Published in final edited form as:

Neurosci Lett. 2016 March 23; 617: 27–31. doi:10.1016/j.neulet.2016.01.056.

Socioeconomic status is associated with striatal dopamine D2/D3 receptors in healthy volunteers but not in cocaine abusers

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Abstract

Positron emission tomography (PET) studies in animals and humans have shown that social status is associated with striatal dopamine D2/D3 receptor (D2/D3R) availability. That is, higher social hierarchy and higher scores on questionnaires assessing social status correlated positively with striatal D2/D3R availability in animals and humans respectively. Furthermore, subordinate monkeys were vulnerable to cocaine self-administration, suggesting that alternations in social hierarchy can change D2/D3R availability and vulnerability to cocaine use. Here, we investigated whether socioeconomic status (SES) measured with the Hollingshead scale is associated with striatal D2D/3R availability using [¹¹C]raclopride PET in 38 cocaine abusers and 42 healthy controls matched for age and education. Compared to controls, cocaine abusers showed lower D2/D3R availability in the caudate, putamen and ventral striatum (all $p < .001$). Despite matching groups for education, SES scores were lower in cocaine abusers than controls ($p < .001$). In the control group only, SES scores significantly correlated with D2/D3R in caudate ($r = .35$, $p = .024$) and putamen ($r = .39$, $p = .011$) but not in ventral striatum ($p = .61$); all corrected for age. The study confirms that SES is associated with striatal D2/D3R availability in healthy human volunteers. However, reductions in D2/D3R availability in cocaine abusers may be driven by factors other than SES such as chronic cocaine exposure.

Keywords

Cocaine; dopamine; PET; socioeconomic status; striatum

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Conflicts of interest

None

Introduction

Animal studies have shown associations between social status and dopamine D2/D3 receptor (D2/D3R) availability in the striatum. That is, dominant monkeys [5, 16] and rats [8] revealed higher striatal D2/D3R availability than subordinate ones. Reductions in striatal D2/D3R have been implicated in the vulnerability for compulsive drug taking in addiction [30], and environment-induced changes in social status in monkeys made subordinate monkeys more vulnerable to the reinforcing effects of cocaine than dominant ones [16].

In humans it has been shown that social status measured on the Barratt Simplified Measure of Social Status (BSMSS) and social support assessed with the Multidimensional Scale of Perceived Social Support (MSPSS) correlated with striatal D2/D3R in 14 healthy volunteers using positron emission tomography (PET) and the radiotracer [^{11}C]raclopride [13]. However, a recent study in 16 healthy volunteers using the radiotracer [^{11}C](+)PHNO found inverse associations between BSMSS and D2/D3R availability in the ventral striatum and substantia nigra/ventral tegmental area [14]. The study furthermore investigated 16 cocaine abusers, and found a negative correlation between social status and D2/D3R in these areas, as well as in the amygdala [14]. The discrepancy in the direction of the association between D2/D3R and social status in these studies may be due to the difference in radiotracers used: while Martinez, et al. [13] measured striatal D2/D3R with [^{11}C]raclopride which has equivalent affinity for D2R and D3R, the PHNO tracer used by Matuskey, et al. [14] has a 20–100 times higher affinity for D3R than D2R and its binding is more sensitive to competition with endogenous dopamine than that of [^{11}C]raclopride.

The first goal of the present study was to replicate the finding of Martinez, et al. [13] that D2/D3R and social status are positively associated in a larger sample of 42 healthy volunteers when measured with PET and [^{11}C]raclopride. For social status we used the Hollingshead scale of socioeconomic status (SES), which is one of the most widely used and cited measures of SES [2]. The second goal was to investigate whether SES was associated with striatal D2/D3R availability in cocaine abusers for which we studied 38 active cocaine abusers who were imaged with PET and [^{11}C]raclopride. We hypothesized positive associations between striatal D2/D3R availability in the healthy and cocaine abusing group.

Material and methods

Participants

Data on SES and PET [^{11}C]raclopride images of 42 controls (4 females) and 38 cocaine abusers (4 females) were acquired as part of previous studies at Brookhaven National Laboratory that measured differences in D2/D3R striatal availability between active cocaine abusers and controls. The main findings from these studies have been reported [22, 27].

Groups were matched for age, education (see Table 1) and gender ($\chi^2=.88$, $p=.59$). There were more smokers among cocaine abusers (30 smokers, 8 non-smokers) than in the control group (8 smokers, 34 non-smokers) ($\chi^2=28.7$ $p<.0001$).

SES assessment

SES was calculated according to the Hollingshead scale, based on a community-based epidemiological study [6]. The SES score is derived from both an Education score (ranging from 1 [i.e., less than 7th grade education] to 7 [i.e., graduate school or professional training]) and an Occupation score ranging from 1 [i.e., menial labor] to 9 [i.e., higher executives, major professionals, large business owners]). SES was then calculated as $([\text{Occupation score} \times 5] + [\text{Education score} \times 3])$, ranging from 8–66, with higher scores reflecting higher SES.

PET imaging, processing and analyses

All [¹¹C]raclopride scans were performed on a Siemens, HR+ scanner (resolution $4.5 \times 4.5 \times 4.5$ mm full width half-maximum, 63 slices) at the BNL PET Imaging Center. The procedures for subjects positioning and scanning protocols have been described previously [25, 28]. In short, emission scans were started immediately after injection of 4–8 mCi (specific activity 0.5–1.5 Ci/ μ M at end of bombardment or EOB). Twenty dynamic emission scans were obtained from time of injection up to 60 min and arterial sampling was used to quantify total carbon-11 and unchanged [¹¹C]raclopride in plasma.

We calculated regional Bmax/KD values for hand-drawn caudate, putamen and ventral striatum (VS) regions of interest (ROIs) using a procedure previously described [29]. ROIs had the same size and shape across subjects. The ratio of the distribution volume in striatal regions was computed to that in the cerebellum to obtain the non-displaceable binding potential (BP_{ND}), which was used as a quantification of D2/D3R availability and corresponds to $B_{\text{max}}/K_d - 1$ [11].

Statistical analyses

Correlations between SES and D2/D3R availability in the caudate, putamen and VS were performed with two-tailed partial correlations using SPSS 22 (IBM, Armonk, New York). Age was included as a covariate, because D2/D2R in all three striatal regions correlated negatively with age (caudate $p=.044$; putamen $p=.018$; VS $p=.055$), which is consistent with previous findings [7, 9, 26].

Since education alone has been shown to correlate with D2/D3R availability in healthy volunteers [13], we also performed exploratory analyses on the relationship between years of education and striatal D2/D3R availability.

Results

SES scores and D2/D3R availability measures were normally distributed in both groups (Kolmogorov–Smirnov tests $p>.16$). Despite matching for education, both SES and IQ scores were lower in cocaine abusers than controls ($p=.003$; see Table 1).

Compared to controls, cocaine abusers showed lower D2/D3R availability in the caudate, putamen and VS (all $p<.001$, see Table 1 and Figure 1). Group differences remained when correcting for smoking status (caudate $p=.002$, putamen and VS $p<.001$).

In healthy volunteers, SES correlated significantly with D2/D3R availability in caudate ($r=.352$, $p=.024$) and putamen ($r=.393$, $p=.011$) but not in VS ($p=.61$) (See Figure 2). However, there were no associations between SES and D2/D3R availability in the group of cocaine abusers in any striatal region ($p>.84$).

Education alone did not correlate with striatal D2/D3R availability in either group ($p>.19$).

Discussion

The study confirms that SES is positively associated with striatal D2/D3R availability in healthy human volunteers. This is in accordance with a previous report that found a positive association between social status and striatal D2/D3R in a smaller sample of 14 healthy human volunteers using [^{11}C]raclopride, and also with pre-clinical findings that socially higher-ranking cynomolgus monkeys [5, 16] and rats [8] have higher levels of D2/D3Rs than subordinate ones. In line with these findings, striatal D2/D3R availability has also been shown to be lower in patients with social anxiety disorder [measured with [(123)I]IBZM SPECT; 20, 21], which correlated with social detachment personality scores (Karolinska Scales of Personality) in these patients [21] as well as in healthy volunteers [with [^{11}C]raclopride; 1, 3].

While social status and social interactions were measured using the BSMSS and MSPSS respectively in previous studies [13], the current study is the first to show an association between striatal D2/D3R and SES measures with the Hollingshead scale, which is one of the most widely-used measures of SES [2]. The scale provides a measure of SES based on both occupation and level of education, whereas the before-mentioned scales were based solely on social factors. Interestingly, education alone was associated with D2/D3R in normal volunteers in Martinez, et al. [13], but not in the current sample. In addition, exploratory analyses showed that the correlation between SES and D2/D3R availability in caudate and putamen became slightly weaker (but remained significant at the $p<.05$ level) if correcting for education, which further strengthens the importance of occupational status in the relationship between SES and D2/D3R. Occupational status will influence not just the economic status of the individual but also their social status and life styles [10].

The second goal of the study was to investigate whether there was a positive relationship between SES and D2/D3R in cocaine abusers. This hypothesis was based on monkey studies that showed that lower D2/D3R binding in monkeys with low social hierarchical status predicted increases in cocaine self-administration [16]. However, a recent study in rats found that dominant rats (with higher D2/D3R levels) maintained higher rates of cocaine self-administration than subordinate ones [8]. Here, we found that cocaine abusers showed lower D2/D3R availability in caudate, putamen and VS compared to controls, which is a consistent finding in cocaine and other drug abusers [e.g., 12, 23, 30]. Despite matching groups for education, SES scores were lower in cocaine abusers than controls, which has been reported before [32]. Contrary to our hypotheses and findings in the control group, however, there was no correlation between SES and striatal D2/D3R in cocaine abusers. Therefore, the reductions in D2/D3R availability consistently found in cocaine abusers may

be driven by factors other than SES, most notable having prior histories of chronic cocaine exposures which can lead to downregulation of D2/D3R [18, 24].

The lack of an effect of social status in D2/D3R availability in cocaine abusers differs from recent findings from a PET study that used the D3R preferring radioligand PHNO that documented an inverse relationship between social status (BSMSS score) and D3R in the VS, as well as in amygdala and midbrain in cocaine abusers [14]. This discrepancy may reflect the difference in the radioligands; for PHNO binding in VS is largely driven by D3R whereas binding of [¹¹C]raclopride reflects both D2R and D3R. In line with this, the binding potential of these tracers show opposite effects in cocaine abusers: while [¹¹C]raclopride binding potential is decreased in cocaine abusers versus controls [12, 30], PHNO binding has been found to be elevated [15, 19]. Since DA release is markedly reduced in cocaine abusers [27] and PHNO is more sensitive to competition with endogenous DA than [¹¹C]raclopride [4], this could lead to reduced competition from endogenous DA in PHNO binding and hence increased binding in cocaine abusers.

Despite matching for education, both groups were not matched for SES. Means and variance of both striatal D2/D3R and SES were therefore significantly lower in the group of cocaine abusers than in controls, which might have limited the likelihood of finding a correlation between these variables in the cocaine abusers. Another limitation is that we used only one measure of SES, the Hollingshead index, to study the association with striatal D2/D3R availability. Future studies with multiple measures of social status, SES and personality scores may help clarify which factor contributes the most to D2/D3R availability. Further, groups were matched for gender, but with the limited number of females (4 in each group), it was not possible to investigate whether the correlations are present in both genders. Previous exploratory analyses of Martinez, et al. [13] suggest, however, no significant gender effects on striatal D2/D3R and social status in healthy volunteers.

In sum, the study shows that SES is associated with striatal D2/D3R availability in healthy human volunteers, but not in cocaine abusers. Since monkey studies have shown that striatal D2/D3 receptor binding can be changed by environmental factors in social hierarchy [16] (though see [17] suggesting that after differences in D2/D3R binding due to social status have been established, this cannot be changed anymore), future studies in humans investigating whether changes in SES covary with changes in striatal D2/D3R availability are relevant for prevention interventions towards improving health outcomes in individuals who are socially deprived.

Acknowledgments

The work was supported by the National Institutes of Health Intramural Research Program. CEW received a scholarship from the German Research Foundation (DFG).

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Highlights

- Socioeconomic status scores of healthy human volunteers correlated positively with striatal dopamine D2/D3 receptor (D2/D3R) availability in the caudate and putamen
- Cocaine abusers showed lower D2/D3R availability in the caudate, putamen and ventral striatum than healthy controls
- Despite matching groups for education, SES scores were lower in cocaine abusers than in controls
- There was no association between socioeconomic status and D2/D3R availability in cocaine abusers, suggesting that the effects of chronic cocaine on D2/D3R override changes from SES

Figure 1.

Dopamine D2/D3 receptor availability in the striatum was lower in cocaine abusers than controls (peak left = $[-26, 6, -10]$, $t=4.13$, $p=.003$; peak right = $[28, 10, -8]$, $t=3.64$, $p=.031$; family-wise error corrected and small-volume corrected for the striatum using a $[^{11}\text{C}]\text{raclopride}$ striatal mask [31]). Activations are shown at $p<.005$ uncorrected. Extracted $[^{11}\text{C}]\text{raclopride}$ in non displaceable binding potentials (BP_{ND}) in the ROIs caudate, putamen and ventral striatum were lower in cocaine abusers than controls (all $p<.001$).

Figure 2.

SES correlated significantly with D2/D3R availability (BP_{ND}) in the caudate ($r = .352, p = .024$) and putamen ($r = .393, p = .011$) but not in the VS ($p = .61$) in healthy volunteers. There were no significant correlations for SES and D2/D3R availability in the group of cocaine abusers in any striatal region ($p > .84$).

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Demographics, clinical characteristics and striatal D2/D3R availability for controls and cocaine abusers. Measures of D2/D3R availability correspond to non-displaceable binding potential (BP_{ND}).

Table 1

Characteristic	Cocaine abusers, N=38		Healthy Control, N=42		p-value
	Mean	SD	Mean	SD	
Age, years	43.86	4.50	42.17	4.54	.10
Years of education	12.95	4.45	14.24	1.85	.90
Full Scale IQ score	92.11 ^a	5.17	95.53 ^b	4.17	.003
BMI	25.95	4.74	26.45	2.78	.57
SES	27.57	10.89	39.32	13.20	<.0001
Cigarette years	24.97 ^c	7.87	13.54 ^d	10.39	.003
Cig # average	6.29	5.01	.90	2.41	<.0001
Cocaine use (g/day)	3.31	2.41	-	-	-
Cocaine use (years)	17.47	7.31	-	-	-
D2/D3R Caudate	2.07	.46	2.42	.47	.001
D2/D3R Putamen	2.48	.53	3.03	.49	<.0001
D2/D3R VS [§]	2.17	.62	2.83	.40	<.0001
BDI	9.00 ^e	9.90	2.34 ^f	3.25	<.0001

Abbreviations: BDI = Beck's depression inventory; BMI = body mass index, D2/D3R = Dopamine D2/D3 receptor availability, SES = socioeconomic status VS = ventral striatum

[§] In VS [¹¹C]raclopride reflects binding to both D2R and D3R whereas in caudate and putamen it largely reflects binding to D2R

^a N=34

^b N=39

^c N=28

^d N=7

^e N=37

^f N=41