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Exploring the relationship between social attachment and dopamine $D_{2/3}$ receptor availability in the brains of healthy humans using [^{11}C]-(+)-PHNO

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Abstract

Differences in striatal dopamine (DA) function may be related to differences in the degree of social attachment to others. Using positron emission tomography (PET), socially detached persons demonstrate reduced DA $D_{2/3}$ receptor ($D_{2/3}$R) availability in the striatum. However, previous PET studies have only used antagonist radiotracers for $D_{2/3}$R and have not specifically examined regions of interest (ROIs) such as the ventral striatum (VS). In 32 healthy persons, we investigated the relationship between self-reported attachment and DA $D_{2/3}$R availability in striatal and extrastriatal ROIs as measured using the agonist radiotracer [^{11}C]-(+)-PHNO. Surprisingly, more social attachment—as measured by the attachment subscale of the temperament and character inventory—was related to less [^{11}C]-(+)-PHNO binding in the VS ($t(30) = -.43$, $p = .01$). This relationship held in a subsample who also completed the detachment subscale of the Karolinska Scales of Personality ($t(10) = .62$, $p = .03$). However, no relationships were observed with BP_{ND} in the dorsal striatum or D_3R-specific ROIs. One potential explanation for these findings is that persons who are more socially detached have less endogenous DA occupying $D_{2/3}$R in the VS. This interpretation warrants investigation by future research. These findings may help us better understand the neurochemical basis of attachment.

Keywords

TCI; KSP; dopamine; [^{11}C]-(+)-PHNO; $D_{2/3}$R; attachment

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Introduction

Engaging in social relationships is fundamental to human well-being and is related to mental health (Bowlby, 1988). The neurochemical dopamine (DA) acting at $D_{2/3}$ receptors ($D_{2/3}R$) in the striatum is hypothesized to be critical for the formation and maintenance of social attachments and their rewarding value (Aragona et al., 2006; Gingrich, Liu, Cascio, Wang, & Insel, 2000). The relationship between striatal $D_{2/3}R$ availability and social detachment in healthy humans has been examined with positron emission tomography (PET) and the antagonist radiotracer [^{11}C]-raclopride. Individuals with high social detachment demonstrate less $D_{2/3}R$ availability in the dorsal striatum (DS) (Breier et al., 1998; Farde, Gustavsson, & Jonsson, 1997). Detachment has also been associated with a D_2R gene promoter variant related to reduced D_2R expression (Jonsson et al., 2003). Consistent with previous work in monkeys (Morgan et al., 2002; Nader & Czoty, 2005), a positive correlation has been observed between social status/support and striatal $D_{2/3}R$ availability in humans measured with [^{11}C]-raclopride (Martinez et al., 2010).

Previous PET studies examining detachment and $D_{2/3}R$ availability have only looked at the DS, not the ventral striatum (VS). This is pertinent given the VS's dual role in social and drug reward (Insel, 2003; Lee et al., 2014; Tops, Koole, H, & Buisman-Pijlman, 2014) and the therapeutic potential of altering social neurocircuits to treat drug addictions (El Rawas et al., 2012; Fritz et al., 2011; Zernig, Kummer, & Prast, 2013). Finally, only antagonist radiotracers have been employed to investigate striatal $D_{2/3}R$ availability and sociability.

[^{11}C]-(+)-PHNO is an agonist radiotracer for $D_{2/3}R$ which has preferential affinity for D_3R over D_2R (Narendran et al., 2006; Wilson et al., 2005). [^{11}C]-(+)-PHNO is currently the only probe available for use in humans that can allow differentiation between D_3R over D_2R. This is relevant because these G-protein-coupled receptors show several differences that may have an impact on behavior. In contrast to D_2R, the D_3R has a unique "rigid" configuration (Vanhauwe, Josson, Luyten, Driessen, & Leysen, 2000) which contributes to its very high affinity for DA (>20-fold higher than D_2) (Freedman et al., 1994). Unlike the D_2R receptor, the D_3R may be activated by tonic DA levels in the brain given its high affinity for DA (Levesque et al., 1992), attenuating any effects of DA fluctuation related to synaptic phasic DA release (Tsukada et al., 1999). Moreover, knock-out mice for the DA D_3R have shown extracellular DA levels twice as high as their wild-type littermates (Joseph et al., 2002). While the D_2R receptor is broadly distributed in the cerebral cortex and subcortical regions (Gurevich & Joyce, 1999), the D_3R receptor has a more restricted distribution to the limbic system, amygdala, hippocampus, thalamus, hypothalamus, and midbrain (substantia nigra and ventral tegmental area), regions known to be involved in modulation of drive, affect, and memory (Nakajima et al., 2013).

[^{11}C]-(+)-PHNO has ~20–40-fold selectivity of D_3R over D_2R (Freedman et al., 1994; Gallezot et al., 2012; Rabiner et al., 2009; G. Searle et al., 2010; Seeman, Ulpian, Larsen, & Anderson, 1993), resulting in a differential contribution of D_2R and D_3R to the [^{11}C]-(+)-PHNO signal across different regions of interest (ROI). The estimated percent of the [^{11}C]-(+)-PHNO signal *in vivo* in humans attributed to D_3R across ROIs are: the substantia nigra (~100%), hypothalamus (~100%), ventral pallidum (~75%), globus pallidus (~65%), VS

(~26%), and dorsal caudate-putamen (negligible) (Graff-Guerrero et al., 2010; Searle et al., 2013; Tziortzi et al., 2011).

Some studies, though few, have examined the relationship between social behavior and D_3R function/expression, noting unique differences from D_2R. For example, unlike antagonism of D_2R, antagonizing D_3R in the prefrontal cortex of rodents increases social recognition and social discrimination (see review: Nakajima et al., 2013). In both healthy persons and cocaine dependent subjects, less D_3R availability in the midbrain has been correlated with greater self-reported social status (Matuskey et al., 2015). Thus, exploring the relationship between attachment and *in vivo* D_3R availability in humans is novel, and may offer new insights as several investigations have noted potential differences in D_2R versus D_3R regulation in several conditions (Boileau, Nakajima, & Payer, 2015; Le Foll, Wilson, Graff, Boileau, & Di Ciano, 2014; Nakajima et al., 2013).

As an agonist [^{11}C]-(+)-PHNO binding to $D_{2/3}R$ is also more sensitive to competition with endogenous DA *in vivo* in humans (Caravaggio, Borlido, Wilson, & Graff-Guerrero, 2015; Caravaggio et al., 2014). For example, it has been demonstrated in humans that [^{11}C]-(+)-PHNO is more sensitive to displacement by amphetamine than [^{11}C]-raclopride (Ginovart et al., 2006; Shotbolt et al., 2012; Willeit et al., 2008). For [^{11}C]-raclopride, it has been reported that 16% of the variance in baseline binding in the striatum can be accounted for by endogenous DA ($t(31) = -.40$, $p = .02$) (Kegeles, Martinez, Slifstein, Laruelle, & Abi-Dargham, 2014). For [^{11}C]-(+)-PHNO this is far greater, with 59% of the variance in baseline binding being explained by endogenous DA in the DS [caudate ($t(8) = -.77$, $p = .01$) and putamen ($r(8) = -.77$, $p = .009$)], and 42% in the VS (Caravaggio et al., 2014). Thus, using [^{11}C]-(+)-PHNO offers a novel probe into how neurochemistry may be related to personality traits and social functioning (Suridjan et al., 2012).

Given the limited ROIs previously examined and the use of only [^{11}C]-raclopride, we explored whether self-reported social attachment in healthy humans is related to DA $D_{2/3}R$ availability with [^{11}C]-(+)-PHNO. Based on previous findings, we hypothesized that attachment would be positively correlated with $D_{2/3}R$ availability in the DS. Furthermore, we explored whether attachment is related to binding in the VS and in the extrastriatal D_3R-specific ROIs.

Elucidating *in vivo* neurochemical correlates of attachment in healthy humans may help us better understand the biological basis of the innate desire for intersubjectivity and how this innate reward may go awry in neuropsychiatric disorders.

Materials and methods

Participants

PET data previously reported in healthy participants were reanalyzed using improved ROI delineation techniques for the purpose of the current investigation (Graff-Guerrero et al., 2009, 2008). Participants were right-handed adults free of any major medical or psychiatric disorders as determined by clinical interview, the Mini International Neuropsychiatric Interview, basic laboratory tests, and electrocardiography. At inclusion and before the PET

scan, participants were required to have a negative urine screen for drugs of abuse and/or pregnancy. All participants provided written informed consent and were nonsmokers. Moreover, history of drug abuse was an exclusion criterion for being scanned. This study was approved by the Research Ethics Board of the Centre for Addiction and Mental Health, Toronto.

Self-reported attachment

Before undergoing a [^{11}C]-(+)-PHNO PET scan, subjects completed the attachment subscale of the Temperament and Character Inventory (TCI) (Cloninger, 1987). This measure is thought to capture the subjective reward value of social relationships. Persons who score high on attachment are characterized as desiring social closeness, eager to help and please others, sympathetic, sentimental, and sensitive to praise and rejection (Cloninger, 1987). Conversely, persons who score low on attachment are characterized as socially and emotionally detached, content to be alone, practical, self-reliant, and independent. They are insensitive to social cues and pressures, and quick to discontinue relationships that are no longer gratifying (Cloninger, 1987). A subset of participants also completed another self-report measure of social attachment, the detachment scale of the Karolinska Scales of Personality (KSP) (Gustavsson et al., 2000). Persons with high detachment scores are described as showing indifference toward social relationships, being socially cold and aloof (Farde et al., 1997). The Cronbach's alpha for the attachment scale of the TCI has been reported to be .71 (Cloninger, Przybeck, & Svrakic, 1994; Miettunen et al., 2004) and .58–.62 for the detachment scale of the KSP (Ortet, Ibáñez, Llerena, & Torrubia, 2002). Given the retrospective nature of our dataset, unfortunately other relevant measures of social cognition were not collected for these [^{11}C]-(+)-PHNO scans.

PET imaging

The radiosynthesis of [^{11}C]-(+)-PHNO and the acquisition of PET images have been described in detail elsewhere (Graff-Guerrero et al., 2008; Wilson et al., 2005). Briefly, [^{11}C]-propionyl chloride was reacted with 9-hydroxynaph-thoxazine to generate a [^{11}C]-amide which was subsequently reduced by lithium aluminum hydride. Purification by HPLC and formulation gave radiochemically pure [^{11}C]-(+)-PHNO as a sterile, pyrogen-free solution suitable for human studies. PET images were acquired using a high-resolution head-dedicated PET camera system (CPS-HRRT; Siemens Molecular Imaging, USA), which measures radioactivity in 207 brain slices with a thickness of 1.2 mm each. The in-plane resolution was ~2.8 mm full-width at half-maximum. Transmission scans were acquired using a ^{137}Cs ($T_{1/2}$ = 30.2 years, E = 662 keV) single photon point source to provide attenuation correction, and the emission data were acquired in list mode. The raw data were reconstructed by filtered-back projection. After completion of the emission acquisition, both the transmission and emission data were transferred to an off-line data processing system for image reconstruction. The emission data were re-binned into a series of 3D sinograms. Scanning time was 90 min in length, wherein 30 frames were defined: 1–15 of 1-min duration and 16–30 of 5-min duration. For each 3D sinogram, gaps were filled and corrections for photon attenuation and detector normalization were applied. The gap-filled sinograms were scatter-corrected before applying Fourier rebinning to convert the 3D sinograms into 2D sinograms. The 2D sonograms were then reconstructed into image space

using a 2D filtered-back projection algorithm, with a Hann filter at Nyquist cutoff frequency and the images calibrated to nCi/mL. A custom-fitted thermoplastic mask (Tru-Scan Imaging, Annapolis) was made for each subject and used with a head fixation system during PET scans to reduce any movement during the acquisition. [^{11}C]-(+)-PHNO was injected as a bolus followed by a flush of 2 mL saline into an intravenous line placed in an antecubital vein. The average time of injection was 12:47 pm. The mean radioactivity dose was 9.63(±1.3) mCi, with a specific activity of 1143.32 (±326.5) mCi/μmol, and an injected mass of 2.1(±.5) μg. None of the participants included in this sample reported nausea given the [^{11}C]-(+)-PHNO injection. The PET data were redefined into 30 frames (1–15 of 1-min duration and16–30 of 5-min duration).

Image analysis

The region of interest (ROI)-based analysis for [^{11}C]-(+)-PHNO has been described in detail elsewhere (Graff-Guerrero et al., 2008; Tziortzi et al., 2011). Time activity curves (TACs) from ROIs were obtained from the dynamic PET images in native space with reference to each subjects co-registered MRI image. The co-registration of each subjects MRI to PET space was done using the normalized mutual information algorithm (Studholme, Hill, & Hawkes, 1997) as implemented in SPM2 (SPM2, Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm). The TACs were analyzed using the Simplified Reference Tissue Method (SRTM) (Lammertsma & Hume, 1996) which has been validated for use with [^{11}C]-(+)-PHNO (Ginovart et al., 2007). The cerebellum was used as the reference region to derive a quantitative estimate of binding—binding potential relative to the non-displaceable compartment (BP_{ND})—as defined by the consensus nomenclature for *in vivo* imaging of reversibly binding radioligands (Innis et al., 2007). The basic function implementation of the SRTM (Gunn, Lammertsma, Hume, & Cunningham, 1997) was applied to the dynamic PET images to generate parametric voxelwise BP_{ND} maps using PMOD (v2.7, PMOD Technologies, Zurich, Switzerland). These images were spatially normalized into Montréal Neurological Institute (MNI) brain space by nearest neighbor interpolation with a voxel size fixed in $2 \times 2 \times 2$ mm^3 using SPM2. Regional BP_{ND} estimates were then derived from ROIs defined in MNI space, except for the hypothalamus and ventral pallidum ROIs. The VS and DS (dorsal caudate, hereafter caudate and dorsal putamen, hereafter putamen) were defined according with the criteria of Mawlawi et al. (2001). The globus pallidus, ventral pallidum, and hypothalamus ROIs were defined according to the criteria of Tziortzi et al. (2011). Regional BP_{ND} estimates for the hypothalamus and ventral pallidum were derived using the SRTM from ROIs drawn by hand, according to the aforementioned criteria of Tziortzi and colleagues.

Statistical analysis

Our a-priori hypothesis was to examine the relationship between self-reported attachment and detachment with [^{11}C]-(+)-PHNO BP_{ND} in the VS and DS in an attempt to extend and replicate previous literature. Notably, the subscale of the TCI measuring attachment is the only subscale of the TCI found to be related to $D_{2/3}R$ availability in previously published PET studies. For the a-priori TCI analyses in the full-sample of subjects, the p-value for significance was set at $p = .02$ (Bonferroni corrected $\alpha = .05/3$ ROIs). Findings with the attachment scale of the TCI and [^{11}C]-(+)-PHNO BP_{ND} were then corroborated within a

subsample of subjects who also completed the detachment scale of the KSP. Since this is the first such investigation with an agonist radiotracer with preferential affinity for D_3R over D_2R, we conducted exploratory analyses examining the relationship between these self-report measures and BP_{ND} in the D_3R specific regions: substantia nigra, globus pallidus, ventral pallidum, and hypothalamus. For these exploratory analyses, the p-value for significance was set at $p = .01$ (Bonferroni corrected $\alpha = .05/4$ ROIs). Age and gender were controlled for using partial Pearson correlations. Statistical analyses were conducted using SPSS (v.12.0; SPSS, Chicago, IL, USA) and GraphPad (v.5.0; GraphPad Software, La Jolla, CA, USA). To our knowledge, this is to date the largest sample ($n = 32$) to examine how [^{11}C]-(+)-PHNO BP_{ND} is related to any self-report measure, not just personality (Boileau et al., 2015; Caravaggio et al., 2014; Di Ciano et al., 2015; Matuskey et al., 2015; Payer et al., 2015; Suridjan et al., 2012). Moreover, this sample is larger than those studies examining the relationship between baseline [^{11}C]-raclopride BP_{ND} and attachment/detachment. As such, our sample size ($n = 32$) was adequately powered ($1 - \beta$ error probability = .80) to detect significant correlations with a medium to large Cohen's d effect size ($d > .46$), given $\alpha = .05$, two-tailed. The a-priori power analysis for a correlation was computed using the statistical software package G*Power (Faul, Erdfelder, Buchner, & Lang, 2009). Normality of variables was determined using the D'Agostino–Pearson test. The significance level for all tests was set at $p < .05$ (two-tailed).

Results

Thirty-two healthy participants (22 males, 10 females; age range: 18–49, mean = 32, SD = 8.9) participated in the study. All 32 participants completed the attachment sub-scale of the TCI, while 12 of these subjects also completed the detachment scale of the KSP (males; age range: 20–39, mean = 30, SD = 6.5). Within the full sample, self-reported attachment was not correlated with age ($r(30) = -.04$, $p = .82$). There was no significant difference in self-reported attachment between men and women ($t(30) = -1.8$, $p = .09$). Attachment was negatively correlated with [^{11}C]-(+)-PHNO BP_{ND} in the VS ($r(30) = -.43$, $p = .01$) (Cohen's $d = -1.06$) (see Figure 1), a relationship that remained statistically significant after controlling for age and gender ($r(28) = -.41$, $p = .02$) (Cohen's $d = -1.03$). Attachment was not correlated with BP_{ND} in the DS: caudate ($r(30) = -.22$, $p = .23$) and putamen ($r(30) = -.16$, $p = .40$). Controlling for age and gender did not significantly affect these null results: caudate ($r(28) = -.16$, $p = .39$) and putamen ($r(28) = -.07$, $p = .71$). Removing an individual who had the lowest attachment score (a score of zero) did not change any of the results, indicating that the relationship between attachment scores and [^{11}C]-(+)-PHNO BP_{ND} in the VS was not being driven by a potential outlier ($r(29) = -.39$, $p = .03$) (Cohen's $d = -.92$).

In the D_3R-specific regions, attachment was not correlated with [^{11}C]-(+)-PHNO BP_{ND} in the substantia nigra ($r(30) = -.29$, $p = .11$), globus pallidus ($r(30) = -.25$, $p = .17$), ventral pallidum ($r(30) = -.35$, $p = .05$), or hypothalamus ($r(29) = .32$, $p = .08$) (note: for one subject [^{11}C]-(+)-PHNO BP_{ND} could not be reliably estimated in the hypothalamus). Controlling for age and gender did not significantly affect any of these null results: substantia nigra ($r(28) = -.23$, $p = .22$), globus pallidus ($r(28) = -.23$, $p = .22$), ventral pallidum ($r(28) = -.29$, $p = .13$), and hypothalamus ($r(27) = .19$, $p = .32$).

Within the subsample of participants who completed both scales, self-reported attachment and detachment were highly negatively correlated ($r(10) = -.71$, $p = .009$). Detachment was not correlated with age ($r(10) = -.14$, $p = .66$). Detachment was positively correlated with [^{11}C]-(+)-PHNO BP_{ND} in the VS ($r(10) = .62$, $p = .03$) (Cohen's $d = 2.01$) (see Figures 2 & 3). This survived statistically controlling for age ($r(9) = .62$, $p = .04$) (Cohen's $d = 2.01$). Detachment was not correlated with BP_{ND} in the DS: caudate ($r(10) = .16$, $p = .61$) and putamen ($r(10) = .17$, $p = .60$). Controlling for age did not significantly affect these null results: caudate ($r(9) = .15$, $p = .65$) and putamen ($r(9) = .13$, $p = .70$).

Detachment was not correlated with [^{11}C]-(+)-PHNO BP_{ND} in the D_3R-specific regions: substantia nigra ($r(10) = .19$, $p = .56$), globus pallidus ($r(10) = .35$, $p = .27$), ventral pallidum ($r(10) = .50$, $p = .10$), and hypothalamus ($r(10) = -.09$, $p = .79$). Controlling for age did not significantly affect any of these null results: substantia nigra ($r(9) = .17$, $p = .62$), globus pallidus ($r(9) = .38$, $p = .26$), ventral pallidum ($r(9) = .49$, $p = .13$), and hypothalamus ($r(9) = -.15$, $p = .65$).

Discussion

We examined whether self-reported attachment in healthy humans was related to DA $D_{2/3}$R availability measured with the agonist radiotracer [^{11}C]-(+)-PHNO. This investigation examined in humans the relationship between attachment and $D_{2/3}$R availability in several striatal and extrastriatal regions. Moreover, it was explored whether there is a relationship between attachment and receptor availability in regions where the majority of the [^{11}C]-(+)-PHNO signal is due to binding to D_3R: the substantia nigra, hypothalamus, ventral pallidum, and globus pallidus. We hypothesized, based on previous findings in humans and animals (Breier et al., 1998; Farde et al., 1997; Martinez et al., 2010; Morgan et al., 2002) that increased attachment would be positively related to [^{11}C]-(+)-PHNO BP_{ND} in the striatum. Surprisingly, we observed using two different scales that attachment was negatively correlated with [^{11}C]-(+)-PHNO BP_{ND} in the VS. While this finding is surprising, it is *prima facie* consistent with work examining the relationship between social status and [^{11}C]-(+)-PHNO BP_{ND} in healthy persons and persons with cocaine-dependence (Matuskey et al., 2015). Notably, low social status has been associated with reduced social attachment through other indirect factors, such as substance abuse, violence, neglect, etc., which has been reviewed elsewhere (Green, Furrer, & McAllister, 2007; Sherry, Adelman, Farwell, & Linton, 2013). Using the Barratt Simplified Measure of Social Status, Matuskey and colleagues found a trend negative correlation between social status and [^{11}C]-(+)-PHNO BP_{ND} in the VS of healthy persons ($r(14) = -.44$, $p = .09$). Notably, using this scale positive correlations have been observed between social status/support and striatal $D_{2/3}$R availability measured with [^{11}C]-raclopride (Martinez et al., 2010).

We did not observe a relationship between social attachment and [^{11}C]-(+)-PHNO BP_{ND} in the DS. A previous PET study failed to find a significant relationship between [^{11}C]-raclopride BP_{ND} in the DS and differences in attachment measured with the TCI, despite finding a significant negative correlation when measured with the KSP (Breier et al., 1998). A subsequent PET study also failed to find a relationship between [^{11}C]-raclopride BP_{ND} in the DS and detachment-like traits measured with the NEO Personality Inventory-Revised

(Kestler, Malhotra, Finch, Adler, & Breier, 2000). It has been suggested that reduced DS $D_{2/3}R$ availability may be related to some specific aspect captured by the KSP not shared by the other attachment scales, or to differences in psychometric properties (Kestler et al., 2000). Similarly, despite these measures being highly correlated with each other in the same persons, a D_2R gene promoter linked to reduced D_2R density was associated with attachment measured with the KSP but not the TCI (Jonsson et al., 2003). In the current investigation, we found converging results with multiple measures: using both the TCI and KSP, less attachment was associated with more [^{11}C]-(+)-PHNO BP_{ND} in the VS. It is possible that we were underpowered due to our sample size to observe a relationship between $D_{2/3}R$ availability in the DS and detachment measured with the KSP. Another potential explanation for this discrepancy with previous literature may be the increased sensitivity of [^{11}C]-(+)-PHNO to endogenous DA in the DS. That is, true differences in receptor number possibly captured by [^{11}C]-raclopride may be masked by concurrent changes in endogenous DA levels.

Differences in radioligand binding *in vivo* are usually explained by changes in at least one of three parameters: the number of available receptors, endogenous DA levels, and receptor affinity for the ligand. While several interpretations exist which are non-mutually exclusive, we speculate that a plausible interpretation of our current findings is that persons who score high on attachment have more endogenous DA occupying $D_{2/3}R$ in the VS, resulting in reduced baseline [^{11}C]-(+)-PHNO BP_{ND}. Subsequently, we outline our rationale.

One interpretation of our findings is that persons who score high on attachment have more endogenous DA occupying $D_{2/3}R$ in the VS, reducing baseline [^{11}C]-(+)-PHNO BP_{ND}. Thus, perhaps persons who do not report receiving reward or pleasure from social relationships have less endogenous DA occupying $D_{2/3}R$ in the VS. Such an interpretation seems biologically plausible for several reasons. First, it is consistent with findings in animals suggesting that increased DA signaling at $D_{2/3}R$ in the VS facilitates social behaviors, while decreased signaling diminishes them (Aragona et al., 2006; Gingrich et al., 2000). Unfortunately, the PET studies, examining how attachment is related to DA synthesis capacity (Laakso et al., 2003) and DA transporter availability (Laakso et al., 2000), have not distinguished between the DS and VS. At least in persons with schizophrenia endogenous DA levels in the VS measured with [^{11}C]-raclopride were found to be inversely correlated with an item on the positive and negative syndrome scale which captures passivity, apathy, and social withdrawal (Kegeles et al., 2010). Second, this interpretation is consistent with the observations that [^{11}C]-(+)-PHNO is more sensitive to changes in endogenous DA than [^{11}C]-raclopride. The high sensitivity of [^{11}C]-(+)-PHNO BP_{ND} to endogenous DA may be capturing changes in endogenous DA levels in the VS at $D_{2/3}R$ across attachment scores which cannot be captured by [^{11}C]-raclopride. Similarly, this sensitivity to endogenous DA may also explain the null result observed between attachment scores and [^{11}C]-(+)-PHNO BP_{ND} in the DS. However, it is possible that we were underpowered to observe a relationship between $D_{2/3}R$ availability in the DS and detachment measured with the KSP. Future studies estimating endogenous DA levels at $D_{2/3}R$ in humans should collect measures of social attachment to validate this interpretation.

Another interpretation of our finding is that persons who score low on attachment have more D_2R and/or D_3R expression in the VS. Notably, while the VS is a mixed D_2R and D_3R region, the majority of the [^{11}C]-(+)-PHNO signal in this ROI is from D_2R (~74%) (Tziortzi et al., 2011). An increase in D_2R expression in the VS with lower attachment would be inconsistent with the aforementioned human and animal literature. For D_3R, it is less clear what would be expected. We did not observe a significant relationship between attachment and [^{11}C]-(+)-PHNO BP_{ND} in the D_3R-specific ROIs. Notably, the trend relationship observed in the ventral pallidum was in the opposite direction of the VS: a positive correlation. However, further human and animal research is required to elucidate the specific role of VS D_3R in the rewarding aspects of affiliative behaviors. Finally, it is important to note that for the D_3R-specific ROIs, the ventral pallidum and hypothalamus, the model fitting (% covariance) and test–retest values are worse than for the D_2R specific ROIs (Gallezot et al., 2014; Searle et al., 2013). This may in part explain our null findings in these regions, and future studies should examine attachment with other D_3R-specific radiotracers. However, [^{11}C]-(+)-PHNO is currently the only *in vivo* probe available to quantify D_3R in the living human brain. Future studies employing agonist radiotracers which are more specific to D_2R—such as [^{11}C]-NPA and [^{11}C]-MNPA—would help clarify the relationship between attachment and availability of striatal D_2R versus D_3R (Finnema, Bang-Andersen, Wikstrom, & Halldin, 2010; Van Wieringen et al., 2014).

We are unaware of any evidence to suggest that reduced affinity at the agonist binding site of the $D_{2/3}R$ in the VS should be related to increased social attachment. *In vitro* studies have yielded inconsistent results regarding the relationship between social isolation in rodents and changes in D_2R affinity (Del Arco, Zhu, Terasmaa, Mohammed, & Fuxe, 2004; King, Seeman, Marsden, & Fone, 2009); a neurocorrelate of increased sensitivity to psychostimulants (King et al., 2009). Therefore, we believe it is unlikely that our findings reflect changes in $D_{2/3}R$ affinity in the VS.

There are several limitations to the current investigation. It has been noted that the injected mass of [^{11}C]-(+)-PHNO is not within ideal radiotracer conditions (i.e., <1.5 ng/kg) (Gallezot et al., 2012). The specific activity required to obtain tracer conditions is not possible with the available radiosynthesis method. While this limitation is currently unavoidable, it is perhaps worth noting that the relationship between attachment and [^{11}C]-(+)-PHNO BP_{ND} in the VS survives controlling for the subjects' injected mass ($t(29) = -.49$, $p = .005$), injected mass per kilogram ($t(29) = -.41$, $p = .03$), amount injected ($t(29) = -.46$, $p = .009$), and specific activity ($t(29) = -.49$, $p = .005$), respectively. It has been suggested that [^{11}C]-(+)-PHNO BP_{ND} in D_3R-rich regions is underestimated if SRTM quantification is used in conjunction with 90 min of data acquisition (Girgis et al., 2011). Thus, using arterial plasma-based kinetic models following 120 min of emission data is more ideal for quantifying [^{11}C]-(+)-PHNO BP_{ND} in D_3R-rich regions (Girgis et al., 2011). Moreover, use of arterial plasma-based kinetic models would circumvent limitations associated with using reference tissue methods, namely concerns about specific binding to D_3R in cerebellar reference tissue (Searle et al., 2013). Future [^{11}C]-(+)-PHNO studies should collect and analyze data accordingly. Moreover, this study was retrospective, reanalyzing previously collected PET data using improved methods to delineate striatal subregions. Unfortunately, other measures were not collected from these subjects such as social status or social support

which would have added further clarification to our results. Further, we only examined the relationship between attachment and $D_{2/3}R$ availability in healthy humans. Future PET studies should examine this relationship in persons with neuropsychiatric illnesses. Several lines of evidence suggest that emotional processing/attachment is sexually dimorphic (Cosgrove, Mazure, & Staley, 2007; Del Giudice, 2011; DeWall et al., 2012). Unfortunately, we only had 10 females in our sample, precluding any meaningful analyses to examine the interactions between gender, attachment, and $D_{2/3}R$ availability. This is something that should be explored by future investigations, using for example, PET and fMRI in the same subjects. Moreover, we did not record the menstrual cycle of our female participants, nor if they were taking contraceptive medications. Given its increased sensitivity to DA over other radiotracers, future [^{11}C]-(+)-PHNO studies should examine the effect of menstrual cycle and contraception use on $D_{2/3}R$ availability, as it has been done with other radiotracers (Kaasinen, Någren, Hietala, Farde, & Rinne, 2001; Nordström, Olsson, & Halldin, 1998; Patrizia Riccardi et al., 2006). We also did not record the relationship status of our participants—a variable which should be investigated by future PET studies. Thus, our findings with [^{11}C]-(+)-PHNO warrant replication with these limitations taken into due consideration.

This is the first investigation to (1) examine whether self-reported attachment in humans is related to DA $D_{2/3}R$ availability in specific subregions of the striatum such as the VS, (2) explore such a relationship with an agonist radiotracer, and (3) explore potential relationships between attachment and receptor availability in D_3R-rich ROIs. We observed a negative correlation between self-reported attachment scores and DA $D_{2/3}R$ availability in the VS of healthy humans as measured with [^{11}C]-(+)-PHNO. Our data, in conjunction with previous research, suggests that persons who are less socially attached—perceiving relationships as less rewarding—have less endogenous DA occupying $D_{2/3}R$ in the VS. However, other interpretations cannot currently be ruled out, requiring investigation by future studies. Such knowledge will have important implications for better understanding the neurochemical basis of social affiliation and how this system may go awry in persons with neuropsychiatric disorders.

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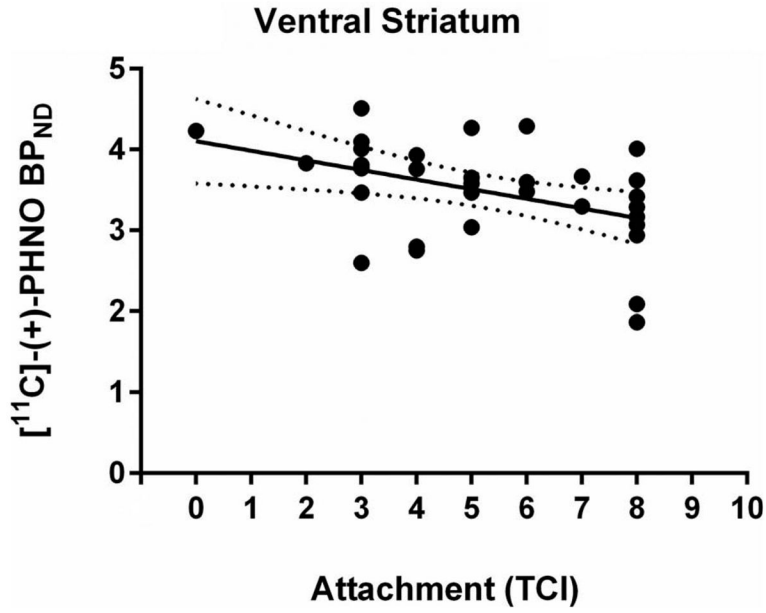

Figure 1.

The relationship between [^{11}C]-(+)-PHNO BP_{ND} in the ventral striatum and attachment measured with the temperament and character inventory. The dashed lines demarcate the 95% confidence interval.

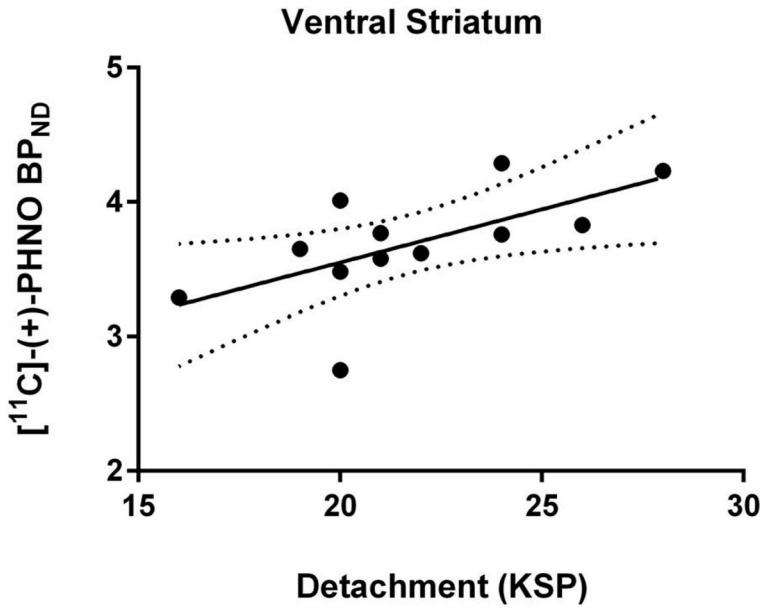

Figure 2.

The relationship between [^{11}C]-(+)-PHNO BP_{ND} in the ventral striatum and detachment measured with the Karolinska Scales of Personality. The dashed lines demarcate the 95% confidence interval.

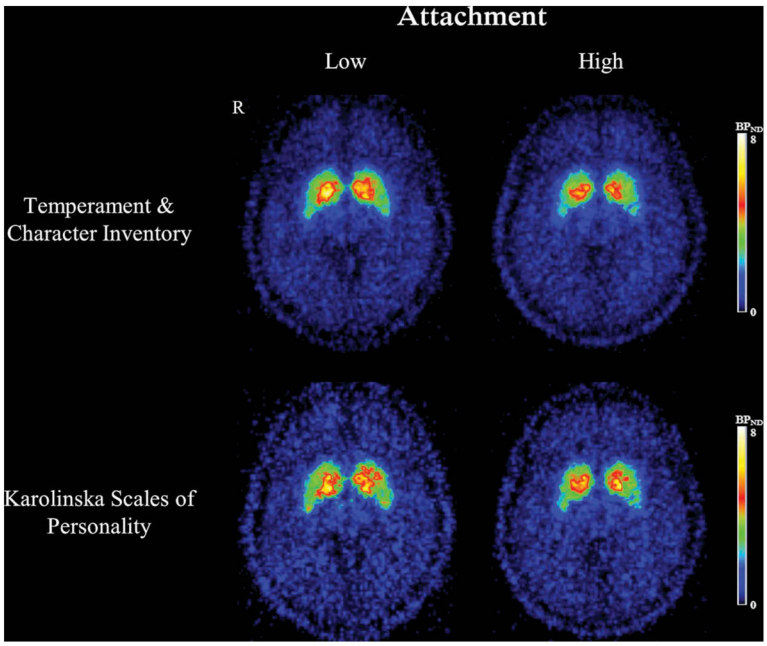

Figure 3.

Averaged [^{11}C]-(+)-PHNO BP_{ND} maps of persons in the first versus fourth quartile of attachment scores measured with the temperament and character inventory (n = 9 per group) and the Karolinska Scales of Personality (n = 4 per group). Depicted is a transaxial slice of the ventral straitum.