
Opioid Receptor PET Reveals the Psychobiologic Correlates of Reward Processing

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Little is known about the neurobiologic correlates of human personality. On the basis of the key role of the central opioidergic system in addiction and substance abuse, we investigated the relationship between certain personality traits that are supposed to be relevant in addiction and the opioid receptor status in healthy subjects. **Methods:** We investigated 23 healthy male volunteers who were extensively clinically tested to exclude substance abuse. All of the subjects underwent 1 PET scan with the subtype-nonspecific opioidergic radioligand ¹⁸F-fluoroethyl-diprenorphine under resting conditions without sensory or cognitive stimulation. Subsequently, the subjects were psychologically tested for the personality traits novelty seeking, harm avoidance, reward dependence, and persistence, according to Cloninger's biosocial model of personality. The binding potential (BP) as a parameter of regional cerebral opioid receptor availability was computed by means of the modified Logan plot using the occipital cortex as a reference region. Further imaging data analysis was performed using statistical parametric mapping; after stereotactic normalization, the correlations were calculated between the regional BP and the psychologic scores on a voxel-by-voxel basis. **Results:** The correlation analysis between personality dimensions and opioid receptor availability showed a significant ($P < 0.001$) positive correlation between the scores of reward dependence and the BP of the bilateral ventral striatum with nucleus accumbens (z scores, 4.52 and 4.33, respectively). The additionally performed region-of-interest-based correlation analysis yielded correlation coefficients of $r = 0.84$ and $r = 0.81$ for the left and right ventral striata, respectively. No further significant correlations were detectable between the other personality dimensions and cerebral opioid receptor binding. **Conclusion:** In healthy subjects, personality traits, which might be predisposing for addictive behavior, are correlated to the opioidergic neurotransmission in core structures of the human reward system.

Key Words: opioid receptor; personality; addiction; drug abuse; positron emission tomography

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The biologic basis of human personality continues to be one of the most interesting and challenging issues of psychobiologic research. Different approaches have shown that certain personality traits are related to neurobiologic parameters (1,2). The development of dimensional models of personality enables a more appropriate description of the complexity and heterogeneity of personality; these models of personality might also be more closely related to the underlying neurobiologic substrate.

One of the most popular models to describe human personality on a dimensional level is Cloninger's biosocial model of personality (3,4). This model comprises the 4 temperament dimensions novelty seeking, harm avoidance, reward dependence, and persistence and involves automatic, preconceptual responses to perceptual stimuli, most probably reflecting heritable biases in information processing. These dimensions are considered to be stable across time, except for novelty seeking, which seems to be age-dependent (5).

Functional imaging using labeled tracers and PET in conjunction with detailed characterization of personality dimensions represents a novel and promising approach for the investigation of the in vivo brain biochemistry of personality. The usefulness of this approach has been documented with radioligands for dopaminergic and serotonergic systems (6). However, little is known about the role of opioidergic neurotransmission for the modulation of human personality, despite the major role that opioidergic neurotransmission plays in the hedonic aspects of reward experience (7). On the basis of this background, it seems challenging to investigate the functional relationship between opioidergic neurotransmission and the level of hereditary personality traits (temperaments) in healthy subjects.

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MATERIALS AND METHODS

This study was performed in accord with the Helsinki Declaration and was approved by the local ethics committee, the Federal Health Administration, and the radiation protection authorities. All PET investigations were performed at the PET Center of the University of Mainz, Germany.

Subjects

For this prospective study, 23 healthy male volunteers (age range, 25–54 y) were included. The subjects had no current or previous history of relevant physical illness, no current or past psychiatric disorders, and no family history of a major psychiatric disorder in first-degree relatives, and they were not regularly taking medication. All control subjects received a mental- and physical-state examination including blood analyses. All subjects gave written informed consent.

The subjects underwent a standardized psychologic assessment for the 4 temperament dimensions novelty seeking, harm avoidance, reward dependence, and persistence, according to Cloninger's temperament and character inventory (3,4).

Radiochemistry and Data Acquisition

¹⁸F-fluoroethyl-diprenorphine (¹⁸F-DPN) was synthesized by applying the secondary labeling precursor 2-¹⁸F-fluoroethyltosylate to 3-*O*-trityl-6-*O*-desmethyl-diprenorphine (8). The 2-¹⁸F-fluoroethyltosylate was synthesized as described elsewhere (9) and obtained in a diethyl ether solution, which was evaporated in a stream of nitrogen. A solution of 4 mg of 3-*O*-trityl-6-*O*-desmethyl-diprenorphine and 10 mg of sodium hydride in 300 μL of *N,N*-dimethylformamide was added to the dried 2-¹⁸F-fluoroethyltosylate, and the resulting mixture was stirred for 8 min at 100°C. Then the reaction mixture was cooled to room temperature, and 600 μL of HCl (2N) were added slowly and stirred for 5 min at 40°C. After the mixture was cooled to room temperature, it was diluted with 8 mL of aqueous ammonia (20%), stirred for 2 min, and loaded on a Sep-Pak C18 cartridge (Waters Corp.). The product was eluted with 2 mL of methanol and purified using semipreparative high-performance liquid chromatography (HPLC) (μBondapak C18 [Waters]: inner diameter, 300 × 7.8 mm; acetonitrile/0.1N ammonium formate, 55:45; 3 mL/min, retention time: 14.9 min). After diluting the HPLC fraction containing the product with 40 mL of 0.1N ammonium formate, the fraction was loaded on a Sep-Pak C18 cartridge, washed with 10 mL of water, eluted with 1 mL of ethanol, and diluted with 9 mL of physiologic saline solution to yield 1,250–1,950 MBq (radiochemical yield, 19% ± 4%) of ¹⁸F-DPN. HPLC analysis (Luna 5μ, C18(2) [Phenomenex]: inner diameter, 250 × 4.6 mm; methanol/0.1N ammonium formate, 70:30, 1 mL/min, retention time: 12.2 min) showed that the radiochemical purity was greater than 99%, whereas the specific activity (determined via ultraviolet-calibration curve) was between 580 and 820 GBq/mmol.

PET and Data Analysis

Images were acquired on a whole-body PET scanner (ECAT EXACT; Siemens). The camera had a field of view of 16.2 cm in 47 planes, with a plane spacing of 3.375 mm, an axial resolution of 6.0-mm full width at half maximum, and an in-plane resolution of 6.0 mm (resolution at center with scanner in 3-dimensional mode). Data acquisition comprised a series of 30 time frames. The scan duration increased progressively from 20 s to 10 min, resulting in a total scanning time of 124 min. A 15-min transmis-

sion scan using a ⁶⁸Ge source was performed before each study for subsequent attenuation correction. A mean of 150 MBq (±30 MBq) of ¹⁸F-DPN was injected intravenously as a bolus into a cubital vein over approximately 30 s. The specific activity at the time of injection was greater than 0.5 GBq/μmol.

Images were reconstructed with filtered backprojection using a ramp filter and a Hanning filter (filter width, 7.3 mm). Frame-by-frame motion correction was applied by matching cortical isodensity contour points. A mean occipital time-activity curve was generated by drawing regions of interest (ROIs) on 3 subsequent transaxial slices.

Binding potentials (BPs) of volumes of interest were calculated using the noninvasive Logan plot (10), with reference region input, according to the following equation:

$$\frac{\int_0^t c_t dt}{c_t} \cong \frac{V_d}{V'_d} \frac{\int_0^t c_r dt}{c_t} + c$$

where C_t is the tissue radioligand activity in the receptor-containing ROI, C_r is the tissue radioligand activity of ¹⁸F-DPN in the reference tissue (occipital cortex), V_d is the volume of distribution of the receptor-rich region, and V'_d is the volume of distribution of the reference region (11). BP was calculated from the ratio V_d/V'_d , which was estimated with a nonlinear least-square minimization procedure. The occipital cortex was chosen as a reference region because it is generally considered of very low opioid receptor density (12). BP images had to be normalized stereotactically for voxelwise analysis of opioid receptor availability (13). First, flow-weighted integral images (summed images between 3 and 12 min after injection) were calculated and spatially normalized using statistical parametric mapping and the standard PET template. The images were realigned and stereotactically normalized into the standard anatomic space by means of linear and nonlinear transformation (14). Then, transformation parameters of the spatial normalization were applied to BP images. Subsequently, the normalized BP images were smoothed with a 3-dimensional gaussian filter using a 12-mm full width at half maximum kernel (voxel size, 2 × 2 × 2 mm).

Statistical Analysis

For the correlation analysis between personality traits and cerebral opioid receptor availability, the scores of novelty seeking, harm avoidance, reward dependence, and persistence were correlated as an external covariate to the corresponding opioid BP data on a voxelwise basis using a statistical threshold of $P < 0.001$ (corrected on a cluster level) and a minimal cluster size of more than 100 voxels. As the image data were stereotactically normalized, the maxima of the activation foci were reported with the respective stereotactic Montreal Neurologic Institute coordinates.

RESULTS

Personality Assessment

The personality assessment of the healthy subjects showed mean scores of 21.6 ± 5.0, 10.7 ± 6.1, 15.4 ± 3.3, and 5.3 ± 2.0 for novelty seeking, harm avoidance, reward dependence, and persistence, respectively. In comparison with the age- and sex-matched normative data group (10), our volunteers scored slightly above the average in novelty seeking (normative data, 19.0 ± 5.9), reward dependence (normative

data, 14.6 ± 3.5), and persistence (normative data, 4.2 ± 1.8), whereas they scored in the lower average range in harm avoidance (normative data, 14.6 ± 5.8). No significant differences between the scores of our volunteers and the normative data were identified. The observed differences between our subjects and the normative database were moderate and might be explained by the different social and educational backgrounds of the 2 groups. Whereas the normative data are based on subjects who are representative of the German population, our study subjects were exclusively recruited by participating scientists and students from our departments.

Correlation Opioid Receptor Status and Personality Traits

The correlation analysis between personality dimensions and opioid receptor availability showed a strong positive correlation between the scores of reward dependence and the BP restricted to the bilateral ventral striata with nucleus accumbens (Fig. 1). The respective stereotactic Montreal Neurologic Institute coordinates of the maximum voxels were $x = -12$, $y = 10$, and $z = -10$ (left) and $x = 16$, $y = 26$, and $z = 2$ (right); the z scores were 4.52 and 4.33, respectively. The corrected P values for both clusters were significant at $P < 0.001$ (corrected for the entire volume). After small-volume correction, the corrected P values were less than 0.005 at a voxel level within each cluster.

To validate these findings, an ROI-based correlation analysis was subsequently performed using predefined ROIs according to Mawlawi et al. (15) for the ventral striatum. Figure 2 shows the anatomically defined ROI

superimposed on significant clusters in the ventral striatum. The corresponding correlation plots are shown in Figure 3; the correlation coefficients were $r = 0.81$ ($P < 0.0001$) and 0.84 ($P < 0.0001$) for the right (Fig. 3A) and left (Fig. 3B) ventral striata, respectively.

In contrast, no correlations passing the given statistical threshold were detectable between opioid receptor binding and the levels of the other personality dimensions.

DISCUSSION

The findings of this study indicate that opiate receptor availability in the ventral striatum, a core area of the brain reward system, is directly correlated with reward dependence, a personality trait that is thought to reflect a bias in the maintenance of ongoing behavior (4). Recent neurobiologic research has emphasized the difference between the anticipation of reward, which is computed by dopaminergic neurotransmission (16) and is thought to be reflected in the personality trait of novelty seeking (4), and the actual pleasant or hedonic experience of reward, which is blocked by opiate receptor antagonists in the ventral striatum of rodents and in human studies (7,17). Our study confirms this difference and suggests that reward dependence but no other personality trait is correlated with opiate receptor availability in the ventral striatum. For novelty seeking, which is attributed to the dopaminergic system, Suhara et al. (18) detected in healthy volunteers a negative correlation between the scores of novelty seeking and the BP of dopamine D_2 receptors in the right insular cortex. Indications for the involvement of the serotonergic

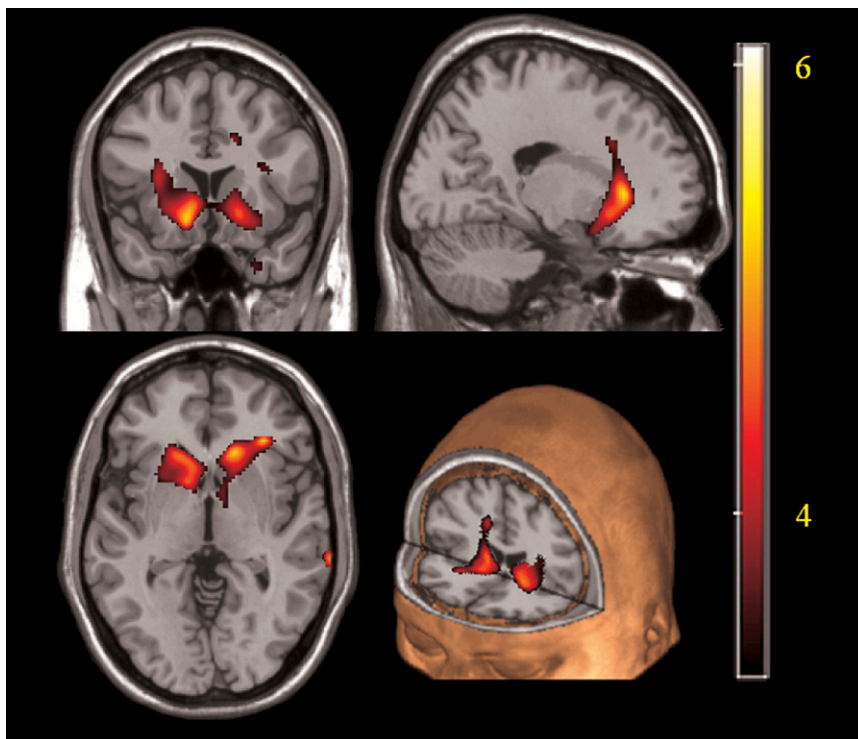


FIGURE 1. Positive correlation (corrected at cluster level at $P < 0.001$) between score for reward dependence and opioid receptor availability in bilateral ventral striata with caudate nucleus and nucleus accumbens. Color scale shows t levels, with $t = 3.55$ corresponding to $P = 0.001$.

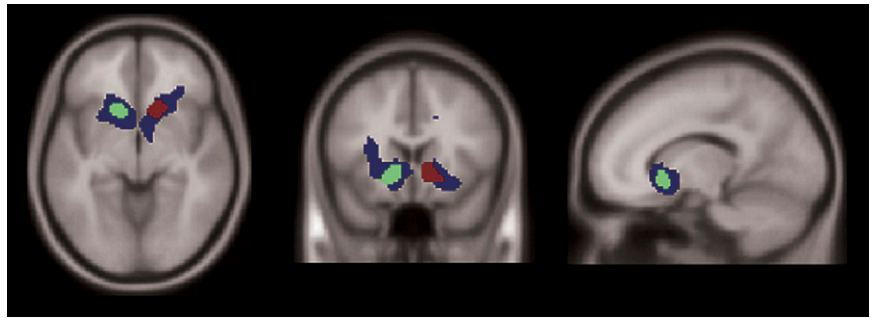


FIGURE 2. Predefined anatomic ROIs of ventral striatum superimposed on clusters significant for reward dependence that are shown in Figure 1.

system in certain human personality traits were found by Moresco et al. (6). These authors revealed an inverse correlation between harm avoidance and the binding of ^{18}F -fluoroethyl-spiperone to 5-hydroxytryptamine receptor 2a in the frontal and the left parietal cortex, whereas no serotonergic correlations were found for novelty seeking and reward dependence (6).

Clinically, reward dependence manifests as individual differences in social attachment, dependence on the approval of others, and sentimentality (4). A study in nonhuman primates also suggested that intimate social contact

between a mother and her infant is regulated by the opiate system (19). Our study supports this notion and indicates that opiate receptor availability may mediate reward dependence in social contact behavior via longer-lasting individual differences that can be clinically defined as human personality traits. The clinical relevance of our study is emphasized by findings that link individual differences in opiate receptor availability with the sensory and affective dimensions of pain and with alcohol dependence (20,21). It was shown in a recent PET study that μ -opiate receptor availability in the ventral striatum was increased in abstinent alcoholic patients and was positively correlated with their craving for alcohol as a relevant risk factor for relapse (21).

The increased dopamine release in the ventral striatum (in particular in the nucleus accumbens) due to drug or alcohol administration is mediated and modulated by opioidergic and GABAergic pathways (22,23). Therefore, increased availability of opioid receptors in brain areas that are relevant for positive-reinforcement effects might be important in initiating and maintaining drug or alcohol abuse (24). Thus, our findings suggest that elevated opiate receptors in the ventral striatum could be one biologic link between personality traits and dependence risk.

Some methodic considerations should be addressed. For this study, we assessed the endogenous opioid receptor status in terms of BPs, which were calculated by means of the noninvasive Logan model (10), with the occipital cortex as a reference region. It has been recently shown that the use of noninvasive models seems an appropriate approach for the quantification of ^{11}C - or ^{18}F -labeled diprenorphine (25,26), although the occipital cortex might not fulfill the criteria of an ideal reference region because it may contain a small amount of opioid receptors as could be shown by naloxone-blocking experiments (27). Expecting the specific occipital binding to be minimal, Spilker et al. (26) also used this area as the reference region and found consistent BP values between invasive and noninvasive quantification methods, with the noninvasive BPs showing less interindividual variability. Therefore, the use of the occipital cortex as a reference region might be problematic in those studies using different (activation) conditions, which might influence the specific binding in the occipital cortex depending on the activation paradigm. However, for the present study

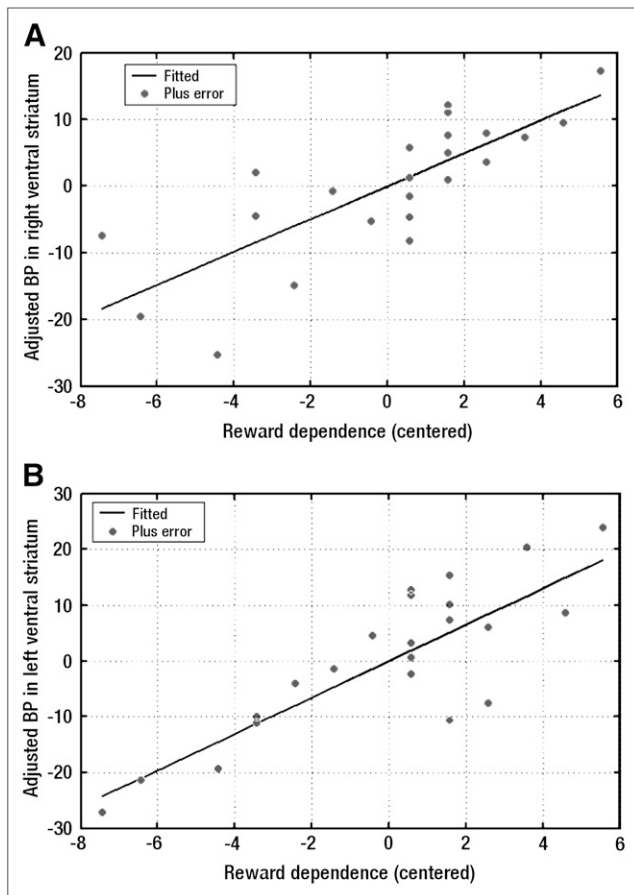


FIGURE 3. Representative plots of extracted binding potential for right (A) and left (B) ventral striata positively correlated to scores of reward dependence (right, $r = 0.81$; left, $r = 0.84$).

we did not use different conditions, and from our a priori hypothesis, it was not expected that the investigated personality dimensions were associated with opioid receptor binding in the occipital cortex.

CONCLUSION

The results of this study suggest that opioidergic neurotransmission in the ventral striatum has a role as a biologic modulator between personality traits (reward dependence as revealed by our study) and addiction-related reward and reinforcement processes.

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