Dopamine Type 2/3 Receptor Availability in the Striatum and Social Status in Human Volunteers

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Background: Previous positron emission tomography (PET) imaging studies in nonhuman primates have shown that striatal dopamine type 2/3 ($D_{2/3}$) receptors correlate with social hierarchy in monkeys and that dominant animals exhibit higher levels of $D_{2/3}$ receptor binding. The goal of the present study was to examine this phenomena in human subjects using PET and the radiotracer [^{11}C]raclopride.

Methods: Fourteen healthy volunteers were scanned with [^{11}C]raclopride to measure $D_{2/3}$ receptor binding potential (BP). Social status was assessed using the Barratt Simplified Measure of Social Status. In addition, participants were asked to assess their level of social support using the Multidimensional Scale of Perceived Social Support (MSPSS).

Results: A correlation was seen between social status and dopamine $D_{2/3}$ receptors, where volunteers with the higher status had higher values for [^{11}C]raclopride BP. A similar correlation was seen with the perceived social support, where higher [^{11}C]raclopride BP correlated with higher scores on the MSPSS.

Conclusions: The results of this study support the hypothesis that social status and social support is correlated with $D_{2/3}$ receptor binding.

Key Words: [^{11}C]raclopride, dopamine 2/3 receptor, PET imaging, social status

Previous studies in animals have shown a correlation between dopamine transmission in the brain and social hierarchy (1). In monkeys, dominant and subordinate social rank are determined by physical and social triumph and defeat. Dominant animals win more physical confrontations and receive more social attention, such as grooming or huddling. Two positron emission tomography (PET) imaging studies have investigated the relationship between social status and $D_{2/3}$ receptors in the striatum in monkeys. Both showed that social dominance was associated with higher $D_{2/3}$ receptor binding compared with subordinate animals (2,3).

In humans, social hierarchy is a more subtle phenomenon that can be approximated by measuring social status and social support (4). Thus, the goal of the present study was to examine the correlation between these factors and dopamine $D_{2/3}$ receptor binding in human subjects. Given the known effect of disease states on striatal $D_{2/3}$ receptors, including substance dependence, schizophrenia, and anxiety disorders (5–7), only healthy control volunteers were included in this study. Social status was measured using the Barratt Simplified Measure of Social Status (BMSSS) (8) and social support was measured using the Multidimensional Scale of Perceived Social Support (MSPSS) (9). Our hypothesis was that low social status and low levels of social support would correlate with low $D_{2/3}$ receptor binding in the striatum measured with [^{11}C]raclopride.

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Methods and Materials

The study was approved by the Institutional Review Board of the New York State Psychiatric Institute and all subjects provided written informed consent. Study participants were nonsmoking healthy control subjects and were required to have no DSM-IV Axis I disorder (including substance abuse or dependence), no significant medical conditions, and no use of medications before the scan (6 months for medications that could affect dopamine, 2 weeks for all others). Subjects (nine men and five women) were recruited from the New York City metropolitan area. Participant screening included a psychiatric assessment with the *Structured Clinical Interview for DSM-IV Axis I Disorders* (10), physical examination, electrocardiogram, and laboratory tests. All subjects were asked for data to complete the Barratt Simplified Measure of Social Status and to complete the Multidimensional Scale of Perceived Social Support. The scans performed on female subjects were not controlled for menstrual cycle phase.

[^{11}C]raclopride was prepared as previously described (11), and PET studies were acquired using a bolus injection of the radiotracer. The PET scans were obtained on the ECAT EXACT HR+ (Siemens/CTI, Knoxville, Tennessee) in three-dimensional (3-D) mode. Emission data were obtained as 15 frames of increasing duration up to 60 minutes. The PET images were reconstructed by filtered backprojection (Shepp .5 filter) with attenuation correction using the data from a 10-minute transmission scan.

All image analysis was performed in MEDx (Sensor Systems, Inc, Sterling, Virginia). Each subject underwent a transaxial T1 magnetic resonance imaging (MRI) scan, acquired on the GE Signa EXCITE 3 T/94 cm scanner (GE Medical Systems, Milwaukee, Wisconsin), for delineation of the regions of interest (ROIs). The regions of interest outlined on the MRI included the subdivisions of the striatum, which have been previously described (12). Briefly, these included the ventral striatum (VST), the dorsal caudate rostral to the anterior commissure (AC) (precommissural dorsal caudate [preDCA]), the dorsal putamen rostral to the AC (precommissural dorsal putamen [preDPU]), the caudate caudal to the AC (postcommissural caudate [postCAU]), and the putamen caudal to the AC (postcommissural putamen [postPUT]).

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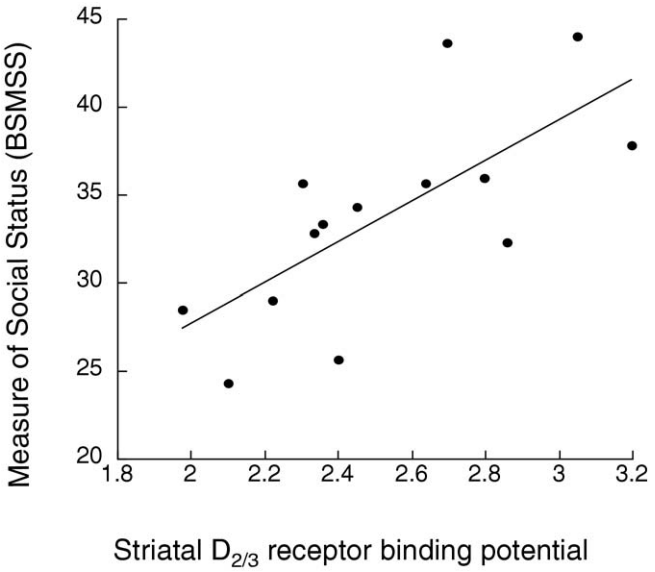

Figure 1. Correlation between [^{11}C]raclopride BP (x axis) and social status, measured with the Barratt Simplified Measure of Social Status (BSMSS). A positive correlation was seen, where higher BP correlated with higher BSMSS ($r = .71$, $p = .004$, age-corrected $p = .007$). BP, binding potential.

The subdivisions were derived based on their cortical and subcortical connections, as described previously (12).

The PET scans were registered to the MRI scans in MEDx (Sensor Systems, Inc) as previously published (11,13). The activity measured in the left and right regions were averaged. The activity in the striatum as a whole (STR) was derived as the spatially weighted average of the five ROIs.

The simplified reference tissue model (SRTM) (14) was used for derivation of the binding potential (BP) implemented in MATLAB (The Math Works, Inc., South Natick, Massachusetts), using the cerebellum as the reference region. The outcome measure for the PET studies was binding potential, defined as the ratio of specifically bound to nondisplaceable radioligand at equilibrium (BP_{ND}) (15). BP_{ND} can also be described as

$$BP_{ND} = f_{ND} * \frac{B_{MAX}}{K_D}$$

where B_{max}. is the concentration of $D_{2/3}$ receptors, K_D is the inverse of the affinity of the radiotracer for the receptor, and fND is the free fraction in the nonspecific distribution volume of the brain (16). [^{11}C]raclopride has a similar affinity for D2 and D3 receptors (17), and the signal from these receptors cannot be distinguished.

Relationships between BP_{ND} and the scores on the BSMSS and MSPSS were analyzed with the Pearson product-moment correlation coefficient. A two-tailed probability value of $p < .05$ was chosen as the level of significance. Since age is known to affect $D_{2/3}$ receptor BP, this factor was included in the regression analysis. Given that previous studies had shown a correlation between social status and the striatum measured as a whole (2,3), there were no specific hypotheses regarding the striatal subregions. Therefore, the primary analysis was restricted to the striatum, with post hoc analyses of the individual subregions.

Results

The research volunteers included nine men and five women with an average age of 30 ± 4 years (range 25–37). The average BSMSS score was 33.2 ± 4.8 (range 24.3–44.0). One subject declined to complete the MSPSS. The average MSPSS score was 19.0 ± 9.5 (range 11.5–20.8). The average decay-corrected injected dose was 439.9 ± 42 MBq and the average specific activity was 579.6 ± 21.7 GBq/mmol.

A positive correlation was seen between [^{11}C]raclopride BP_{ND} and social status for the striatum ($r = .71$, $p = .004$, age-corrected $p = .007$), as shown in Figure 1. A post hoc analysis was performed with the striatal subregions, and a positive correlation was seen in the ventral striatum ($r = .73$, $p = .003$, age-corrected $p = .004$), precommissural caudate ($r = .63$, $p = .015$, age-corrected $p = .018$), and postcommissural putamen ($r = .85$, $p = .001$, age-corrected $p = .003$). Correlations did not reach significance in the precommissural putamen ($r = .48$, $p = .08$) or postcommissural caudate ($r = .20$, $p = .5$).

A positive correlation was seen between [^{11}C]raclopride BP_{ND} and the MSPSS for the striatum ($r = .73$, $p = .005$, age-corrected $p = .02$), as shown in Figure 2. A post hoc analysis was performed with the striatal subregions, and a positive correlation was seen in the ventral striatum ($r = .63$, $p = .02$, age-corrected $p = .05$), precommissural putamen ($r = .78$, $p = .002$, age-corrected $p = .09$), precommissural caudate ($r = .67$, $p = .02$, age-corrected $p = .05$), and postcommissural putamen ($r = .55$, $p = .05$, age-corrected $p = .15$). Correlation did not reach significance in the postcommissural caudate ($r = .28$, $p = .35$). Thus, within the subdivisions of the striatum, this correlation was seen in most, but not all, of the subdivisions. A correlation was seen between the BSMSS and MSPSS ($r = .53$, $p = .05$), showing that these are scales that measure factors that are related, but not identical.

Discussion

In this study, a positive correlation was seen between $D_{2/3}$ receptor binding potential and measures of social status and

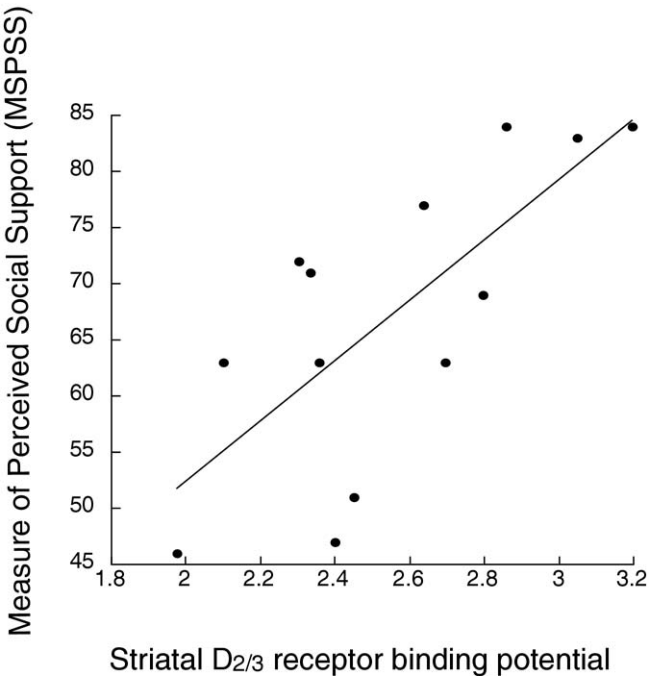

Figure 2. Correlation between [^{11}C]raclopride BP (x axis) and score on the Multidimensional Scale of Perceived Social Support (MSPSS). A positive correlation was seen, where higher BP correlated with higher score on the MSPSS ($r = .73$, $p = .005$, age-corrected $p = .02$). BP, binding potential.

perceived social support. These results are similar to those reported previously in nonhuman primates, which showed that striatal $D_{2/3}$ receptors were higher in rhesus monkeys who were dominant in a social hierarchy compared with subordinate monkeys (2,3). However, to our knowledge, this is a first demonstration of this type of association in human volunteers.

Striatal $D_{2/3}$ receptor availability has also been shown to correlate with measures of social detachment in healthy human volunteers and is low in patients with social phobia (7,18–20). These studies have shown that low $D_{2/3}$ receptor availability is associated with personal detachment and aloofness, measured with the detachment subscale of the Karolinska Scales of Personality. In the present study, we found a correlation with the volunteer's score on the Multidimensional Scale of Perceived Social Support (9), a scale that assesses three sources of social support: family, friends, and significant other. While the MSPSS and the detachment subscale of the Karolinska Scales of Personality ask about different aspects of social behavior, they can both be viewed as measuring the extent of social interaction. Taken together, these data suggest that striatal $D_{2/3}$ receptor binding is associated with an individual's social capital, which can be thought of as a balance of social rank and stress offset by social support and attachment (21). Overall, these data suggest that higher social status, a greater sense of perceived social support, and lower levels of social avoidance are associated with higher $D_{2/3}$ receptor binding.

The study in nonhuman primates by Morgan *et al.* (2) showed that $D_{2/3}$ receptor binding was modulated by the environment. In that study, $D_{2/3}$ receptors did not differ between the animals before the establishment of a social hierarchy, but once the social structure was established, the animals that became dominant developed higher $D_{2/3}$ receptor binding. At this point, it is unknown if $D_{2/3}$ receptor binding in human beings can be modulated by changes in the environment. Nader *et al.* (22) recently reported that rearrangement of the social hierarchy, such that some previously subordinate monkeys became dominant (and some dominant became subordinate) did not produce significant differences in $D_{2/3}$ receptor binding, suggesting that this neurobiological marker, once established, may become unchangeable.

A number of previous studies have investigated the behavioral significance of high and low striatal $D_{2/3}$ receptor availability in humans. This has been of particular interest to the field, given that low $D_{2/3}$ receptor BP is the most replicated finding in imaging studies of drug and alcohol addiction (for review see [6]). In addition, the study of rhesus monkeys showed that low $D_{2/3}$ receptor binding predicted increased cocaine self-administration (2) and similar results have been shown in rodents (23). Taken together, these data suggest that $D_{2/3}$ receptor binding may provide a molecular marker that reflects the interaction between genes and environment and the predisposition to drug abuse (24).

A potential significant limitation of this study is the use of the BSMSS, which provides an estimate of social status across society but does not provide an accurate measure of social prominence with respect to one's peers or a measure of socioeconomic status. However, while there is a clear consensus in the literature regarding the importance of these factors on health and disease, there is a lack of consensus of how to measure social status. Many studies investigating the effects of social status on health have used the Hollingshead (25) index, which provides a composite score of social status based on the subject's occupation and level of education. However, this scale uses a list of occupations generated from the 1970 census data, and many of our subjects' occupations were not included in this list. The BSMSS is based on the Hollingshead (25) scale, in that it generates a composite score based on level of education and occupation but uses an updated list of occupations. In addition, the BSMSS includes the education/occupation scores of the subjects' parents, which are weighted to a lesser degree that the subjects' own educational and occupational achievement, recognizing that social status is partly determined by the opportunities provided by one's background. Another more simple determination of social status that is sometimes used is years of education. In this dataset, a post hoc analysis of years of education and [^{11}C]raclopride binding in the striatum also showed a significant positive correlation ($r = .54$, $p = .04$), suggesting that this correlation was not simply a function of error within the BSMSS.

Other potential limitations include the fact that baseline measures of $D_{2/3}$ receptor binding potential do not account for occupancy of the receptor by endogenous dopamine, and studies using the acute depletion of dopamine would be needed to answer this question. Another potential limitation of the present study is the possibility of gender differences. This study included only five females, which does not allow a full analysis of the effects of gender. However, a post hoc analysis of the correlation between BSMSS and MSPSS and BP_{ND} within each sex showed that the correlation was not gender-specific; male subjects: 1) BSMSS and BP_{ND} $r = .69$, $p = .04$; and 2) MSPSS and BP_{ND} $r = .81$, $p = .01$; female subjects: 1) BSMSS and BP_{ND} $r = .74$, $p = .18$; and 2) MSPSS and BP_{ND} $r = .99$, $p = .005$). In addition, the scans obtained in the female participants did not control for menstrual cycle, and it is possible that this factor could have affected our results. However, previous studies have investigated this question and have not shown a consensus with respect to the effect of cycle on $D_{2/3}$ receptor binding (26–28). Lastly, in this study, we did not include measures of other factors that could affect social status, such as intelligence or anxiety. While attributes such as these may affect the BSMSS score, the degree of their impact is not known, and an investigation of these factors is needed in future studies.

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