Relationship of Type 1 Cannabinoid Receptor Availability in the Human Brain to Novelty-Seeking Temperament

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Context: Brain neurochemistry can partially account for personality traits as a variance of normal human behavior, as has been demonstrated for monoamine neurotransmission. Positron emission tomography using fluorine 18–labeled MK-9470 now enables quantification of type 1 cannabinoid receptors (CB1R) in the brain.

Objective: To investigate whether there is a relationship between human temperament traits and regional cerebral CB1R availability.

Design: Forty-seven [^{18}F]MK-9470 baseline scanning sessions were performed and correlated with the temperament dimensions and subdimensions of the 240-item Cloninger Temperament and Character Inventory.

Setting: Academic brain imaging center.

Participants: Forty-seven nonsmoking, healthy volunteers (paid).

Main Outcome Measure: Voxel-based correlation of temperament variables of the inventory with regional CB1R availability.

Results: Novelty seeking was inversely correlated with global CB1R availability ($r=-0.33$, $P=.02$), with the most significant correlation in the left amygdala ($r=-0.41$, $P=.005$). In particular, the subdimension extravagance showed a highly significant inverse correlation to global CB1R availability ($r=-0.53$, $P<.001$), most pronounced in the amygdala, anterior cingulate, parietal cortex, and precuneus. Also, disorderliness was inversely correlated with global CB1R availability ($r=-0.31$, $P=.04$).

Conclusions: Low baseline cerebral CB1R availability is related to a high novelty-seeking personality, in particular to extravagance, most pronounced in the amygdala. Further investigation of the functional role of the CB1R is warranted in pathological behavior known to be strongly related to novelty seeking, such as addiction and eating disorders.

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HUMAN BEHAVIOR VARIES widely among individuals, and there is increasing support for the view that interindividual differences may be, at least in part, explained by neurobiological and genetic factors.[1] Independent, heritable temperament traits, involving preconceptual biases in perceptual memory and habit formation, have been identified and validated.[2,3] These temperament traits are thought of as a genetically influenced aspect of personality, are relatively stable over a lifetime, and are heritable to a high degree. This contrasts to character, which reflects a more developmental outcome of the interplay of environmental factors with temperament over time.

Based on genetic studies of personality in humans and neurobiological studies of functional brain networks in rodents, Cloninger's biosocial theory of personality[4] involves 4 grossly independent temperament dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P).[4,5] On the basis of neuropharmacologic, neuroanatomic, and neurochemical data, these dimensions are thought to be related to activity in specific central monoamine neurotransmitter systems. Driven by the availability of radioligands to investigate presynaptic and postsynaptic dopaminergic and serotonergic neurotransmission, neuroimaging, in particular positron emission tomography (PET), has contributed to this view.[1,6] However, personality is a very complex phenotype, and little is known about how genetic and environmental or social factors during brain development and aging may contribute to regional alterations in neurochemistry. Furthermore, such monoamine neurotransmitter relations are not exclusive. For example, in the Karolin-

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ska Scales of Personality,[7,8] dopamine function has been linked to personal detachment (social withdrawal), which is regarded to be the opposite of NS, but also to HA.[7]

Since the discovery of endogenous cannabinoids in the early 1990s, considerable interest in the endocannabinoid system has arisen.[9,10] Experimental studies in animals and observational studies on the effects of cannabis in humans have implied important functions for the endocannabinoid system in cognitive, motor, reward, and motivation circuitries. The majority of the cannabinoid effects in the central nervous system are mediated by the type 1 cannabinoid receptor (CB1R), one of the most ubiquitously expressed G-coupled receptors in the brain. The CB1R is thought to play a major role in modulation of neurotransmission by a predominantly inhibitory presynaptic action on other transmitter systems, mainly glutamate, γ-aminobutyric acid, and dopamine.[9] Because of a presumed central role of CB1R in the reward circuitry, elective CB1R inverse agonists are being marketed as antiobesity agents,[11,12] mediating weight loss likely by a combination of central and peripheral mechanisms,[13] and are also investigated as drug therapy for several forms of substance dependence.[14,15]

Previously, our group has characterized the in vivo CB1R availability in the human brain by using the novel high-affinity, highly selective radioligand MK-9470 labeled with fluorine 18[16] and investigated its variation with age and sex.[17] A large intersubject variability, up to 230%, was found, even within the same sex and age groups. Such interindividual variability is common to many neurotransmitter systems. For example, the dopamine_2,[1] serotonin_{1A},[18] and serotonin_{2A}[6] receptors show a similar variation in availability of up to 250% in healthy adults.

Because strong correlations have been found between molecular imaging parameters of brain monoamine neurotransmitter activity and personality or personality disorders, we have used an explorative data-driven voxel-based design in this study to search for associations between baseline CB1R availability in healthy subjects and temperament traits to explain part of this intersubject variability and to provide evidence of neurochemical correlates of personality beyond the classic monoamine systems.

METHODS

SUBJECTS

The study was approved by the local ethics committee and performed in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all volunteers before the study. Members of the local community were recruited via newspaper and Internet advertisements. A total of 50 white volunteers were included in the imaging study. This sample was previously described in another study.[17] Eighteen of the volunteers were also involved in further studies on experimental drug trials[13]; only their baseline data obtained during drug-naïve conditions were used for this study.

All volunteers were healthy, according to a detailed medical history, physical examination, extended psychiatric interview to exclude Axis I and II disorders, routine blood and urine analysis, and T2- and volumetric T1-weighted brain magnetic resonance (MR) imaging. Handedness was determined according to Briggs and Nebes.[19] Furthermore, all subjects underwent urine drug screening including cannabis, amphetamines, opiates, sedatives, and neuroleptics. Exclusion criteria were smoking or cessation of less than 6 months, history of alcohol consumption of more than 10 units per week, history of psychiatric disorder in the subject or in a first-degree relative, intake of psychotropic drugs, or history of other substance addiction or previous use of cannabis. All subjects abstained from alcohol during the 48 hours before scanning, and from eating and drinking for at least 6 hours before PET imaging.

PET IMAGING

Tracer synthesis, validation, and human imaging procedures were described previously.[16] In short, the radioligand [^{18}F]MK-9470 (*N*-[2-(3-cyano-phenyl)-3-(4-(2-[^{18}F]fluoroethoxy)phenyl)-1-methylpropyl]-2-[5-methyl-2-pyridyloxy]-2-methylproponamide) was synthesized on site on the basis of a precursor donated by Merck Research Laboratories (West Point, Pennsylvania). The PET acquisitions were performed on a PET scanner (ECAT EXACT HR+; Siemens, Erlangen, Germany), and subjects received on average 271 MBq of [^{18}F]MK-9470 in slow bolus intravenous injection (to convert to curies, multiply by 2.7×10^{-4}).[17] The specific radioactivity at the time of injection was greater than 37 GBq/μmol (injected tracer mass in all subjects was <5 μg).

Regional tracer activity in the brain was measured in a series of 30 consecutive frames for at least 120 minutes.[16] A transmission scan using germanium 68 rod sources was performed to correct for attenuation. The in-plane resolution of the reconstructed images was 4 mm full-width at half-maximum. Data were reconstructed by means of filtered back-projection in a $128 \times 128 \times 63$ matrix with a plane separation of 3.4 mm.

IMAGE PROCESSING

On the basis of previously validated kinetic modeling,[16] receptor availability was calculated from the area under the curve in the interval between 90 and 120 minutes after injection. In this way, standardized uptake values (SUVs) were determined as an index of receptor availability by dividing the calibrated activity concentration at this time frame by the amount of tracer injected and by normalizing on the subject's weight: SUV = activity concentration (kBq/cm^3)/(injected dose [MBq]/weight [kg]). For each subject, parametric SUV images were coregistered to a specific CB1R template[17] constructed in Montreal Neurological Institute (MNI) space, with a voxel size of $2 \times 2 \times 2$ mm, using statistical parametric mapping (SPM2) (Wellcome Department of Cognitive Neuroscience, London, England). Spatial normalization to this standard MNI template with the use of nonlinear warping ($7 \times 9 \times 7$ basis functions, 16 iterations) was carried out. Data were masked within the brain 80% isocontour of the CB1R template before further analysis.

The SPM voxel-based analysis was the primary analysis. For specific anatomic volume-of-interest (VOI) correlations with scores on the Cloninger Temperament and Character Inventory (TCI) and assessment of association strength, a VOI-based analysis using the Wake Forest University Pick Atlas SPM toolbox (version 2.4)[20] was used additionally. The Talairach Deamon "Brodmann area +" definitions (using a 2-dimensional dilation of 2) and "Lobes" definition files were used for bilateral and unilateral VOI data sampling.

PERSONALITY ASSESSMENT: TCI QUESTIONNAIRE

After completion of the imaging study, TCI questionnaires were presented to all participants and 47 responses were received

Table 1. Demographic Characteristics and Temperament *z* Scores of the Studied Sample Compared With the Reference Population[a]

	Subject Group	
	Male (n=23)	Female (n=24)
Handedness, No. L/R/ambi	2/20/1	0/23/1
Age, y	38.1 (15.5)	32.7 (16.9)
Temperament dimension, *z* score		
Novelty seeking (NS)	0.65 (1.31)	0.28 (1.18)
Exploratory excitability (NS1)	0.21 (1.05)	0.45 (1.09)
Impulsiveness (NS2)	0.37 (1.12)	0.02 (0.92)
Extravagance (NS3)	0.29 (1.35)	−0.03 (0.97)
Disorderliness (NS4)	0.90 (1.08)[b]	0.29 (1.08)
Harm avoidance (HA)	−0.08 (1.18)	−0.11 (1.03)
Anticipatory worry (HA1)	−0.06 (1.05)	−0.24 (1.15)
Fear of uncertainty (HA2)	−0.09 (1.03)	−0.11 (1.09)
Shyness (HA3)	0.05 (1.02)	0.04 (1.07)
Fatigability (HA4)	−0.16 (1.17)	−0.04 (0.98)
Reward dependence (RD)	−0.39 (1.03)	0.28 (1.02)
Sentimentality (RD1)	−0.50 (0.86)	0.04 (0.90)
Attachment (RD2)	−0.05 (1.10)	0.39 (0.93)
Dependence (RD3)	−0.29 (1.13)	0.10 (0.93)
Persistence (P)	0.09 (1.06)	−0.21 (0.96)

Abbreviation: ambi, ambidextrous.
[a] Values are given as mean (SD) unless otherwise specified.
[b] $P=.01$ (*t* test vs $z=0$, corrected for multiple Cloninger Temperament and Character Inventory subdimension comparisons).

(23 men and 24 women; age range, 18-69 years). Demographic data of these subjects are summarized in **Table 1**. The Dutch translation of the 240-item (true-false) TCI[2] was used. This Dutch version (version 1.3; Datec Psychological Tests, Leiderdorp, the Netherlands) of the TCI is a validated translation for which in 2004 normalization data are based on a representative population sample of 1034 Flemish and Dutch persons.

All questionnaires were filled out completely and answers to the validity items were checked. Data were analyzed on the basis of normal scores of the global (male + female) population by means of an in-house written Excel analysis macro (Microsoft Corp, Redmond, Washington). The TCI results were calculated as *z* scores based on tabulation of the mean and standard deviation values. We report herein only the temperament scales that are known to reflect stable behavioral dimensions because some questionnaires were filled in up to 12 months after the PET study for the volunteers who participated in the drug study.

DATA ANALYSIS: STATISTICAL ANALYSIS AND SPM

Before SPM2 analysis, imaging data were smoothed with a kernel with full-width at half-maximum of 10 mm to account for interindividual gyral variability and to allow use of the general linear model in SPM.[21] No global normalization or proportional scaling was used.

For SPM analysis, age and sex were used as nuisance variables because an age-related increase in [^{18}F]MK-9470 SUV has been documented and differences between sexes exist.[17] Data were standard interrogated at a voxel-level $P_{height}<.001$ (uncorrected) and cluster-level $P_{cluster}<.05$ (corrected) with a cluster size extent of 100 (approximately 0.8 cm^3), unless specified otherwise. To reduce the chance of false-positive findings, we evaluated correlations with the 4 main temperament dimensions in a multivariate correlation design first. When positive findings were obtained for a main dimension, its subdimensions were also evaluated. The MNI coordinates were nonlinearly converted to Talairach space by means of the same Wake Forest University Pick Atlas tool. Conventional statistical analyses were performed with Statistica version 7.1. for Windows (StatSoft, Tulsa, Oklahoma). Scale and subscale means and their distributions were examined for normality distribution by Kolmogorov-Smirnov testing, and partial Pearson correlations were assessed between TCI scales and specific VOIs.

RESULTS

TCI RESULTS

We first evaluated the distribution of the studied population with respect to the reference sample of 1034 subjects. Table 1 shows the results of the TCI questionnaire in the studied population. All variables followed an expected normal distribution after conversion to *z* scores (Kolmogorov-Smirnov test). After Bonferroni correction for multiple comparisons, participants scored significantly higher on disorderliness (an NS subdimension) than the reference population sample (mean [SD], 0.59 [1.11]; *t* test, $P<.001$). As for age, only attachment (a subdimension of reward dependence) decreased significantly with age (Pearson $r_{45}=-0.41$, $P=.004$). No sex differences or age × sex interactions for the TCI results were present in this sample.

There was no significant correlation between the 4 main temperament dimensions (all $P>.2$).

For the main dimensions (NS, HA, and RD), there was a significant correlation (all $P<.01$) between their subdimensions in the studied group. In particular, global NS scores were highly correlated with the subdimension scores extravagance (Pearson $r_{45}=0.82$, $P<.001$) and impulsivity (Pearson $r_{45}=0.85$, $P<.001$) and, to a lesser extent, to disorderliness (Pearson $r_{45}=0.57$, $P<.001$) and exploratory excitability (Pearson $r_{45}=0.65$, $P<.001$).

CORRELATION OF TEMPERAMENT WITH CB1R PET FINDINGS

Regional mean (SD) SUV values varied from 0.84 (0.12) (range, 0.58-1.12) in the pons to 1.20 (0.18) (range, 0.79-1.57) in the frontal cortex regions and 1.36 (0.24) (range, 0.82-1.85) in the striatum.[17]

The SPM analysis showed that NS was inversely correlated with global cerebral CB1R availability in a cerebral-wide cluster at the $P_{height}=.005$ level (*t* statistic >3.0). At a more stringent threshold of $P_{height}<.001$, a single significant cluster was found located at the left amygdala (peak maximum [x, y, z] = [−16, −7, −25], $t=3.49$) (**Figure 1**).

Table 2 gives the partial correlation coefficients for a whole-brain VOI, bilateral lobar areas, and amygdala VOIs. These indicate that, although the strength of the correlation is strongest in the left amygdala, the observed correlations are mainly global. Individual data for the whole-brain VOI are shown in **Figure 2**A (partial correlation $r_{43}=-0.33$, $P=.02$).

There were no significant relationships between CB1R availability and HA, RD, or P dimensions (Table 2). Within the NS dimension, SPM analysis showed that both extravagance (NS3) and disorderliness (NS4) were inversely correlated with CB1R availability.

For extravagance, this was the case in a global cerebral cluster even at a very stringent uncorrected threshold of P_{height}<.001. The most significant regional clusters at P_{height}=.05 (corrected) were found at the left amygdala (extending to the hippocampus and posterior pons covering the locus ceruleus), bilaterally in the anterior temporal poles, bilaterally at the high parietal and precuneus cortex, and at the anterior cingulate, including its pregenual part (Brodmann area 25). Peak T locations for this correlation design with NS3 are given in **Table 3** and are also shown in **Figure 3**. Figure 2B shows the individual response curve for the predefined VOI over the left amygdala (partial correlation r_{43}=−0.59, P<.001). **Figure 4** shows a group parametric image comparison of mean CB1R availability of the 10 highest vs 10 lowest NS3-scoring individuals. **Table 4** shows CB1R availability values between low and high novelty seekers for the lobar VOIs.

The NS subdimension disorderliness (NS4) also showed an inverse correlation to CB1R availability in a cluster comprising the full cerebrum at P_{height}=.005. Borderline significance was reached for most lobar VOIs (Table 2).

For the other NS subdimensions, only NS2 showed a trend toward significance in the VOI analysis (Table 2) in the limbic system, most pronounced in the left amygdala (P=.04).

As for sex effects, the correlations with NS, extravagance, and disorderliness were retained for the subgroup of female subjects. No other correlations were found. For the subgroup of men, only extravagance remained above the statistical threshold of P_{height}<.001 uncorrected.

COMMENT

Several lines of evidence point to an important role of genetic determinants of receptor expression and neuronal function in the normal variation of human behavior.[22] The genetics of complex human phenotypes are complicated because of small effect sizes of nonmendelian traits, polygenic patterns, and true heterogeneity between studies. Therefore, as an alternative paradigm, the approach of combining functional neuroimaging with personality assessments enables a complementary and more direct in vivo exploration of neurochemical markers of personality.

In this study, we found that in normal adult human subjects global CB1R availability in the brain correlates inversely with NS and more specifically with its subdimension extravagance.

The NS dimension reflects a heritable bias in the initiation or activation of appetitive approach in response to novelty and approach to signals of reward.[4] Specifically, extravagance in approach to cues of reward is characterized by a strong tendency toward spending money, energy, and emotional feelings. In this sense, extravagance is regarded as a form of action impulsivity (in contrast to the subscale impulsivity, which more reflects a cognitive component).[23]

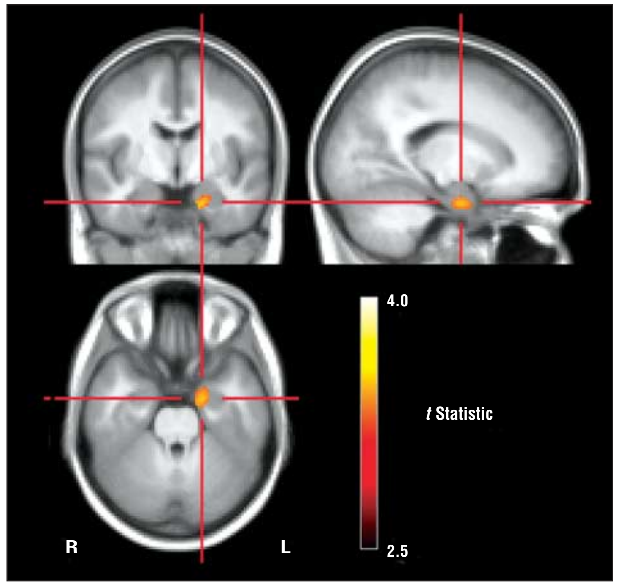

Figure 1. Statistical parametric maps showing the inverse correlation of the temperament dimension novelty seeking with type 1 cannabinoid receptor availability on positron emission tomography at the P_{height} level of P<.001 (uncorrected for multiple comparisons) and cluster size extent greater than 100. Clusters are overlaid on the average T1-weighted magnetic resonance image of the studied group. Images are in radiologic orientation.

Cloninger[23] previously postulated that NS is specifically related to the amygdaloid subdivision of the limbic system, which is in striking agreement with the most significant regional correlations found in the present study. Selective amygdala lesions have shown to yield personality changes such as increased exploration and excitability.[24] The amygdala influences drive-related behavioral patterns and the corresponding subjective feelings, and regulates the tonic opposition of drives for feeding and aggression vs satiety and satisfaction. The CB1R is of primary importance for fear extinction,[25] and endocannabinoids facilitate extinction of aversive memories through selective inhibitory effects in the amygdala.[26] When assuming low CB1R availability is based on compensatory downregulation of a high endocannabinoid tone, we can hypothesize that such findings, in combination with our results, suggest that facilitated fear extinction could be related to increased emotional impulsivity and exploratory behavior less inhibited by aversive memories. Such a hypothesis would be testable, for example, by measuring fear extinction (eg, startle reflex or skin conductance responses) in relation to temperament and imaging parameters. On the other hand, recently a central role for CB1R in the amygdala-medial prefrontal circuit in the encoding and acquisition of emotional learning has been shown.[27] Thus, low CB1R availability could also result in disrupted emotional associative learning of this circuit.

Although a predominance toward the left-sided amygdala was found and a left-lateralized hemispheric specialization for positive affect or approach-oriented behavior has been described,[28] we did not test for specific asymmetries in the study design,[29] and the correlation in the left amygdala is only the maximum of an extended significant cluster (Figure 2) that points to spe-

Table 2. Partial Correlation Coefficients and *P* Values for Regional [18F]MK-9470 CB1R Availability (SUV) vs Temperament Dimensions and NS Subdimensions

	NS		NS1		NS2		NS3		NS4		HA		RD		P	
	r Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
Global gray matter VOI	−0.33	.02	0.09	.56	−0.24	.11	−0.53	<.001	−0.31	.04	−0.08	.61	−0.05	.71	0.11	.44
Frontal																
Left	−0.33	.03	0.08	.59	−0.24	.11	−0.53	<.001	−0.32	.03	−0.08	.58	−0.05	.73	0.12	.45
Right	−0.32	.03	0.09	.56	−0.24	.12	−0.53	<.001	−0.30	.05	−0.08	.61	−0.07	.64	0.09	.54
Temporal																
Left	−0.34	.02	0.08	.61	−0.24	.11	−0.53	<.001	−0.33	.03	−0.08	.59	−0.05	.76	0.12	.42
Right	−0.32	.04	0.09	.56	−0.24	.12	−0.52	<.001	−0.28	.06	−0.09	.55	−0.08	.62	0.09	.55
Limbic[a]																
Left	−0.34	.02	0.08	.60	−0.25	.10	−0.54	<.001	−0.31	.04	−0.07	.64	−0.07	.63	0.09	.54
Right	−0.33	.03	0.10	.54	−0.25	.10	−0.53	<.001	−0.32	.03	−0.09	.57	−0.07	.63	0.09	.55
Amygdala																
Left	−0.41	.005	0.00	>.99	−0.32	.04	−0.59	<.001	−0.32	.03	0.01	.97	−0.06	.69	0.05	.72
Right	−0.34	.02	0.05	.72	−0.27	.08	−0.52	<.001	−0.29	.06	−0.09	.55	−0.10	.50	−0.01	.97
Parietal																
Left	−0.33	.03	0.09	.56	−0.24	.11	−0.53	<.001	−0.31	.04	−0.05	.73	−0.04	.79	0.11	.47
Right	−0.33	.03	0.07	.64	−0.24	.12	−0.55	<.001	−0.28	.06	−0.05	.76	−0.08	.60	0.09	.55
Occipital																
Left	−0.33	.03	0.08	.61	−0.24	.11	−0.52	<.001	−0.31	.04	−0.08	.60	−0.06	.71	0.12	.43
Right	−0.31	.04	0.09	.56	−0.23	.13	−0.52	<.001	−0.29	.05	−0.08	.61	−0.05	.74	0.12	.42
Striatum																
Left	−0.31	.04	0.11	.48	−0.25	.09	−0.48	.001	−0.33	.03	−0.11	.49	−0.03	.83	0.14	.38
Right	−0.29	.06	0.14	.37	−0.23	.13	−0.47	.002	−0.33	.03	−0.12	.43	−0.04	.78	0.12	.42
Midbrain																
Left	−0.33	.03	0.07	.65	−0.24	.11	−0.53	.001	−0.31	.04	−0.06	.69	−0.04	.77	0.09	.54
Right	−0.28	.06	0.14	.37	−0.22	.14	−0.49	.001	−0.27	.07	−0.07	.66	−0.01	.94	0.06	.68
Cerebellum																
Left	−0.32	.03	0.09	.57	−0.24	.11	−0.51	.001	−0.33	.03	−0.05	.72	−0.03	.84	0.12	.43
Right	−0.31	.04	0.09	.55	−0.23	.14	−0.50	.001	−0.32	.03	−0.07	.67	−0.04	.79	0.11	.48

Abbreviations: CB1R, type 1 cannabinoid receptor; [18F]MK-9470, fluorine 18–labeled MK-9470; HA, harm avoidance; NS, novelty seeking; NS1, exploratory excitability; NS2, impulsiveness; NS3, extravagance; NS4, disorderliness; P, persistence; RD, reward dependence; SUV, standardized uptake value; VOI, volume of interest.

[a]The limbic VOI is the sum of the mesial temporal and cingulate VOIs.

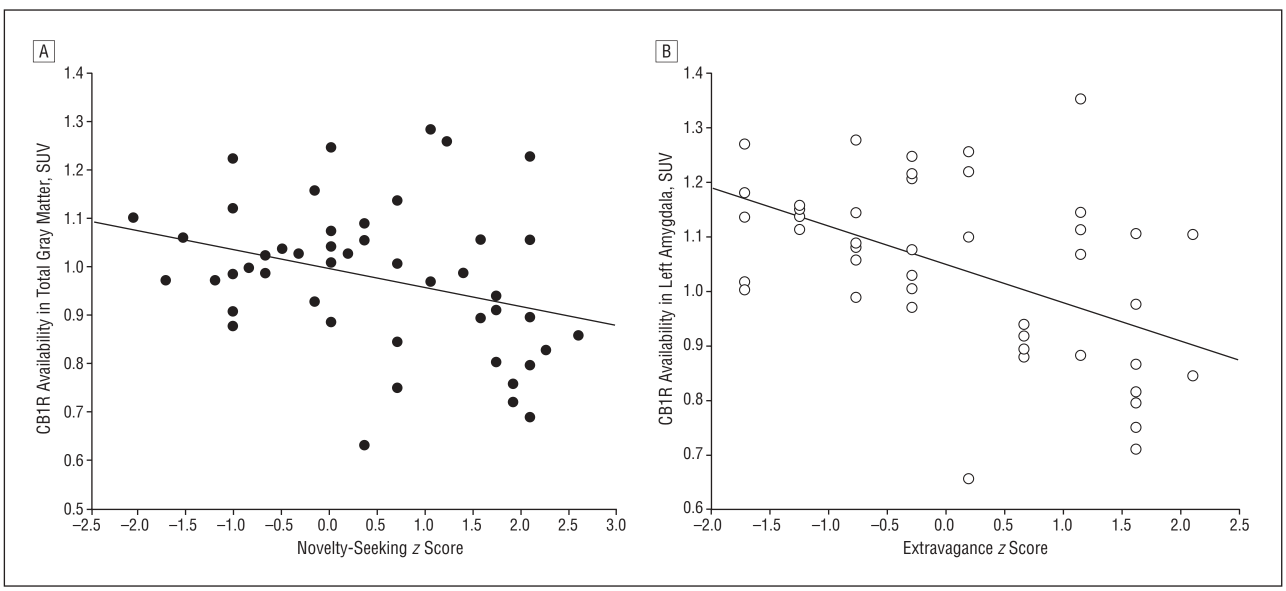

Figure 2. Individual correlation scatterplots showing the relation between novelty-seeking and type 1 cannabinoid receptor (CB1R) availability at a cerebral-wide volume of interest (A) and between the novelty-seeking subdimension extravagance and CB1R availability at a predefined volume of interest of the left amygdala (based on the Wake Forest University Pick Atlas in Montreal Neurological Image space) (B). SUV indicates standardized uptake value.

cific involvement of the CB1R in an integrated limbic-sensory neurocircuitry regarding NS.

The observed differences in CB1R availability may be due to genetically regulated receptor concentration (eg, in relation to CB1R gene polymorphisms [OMIM 114610]), differences in receptor affinity, endogenous competition, or alterations in receptor trafficking. Direct endogenous competition is less likely because the affinity of endogenous cannabinoids is in the micromolar range, compared with 0.7nM for [18F]MK-9470. Theoretically, local high con-

Table 3. Peak Locations for the Inverse Correlation Between [¹⁸F]MK-9470 Availability and the Novelty-Seeking Subdimension Extravagance

Cluster Location	Cluster Level		Voxel Level		Peak Voxel Talairach Coordinate		
	k_E	$P_{cluster}$, Corrected	*t* Value	P_{FWE}, Corrected	x	y	z
Left amygdala/entorhinal cortex (BA28)	5939	<.001	5.20	.005	−16	−20	−24
Left temporopolar cortex (BA38)					−36	24	−24
Right temporopolar cortex (BA38)	1124	.002	5.11	.007	48	20	−17
Right anterior cingulate (BA24)	676	.005	5.01	.009	22	15	32
Right parietal inferior (BA40)	2945	<.001	4.95	.01	52	−44	54
Left parietal inferior/precuneus (BA7/40)	1266	.002	4.78	.02	−24	−54	56
Right frontal gyrus superior (BA6)	527	.007	4.77	.02	12	12	56
Right gyrus cingulus posterior (BA23/31)	413	.01	4.69	.02	20	−56	4

Abbreviations: BA, Brodmann area; [¹⁸F]MK-9470, fluorine 18–labeled MK-9470; FWE, family-wise error (peak height corrected for multiple voxel comparisons); k_E, cluster size extent (number of $2 \times 2 \times 2$-mm³ voxels).

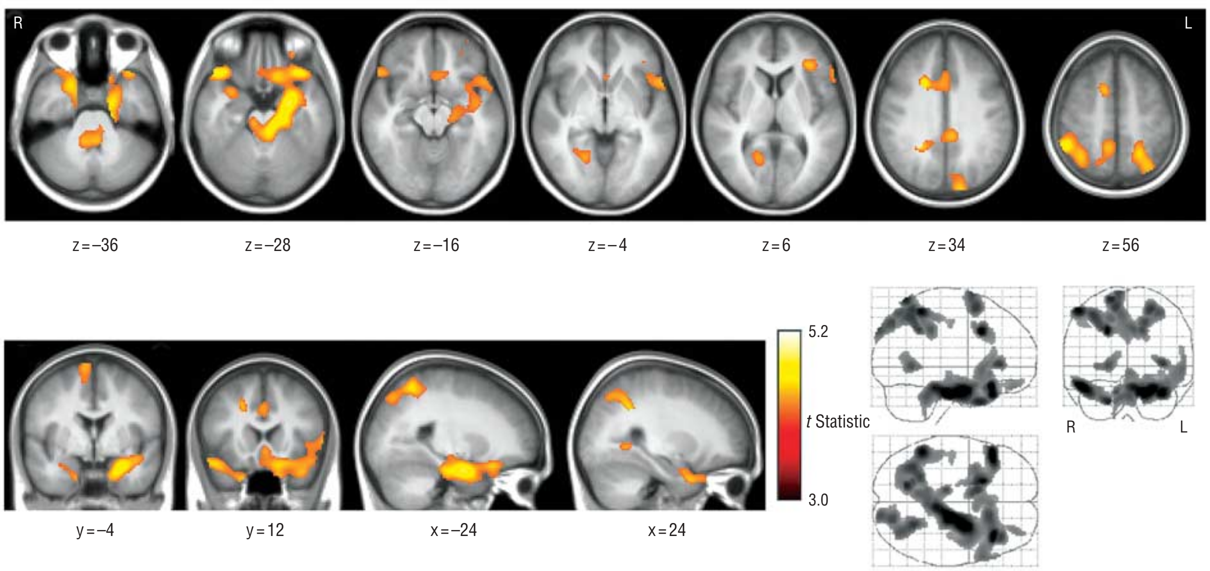

Figure 3. Statistical parametric maps showing the inverse correlation of the novelty-seeking subdimension extravagance with type 1 cannabinoid receptor availability. Clusters are shown at the level of $P<.05$ (corrected for multiple comparisons), with a cluster size extent greater than 400. Clusters are overlaid on an average T1-weighted magnetic resonance image of the studied group and are also shown in glass brain representations on the right. Images are in radiologic orientation.

centrations of endocannabinoids could compensate for this lower affinity, but a recent study using carbon 11–labeled MePPeP ([3*R*,5*R*]-5-[3-methoxy-phenyl]-3-[(*R*)-1-phenylethylamino]-1-[4-trifluoromethyl-phenyl]-pyrrolidine-2-one), a rimonabant-based radioligand with similar affinity and binding the same docking site of the CB1R, showed that high doses of anandamide or fatty acid amide hydrolase inhibitor URB597 were unable to displace the radioligand.[30]

The effect of long-term selective CB1R blockade by inverse agonist treatment on personality dimensions could provide valuable information but has not been assessed so far. To our knowledge, for this as well as for other neurotransmitter systems related to personality dimensions, such as dopamine and serotonin, there are no observational studies on changes in personality dimensions after experimental drug administration in healthy volunteers. In rodents, inconsistent results of CB1R blockade on behavior have been observed regarding anxiolytic and mood-altering effects.[31]

As a complementary strategy in unraveling the complexity of personality neurobiologic mechanisms, subjects with extreme personality phenotypes are also of interest. Individuals high in NS are particularly prone to thrill-seeking behavior, overeating, and substance dependence as well as to irritability and impulsive aggression.[23] In particular, high scores for extravagance are associated with alcohol and nicotine addiction (for review, see Hiroi and Agatsuma[32]). On the basis of behavioral, imaging, genetic, and pharmacologic studies, there are compelling arguments that CB1R is involved in several aspects of substance abuse.[14,15,33-35]

As for methodology, the results found were robust and independent of several potential confounds. A previous

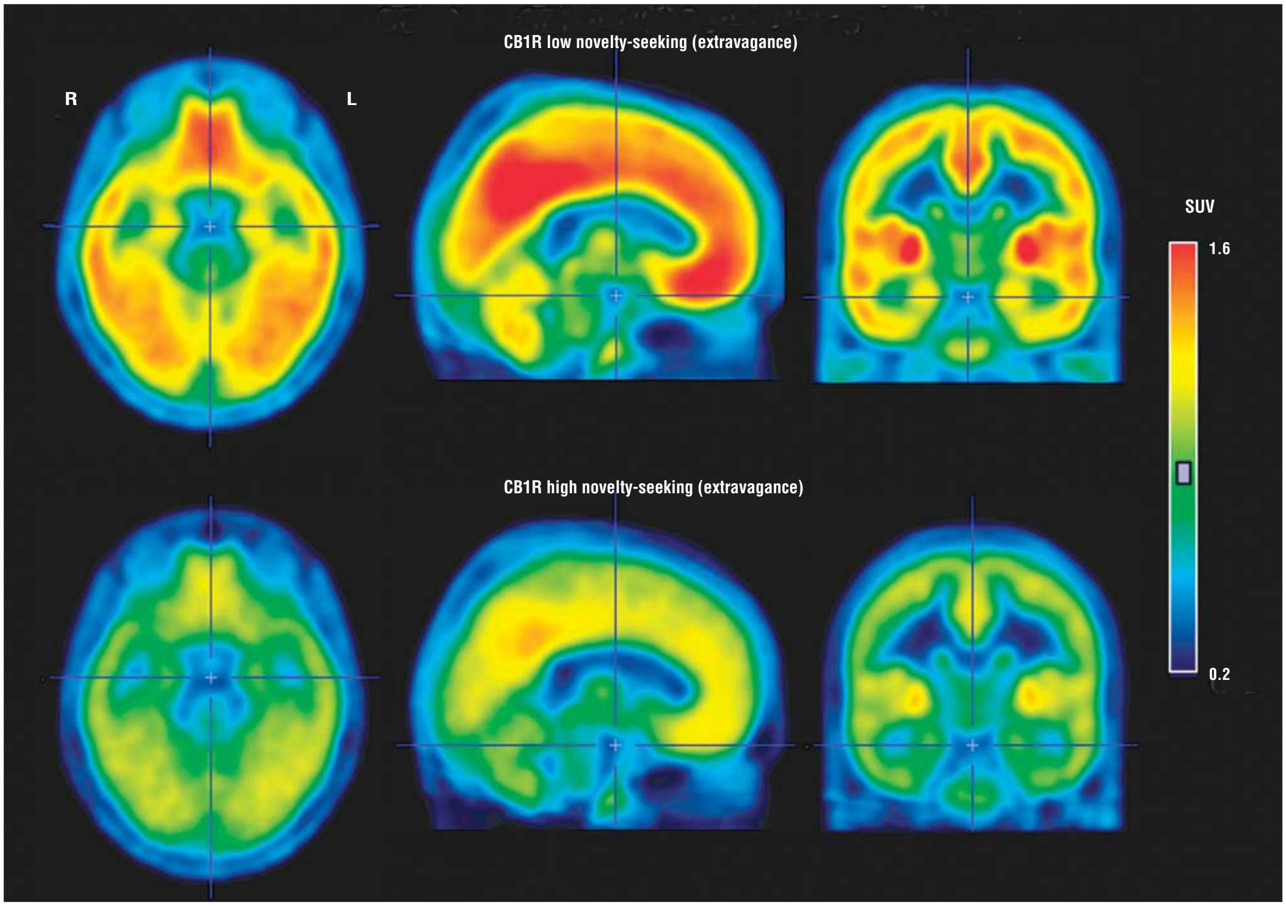

Figure 4. Group comparison of average parametric type 1 cannabinoid receptor (CB1R) availability maps of 10 highest vs 10 lowest scorers on the novelty-seeking subdimension extravagance of the Cloninger Temperament Character Inventory. SUV indicates standardized uptake value.

Table 4. CB1R Availability Between Low and High Novelty Seekers

	CB1R Availability, Mean (SD)	
	Lowest 10 Novelty Seekers	Highest 10 Novelty Seekers
Frontal	1.02 (0.10)	0.86 (0.16)
Temporal	1.09 (0.11)	0.92 (0.18)
Limbic	1.10 (0.12)	0.92 (0.17)
Amygdala	1.08 (0.11)	0.89 (0.18)
Parietal	1.15 (0.12)	0.97 (0.18)
Occipital	1.13 (0.11)	0.95 (0.19)
Striatum	1.16 (0.14)	0.97 (0.20)
Cerebellum	0.98 (0.11)	0.83 (0.15)

Abbreviation: CB1R, type 1 cannabinoid receptor.

study[17] showed an increase of CB1R availability with age in women. However, although age and sex were used as nuisance variables, analysis of the data without these variables resulted in the same outcome. Similarly, inclusion of tracer activity, tracer mass, body weight, or body mass index as nuisance variables did not alter the findings. The results were also not dependent on the CB1R availability PET modeling method or partial volume correction. Normalization on white matter or pons as the reference region (because these have very low CB1R availability) showed similar correlations. Finally, the SUV value for [^{18}F]MK-9470 is not dependent on blood flow or tracer influx, and PET and single-photon emission computed tomographic studies using glucose or perfusion measures have not shown concordant or consistent differences regarding metabolism or perfusion in the observed regions linked to temperament.[36]

Although this study was restricted to a relatively small sample of healthy individuals, most other PET studies on personality were limited to 10 to 30 individuals. Only 1 previous neuroimaging study relating personality characteristics to serotonin$_{1A}$ receptor density has included as many as 49 subjects.[37] A trend toward higher NS and significantly higher value in NS4 (disorderliness) was present in the studied population. Higher NS in patients recruited for imaging studies has been described before and may be related to more openness toward new methodology and investigations.[38] However, because sufficient spread of the population was also present for these dimensions and subdimensions (Table 1), it is unlikely that this has introduced bias in the observed correlations.

Previously, temperament theories have implicated dopamine as the primary neurotransmitter that drives NS behavior, both in normal subjects[1,39,40] and in patients with alcoholism,[41] cocaine abuse,[42] and Parkinson disease.[43] The endocannabinoid system has close connections with the dopaminergic system, but its interaction mechanism is complex and region-specific.[44] Although cannabinoids, applied in vivo, can increase striatal dopaminergic transmission[45] and CB1R inverse agonists can block this, as well as increase the dopamine-releasing and motivational effects of nicotine and ethanol administration,[14,46] there is most likely no direct control of endocannabinoids on dopaminergic neurons.[44,47] Activation of CB1Rs can facilitate the nigrostriatal and mesolimbic dopaminergic systems through a multisynaptic neuronal circuit, eg, by reducing tonic inhibitory control of γ-aminobutyric acid–containing neurons that can occur in the hippocampus, neocortex, and striatum.[48-50] Further studies are needed to elucidate the potential interaction of dopaminergic-cannabinoid neurotransmission regarding personality phenotypes.

In conclusion, we have found a strong relationship between various aspects of human NS and in vivo baseline brain CB1R availability. These findings suggest that biological correlates of personality not only are restricted to various monoamine neurotransmitter systems but also are present in the modulatory endocannabinoid system. This link with NS deserves replication and intensified investigation, especially in light of the association of the endocannabinoid system with addictive behavior and eating disorders.

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