we had BMI information available, see supplementary **Table S1**).

Three subjects with low injected dose < 90 megabecquerel (MBq) and seven without dose information were excluded from the sample to avoid low signal to noise ratio. The excluded subjects were from healthy control, PD, schizophrenia, and overweight groups. Due to lost or noisy data from interrupted PET scanning, we discarded eight subjects (including subjects from PD, schizophrenia, and severe violent

behavior groups) whose kinetic model fits were inadequate. Altogether 18 subjects were excluded from the data due to aforementioned reasons.

	Males (n= 294)				Females (n= 143)			
	N	Mean	SD	Range	N	Mean	SD	Range
Healthy controls	174	28	11	19-78	65	41	16	19-82
Parkinson's disease	31	62	12	34-82	29	60	11	41-81
Schizophrenia	3	22	3	19-25	4	36	13	24-53
Violence	10	31	7	24-46	0	-	-	-
Pathological gambling	12	32	8	23-49	0	-	-	-
Depression	3	38	10	25-48	9	41	5	34-50
Overweight	61	29	9	19-56	36	43	13	23-74

Table 1. Age of the sample groups separately for males and females.

PET data preprocessing and kinetic modelling

PET image preprocessing and kinetic modelling were carried out in MATLAB (The Mathworks Inc., 2021) using an in-house brain image processing pipeline Magia (Karjalainen et al., 2020) (https://github.com/tkkarjal/magia). We spatially normalized the dynamic PET images into MNI152 space with an in-house [11C]raclopride PET-template created using a subset (n=187) of healthy control subjects, because only a subset of the sample had magnetic resonance (MR) image available (n=249) (Karjalainen et al., 2020). Four bilateral regions of interest (ROI) from Harvard-Oxford atlas, caudate nucleus (caudate), nucleus accumbens (accumbens), putamen, and thalamus, were applied to the normalized PET-images. [11C]raclopride binding to D_2Rs in these regions is reliable, while negligible elsewhere (Hirvonen et al., 2003; Svensson et al., 2019). Regional specific binding of [^{11}C]raclopride was quantified as nondisplaceable binding potential (BP_{ND}) using simplified reference tissue model (SRTM) (Lammertsma & Hume, 1996). BP_{ND} resembles receptor availability, being a measure of receptor density, affinity, and the receptor occupancy by endogenous dopamine (Cumming et al., 2002; Mintun, Raichle, Kilbourn, Wooten, & Welch, 1984). Parametric BP_{ND} images were also calculated for illustrative purposes with basis function implementation of SRTM (bfSRTM) with 300 basis functions. Lower and upper bounds for theta parameter were set to 0.082 1/min and 0.6 1/min. Before the parametric image calculation, the dynamic PET images were smoothed using Gaussian kernel with 4 mm full width at half maximum to reduce the effect of noise in the voxel-level bfSRTM fit.

Statistical analysis

Statistical analysis was carried out in R (R Core Team, 2021). We analyzed the regional data using Bayesian modeling tools of brms (Bürkner, 2017, 2018, 2021) utilizing rstan (Stan Development Team, 2020). We analyzed the interregional BP_{ND} correlation in each subject group using (Pearson) correlation matrix with corrplot (Wei & Simko, 2021), and Mantel test for similarity of two matrices using ape (Paradis & Schliep, 2019).

Regional group differences in D_2R availability

We used linear mixed effects regression to compare regional D_2R availability across the seven subject groups. In the analysis, we adjusted for the scanner used in the image acquisition, and the subject age and sex that affected striatal BP_{ND} estimates in healthy controls (Malén et al., 2022).

The regional binding potentials (BP_{ND}) were modeled as a dependent variable. We analyzed the group differences in BP_{ND} in caudate, accumbens, putamen, and thalamus, while adjusting for age, sex, and

scanner. Specifically, we applied group, standardized age, and sex as fixed effects and allowed these effects to vary between ROIs (regionally varying a.k.a. random slopes). We allowed the BP_{ND} intercept to vary between subjects, scanners, ROIs, and the scanners within each ROI (random intercepts for subjects, scanners, ROIs, and scanner-ROI combinations). For the residual variances, we similarly applied random intercepts for scanners, ROIs, and the scanner-ROI combinations, but not for subjects as we did not expect the residual variances to depend on subject. We validated the model by comparing it with three other candidate models (see **Model diagnostics and comparison** in supplementary material).

We log-transformed the dependent variable BP_{ND}, and did not expect non-linear associations between the predictors and log-BP_{ND} (Malén et al., 2022). Modeling higher-degree associations increases the risk of overfitting, potentially resulting in poor generalization of the results (McElreath, 2020). In the absence of appropriate priors for Bayesian statistical inference from independent data, we gave a normal distribution prior (with expected value= 0 and variance= 1) for the fixed effects (age, sex, group). Such zero-centered normal prior assigns symmetrical probabilities for both positive and negative regression coefficients and does not restrict the parameter to certain values (i.e., no regression coefficient is given zero probability). For the standard deviations of the random effects, we set the same normal prior. As standard deviation is always positive, brms-package automatically restricts this prior to positive values, making it a half-normal distribution (Bürkner, 2017, 2018, 2021). For the rest of the modeling parameters, we used weakly informative default priors of brms (Bürkner, 2017). The model was carried out using Markov Chain Monte Carlo sampling with each four chains running 4000 iterations (including 1000 warm-up samples).

Validation of the age and sex effects on regional D_2R availability

For validation purposes, we assessed the age and sex effects in the current sample. We tested the replicability of the age and sex effects (Malén et al., 2022) in the i) healthy control sample (almost identical sample to our earlier work (Malén et al., 2022)) and ii) groups of interest together (subjects with PD, schizophrenia, severe violent behavior, pathological gambling, depression, and overweight) (**Validation of the age and sex effects on regional D_2R availability** in supplementary material).

Between-region correlation of the D_2R availability

We formed a 4×4 between-region BP_{ND} correlation matrix for each subject group. After that, we tested for the similarity of each correlation matrix (subject group) pair. These analyses allowed us to assess, whether interregional D_2R coupling is altered in neuropsychopathology, and whether different neuropsychiatric conditions share or differ in their striatal and thalamic 'connectivity' patterns.

Results

Descriptives

Mean group specific D_2R maps revealed broadly similar receptor distribution in the subject groups (**Figure 1**; the mean D_2R maps are also available in NeuroVault (https://identifiers.org/neurovault.collection:12799)). Mean regional non-transformed BP_{ND} estimates for each group are shown in **Figure 2**. The non-transformed BP_{ND} estimates as a function of PD duration are shown in **Figure S1**. In all four regions, the (Pearson) correlation of PD duration and non-transformed BP_{ND} was negative, but the 95% confidence level crossed zero.

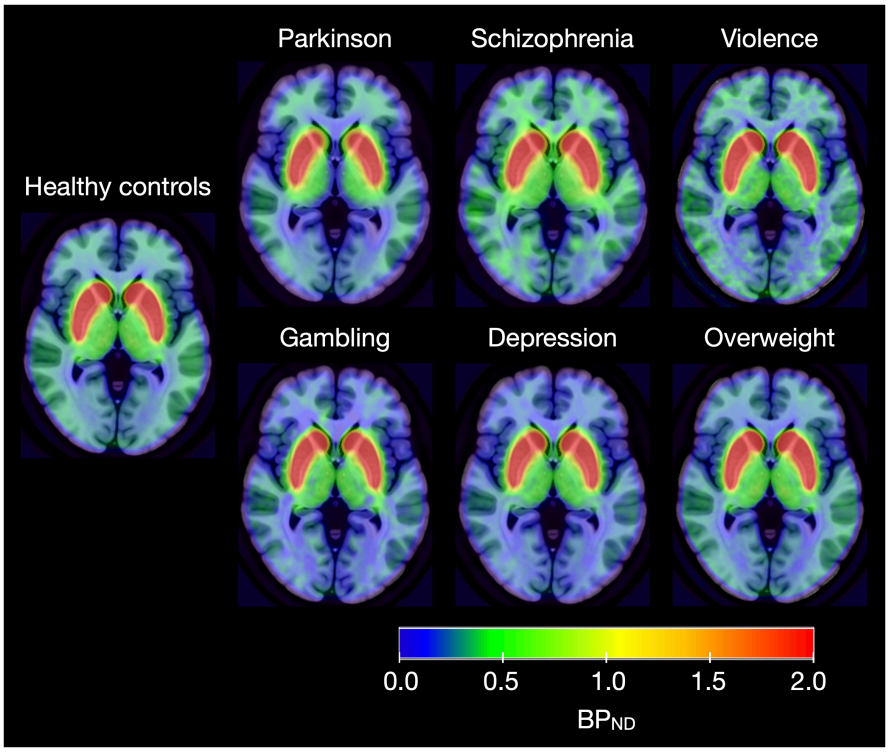

Figure 1. Mean [11C]raclopride non-transformed BP_{ND} of the subject groups.

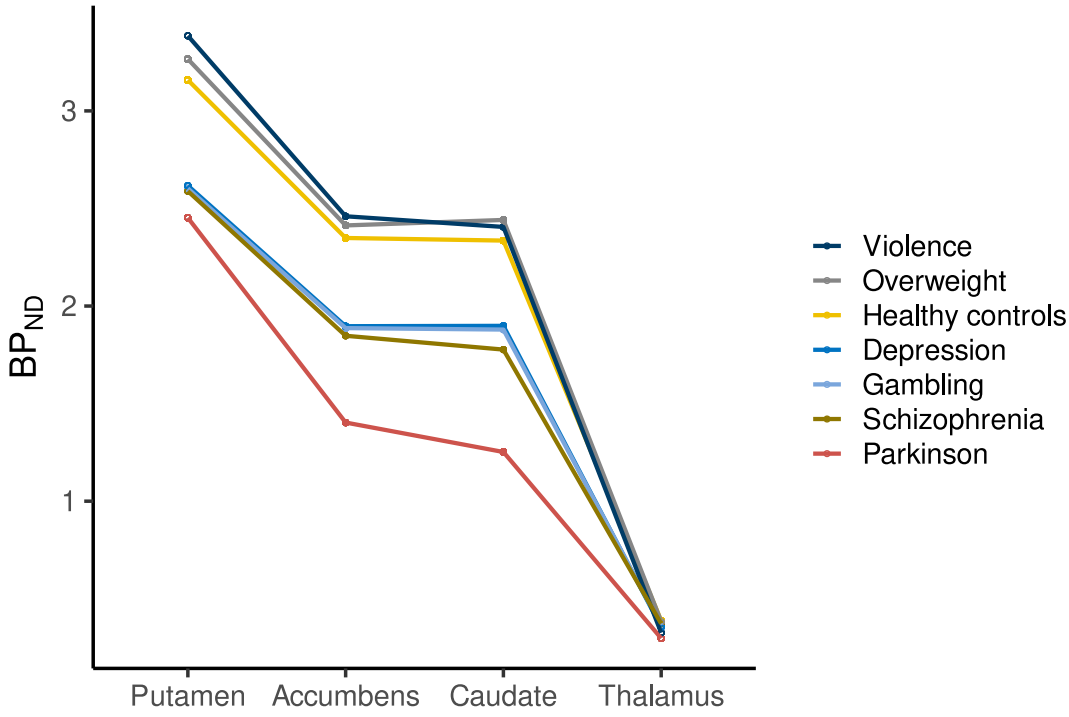

Figure 2. The group specific BP_{ND} profiles (non-transformed values). The lines connect the group specific mean points to aid in visualization of the group-specific binding profiles.

Regional group differences in D_2R availability

Bayesian linear mixed effects modeling (**Figure 3**), adjusting for age, sex, and scanner, revealed that compared to the other groups, PD patients had approximately 10-20% lower [11C]raclopride BP_{ND} (values transformed back to original scale) in caudate, accumbens and thalamus, while the BP_{ND} in putamen was approximately 10% higher (**Figure 4**). The other groups of interest (schizophrenia, severe violent behavior, pathological gambling, depression, and overweight) did not show clear differences in regional D_2R availability when compared with healthy controls or each other. However, subjects with schizophrenia and severe violent behavior showed more support for lowered than elevated D_2R availability (more probability mass below zero), although the 80% posterior intervals (i.e. probability mass) crossed zero. Pathological gambling, depression and overweight groups showed the least support for altered D_2R availability with practically non-existent difference compared to healthy controls.

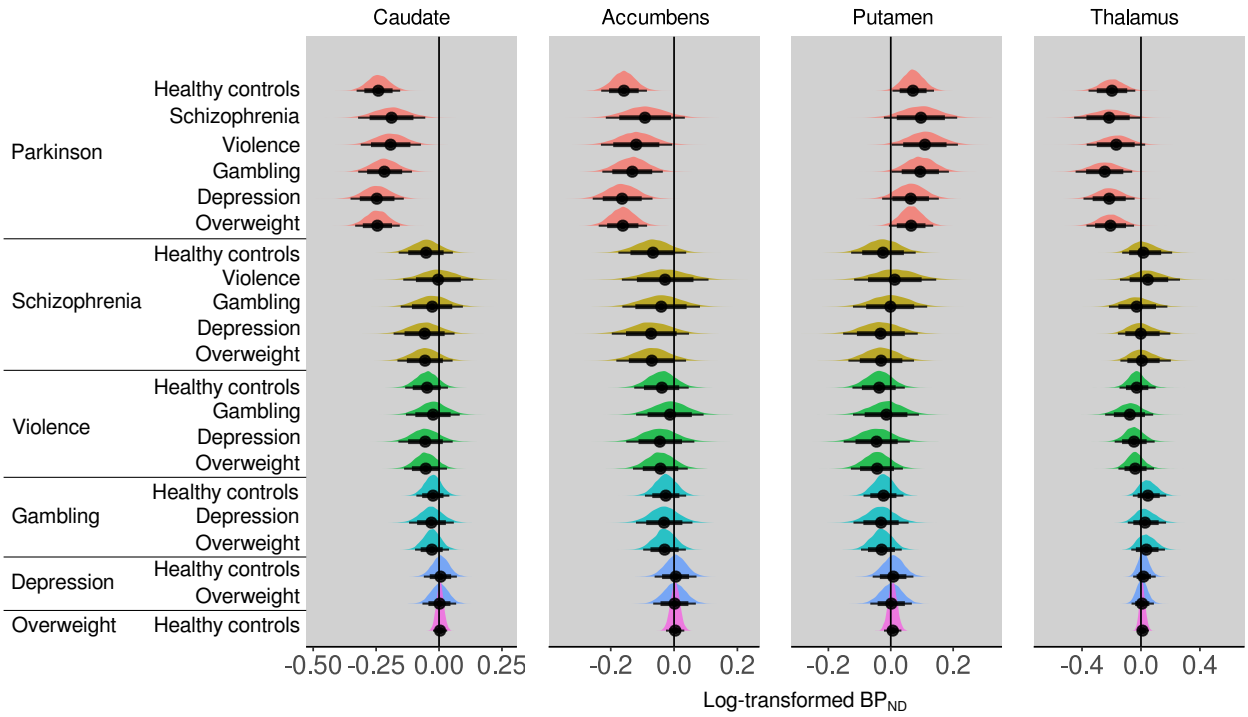

Figure 3. The figure shows colored posterior probability distributions (posteriors), as well as their median (point), 80% (thick line) and 95% (thin line) posterior intervals, describing the between-group differences in log-transformed BP_{ND}. Posterior located on the negative side of the zero line suggests lower BP_{ND} in the reference group on the left compared with the group on the right.

		Caudate	Accumbens	Putamen	Thalamus
Parkinson	Healthy controls	0.79 **	0.85 **	1.07 **	0.82 **
	Schizophrenia	0.83 **	0.91 *	1.1 *	0.81 **
	Violence	0.82 **	0.89 **	1.12 **	0.85 *
	Gambling	0.8 **	0.88 **	1.1 **	0.78 **
	Depression	0.78 **	0.85 **	1.07 *	0.81 **
	Overweight	0.78 **	0.85 **	1.07 *	0.81 **
Schizophrenia	Healthy controls	0.95	0.94	0.98	1.02
	Violence	1	0.97	1.01	1.05
	Gambling	0.97	0.96	1	0.97
	Depression	0.94	0.93	0.97	1
	Overweight	0.95	0.93	0.97	1.01
Violence	Healthy controls	0.95	0.96	0.96	0.97
	Gambling	0.98	0.99	0.99	0.93
	Depression	0.95	0.96	0.96	0.95
	Overweight	0.95	0.96	0.96	0.96
Gambling	Healthy controls	0.95	0.93	0.97	1.01
	Depression	0.97	0.97	0.97	1.03
	Overweight	0.97	0.97	0.97	1.04
Depression	Healthy controls	1.01	1.01	1.01	1.02
	Overweight	1	1	1	1.01
Overweight	Healthy controls	1	1	1.01	1.01

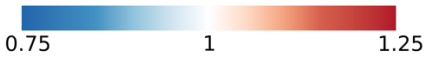

Figure 4. Summary of the regional group comparisons. The values represent the (median) proportional BP_{ND} (values transformed back to original scale) of the reference group (on the left) compared with the group on the right. Asterisks represent comparisons were 80% (*) and 95% (**) posterior interval did not cross zero.

Validation of the age and sex effects on regional D_2R availability

Similarly as in our previous analysis with healthy subjects (Malén et al., 2022), D_2R availability decreased through age, both in the healthy control group that is almost identical to the sample in our previous work (Malén et al., 2022) and in the groups of interest. The lower striatal D_2R availability in males versus females was only found in healthy controls. However, in thalamus, females had higher thalamic availability in both the healthy controls and the groups of interest. Detailed results are shown in **Figure S2**.

Between-region correlation of the D_2R availability

The interregional correlations of non-transformed BP_{ND} are shown in **Figure 5**. Despite the regional BP_{ND} changes, PD patients showed high between-region BP_{ND} correlation, similarly as healthy controls, and subjects with pathological gambling and overweight. Subjects with schizophrenia, severe violent behavior, and depression showed the weakest (Pearson) correlation between the ROIs, most notably manifested as hypoconnectivity of putamen. For the healthy control, Parkinson's disease and overweight groups, the p-value for each correlation was < .001. For the other groups, the p-value at maximum for the between-ROI correlation was 0.02 for gambling (putamen-thalamus), 0.28 for schizophrenia (putamen-caudate), 0.43 for violence (putamen-caudate), and finally 0.35 for depression (putamen-thalamus). When we compared the correlation matrixes of the groups (**Figure 5**), there was no clear support for similarity between any of the matrices. Mantel test p-value was at minimum 0.06 (depression versus overweight) and at maximum 0.88 (Parkinson versus pathological gambling), thus indicating different connectivity profiles across all studied pairs of groups.

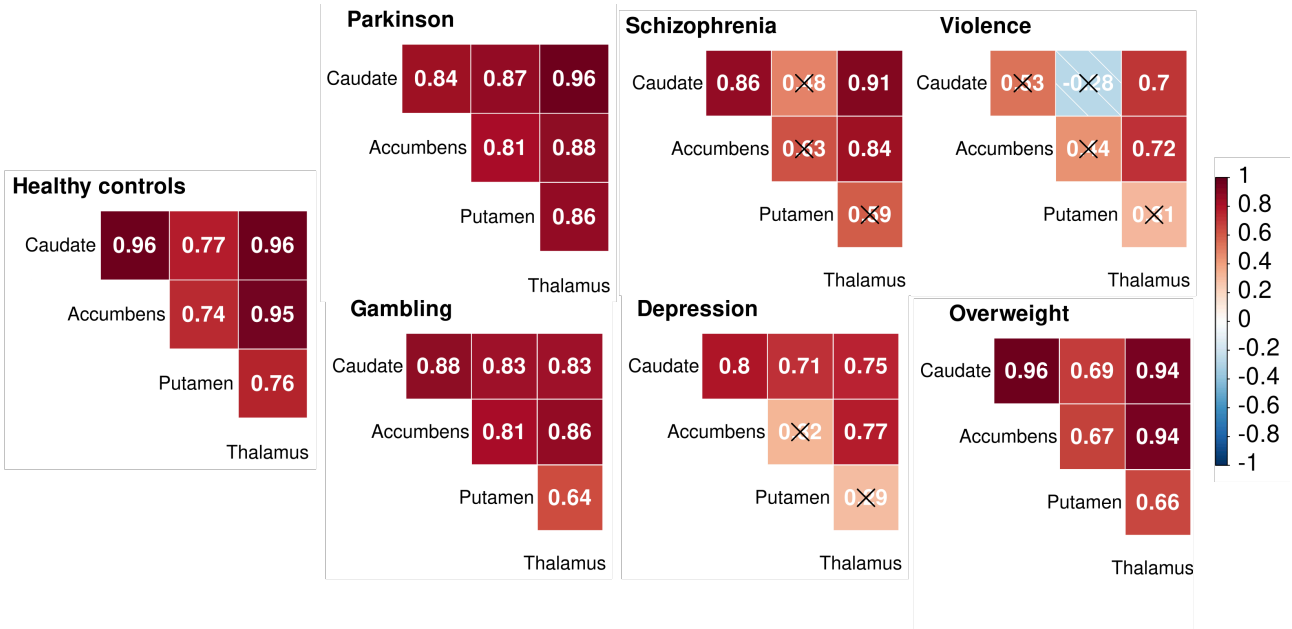

Figure 5. Group specific interregional BP_{ND} correlations (Pearson, p-values > 0.05 marked with a cross, while the lower the p-value, the more support for non-zero correlation).

Discussion

Striatal dopamine neurotransmission has a central role in motor function that is disturbed particularly in PD (Kaasinen & Vahlberg, 2017; Kaasinen, Vahlberg, Stoessl, Strafella, & Antonini, 2021), and motivational processes that are impaired in many neuropsychiatric disorders (Bressan & Crippa, 2005; Knable et al., 1997; Schmidt et al., 2005; Schultz, 1998; Volkow et al., 2004). Our findings show that in PD, striatal (caudate and accumbens) and thalamic D_2R availability is downregulated, while interregional correlation might be lowered in antipsychotic-naïve schizophrenia, severe violent behavior, and depression. These results suggest that specific regional decoupling patterns in the striatothalamic dopamine circuit associate to a broader variety of neuropsychiatric conditions than overall changes in receptor levels.

Regional D_2R changes in Parkinson's disease

Striatal (caudate and accumbens) and thalamic downregulation in D_2R availability was most salient in PD patients. There was weak evidence for striatal downregulation also in schizophrenia and severe violent behavior, but even the 80% posterior intervals for these groups overlapped with zero, leaving the support subtle. Our finding supports a previous meta-analysis describing that the effect of the striatal D_2R in schizophrenia is negligible (and possibly linked to the antipsychotic treatment) compared to the presynaptic dopamine synthesis and release (Howes et al., 2012). The other groups did not show clear alterations in striatum nor thalamus.

Compared with the other groups, PD patients exhibited both lowered (accumbents, caudate, thalamus) and elevated (putamen) striatal D_2R availability when adjusting for age and sex. PD subjects had lowered D_2R availability in nuclei caudate and accumbens, and thalamus. In putamen PD patients had high D_2R availability, although this effect is not discernible in the raw data where age and sex are not adjusted for. The implemented statistical model however adjusted for the general decline in D_2R as a function of ageing, and patients with PD were in general among the oldest individuals in the sample. Thus, it is possible that in putamen the PD subjects have high receptor availability for their age. However, this finding requires additional validation, as D_2R changes in putamen are dynamic and dependent on the disease stage. Compensatory D_2R upregulation in putamen changes to downregulation around four years

from PD onset (Kaasinen et al., 2021; Rinne et al., 1990). The PD duration greatly varied between the studies subjects (range: 0-29 years) and our findings cannot directly discern the effects in early and late stages, as the disease duration information was available for only half of the patients. Thus, we are unable to specify the weight of early and late stage patients in our data and analysis. For the subjects with available information, the correlation between disease duration and BP_{ND} was subtle but nevertheless negative in all tested regions (-0.16 in putamen) suggesting no prolonged upregulation with progressed PD. Consequently, our findings do not provide clear evidence against late stage D_2R downregulation in putamen. Overall, the findings nonetheless highlight the region and motor symptom specificity of within-region D_2R changes.

Lowered between-region connectivity in schizophrenia, severe violent behavior, and depression

Our data suggests that the dopaminergic changes in schizophrenia, severe violent behavior, and depression were more salient in the regional coupling in dopaminergic function, rather than in the overall regional receptor availability. The regional coupling was lower in subjects with schizophrenia, severe violent behavior, and depression. Aberrant coupling in this striatal dopamine network might reflect altered communication and weakened links between the regional nodes. Particularly, affective flattening (e.g. lowered mood and interest) is characteristic for depression and schizophrenia (Berenbaum & Oltmanns, 1992), and mental health problems overall are over-represented among imprisoned (Fazel, Hayes, Bartellas, Clerici, & Trestman, 2016). Thus, potentially, the shared regional D_2R hypoconnectivity associate with affective disturbance common to these subject groups, whereas the overall downregulation of D_2R levels link to motor problems as was the case in PD. We nevertheless stress that the correlations are dependent on the number of observations, and we had limited sample sizes of schizophrenia, severe violent behavior, and depression groups, which might limit the generalizability of our findings. However, they nevertheless indicate different dopaminergic connectivity profiles between motor and affective symptoms, and this between-region connectivity in affective disorders should be further examined in larger studies.

Unaltered baseline D_2R in pathological gambling and overweight

We observed neither regional D_2R changes nor aberrant regional coupling in the pathological gambling and overweight groups. Although "food addiction" is not the primary cause of obesity, addiction related D_2R function has been proposed to underlie obesity (Volkow, Wise, & Baler, 2017). Our results however underline that dopaminergic mechanisms do not notably contribute to neither weight gain nor pathological gambling. In patients with pathological gambling and overweight, we did not observe lowered regional D_2R coupling as in affective disorders, although lowered mood and addictions are often comorbid (Hasin, Goodwin, Stinson, & Grant, 2005). More precise comorbidity information of the exact subjects in our data might have allowed us to clarify the link between regional coupling and blunted affect. However, our findings accords with previous reports of no clear connections between D_2R availability and behavioral addictions, such as gambling (Linnet, Møller, Peterson, Gjedde, & Doudet, 2011), and also with those finding no links between altered D_2R availability and obesity / overweight (Karlsson et al., 2015; Malén et al., 2022).

Altogether, our results highlight that motor symptoms, rather than disturbance in affect and behavioral control, are the most consistently linked with regional alterations in D_2R availability. According to our data, PD is associated with changes in regional D_2R availability, while antipsychotic-naïve schizophrenia, severe violent behavior, and depression might link to disturbed correlation between the regional availability. Overall, our results of unaltered D_2R in pathological gambling and overweight suggests that the postsynaptic type 2 dopamine receptor in the striatum and thalamus is not a central contributor of behavioral addictions. Overall, this large multi-group dataset suggests that the dopaminergic changes observed in neuropsychiatric pathology are multifaceted, involving region-specific and between-region

mechanisms of the D_2R. We conclude that the changes in baseline D_2R might be more profoundly linked with motor and affective symptoms than with behavioral addictions.

Effects of age and sex on D_2R availability

We found that baseline striatal D_2R availability is lowered through age both in healthy controls and in the groups of interest. Previously we observed sex differences (female > male) in healthy controls consistently in the striatothalamic regions (Malén et al., 2022), whereas here in the groups of interest, sex differences were only found in the thalamus. However, this effect pertains to the joint analysis of the groups of interest together. Because all the groups did not include both males and females, we pooled the groups together for the analysis of age and sex, which might have overlooked group specific sex differences. Nevertheless, our data indicate that the effects of age on D_2R are more consistent than those of sex, and generally found also in clinical populations. Accordingly, adjusting for age and sex is necessary when assessing the effects of other variables on striatothalamic D_2R availability.

Limitations

First, our data were not fully balanced. Although the dataset was large, the group size, age, sex, and scanner distribution were compromised in some of the studied groups. Combined with our statistical analysis of the group differences that adjusted for the age, sex, and scanner related variation in the data, some group differences were possibly left undetected (McElreath, 2020). Second, in a single PET scan, it is not possible to demonstrate the exact molecule-level mechanism for altered receptor availability. Finally, not all subjects were drug naïve. Due to the retrospective nature of the data derived from multiple projects, the collection of clinical characteristics of patient populations were not standardized. Patient categorization was based on their enrollment criteria in the original studies. Finally, it must be noted that unaltered baseline D_2R level does not mean the dopaminergic responses in different environmental contexts would be similar across all studied groups. It is possible that differential patterns of dopamine firing in motivationally triggering environments exist for example, towards gambling in pathological gamblers and towards feeding in obese individuals (Grace, 2016). Investigating such effects however requires standardized challenge or activation paradigms, which could not be incorporated in the current analysis.

Conclusions

Dopaminergic function is altered across multiple psychiatric and neurological conditions, and the regional receptor availability patterns, as well as interregional coupling of D_2R levels, might distinguish between the specific conditions. PD was associated with region-specific changes in D_2R availability. The role of D_2R in schizophrenia, severe violent behavior, and depression might rather relate to the interregional connections as in these subject groups, the between-region receptor availabilities were less correlated. In pathological gambling and overweight groups, no clear changes were observed in the striatothalamic D_2R level nor the correlation structure. Our results suggest that in striatum and thalamus, motor symptoms are more profoundly linked to the region-specific D_2R availability, while affective symptoms might be more associated with lowered correlation between the regions.

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