ORIGINAL ARTICLE
Dopaminergic function and intertemporal choice

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The discounting of delayed rewards, also known as temporal or delay discounting, is intrinsic to everyday decisions and can be impaired in pathological states such as addiction disorders. Preclinical and human studies suggest a role for dopaminergic function in temporal discounting but this relationship has not yet been verified using molecular imaging of the living human brain. Here, we evaluated dopaminergic function in temporal discounting using positron emission tomography (PET) with two different dopaminergic ligands assessing three populations in whom temporal discounting has been shown to be impaired. First, we show using [11C]raclopride PET that in pathological gamblers, greater temporal discounting correlates with decreased ventral striatal binding potential, convergent with translational findings of lower nucleus accumbens D2/D3 receptor density in high-impulsive rodents. Temporal discounting also correlates with lower ventral striatal dopamine release in response to high-reward magnitude suggesting that dopamine-mediated devaluation of larger delayed rewards may drive choice preferences. Second, we show using [18F]fluorodopa PET that in Parkinson's disease, temporal discounting correlates with greater left caudate dopaminergic terminal function. Finally, in subjects with Parkinson's disease and dopamine medication-induced behavioral addictions, temporal discounting is further correlated with greater dopaminergic terminal function in the anterior putamen. These findings provide insights into the relationship between striatal dopamine function and temporal discounting, and its potential role in pathological disorders and mechanisms underlying treatment interventions.

INTRODUCTION

The weighting of choices as a function of time is intrinsic to everyday decisions. These choices include daily decisions, about whether to diet, to fit into a swimsuit for the summer or more substantial decisions, such as choosing to stay in school for future career plans. Delay or temporal discounting is a form of decisional impulsivity characterized by a choice of an immediate smaller reward over a larger delayed reward. Temporal discounting can be measured using intertemporal choice tasks in which subjects choose between immediate and larger delayed rewards.[1] There is much interindividual variability and the discounting of delayed rewards is a core impairment across diverse behavioral addictions (BA), such as pathological gambling (PG), and substance addictions in humans.[2] In rodents, greater temporal discounting predicts the inability to inhibit nicotine seeking during abstinence and greater sensitivity to nicotine cues,[3] faster acquisition of cocaine self-administration,[4] persistent cocaine seeking during extinction and greater context-associated relapse.[5] Greater temporal discounting has also been shown to be increased in Parkinson's disease (PD) patients compared with healthy volunteers[6] suggesting that there may be a potential pathophysiological role for the neurobiology of PD in temporal discounting, although psychosocial mechanisms are likely to contribute as well.[7] Furthermore, PD patients with dopaminergic medication-related PG or compulsive shopping have been shown to have greater temporal discounting compared with those without BAs.[8–10]

Converging evidence implies a role for dopamine in temporal discounting. Single-unit striatal recordings in primates during the presentation of reward-predicting stimuli show that dopaminergic activity increases monotonically with magnitude and also decreases with delay to reflect the subjective devaluation of the delayed reward.[11] Greater temporal discounting is also associated with lower dopamine reactivity in the nucleus accumbens core and shell measured using electrically evoked dopamine release.[3] Nucleus accumbens lesions are also associated with increased temporal discounting.[12] These observations suggest that enhanced temporal discounting may be associated with a decrease in endogenous dopaminergic activity.

The relationship to exogenously administered dopamine is more complex. Acute administration of low and moderate doses of amphetamine has been shown to decrease impulsive choice in rodents.[13–15] In contrast, high chronic doses of methamphetamine and cocaine also increase impulsive choice in rodents,[14,16] which may be related either to a dose related effect or chronic adaptation. Similarly, levodopa, a precursor to dopamine, is associated with increased impulsive choice in healthy humans[17] and increased delay aversion in PD patients.[18]

Taken together, this evidence suggests a possible role for a U-shaped curve in the relationship between dopamine and temporal discounting.[19] Lower endogenous dopamine levels in preclinical studies and lower dopaminergic tone in PD patients are associated with greater temporal discounting. Acute administration of low and moderate doses and chronic high doses of exogenously administered drugs may have differential effects on temporal discounting dependent on how the administration shifts dopaminergic activity on this U-shaped curve.

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Previous [11C]raclopride studies, including our earlier studies based on this imaging data, have remained inconclusive about group differences in striatal dopamine function in PG patients compared with healthy volunteers.[20,21] However, in PD patients, BAs seem to be related with increased cue- and reward-related striatal dopamine release[22,23] and lower dopamine transporter density,[24,25] but not with alterations in striatal dopamine synthesis capacity as shown in our earlier study from this sample.[26]

Here, we focus on the relationship between temporal discounting and measures of striatal dopamine function. We assess disorders shown to have abnormal temporal discounting, including PG subjects and PD subjects with and without BAs. Our first study focused on interindividual differences in temporal discounting and their relationship with [11C]raclopride PET in healthy volunteers and PG subjects. Subjects were tested with a baseline control and a gambling task with reward magnitude manipulation. Greater temporal discounting has been shown to correlate with premature or anticipatory responding,[27] which is associated with lower nucleus accumbens D2/D3 receptor density in rodents without any associated changes in presynaptic dopamine release at baseline.[28] Thus, we hypothesize that greater temporal discounting is associated with lower ventral striatal D2/D3 receptor density.

In the second study, we assessed the relationship between temporal discounting and striatal dopamine terminal function, which reflects dopamine synthesis capacity (aromatic amino acid carboxylase activity), by measuring the [18F]fluorodopa PET at rest.[29] We investigated interindividual differences in temporal discounting in patients with PD with and without medication-induced BAs. Previous studies with [11C]raclopride PET have shown that PD patients with BAs have enhanced presynaptic striatal dopamine release in response to a gambling task or reward-related cues.[22,23] We hypothesized that greater temporal discounting would be associated with higher dopamine function particularly in PD subjects with BAs.

MATERIALS AND METHODS

Subjects

Twelve pathological gamblers, 12 healthy volunteers and 20 PD patients with ($n = 10$) and without ($n = 10$) medication-induced BAs participated in the study. The group comparisons of the imaging data between gamblers and healthy volunteers, and PD patients with and without BAs have been published earlier.[20,26] All subjects were male. For PD patients, the diagnosis had been established by a neurologist according to the UK Brain Bank Criteria[30] and BA diagnoses were made by a consultant psychiatrist (SN) according to previously published criteria.[31] The BAs in PD patients included PG in five patients, hypersexuality in four patients and binge eating disorder in one patient. All BAs had emerged following the initiation of dopamine replacement therapy and were active during the study. PD subjects were tested behaviorally on medication. Dementia, substance dependence, major axis-I disorders, clinically relevant medical conditions, medications known to affect dopamine function and substance use within 36 h or caffeine consumption within 12 h before the PET imaging were considered as exclusion criteria. The studies received approval from the local ethical committee, informed written consent was obtained and the study was conducted according to the principles of the Declaration of Helsinki.

Temporal discounting

Temporal discounting was assessed using a 27-item monetary choice questionnaire,[1] where subjects were asked to choose between an immediate reward and a larger delayed reward. The hyperbolic temporal discounting rate k can be calculated with the formula (1)

$$V = A/(1 + kD),\qquad(1)$$

where V is the present value of the delayed reward A at delay D. To estimate the magnitude effect, delayed rewards were divided into small, medium and large delayed rewards.[1] The indifference points of the k-values were established and the k-value calculated as the geometric mean

of the three magnitude categories. The subjects were instructed to carefully make the choices as they would in real life situations. Written instructions were given and the task was also explained by one of the investigators (J. Joutsa). Two PD subjects (one patient with pathological gambling and one without BAs) were excluded from the analyses because they had more than two choices inconsistent with their temporal discount rate in one or more of the reward magnitude categories.[32] In addition, the task was too hard for one patient without BAs with cognitive impairment (Mini-Mental State Examination score of 22), leaving 17 PD patients in the final sample.

Imaging

All subjects underwent a 1.5T brain MRI scan to provide a structural reference for PET image analyses and to exclude structural brain abnormalities. T1, T2, DWI and FLAIR sequences were obtained and inspected by a consultant neuroradiologist.

The PG and healthy volunteer subjects were scanned repeatedly under different conditions (a control task and two gambling tasks with a slot machine) with [11C]raclopride PET on the same day, and the order of the scans was fully counter balanced. The control task included pressing buttons A and B when lit with combined auditory stimulus, but without any gambling-related cues or monetary gain/loss. In the gambling tasks, subjects were instructed to gamble with ecologically valid slot machine software under two scenarios: high reward and low reward. The magnitude (but not the frequency) of wins was modified, resulting in a mean payback rate of 371% in the high-reward task and 93% in the low-reward task. The subjects were blinded to the gambling task outcomes. The tasks have been described in detail previously.[20]

PD patients were scanned once with [18F]fluorodopa in the resting condition in off-medication state. All dopaminergic medications were discontinued at least 12 h (24 h for extended release medications) before the tracer injection and a 150 mg oral dose of carbidopa was given 1 h before [18F]fluorodopa bolus administration to prevent peripheral decarboxylation of the tracer.

[11C]raclopride scanning was performed using GE Advance (General Electric Medical Systems, Milwaukee, WI, USA) and [18F]fluorodopa scanning using Siemens ECAT EXACT HR+ (Siemens, Münich, Germany) scanner, and preprocessing performed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK; http//www.fil.ion.ucl.ac.uk/spm/) software, as described earlier.[20,26] Briefly, between-frame motion was corrected, and images were coregistered with individual structural images using the mutual information algorithm, and the images were normalized to Montreal Neurological Institute standard space using the structural information of the T1-weighted MR images. Regions of interest (ROIs) were drawn with Carimas software (version 2.0, Turku PET Centre, Turku, Finland) on the normalized T1-weighted MR images including the ventral striatum, caudate and putamen. The subdivision of the striatum was performed as described my Mawlawi et al.[33] In addition, for [18F]fluorodopa images of PD patients, the putamen was divided into anterior and posterior parts. [18F]fluorodopa uptake (K_i^{ref}) was quantified by applying the Patlak plot to data from 15 to 90 min from the injection using the occipital cortex as the reference region.[34] [11C] raclopride non-displaceable binding potential (BP_{ND}) was calculated using the simplified reference tissue model with cerebellar cortex as the reference region.[35]

Dopamine release was estimated from the change in [11C]raclopride BP_{ND} between the control and gambling task using the formula (2):

$$\Delta BP_{ND} = \left(BP_{ND(control)} - BP_{ND(gambling)}\right)/BP_{ND(control)}\qquad(2)$$

Thus, as [11C]raclopride competes for binding sites with dopamine, positive ΔBP_{ND} were considered to indicate endogenous dopamine release in the corresponding striatal subregion.[36]

Statistical analyses

The normality of the distributions was estimated by visual inspection of the histograms and using Shapiro–Wilk tests. Differences between the groups were analyzed using Student's t-tests or Mann–Whitney U-tests, when appropriate. Within-subject differences were examined using paired t-tests or Wilcoxon signed-rank order tests. The differences in temporal discounting between the reward magnitude categories were tested using Friedman's analysis of variance. The associations between striatal dopamine synthesis capacity and temporal discounting were analyzed with Spearman's rank order correlation coefficients. Group differences in

correlation coefficients were investigated using Fisher's r-to-z transformations, which can also be applied for nonparametric tests. Due to the distribution of temporal discounting k-values and the number of subjects, logistic regression analyses or partial correlation analyses could not be performed. Instead, potential confounding variables were tested using Spearman correlation analyses. The statistical analyses were performed with PASW Statistics (version 19; SPSS, Chicago, IL, USA) and P-values < 0.05 were considered statistically significant.

The issue of multiple comparisons due to several analyzed brain regions was addressed by voxel-wise analyses using Statistical nonParametric Mapping (SnPM5) run in SPM8. The images were smoothed with an 8 mm Gaussian kernel. Simple regression analyses were conducted using 10 mm variance smoothing. The analyses were restricted to the striatum and family-wise error (FWE) corrected P-values < 0.05 were considered statistically significant.

RESULTS

Demographics
The demographic data and discounting rates are presented in Table 1. The temporal discounting rate did not correlate with age, duration of PG, SOGS score or age of PG onset in PG or healthy volunteers. However, in PD patients, temporal discounting correlated with age ($r = -0.68$, $P = 0.003$) and age of PD onset ($r = -0.66$, $P = 0.006$) but not with PD duration, Unified Parkinson's Disease Rating Scale off-motor score, levodopa equivalent daily dose or dopamine agonist levodopa equivalent daily dose. Subject age and age of PD onset were strongly intercorrelated ($r = 0.96$, $P < 0.001$).

[11C]raclopride binding and dopamine release
In Study 1, in the entire sample ($n = 24$), there was a negative correlation between k-value and the bilateral ventral striatum BP_{ND} ($r = -0.44$, $P = 0.03$; Figure 1), which was verified in voxel-wise analyses (FWE corrected $P < 0.05$, cluster extent 34 voxels, peak pseudo-T = 3.58 at -9 15 -9). The correlation was, however, significantly different between groups ($z = 3.36$, $P < 0.001$), and it

was observed in PG ($r = -0.89$, $P < 0.001$) but not in healthy volunteers ($r = 0.15$, $P = 0.65$; Figure 1). Again, the findings were confirmed using voxel-wise analysis revealing a significant cluster in PG but not in healthy volunteers (Figure 2). The BP_{ND} in the right ventral striatum (ipsilateral to the hand controlling the sensorimotor task in all except one subject) was lower compared with the left side (mean (s.d.) 2.15 (0.29) vs 2.37 (0.29), $P < 0.001$). In addition, the caudate BP_{ND} correlation with k-value differed between the groups ($z = 2.15$, $P = 0.03$), but k-value did not correlate with BP_{ND} in either of the groups ($r = -0.46$, $P = 0.13$ in gamblers; and $r = 0.47$, $P = 0.12$ in controls). In the voxel-wise analysis, there was also a correlation in the PG group, but not in the control group, in the left dorsal caudate in addition to the ventral striatum (Figure 2).

Temporal discounting values correlated negatively with high-reward ΔBP_{ND} (that is, the higher the k-value, the lower the dopamine release) in the bilateral ventral striatum over the whole sample ($r = -0.45$, $P = 0.03$). The correlation was observed only in PG ($r = -0.70$, $P = 0.01$; control group $r = -0.01$, $P = 0.98$; Figure 1). However, the difference in correlation coefficients between the groups did not reach statistical significance ($z = 1.84$, $P = 0.07$). There were no correlations between temporal discounting and ΔBP_{ND} in other regions in the high-reward task or any of the ROIs in the low-reward task.

[18F]fluorodopa uptake
In Study 2, there was a positive correlation between k-value and [18F]fluorodopa Ki^{ref} in the left caudate nucleus over the whole sample ($r = 0.64$, $P = 0.005$; Figure 3). The correlation between k-value and [18F]fluorodopa uptake was also significant in the left anterior putamen ($r = 0.51$, $P = 0.04$). There were no correlations between k-value and [18F]fluorodopa uptake in other ROIs. The correlation was verified and spatial extent of the correlation explored using voxel-wise analysis, which revealed significant clusters located in the left dorsal caudate and anterior putamen confirming the ROI findings (Figure 3).

Table 1. Demographics

	PG (n = 12)	Healthy volunteers (n = 12)	P
Age	31.3 (8.2)	30.1 (9.3)	0.73
BMI	27.7 (3.5)	27.3 (3.5)	0.82
k	0.0252 (0.002–0.087)	0.0112 (0.000–0.035)	0.06
Small	0.0651 (0.002–0.159)	0.0256 (0.000–0.065)	0.04
Medium	0.0252 (0.002–0.158)	0.0097 (0.000–0.064)	0.04
Large	0.0098 (0.002–0.026)	0.0068 (0.000–0.026)	0.06

	PD with BA (n = 9)	PD without BA (n = 8)	P
Age	59.3 (8.4)	60.1 (5.9)	0.83
BMI	25.8 (3.7)	27.8 (2.9)	0.25
MMSE	27.6 (2.0)	28 (1.5)	0.62
Age of PD onset	53.1 (8.7)	55.3 (5.1)	0.56
PD duration	6.1 (1.8)	5.1 (2.0)	0.32
UPDRS-III off	38.7 (7.1)	39.8 (9.8)	0.26
UPDRS-III on	31.7 (4.9)	30.1 (10.7)	0.77
LEDD (mg)	628 (186)	762 (269)	0.25
DA LEDD (mg)	173 (80)	216 (67)	0.27
Levodopa use	$n = 8$	$n = 7$	
DA use	$n = 8$	$n = 8$	
k	0.0062 (0.001–0.040)	0.0094 (0.001–0.035)	0.70
Small	0.0256 (0.002–0.101)	0.0177 (0.002–0.065)	0.56
Medium	0.0039 (0.001–0.025)	0.0039 (0.002–0.025)	0.80
Large	0.0039 (0.001–0.026)	0.0098 (0.001–0.026)	0.38

Abbreviations: BA, behavioral addiction; BMI, body mass index; DA, dopamine agonist; k, temporal discounting rate constant; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PG, pathological gambling; UPDRS, Unified Parkinson's Disease Rating Scale. Mean (s.d.) or median (range) values are presented and group differences were tested using Student's t-test or Mann–Whitney U-test, as appropriate.
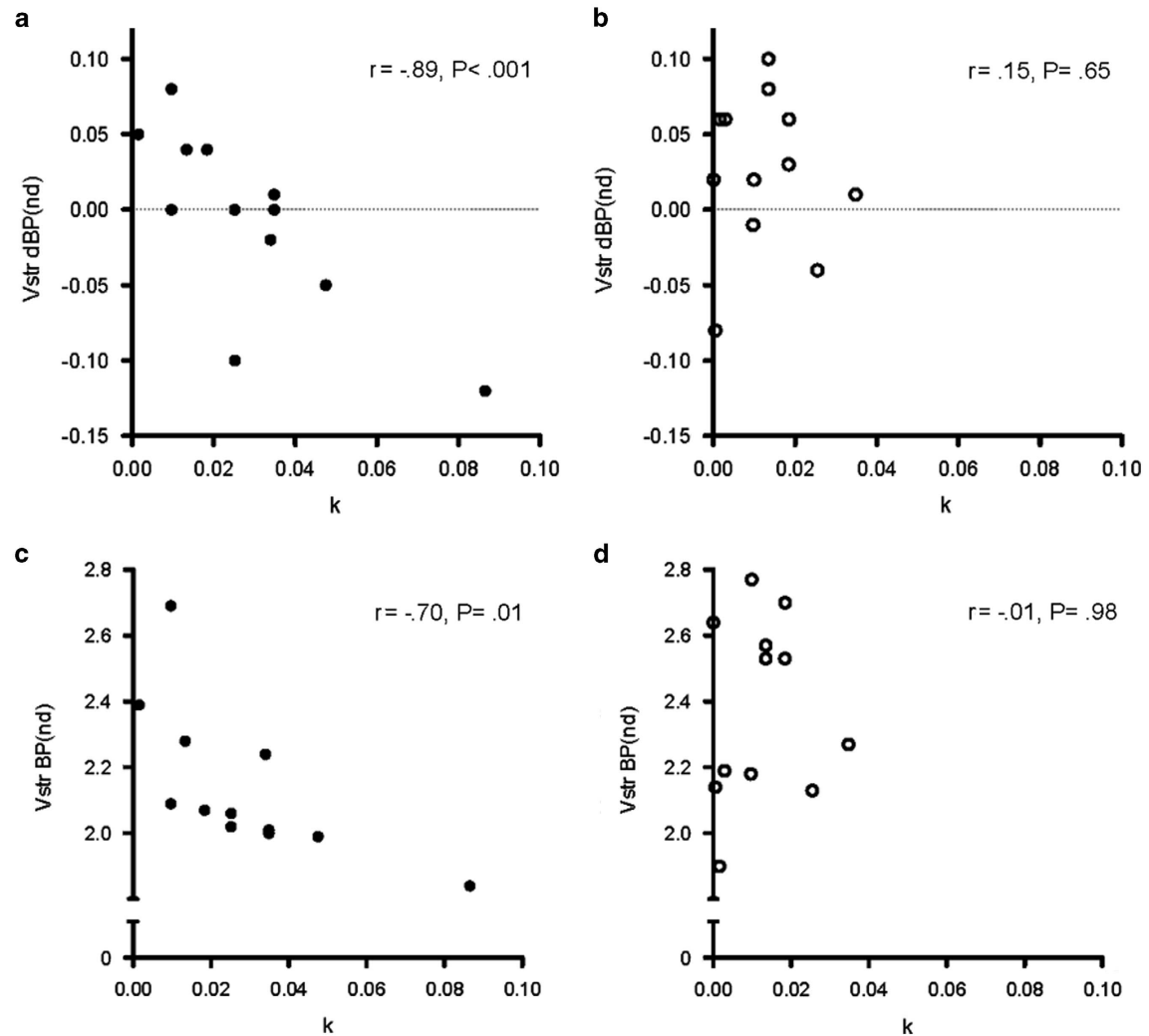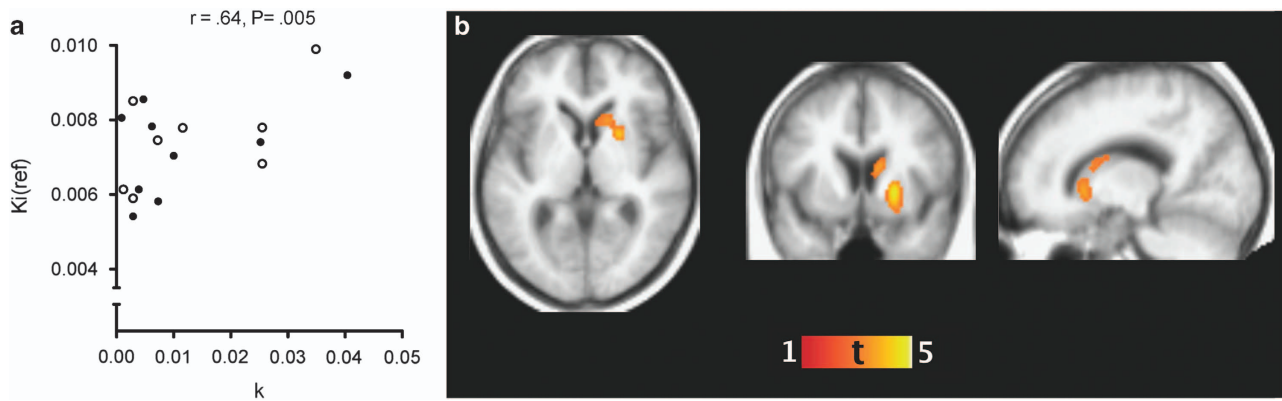
Figure 1. Temporal discounting and dopamine function in the ventral striatum. Spearman nonparametric correlations between temporal discounting rate (k) and dopamine release (Vstr dBP$_{ND}$; positive values indicate dopamine release) in pathological gamblers (**a**) and controls (**b**). Correlations between the baseline ventral striatum D2/D3 availability (Vstr BP$_{ND}$) and k in pathological gamblers (**c**) and controls (**d**). Solid circles represent PG subjects. Open circles represent healthy volunteers. BP$_{ND}$, non-displaceable binding potential; Vstr, ventral striatum; PG, pathological gambling.
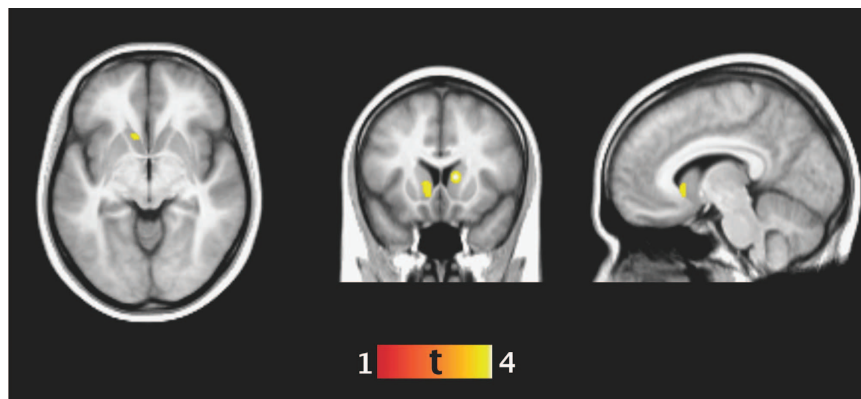
Figure 2. Lower ventral striatal D2/D3 binding associated with higher temporal discounting. The t-values for negative correlation between [11C]raclopride BP$_{ND}$ and overall temporal discounting rate k in PG subjects ($n = 12$) overlaid on the average T1-weighted image of the studied sample in Study 1. The images are thresholded to $P_{FWE} < 0.05$, showing clusters of 147 voxels with peak pseudo-T 4.06 at 12, 15, 7 and 126 voxels with peak pseudo-T 4.03 at − 10 16 − 2. Pseudo-T values are indicated with a red–yellow scale. The images are displayed in radiological convention (that is, the right side of the image corresponds to the left side of the patient) and coordinates are in Montreal Neurological Institute space (mm). BP$_{ND}$, non-displaceable binding potential; FWE, family-wise error.

Figure 3. Higher dorsal striatal dopamine synthesis capacity associated with higher temporal discounting in Parkinson patients. (**a**) The correlation between the left caudate FDOPA uptake (Ki^{ref}) and temporal discounting rate (k). Solid circles represent patients with BAs. Open circles represent patients without BAs. (**b**) The pseudo-T values (red–yellow scale) for positive correlations between FDOPA Ki^{ref} and temporal discounting rate k (peak at 22 30 − 23, cluster size $k = 494$, $P_{FWE} = 0.003$). The image is thresholded to show only clusters with $P_{FWE} < 0.05$. The background image is the average normalized T1-weighted MRI of the subjects in Study 2. The images are displayed in radiological convention (that is, the right side of the image corresponds to the left side of the patient). BA, behavioral addiction; FDOPA, fluorodopa; FWE, family-wise error.

When examining the PD patients with and without BAs separately, the correlation between the left caudate Ki^{ref} and overall temporal discounting was similar in both groups ($r = 0.67$, $P = 0.05$ for patients with and $r = 0.74$, $P = 0.04$ for patients without BAs). In addition, the left anterior putamen Ki^{ref} correlated with k-value in patients with BAs ($r = 0.75$, $P = 0.02$). There were no significant differences in the correlation coefficients between the groups. Correlation analyses were not performed separately by specific BAs due to the low number of patients in these subgroups.

The left hemihere was contralateral to the predominant motor symptoms in 8/17 patients and the k-value did not differ according to the side of the predominant motor symptoms ($P = 0.81$). When examining the effect of PD-related factors on [18F]fluorodopa uptake, Ki^{ref} values correlated with PD duration only in the posterior putamen ($r = −0.65$, $P = 0.007$). Off-medication Unified Parkinson's Disease Rating Scale motor scores did not correlate with striatal [18F]fluorodopa uptake in any of the regions ($P > 0.08$) in the present sample.

DISCUSSION

Converging evidence suggests that temporal discounting is associated with dopaminergic mechanisms. We assessed temporal discounting using two different dopaminergic ligands and three populations in which temporal discounting has been shown to be impaired. Consistent with rodent studies, we showed a relationship between greater temporal discounting and lower ventral striatal D2/D3 receptor density.[28] We further showed a relationship between greater temporal discounting and lower ventral striatal dopamine release as a function of high-reward magnitude in a gambling task, suggesting a role for dopamine-mediated interindividual discounting of delayed rewards in influencing intertemporal choice preference. In contrast, in all PD subjects, higher temporal discounting correlated with greater left caudate dopaminergic terminal function suggesting a role for abnormal dopaminergic dorsal striatal function possibly related to the neuropathology of PD. In PD subjects with BA, higher temporal discounting also correlated with greater left anterior putamen dopaminergic terminal function, suggesting a further engagement of dorsal striatal regions. Our findings can be explained by a U-shaped relationship between temporal discounting and dopamine function.[19]

Ventral striatal D2/D3 receptors

PG subjects, as expected, had greater temporal discounting compared with healthy volunteers.[37] We found that greater temporal discounting correlated with lower ventral striatal [11C] raclopride binding potential during the motor control task across all the subjects. We suggest that this may reflect lower D2/D3 receptor density at baseline rather than greater presynaptic dopamine release at baseline or to a simple motor task. As the right ventral striatal binding potentials were lower compared with left and all but one of the subjects used their right hand for motor responses, it is highly unlikely that the findings were related to motor activation during a simple control task. In rodent studies, premature responding (responding before target onset) is correlated with delay discounting.[27] Premature responding (and delay discounting) is associated with lower [18F]fallypride binding potential in the nucleus accumbens but not with changes in dopamine metabolites, indicating a specific relationship with lower D2/D3 receptors rather than presynaptic dopamine release.[28] Given the relationship between premature responding and delay discounting, our findings in humans provide translational support for the preclinical findings. A questionnaire-based subtype of impulsivity, specifically the factor of mood-related 'urgency', has also been shown to be negatively correlated with striatal D2/D3 receptor availability in PG.[38] Similarly, questionnaire-based impulsivity was associated with lower striatal midbrain D2/D3 receptors in healthy volunteers.[39] Our study extends these findings to a form of decisional impulsivity.

Ventral striatal presynaptic dopamine release

We also showed that across all subjects greater temporal discounting correlated with lower ventral striatal dopamine release to a simulated gambling task to high but not low-reward magnitude. Temporal discounting can be parcellated into several cognitive mechanisms including but not limited to the incentive salience of the immediate choice, the discounting effects of the delay, the uncertainty of the delayed choice or decreasing subjective valuation of increasing magnitude.[2,40] The fact that the findings are specific to the anticipation and receipt of a high but not low-reward magnitude is argumentative against an effect of uncertainty, cue conditioning (as a function of the gambling task design) or motor response, all of which were equal across high and low magnitude conditions.

Lesions of the rodent nucleus accumbens core, amygdala and hippocampus increase impulsive choice, suggesting that these

structures are critical to the evaluative process.[12,41,42] In human functional magnetic resonance imaging studies, the ventral striatum, prefrontal cortex, insula, amygdala, posterior cingulate and parietal cortex have been implicated in intertemporal choice for secondary[43–46] and primary rewards.[47] The ventral striatum is a key structure implicated in valuation theories of temporal discounting. The ventral striatum and medial prefrontal cortex have been implicated in overvaluing immediate reward choice, whereas lateral prefrontal and parietal cortices are activated across all decisions.[46] Delay has been suggested to be coded in the lateral prefrontal cortex and magnitude coded in the ventral striatum.[43] In contrast, the ventral striatum has also been suggested to represent the subjective value of the delayed choice.[45] Along these lines, single-unit striatal recordings of cue-predicting rewards in primates show that dopaminergic neuronal activity both increases monotonically with magnitude and decreases with delay, reflecting the subjective devaluation of the delayed reward.[11] Our findings suggest that ventral striatal dopaminergic activity may reflect choice preference and encode the devalued delayed reward. Were this to represent the incentive value of the immediate reward, one might anticipate the opposite correlation with increased temporal discounting and increased dopaminergic activity representing enhanced incentive value of the immediate reward. We speculate that the relationship between dopaminergic activity and temporal discounting may be driven by the enhanced ventral striatal discounting of delayed rewards.

Our findings are consistent with preclinical studies on endogenous dopamine activity showing that greater temporal discounting is associated with lower dopamine reactivity in the nucleus accumbens core and shell[3] and that single-unit striatal recordings encode the subjective devaluation of a delayed reward.[11] These findings suggest that interindividual endogenous dopamine release to delayed high-reward magnitude may influence choice preference for intertemporal choices. In contrast, exogenous administration of dopaminergic agents presents a mixed picture, with low and moderate doses of amphetamine decreasing impulsive choice in rodents[13–15] but high chronic doses of stimulants increasing impulsive choice.[14,16] Exogenous levodopa in healthy humans increases impulsive choice.[17] In healthy humans, questionnaire-based impulsivity is associated with enhanced amphetamine-induced striatal dopamine release.[39] These inconsistent findings may be related to dose differences, with a U-shaped relationship between dopamine activity and temporal discounting.[19]

Dorsal striatal dopamine function

Using [18F]fluorodopa PET, we further showed that greater temporal discounting is associated with greater left caudate dopaminergic terminal function in PD patients with and without BA. The fact that PD has been associated with temporal discounting irrespective of dopaminergic medication status[6,7] suggests that the neuropathology of PD affecting dorsal striatal functioning might have a role in temporal discounting. In line with this, caudate activity has been associated with greater temporal discounting in healthy volunteers.[48,49] In addition, in PD patients, levodopa administration has been shown to change their betting strategies to more impulsive and dopamine agonists increase impulsive choice rather than diminish behavioral control.[18,50] In PD subjects and healthy controls, the caudate is anatomically connected to the lateral prefrontal cortex.[51] The dorsolateral prefrontal cortex (DLPFC) is implicated in temporal discounting, particularly in the representation of the delay.[43,46] Studies using low-frequency repetitive transcranial magnetic stimulation (rTMS), which inhibits cortical excitability, show that disruption of the left, but not right DLPFC increases choice preference for the immediate reward but does not affect valuation processes.[52]

Similarly, in smokers, high frequency repetitive transcranial magnetic stimulation to increase left DLPFC activity was associated with greater preference for the delayed reward.[53] Repetitive transcranial magnetic stimulation inhibition of the left DLPFC is associated with caudate dopamine release in depressed patients[54] and healthy volunteers.[55] Our findings being lateralized to the left caudate dovetails with these reports, suggesting that inhibition of left DLPFC activity via stimulation may increase preference for the immediate reward possibly by increasing downstream left caudate dopaminergic function.

In our study, greater temporal discounting was also associated with greater presynaptic dopaminergic availability in the left anterior putamen in PD patients with BA but not in those without BA. We have previously shown in this same population that PD subjects with and without BAs exhibited no differences in striatal presynaptic dopaminergic function.[26] In PD subjects and healthy controls, the anterior putamen is functionally connected to the pre-supplementary motor area.[51] An imbalance in dopaminergic function in associative, relative to motor, striatal regions may contribute to the emergence of BAs.

Limitations

We did not compare PG patients using [18F]fluorodopa or PD patients using [11C]raclopride. The study was also limited by relatively small sample size and lack of healthy volunteer group matched to PD patients. Several correlation analyses with multiple ROIs were performed, which might increase the type I error rate. However, the issue of multiple comparisons was stringently addressed in the voxel-wise analyses by using family-wise error correction.

Conclusions

Our results support the concept of a U-shaped relationship between striatal dopaminergic function and intertemporal choice and provide insight into its potential role in pathological disorders and the mechanisms underlying treatment interventions.

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