

# Positron Emission Tomography Measures of Endogenous Opioid Neurotransmission and Impulsiveness Traits in Humans

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**Context:** The endogenous opioid system and opioid  $\mu$  receptors ( $\mu$ -receptors) are known to interface environmental events, positive (eg, relevant emotional stimuli) and negative (eg, stressors), with pertinent behavioral responses and to regulate motivated behavior.

**Objective:** To examine the degree to which trait impulsiveness (the tendency to act on cravings and urges rather than to delay gratification) is predicted by baseline  $\mu$ -receptor availability or the response of this system to a standardized, experientially matched stressor.

**Design, Setting, and Patients:** Nineteen young healthy male volunteers completed a personality questionnaire (NEO Personality Inventory, Revised) and underwent positron emission tomography scans with the  $\mu$ -receptor-selective radiotracer carfentanil labeled with carbon 11. Measures of receptor concentrations were obtained at rest and during receipt of an experimentally maintained pain stressor of matched intensity between subjects.

**Main Outcome Measures:** Baseline receptor levels and stress-induced activation of  $\mu$ -opioid system neurotransmission compared between subjects scoring above and below the population median on the NEO Personality Inventory, Revised, impulsiveness subscale and the

orthogonal dimension (deliberation) expected to interact with it.

**Results:** High impulsiveness and low deliberation scores were associated with significantly higher regional  $\mu$ -receptor concentrations and greater stress-induced endogenous opioid system activation. Effects were obtained in the prefrontal and orbitofrontal cortices, anterior cingulate, thalamus, nucleus accumbens, and basolateral amygdala—all regions involved in motivated behavior and the effects of drugs of abuse. Availability of the  $\mu$ -receptor and the magnitude of stress-induced endogenous opioid activation in these regions accounted for 17% to 49% of the variance in these personality traits.

**Conclusions:** Individual differences in the function of the endogenous  $\mu$ -receptor system predict personality traits that confer vulnerability to or resiliency against risky behaviors such as the predisposition to develop substance use disorders. These personality traits are also implicated in psychopathological states (eg, personality disorders) in which variations in the function of this neurotransmitter system also may play a role.

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**T**HERE IS SUBSTANTIAL INTEREST in the mechanistic understanding of traits that may predispose individuals to the development of specific behaviors or psychopathologies. Trait impulsivity has received substantial attention because of its association with risky behaviors (eg, experimentation with drugs, sex, problem gambling, and reckless driving), personality disorders, or even the mortality associated with the mood disorders. Impulsivity, although frequently referred to as a single trait, is better conceptualized as a heterogeneous characteristic consisting of multiple dimensions that include sensation seeking, lack of planning, lack of persistence, and urgency.<sup>1,2</sup> The nonplanning dimension in particular appears

to be more strongly associated with negative risk taking (eg, binge eating and problem gambling).<sup>2</sup> The same holds true for the urgency dimension, which predicts problem behaviors (problem gambling and drinking), whereas factors such as sensation seeking are perhaps more related to risk taking in general.<sup>2,3</sup>

Impulsivity as it refers to pathological behavior has been well studied in current and former substance users. In humans, opiate addicts are more impulsive than nonaddicts, as measured by an increase in the discounting of delayed rewards (ie, the devaluation of rewards as a function of time)<sup>4</sup> and by a reduction in reflection (ie, the tendency to use information when making a decision).<sup>5</sup> In animals, it has been shown that in rodents a preference for im-

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mediate reward over a larger, delayed reward predicted the development of nicotine self-administration and maintenance of use,<sup>6</sup> suggesting that this is a trait that predisposes one to substance dependence. This form of impulsive choice in rats has also been demonstrated to predict cocaine self-administration.<sup>7</sup> Other clinical populations are also characterized by or associated with impulsive behavior such as those with attention-deficit/hyperactivity disorder,<sup>8</sup> borderline personality disorder,<sup>9</sup> eating disorders,<sup>10</sup> and pathological gambling.<sup>11</sup> Whether impulsivity represents a predisposing factor exclusively or is at least partially the result of prior exposure to drugs or ongoing disease is a matter of current debate.

Impulsive characteristics probably do not affect behavior in isolation but are also likely to interact with other factors such as stress. Stressors have a negative effect on initiation and maintenance of drug use, craving, and relapse.<sup>12</sup> Gamblers with high impulsivity also show greater neuroendocrine stress axis and cardiovascular responses to gambling situations relative to their low-impulsivity counterparts.<sup>13</sup> In addition, stressors, particularly when combined with substance abuse, are thought to be modulated by individual impulsivity traits to increase the risk of completed suicides,<sup>14</sup> particularly in younger individuals.<sup>15</sup>

Although it is increasingly clear that impulsivity and stress responses confer vulnerability to substance abuse and other risky behaviors, the neurobiological processes underlying these effects are still poorly understood, particularly in humans. Dopamine neurotransmission appears to be one of the mechanisms involved. Using an animal model of impulsivity that examines anticipatory responses to a food reward as proxy, Dalley and colleagues<sup>16</sup> observed that rats demonstrating greater impulsivity before drug exposure exhibited lower dopamine D<sub>2/3</sub> receptor concentrations in the nucleus accumbens and increased escalation and maintenance of drug self-administration relative to their lower-impulsivity counterparts. Although dopamine function in the ventral basal ganglia is thought to play an important role,<sup>17-19</sup> it is unlikely to take place in isolation. The nucleus accumbens lies at the interface of sensorimotor and limbic systems and, through its connections with the ventral pallidum and the amygdala, forms part of a circuit involved in the integration of cognitive, affective, and motor responses.<sup>20,21</sup> This pathway and interconnected regions (eg, the insular and prefrontal cortices and medial thalamus) are heavily modulated by the endogenous opioid system and opioid  $\mu$  receptors ( $\mu$ -receptors). For example, this neurotransmitter system is recruited when drug-induced dopamine release takes place in the context of environmental novelty and stressors.<sup>22-26</sup> Furthermore, the motivated pursuit and positive behavioral responses to rewards<sup>27,28</sup> are enhanced by the selective administration of  $\mu$ -receptor agonists in the nucleus accumbens/ventral pallidum, nuclei that are central to the regulation of motivated behavior.

The present report examined the orthogonal behavioral traits of impulsiveness (IMP) and deliberation (DLB) as defined by the NEO Personality Inventory, Revised (NEO PI-R), facets<sup>29</sup> as a function of in vivo measures of  $\mu$ -receptor neurotransmission in humans. As defined by the NEO PI-R, the IMP facet refers to the tendency to

act without careful consideration for the consequences of immediate gratification and maps onto urgency, which appears related to problem behaviors such as drug use.<sup>2</sup> The DLB facet, which corresponds to the lack of planning dimension, is thought to act as a moderating, opposing trait.<sup>30</sup>

We used positron emission tomography (PET) and the  $\mu$ -receptor-selective radiotracer carfentanil labeled with carbon 11 while participants were at rest and during the experience of a physical and emotional stressor (moderate levels of sustained pain). Under these experimental conditions, reductions in the availability of  $\mu$ -receptors during the stress challenge reflect the activation of endogenous opioid neurotransmission and  $\mu$ -receptors.<sup>31</sup> We hypothesized that individual levels of IMP and DLB would be positively and negatively associated, respectively, with the functional response of the  $\mu$ -opioid system during the stressor. Furthermore, these effects would take place in motivational circuits modulated by this neurotransmitter system, namely, the rostral anterior cingulate and adjacent medial prefrontal cortex, nucleus accumbens/ventral pallidum, medial thalamus, and amygdala.

## METHODS

### SUBJECTS

Nineteen healthy right-handed, nonsmoking men (age range, 20-30 years; mean [SD] age, 23 [3] years) were recruited via advertisement. In addition to completing physical and neurological examinations, study participants underwent screening using the nonpatient version of the Structured Clinical Interview for DSM-IV. Participants had no history of or current medical, neurological, or psychiatric illnesses, including substance abuse or dependence, and had alcohol intake of less than 5 drinks/wk. Participants reported no current or recent ( $\leq 6$  months) exposure to centrally active prescription or illicit drugs and were asked not to drink alcohol for 48 hours before scanning. Urine drug screens were performed immediately before imaging. Participants reported no family history of psychiatric disease in first-degree relatives. The sample was restricted to men owing to the known sex differences in the regional concentration of  $\mu$ -receptors<sup>32</sup> and in the activity of this neurotransmitter system in response to stress,<sup>33</sup> an effect that is influenced by circulating gonadal steroids.<sup>34</sup> Furthermore, a link between impulsivity and substance use disorders has been shown most conclusively in men.

Protocols were approved by the investigational review boards of the University of Michigan and the University of Maryland and the Radioactive Drug Research Committee at the University of Michigan. Written informed consent was obtained in all participants.

### PERSONALITY INVENTORIES

Participants were administered the NEO PI-R.<sup>29</sup> The facets of IMP (defined as "a lack of control over cravings or desires") and DLB (defined as the "tendency to think carefully before acting") were used as the primary scales of interest. These facets have been previously demonstrated to reflect the dimensions of impulsivity that have been associated with negative risk taking.<sup>2,3</sup> Individuals endorsing less behavioral control or a lack of reflection would display higher IMP and lower DLB scores. The median scores in population samples of comparable age were used to separate the study sample into high- and low-scoring groups (population data: mean [SD] IMP, 15 [4] and

DLB, 18 [4]<sup>29</sup>; study sample data: IMP, 15 [3] and DLB, 18 [3] (median IMP score, 15; high in 9 subjects and low in 10; median DLB score, 18; high in 9 subjects and low in 10).

## STRESS CHALLENGE

We used a physical and emotional stressor consisting of moderate levels of sustained pain of experientially adjusted intensity to activate endogenous opioid/ $\mu$ -opioid system-mediated neurotransmission, as previously described.<sup>31,35</sup> In short, a steady state of moderate muscle pain was maintained from 45 to 65 minutes after the radiotracer administration by a computer-controlled delivery system through the infusion of medication-grade hypertonic saline solution (5%) into the left masseter muscle. In this model of sustained deep somatic pain, the intensity of the painful stimulus is standardized across subjects, as described in detail previously.<sup>36,37</sup> Pain intensity was rated every 15 seconds from 0 (no pain) to 100 (most intense pain imaginable). During the baseline control condition, no infusions took place, and the participant was instructed to lie quietly in the scanner. The pain intensity ratings, obtained every 15 seconds, were recorded in the computer controller and averaged for statistical analyses.

Integrative measures of the pain experience (the sensory and pain affect components) were obtained using the McGill Pain Questionnaire, administered on completion of the challenge.<sup>38</sup> The Positive and Negative Affectivity Scale,<sup>39</sup> assessing the internal affective state of the volunteers, was obtained before and after the challenge. The infusion volume required for pain maintenance was also recorded and provided a measure of sustained pain sensitivity for the individual participant.

## SCANNING PROTOCOLS

Two PET scans per participant were acquired (Siemens HR<sup>+</sup> scanner; Siemens/CTI, Knoxville, Kentucky) in 3-dimensional mode (reconstructed full-width half-maximum resolution, 5.5 mm in plane and 5.0 mm axially), one at baseline and another during the stress challenge. Radiotracer synthesis, image acquisition, coregistration, and reconstruction protocols were identical to those used in previous publications.<sup>31,33,35</sup>

The mean (SD) total radioactivity of the [<sup>11</sup>C]carfentanil administered to each participant in each scan was 535.0 (100.9) MBq (to convert to millicuries, multiply by 0.027), with an average (SD) mass injected of 0.02 (0.01)  $\mu$ g/kg, ensuring that the compound was administered in tracer quantities (ie, subpharmacological doses). Fifty percent of the [<sup>11</sup>C]carfentanil dose was administered as a bolus, with the remainder delivered as a continuous infusion by a computer-controlled automated pump to more rapidly achieve steady-state tracer levels.

Dynamic image data for each of the receptor scans were transformed, on a voxel-by-voxel basis, into the following 2 sets of parametric maps, coregistered to each other: (1) a tracer transport measure ( $K_1$  ratio) proportional to regional cerebral blood flow and (2) a receptor-related measure, the distribution volume ratio at equilibrium. To avoid the need for arterial blood sampling, these parametric images were calculated using a modified Logan graphical analysis,<sup>40</sup> using the occipital cortex (an area devoid of  $\mu$ -receptors) as the reference region. The Logan plot became linear 5 to 7 minutes after the start of radiotracer administration, with a slope proportional to the  $(B_{\max}/K_d) + 1$  for this receptor site, where  $B_{\max}/K_d$  is the receptor-related measure of  $\mu$ -receptor availability or  $\mu$ -receptor nondisplaceable binding potential ( $BP_{ND}$ ),  $B_{\max}$  is the receptor concentration, and  $K_d$  is the receptor affinity for the radiotracer.

Magnetic resonance (MR) images were acquired on a 1.5-T scanner (Signa; General Electric Systems, Milwaukee, Wisconsin) for anatomical localization and coregistration to standard-

ized stereotactic coordinates. Acquisition sequences were axial spoiled gradient recalled MR (echo time, 5.5 milliseconds; repetition time, 14 milliseconds; inversion time, 300 milliseconds; flip angle, 20°; number of excitations, 1; 124 contiguous images; thickness, 1.5 mm; field of view, 24 cm; image matrix, 256  $\times$  256 pixels; pixel size, 0.94 mm). The T1-weighted MR and PET images of each subject were then coregistered to each other using a mutual information algorithm as previously described.<sup>31,35</sup>

## IMAGE ANALYSES

Differences between groups (high IMP/low IMP and low DLB/high DLB, using 2-tailed unpaired *t* tests) were mapped into stereotactic space using *z* maps of statistical significance with a modified version of the Statistical Parametric Mapping software (SPM99; Wellcome Department of Cognitive Neurology, University College, London, England), MATLAB software (MathWorks, Natick, Massachusetts), and a general linear model. No global normalization was applied to the data, and therefore the calculations presented are based on absolute  $B_{\max}/K_d$  estimates. Only regions with specific  $\mu$ -receptor binding were included in the analyses (voxels with  $BP_{ND} > 0.2$  as calculated with SPM99). A priori hypothesized regions were deemed significant at  $P < .0001$  uncorrected for multiple comparisons. For other regions, significant differences were detected using a statistical threshold that controls for a type I error rate at  $P = .05$  for multiple comparisons.<sup>41</sup> Numerical values for each region were obtained by averaging the values of voxels contained in each significant cluster, up to  $P = .001$ . These data were extracted for quantification of regional changes in  $BP_{ND}$ , graphing, determination of correlation coefficients (Pearson correlations at  $P < .05$ ), ruling out the presence of outliers, and further statistical analyses with commercially available statistical software (SPSS for Macintosh, version 11.0.3; SPSS Inc, Chicago, Illinois).

## RESULTS

### PSYCHOPHYSICAL MEASURES

The use of the adaptive, experientially adjusted stimulus delivery system produced comparable perceptions of the pain stressor among participants by individually titrating the rate of infusion of the algescic substance. No significant group differences were obtained in psychophysical measures of pain or affective state during the stress challenge (high vs low IMP and high vs low DLB) (**Table 1**). As would be expected, IMP and DLB scores were negatively correlated ( $r = -0.55$ ;  $P = .02$ ).

### BASELINE $\mu$ -RECEPTOR $BP_{ND}$

#### Impulsiveness

Significant differences in baseline  $\mu$ -receptor  $BP_{ND}$  were observed between high and low IMP groups. Specifically, greater regional  $\mu$ -receptor  $BP_{ND}$  was observed in the participants with high IMP scores compared with those with low IMP scores, in the right anterior cingulate and adjacent medial frontal cortex, right ventral basal ganglia (nucleus accumbens, extending into the ventral pallidum), and basolateral area of the right amygdala (**Table 2** and **Figure 1**). No effects were obtained in the opposite direction.

Significant positive correlations were obtained between  $\mu$ -receptor  $BP_{ND}$  and IMP scores within the right dorsal anterior cingulate ( $r = 0.59$ ;  $P < .01$ ), right ventral

**Table 1. Psychophysical Measures<sup>a</sup>**

	IMP			DLB		
	High Scores (n=9)	Low Scores (n=10)	P Value <sup>b</sup>	Low Scores (n=10)	High Scores (n=9)	P Value <sup>b</sup>
Average visual analog scale intensity	32 (16)	29 (12)	.60	34 (13)	26 (13)	.20
McGill Pain Questionnaire total score	21.7 (8.4)	20.4 (3.1)	.66	23.3 (6.41)	18.4 (4.61)	.08
Positive and Negative Affectivity Scale						
Positive affect	16.9 (10.1)	16.2 (9.2)	.90	18.8 (10.6)	14.0 (7.6)	.30
Negative affect	2.6 (3.5)	3.3 (2.9)	.60	2.7 (3.3)	3.2 (3.2)	.70
Total volume of hypertonic saline solution (5%), $\mu$ L	2654 (1568)	3296 (878)	.28	2532 (1532)	3503 (609)	.09

Abbreviations: DLB, deliberation; IMP, impulsiveness.

<sup>a</sup>Data are expressed as mean (SD).

<sup>b</sup>Calculated using 2-sample *t* tests for differences between high and low IMP and DLB.

basal ganglia ( $r=0.50$ ;  $P=.03$ ), and right amygdala ( $r=0.49$ ;  $P=.03$ ).

### Deliberation

Participants with high DLB scores showed significantly lower baseline regional  $\mu$ -receptor BP<sub>ND</sub> compared with the low DLB group in the right dorsolateral prefrontal cortex, right dorsal anterior cingulate and medial frontal gyrus, left ventral basal ganglia, right thalamus extending inferiorly into the hypothalamus, and right basolateral amygdala (Table 2 and Figure 1). No effects were observed in the opposite direction.

Significant negative correlations between  $\mu$ -receptor BP<sub>ND</sub> and DLB scores were noted within the right prefrontal cortex ( $r=-0.65$ ;  $P=.003$ ), right anterior cingulate (2 peaks in the *x, y, z* coordinates, 16, 10, 39 mm [ $r=-0.56$ ;  $P=.01$ ] and 8, 14, 26 mm [ $r=-0.46$ ;  $P=.04$ ]), and right amygdala ( $r=-0.54$ ;  $P=.02$ ).

### STRESS-INDUCED ACTIVATION OF $\mu$ -OPIOID NEUROTRANSMISSION

#### Impulsiveness

Participants with higher IMP scores demonstrated significantly greater stress-induced activation of  $\mu$ -opioid receptor-mediated neurotransmission, compared with subjects in the low IMP group, in the left orbitofrontal cortex, right dorsal anterior cingulate, and ventral basal ganglia bilaterally with extension into the hypothalamus, left anterior thalamus, and basolateral amygdala bilaterally (Table 3 and Figure 2). There were no regions where the high IMP group showed significantly lower stress-induced changes in  $\mu$ -receptor BP<sub>ND</sub> relative to the low IMP group.

Significant positive correlations between  $\mu$ -opioid system activation (baseline BP<sub>ND</sub>-pain BP<sub>ND</sub>) and IMP scores were noted in the left orbitofrontal cortex ( $r=0.63$ ;  $P=.005$ ), right ventral basal ganglia ( $r=0.49$ ;  $P=.03$ ), left anterior thalamus ( $r=0.61$ ;  $P=.006$ ), and right amygdala ( $r=0.50$ ;  $P=.03$ ).

#### Deliberation

Significant differences in stress-induced activation of endogenous opioid neurotransmission were also detected

**Table 2. Differences in Baseline Regional Opioid  $\mu$ -Receptor BP<sub>ND</sub>**

Brain Region	<i>x, y, z</i> Coordinates, mm <sup>a</sup>	Cluster Size, mm <sup>3b</sup>	<i>z</i> Score
High IMP > low IMP			
Right anterior cingulate/medial frontal cortex <sup>c</sup>	15, 3, 47	1294	4.37
Right ventral basal ganglia extending into ventral pallidum <sup>c</sup>	7, -3, -3	2660	5.85
Right basolateral amygdala	31, -2, -23	440	3.70
Low DLB > high DLB			
Right prefrontal cortex	46, 7, 52	2676	4.84
Right anterior cingulate/medial frontal cortex <sup>c</sup>	16, 10, 39	1294	4.02
Right thalamus <sup>c</sup>	12, -9, 7	3218	4.19
Right ventral basal ganglia/hypothalamus	6, -3, -4	222	5.45
Left ventral basal ganglia	-4, 5, -14	1361	4.18
Right basolateral amygdala	28, 0, -26	416	4.56

Abbreviations: BP<sub>ND</sub>, nondisplaceable binding potential; DLB, deliberation; IMP, impulsiveness.

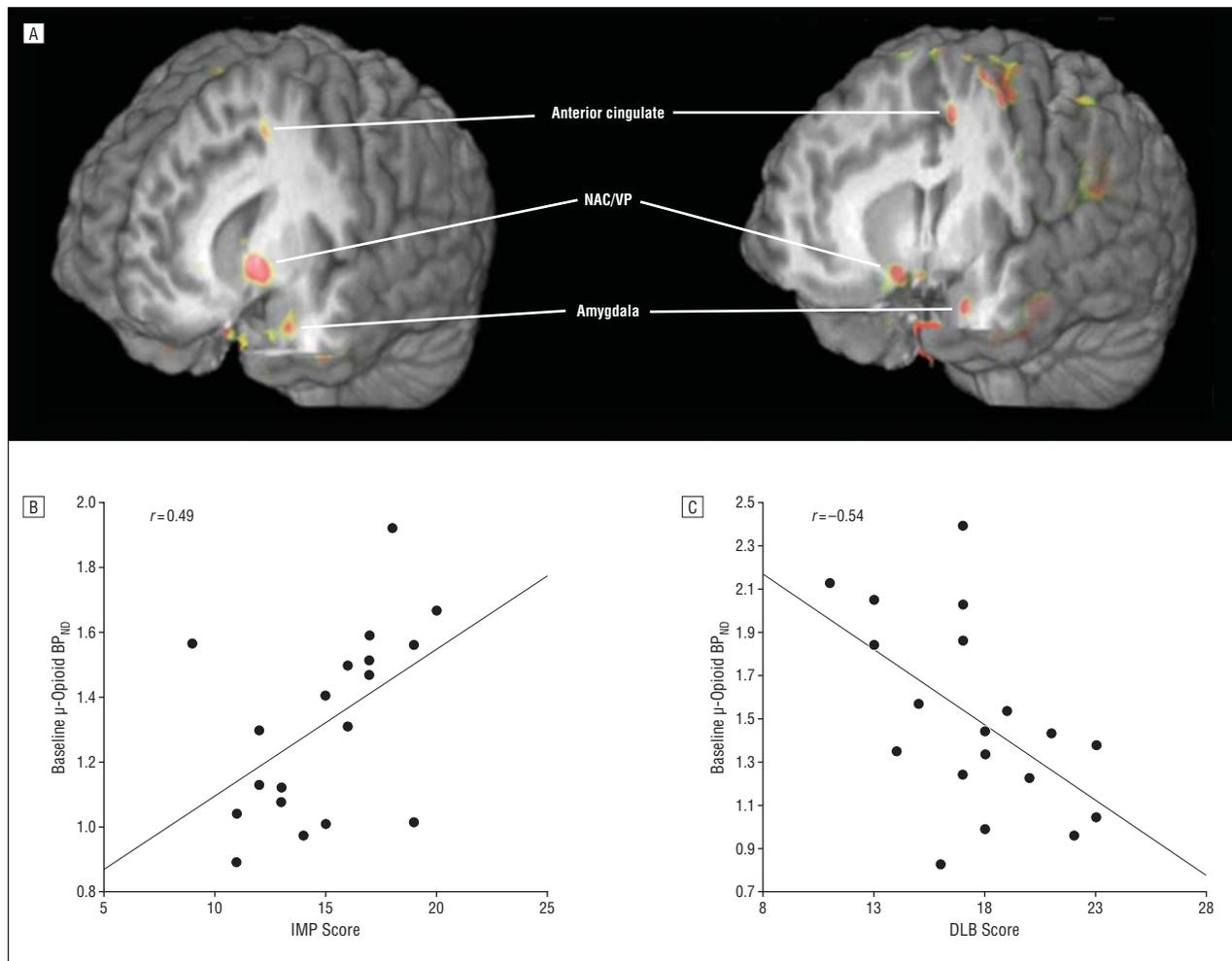
<sup>a</sup>Indicates the Montreal Neurological Institute coordinates, for significant peaks.

<sup>b</sup>Diencephalic regions included the thalamus and hypothalamus.

<sup>c</sup>Multiple peaks were detected in this region. Coordinates indicate center of largest peak.

between the high DLB and low DLB groups. Opposite the high IMP group and in a direction similar to that observed for baseline binding measures, the high DLB group showed lower stress-induced activation of the endogenous opioid system compared with the low DLB group in a number of brain regions. These included the left dorsolateral prefrontal cortex, right anterior cingulate and medial frontal cortex, orbitofrontal cortex bilaterally, ventral basal ganglia bilaterally with extension into the anterior hypothalamus, and basolateral amygdala bilaterally. No effects were obtained in the opposite direction (Table 3 and Figure 2).

Significant negative correlations between  $\mu$ -opioid system activation and DLB scores were observed within the left dorsolateral prefrontal cortex ( $r=-0.69$ ;  $P=.001$ ), right anterior cingulate ( $r=-0.61$ ;  $P=.005$ ), right ( $r=-0.54$ ;  $P=.02$ ) and left ( $r=-0.60$ ;  $P=.01$ ) ventral basal ganglia,



**Figure 1.** Association between impulsiveness (IMP) and deliberation (DLB) scores and baseline  $\mu$ -opioid receptor ( $\mu$ -receptor) availability. A, Areas in which significant differences in  $\mu$ -receptor availability in vivo were observed between individuals with high and low IMP scores (left) and DLB scores (right). B and C, Correlations between  $\mu$ -receptor nondisplaceable binding potential ( $BP_{ND}$ ) and IMP and DLB scores for the cluster centered in the nucleus accumbens/ventral pallidum (NAC/VP).

and right amygdala ( $r = -0.70$ ;  $P = .001$ ). The left amygdala cluster followed a similar pattern at trend levels of correlation ( $r = -0.41$ ;  $P = .08$ ).

#### INTERACTIONS AMONG MEASURES: CONJUNCTION ANALYSES

These data suggested the presence of some but not complete regional overlap for the effects of the related traits IMP and DLB, with neurochemical findings in opposite directions, as would be expected for opposing traits. In an additional analysis, we sought to determine how the individual combination of these 2 behavioral traits segregated at the levels of anatomical and neurochemical substrates ( $\mu$ -receptor availability and neurotransmitter responses to stress). Individuals were divided into behavioral risk groups based on their IMP and DLB classifications, resulting in 3 groups with relatively high (high IMP/low DLB,  $n = 7$ ), low (low IMP/high DLB,  $n = 7$ ), or intermediate (high IMP/high DLB or low IMP/low DLB,  $n = 5$ ) behavioral trait vulnerability. Intermediate groups were not separated because of the small sample sizes in those cells. Then, for the baseline and activation conditions, we identified brain areas

of coincidence where  $BP_{ND}$  and stress-induced release were greater in the high IMP and low DLB groups. For this purpose, the ImCalc function within SPM99 was used to generate a mask that contained only those voxels that were significantly different above the level of  $P = .007$  ( $t = 1.99$ ) in both of the contrasts using the following formula:

$$(\text{Contrast 1 } t \text{ Score} > 1.99) \times (\text{Contrast 2 } t \text{ Score} > 1.99),$$

where Contrast 1 indicates high vs low IMP and Contrast 2, low vs high IMP. The resulting area of coincidence contained voxels that were independently significant in each and both of the contrasts, for which joint probability is given by multiplying the probabilities for each contrast ( $0.007 \times 0.007 = P \leq .000049$ ) (eg, in Dolcos et al<sup>42</sup>). Measurement values for the regions identified were then extracted for quantification of regional changes in  $BP_{ND}$ , graphing, and statistical analyses.

#### BASELINE

The following 3 regions showed significant overlap between the 2 traits: right anterior cingulate, right ventral pallidum, and right amygdala. The baseline  $BP_{ND}$  for each

**Table 3. Differences in Stress-Induced Changes in Regional Opioid  $\mu$  Receptor BP<sub>ND</sub><sup>a</sup>**

Brain Region	x, y, z Coordinates, mm <sup>b</sup>	Cluster Size, mm <sup>3</sup>	z Score	Baseline BP <sub>ND</sub>		Pain BP <sub>ND</sub>		Change, % <sup>c</sup>	
				High IMP	Low IMP	High IMP	Low IMP	High IMP	Low IMP
High IMP > low IMP <sup>d</sup>									
Left orbitofrontal cortex	-13, 29, -25	434	3.87	0.87 (0.32)	0.76 (0.21)	0.62 (0.17)	0.82 (0.19)	-33.4	7.3
Right anterior cingulate	15, 2, 47	661	4.59	0.76 (0.29)	0.41 (0.13)	0.55 (0.18)	0.53 (0.13)	-32.0	24.5
Left thalamus	-10, 0, 5	629	3.98	1.10 (0.22)	1.02 (0.10)	0.98 (0.17)	1.24 (0.20)	-11.9	18.9
Right ventral basal ganglia extending into ventral pallidum <sup>e</sup>	6, -3, -4	2776	7.46	1.97 (0.47)	1.54 (0.19)	1.41 (0.15)	1.57 (0.20)	-33.3	1.8
Left ventral basal ganglia	-8, 15, -5	233	3.69	2.32 (0.34)	2.06 (0.20)	2.01 (0.32)	2.16 (0.34)	-14.3	4.9
Right basolateral amygdala	29, -1, -27	466	4.83	1.47 (0.28)	1.18 (0.25)	1.09 (0.24)	1.19 (0.11)	-29.5	0.6
Left basolateral amygdala	-20, 3, -30	337	5.61	1.16 (0.35)	0.86 (0.27)	0.86 (0.22)	0.97 (0.24)	-29.4	12.1
Low DLB > high DLB <sup>d</sup>									
Bilateral orbitofrontal cortex <sup>e</sup>	-7, 34, -26	2206	3.73	0.69 (0.21)	0.88 (0.13)	0.83 (0.09)	0.66 (0.09)	18.5	-27.7
Left prefrontal cortex	-33, 7, 38	2266	3.90	0.42 (0.12)	0.59 (0.22)	0.59 (0.15)	0.44 (0.13)	34.1	-30.0
Right anterior cingulate	16, 10, 39	3596	4.48	0.54 (0.09)	0.76 (0.18)	0.63 (0.12)	0.56 (0.14)	25.8	-44.2
Right ventral basal ganglia extending into ventral pallidum <sup>e</sup>	6, -3, -4	2449	4.64	1.25 (0.11)	1.57 (0.23)	1.41 (0.15)	1.26 (0.11)	12.0	-22.0
Left ventral basal ganglia	-2, 4, -15	578	4.57	0.84 (0.27)	1.15 (0.24)	1.03 (0.25)	0.85 (0.28)	19.9	-29.0
Right basolateral amygdala	28, 0, -26	599	4.40	1.21 (0.18)	1.55 (0.39)	1.30 (0.11)	1.17 (0.23)	7.0	-28.3
Left basolateral amygdala	-21, 6, -30	145	4.61	0.86 (0.19)	1.03 (0.36)	1.12 (0.26)	0.74 (0.19)	26.4	-32.9

Abbreviations: BP<sub>ND</sub>, nondisplaceable binding potential; DLB, deliberation facet of the NEO Personality Inventory, Revised (NEO PI-R); IMP, impulsiveness facet of the NEO PI-R.

<sup>a</sup>Unless otherwise indicated, data are expressed as mean (SD).

<sup>b</sup>Indicates the Montreal Neurological Institute coordinates, in millimeters, for significant peaks.

<sup>c</sup>Represents the mean percentage of change in regional opioid  $\mu$  receptor BP<sub>ND</sub> between baseline and stress conditions.

<sup>d</sup>Measured by baseline pain.

<sup>e</sup>Multiple peaks were detected in this region. Coordinates indicate the center of the largest peak. Diencephalic regions included the thalamus and hypothalamus.

of the regions analyzed increased in a stepwise progression from the group with the lowest vulnerability traits (low IMP/high DLB) to the highest (high IMP/low DLB) (**Figure 3** and **Table 4**). Analysis of variance showed significant effects of risk classification for the right anterior cingulate ( $F_{2,16}=8.009$ ;  $P=.004$ ), right nucleus accumbens/ventral pallidum ( $F_{2,16}=8.157$ ;  $P=.004$ ), and right amygdala ( $F_{2,16}=5.280$ ;  $P=.02$ ). Results of the post hoc tests (Tukey honestly significantly different test) are shown in Table 4. The intermediate high IMP/high DLB and low IMP/low DLB groups showed similar results for these regions (data not shown).

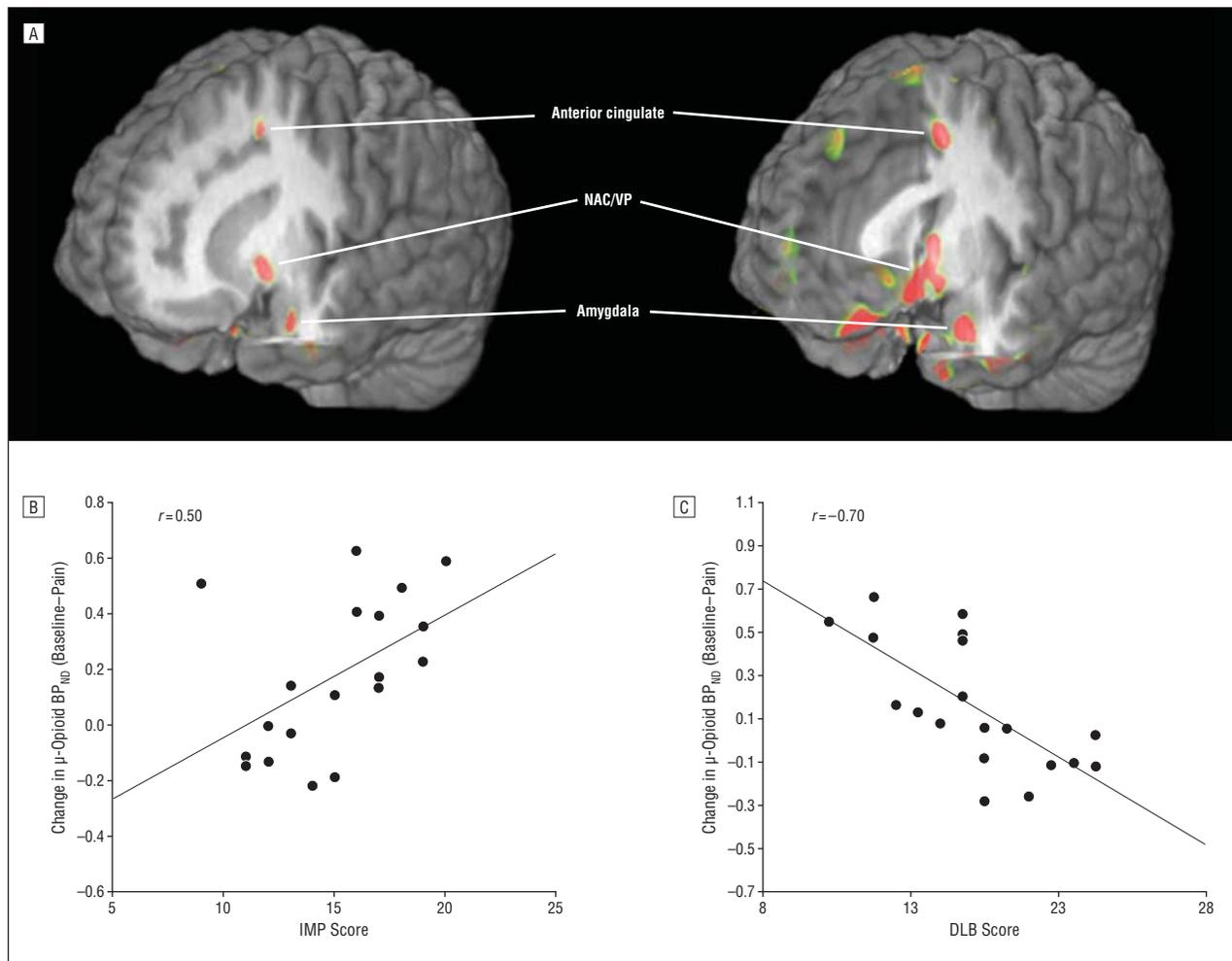
### STRESS-INDUCED ACTIVATION OF $\mu$ -OPIOID SYSTEM NEUROTRANSMISSION

The following 5 regions showed significant activation overlap among traits: right anterior cingulate, right and left nucleus accumbens/ventral pallidum, and right and left amygdala. Again, we observed a stepwise progression in stress-induced endogenous opioid system activation, with the smallest change in the group with the fewest vulnerable behavioral traits (low IMP/high DLB) and the greatest from the group with the most (high IMP/low DLB) (**Figure 3** and **Table 5**). A significant main effect of group on stress-induced activation of  $\mu$ -opioid system neurotransmission was present for the right anterior cingulate ( $F_{2,16}=10.53$ ;  $P=.001$ ), right ventral pallidum ( $F_{2,16}=40.91$ ;  $P<.001$ ), left ventral pallidum ( $F_{2,16}=5.10$ ;  $P=.02$ ), right amygdala ( $F_{2,16}=23.54$ ;

$P<.001$ ), and left amygdala ( $F_{2,16}=5.05$ ;  $P=.02$ ). Post hoc test results are shown in Table 5. As with the baseline data, intermediate groups showed similar results for the overlapping regions (data not shown).

### COMMENT

The present study demonstrates that IMP and DLB are highly predicted by measures of endogenous opioid function in limbic regions. The personality facets studied herein refer to the tendency to act rashly and without forethought and have been associated with various psychopathologies and risky phenotypes (eg, drug consumption, pathological gambling, and personality disorders).<sup>2,3,9,11</sup> We have 3 major findings. First, we found that individuals displaying these risky phenotypes (eg, high IMP or low DLB) have higher  $\mu$ -receptor BP<sub>ND</sub> at rest within regions implicated in decision making, reward seeking, and emotional responsivity. This higher BP<sub>ND</sub> reflects a greater availability of  $\mu$ -receptors in a high-affinity state (eg, binding to an agonist radiotracer at low tracer concentrations).<sup>43</sup> Second, after a pain stress challenge, we found larger reductions in BP<sub>ND</sub> from baseline in individuals displaying high IMP/low DLB in overlapping regions. These reductions reflect processes related to the release of endogenous opioids interacting with  $\mu$ -receptors; thus, these receptors are no longer available for binding to the radioligand.<sup>43,44</sup> Third, we demonstrated a cumulative effect of personality traits on in vivo measures of  $\mu$ -receptor-



**Figure 2.** Association between impulsiveness (IMP) and deliberation (DLB) scores and stress-induced activation of  $\mu$ -opioid receptor ( $\mu$ -receptor)-mediated neurotransmission. A, Areas in which significant differences in endogenous opioid activity during stress were observed between individuals with high and low IMP scores (left) and DLB scores (right). B and C, Correlations between opioid system activation and IMP and DLB scores for the cluster centered in the nucleus accumbens/ventral pallidum (NAC/VP).  $BP_{ND}$  indicates nondisplaceable binding potential.

mediated neurotransmission. We found that individuals exhibiting extreme traits (high IMP/low DLB and low IMP/high DLB) display the greatest and smallest, respectively, baseline  $\mu$ -receptor availability and endogenous opioid system responses to the pain stressor used.

Personality traits, such as IMP, likely manifest as a result of a variety of biological and genetic factors. Converging lines of evidence point to the opioid system as a candidate system involved in the expression of the nonplanning dimension of impulsiveness. Previous research on a measure related to the nonplanning dimension of impulsiveness, delayed discounting, which refers to the devaluation of rewards as a function of time, has indicated prominent roles for several neurotransmitters, including serotonin,<sup>45</sup> dopamine,<sup>45</sup> and, based on the present results, opioids. Manipulation of the opioid system affects preferences for immediate rewards; for instance, in animal models, Kieres and colleagues<sup>46</sup> demonstrated that morphine could increase the rate of delayed discounting among rats, an effect blocked by naloxone hydrochloride. Few human studies have directly addressed this issue; however, multiple studies have shown that several psychiatric groups, such as pathological gam-

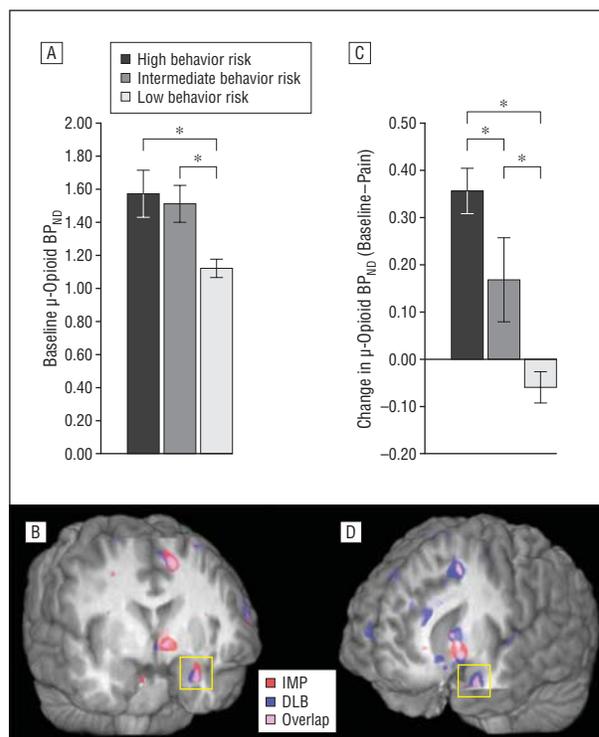
blers<sup>47</sup> and those with drug addiction (eg, to opiates<sup>4</sup>), show steeper discounting of delayed rewards. In addition, individuals with opiate addiction show a greater preference for immediate monetary rewards relative to those without an addiction,<sup>4</sup> a preference that is potentiated after mild opiate deprivation.<sup>48</sup>

In the present work, we show that individuals displaying risky personality traits (high IMP/low DLB) showed significantly greater regional  $\mu$ -receptor availability at baseline and stress-induced regional  $\mu$ -opioid system activation when compared with individuals endorsing low IMP/high DLB. These effects were observed in multiple brain regions, including the amygdala, nucleus accumbens/ventral pallidum, and orbitofrontal, medial prefrontal, and cingulate cortices. Individually, these regions are known to be involved in impulsive choice, reward seeking, and cognitive-emotional integration and are heavily modulated by  $\mu$ -receptors.<sup>49-51</sup> Many of these regions, particularly the prefrontal cortex and nucleus accumbens, have been implicated in disorders characterized by or associated with impulsive behavior such as attention-deficit/hyperactivity disorder,<sup>52</sup> substance abuse disorders,<sup>53</sup> and pathological gambling.<sup>54</sup> Manipulation

of nucleus accumbens activity can directly influence impulsive behavior (ie, stimulation of the nucleus accumbens core has been shown to decrease impulsive choice),<sup>55</sup> whereas lesions increase impulsive choice.<sup>56</sup> Similar roles have been ascribed to the prefrontal and orbitofrontal cortices and amygdala, thought to contribute to decision making by the cognitive and emotional evaluation of future consequences.<sup>57,58</sup> Collectively, these regions are thought to be involved in the pursuit and receipt of natural rewards, decision making, and, more generally, motivated behavior.<sup>25,59-65</sup> Neurobiologically, this regulation of motivated behavior is thought to take place as a result of their extensive reciprocal connections, which are well described among the amygdala, prefrontal cortex, nucleus accumbens, ventral pallidum, and mediodorsal nucleus of the thalamus.<sup>66,67</sup>

We also observed greater stress-induced activation of this neurotransmitter system in subjects scoring above the population average of NEO PI-R IMP scores, compared with subjects scoring below, in regions at least partially overlapping with those where baseline differences were observed. Opposite effects (lower stress-induced opioid system activity in high-scoring subjects) were observed for the orthogonal domain, DLB. These data then support the contention that there are interactions between neurobiological processes related to stress responsiveness and impulsivity. Physiological stress responses seem greater in more impulsive individuals, even among risky populations (eg, pathological gamblers<sup>13</sup>) and therefore point to factors that may contribute to interindividual variations in risky behavior in various pathological states. Outbred rats exposed to the mild stress of a novel environment may show high or low rates of exploratory locomotion, and rats with high rates learned to self-administer psychostimulants faster than those with low rates.<sup>68-71</sup> Activation of DA neurotransmission and stress responses during risky behavior has been proposed as the critical variable underlying the reinforcement of this behavior in the more impulsive individuals,<sup>72</sup> an effect that may be mediated by the increase in corticosterone induced by the stressor.<sup>73-76</sup> Relevant to the results presented herein, rats with high rates, which are more prone to acquire drug self-administration, also show increased nucleus accumbens proenkephalin gene expression.<sup>77</sup>

A conjunction analysis more formally determined the overlap in the processes and brain regions where IMP and DLB effects were obtained. It demonstrated a cumulative effect of personality risk factors on measures of  $\mu$ -opioid system neurotransmission. Extreme traits (high IMP/low DLB and low IMP/high DLB) demonstrated greatest and smallest endogenous opioid system responses, respectively, to a standardized stressor and  $\mu$ -receptor availability at baseline. Intermediate compounded traits (high IMP/high DLB and low IMP/low DLB) showed intermediate effects for both measures. This is consistent with the observation that the accumulation of risky traits is associated with a greater probability of problem behaviors and substance use problems.<sup>78</sup> The coalescence of IMP and DLB effects were observed in the dorsal anterior cingulate, nucleus accumbens/ventral pallidum, and amygdala, centrally implicated in decision making and motivated behavior, as noted in the preceding paragraphs.<sup>20,21,79</sup>



**Figure 3.** Conjunction analysis of impulsiveness (IMP) and deliberation (DLB) effects on  $\mu$ -opioid receptor ( $\mu$ -receptor) nondisplaceable binding potential (BP<sub>ND</sub>) and stress-induced endogenous opioid system activity. A, The  $\mu$ -receptor BP<sub>ND</sub> for high (high IMP/low DLB), intermediate (low IMP/low DLB or high IMP/high DLB), and low (low IMP/high DLB) behavioral risk groups in the amygdala. \* $P < .05$ . Bars indicate mean values; error bars, standard error of the mean. B, Areas with color overlap show coincidence regions for IMP and DLB effects on  $\mu$ -receptor BP<sub>ND</sub>. The amygdala (the baseline  $\mu$ -opioid BP<sub>ND</sub> that is shown in A) is highlighted by the yellow square. C, Stress-induced  $\mu$ -opioid system activation for high, intermediate, and low behavioral risk groups in the amygdala. \* $P < .05$ . D, Areas with color overlap show coincidence regions for IMP and DLB effects on stress-induced  $\mu$ -opioid system activation. The amygdala (the stress-induced  $\mu$ -opioid system activation that is shown in C) is highlighted by the yellow square.

Regional  $\mu$ -receptor availability and  $\mu$ -opioid system activation during the stressor accounted for 24% to 40% of the variance in IMP scores and 17% to 49% of the variance in DLB scores. In contrast, no significant relationships have been reported between NEO PI-R IMP scores and dopamine D<sub>2/3</sub> receptor binding in the basal ganglia as measured with [<sup>11</sup>C]raclopride<sup>80</sup> or with dopamine turnover as measured with fluorodopa F 18.<sup>81</sup> Amphetamine-induced dopamine release in the ventral basal ganglia accounted for 9% to 20% of the variance in NEO PI-R IMP scores in a healthy sample similar to the one studied in the present report.<sup>80</sup>

Because the study sample was restricted to male subjects to reduce experimental complexity, additional questions remain that will need to be addressed in subsequent work. The effects of sex, gonadal steroids, and age  $\times$  sex interactions have been described for  $\mu$ -receptors and stress-induced  $\mu$ -opioid system activation.<sup>32-34</sup> These effects may or may not be related to IMP and DLB traits and will require specific studies addressing their effects. From a different perspective, impulsive behavior has been suggested to be a result of prefrontal cortex dysfunction. For instance, Bechara and others<sup>57,58</sup> have described prob-

**Table 4. Conjunction Analyses at Baseline<sup>a</sup>**

Region	Baseline BP <sub>ND</sub> by Risk Group, Mean (SEM)			Group Comparison, P Value		
	High	Intermediate	Low	High vs Low	High vs Intermediate	Low vs Intermediate
Right anterior cingulate	0.87 (0.09)	0.63 (0.12)	0.50 (0.05)	.003	.08	.43
Right ventral basal ganglia extending into ventral pallium <sup>b</sup>	1.76 (0.11)	1.54 (0.11)	1.29 (0.08)	.003	.22	.16
Right basolateral amygdala	1.58 (0.14)	1.52 (0.11)	1.13 (0.06)	.02	.93	.70

Abbreviation: BP<sub>ND</sub>, nondisplaceable binding potential.

<sup>a</sup>Post hoc analyses were used to calculate the P values. High, intermediate, and low risk groups are described in the "Interactions Among Measures: Conjunction Analyses" subsection of the "Results" section.

<sup>b</sup>Multiple peaks were detected in this region. Diencephalic regions included the thalamus and hypothalamus.

**Table 5. Conjunction Analyses of Stress-Induced Changes<sup>a</sup>**

Region	Baseline BP <sub>ND</sub> by Risk Group, Mean (SEM)			Pain BP <sub>ND</sub> by Risk Group, Mean (SEM)			Group Comparison, P Value		
	High	Intermediate	Low	High	Intermediate	Low	High vs Low	High vs Intermediate	Low vs Intermediate
Right anterior cingulate	0.79 (0.09)	0.53 (0.07)	0.43 (0.05)	0.53 (0.07)	0.51 (0.07)	0.56 (0.05)	.001	.046	.30
Right ventral basal ganglia extending into ventral pallium <sup>b</sup>	1.42 (0.05)	1.32 (0.06)	1.20 (0.06)	1.06 (0.04)	1.31 (0.04)	1.28 (0.07)	<.001	<.001	.22
Left ventral basal ganglia	2.26 (0.13)	2.04 (0.09)	1.94 (0.08)	1.88 (0.13)	2.03 (0.16)	2.09 (0.10)	.02	.15	.66
Right basolateral amygdala	1.33 (0.09)	1.31 (0.10)	1.08 (0.04)	0.97 (0.06)	1.14 (0.05)	1.14 (0.02)	<.001	.03	.01
Left basolateral amygdala	1.75 (0.11)	1.66 (0.28)	1.69 (0.08)	1.51 (0.12)	1.65 (0.22)	1.90 (0.16)	.02	.32	.36

Abbreviation: BP<sub>ND</sub>, nondisplaceable binding potential.

<sup>a</sup>Post hoc analyses were used to calculate the P values. High, intermediate, and low risk groups are described in the "Interactions Among Measures: Conjunction Analyses" subsection of the "Results" section.

<sup>b</sup>Multiple peaks were detected in this region. Diencephalic regions included the thalamus and hypothalamus.

lems with decision making, specifically, insensitivity to future consequences, following damage to the ventromedial prefrontal cortex. The relationship between ventral prefrontal cortex function and endogenous opioid system activity measures are presently unexplored.

It is also unlikely that complex personality domains are solely related to a single neurotransmitter system. Dopamine D<sub>2/3</sub> receptor concentration within the ventral basal ganglia has been demonstrated to predict impulsive anticipatory responses to food reward in an animal model of impulsivity.<sup>16</sup> The involvement of dopamine mechanisms, however, is not exclusive of effects by other systems, such as the endogenous opioid system. Dopamine-opioid interactions have been described in the striatopallidal pathway and interconnected regions, where short- and long-term dopamine receptor stimulation induces opposite effects on the functional capacity of the μ-opioid system in animal models<sup>82-87</sup> and humans.<sup>35,88</sup> These and other still undescribed neurotransmitter systems may underlie the psychophysical differences, such as heart rate and pupillary responses, classically noted between otherwise healthy shy and uninhibited children.<sup>89</sup>

In summary, the present study provides the first evidence in humans that IMP and DLB—behavioral facets relevant to motivated behavior, the pursuit of reward, and risk taking, including the development of substance use disorders—are related to the individual function of the endogenous opioid system. Baseline measures of

μ-receptor availability and the capacity to activate this neurotransmitter system in limbic and paralimbic regions in response to stress accounted for up to half of the variance in trait IMP and DLB scores in a healthy sample.

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