A Preliminary Study of the Opioid System and Personality Traits Using Positron Emission Tomography

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Abstract

Background: Personality traits, such as Neuroticism and Extraversion, have been implicated in the processing of emotion. The neural correlates most often associated with Neuroticism and Extraversion are the insular cortex, orbitofrontal cortex, amygdala, and ventral striatum. Objective: The aim of the current study was to explore neurotransmitter systems underlying those neural correlates and investigate the relationship between personality traits and opioid receptor binding potential. Method: Twelve healthy participants completed an [11C]diprenorphine positron emission tomography scan at rest. Endogenous opioid levels as indicated by opioid receptor binding potential was examined in relation to personality phenotype. Results: A high score of Neuroticism, a personality trait characterized by negative affect, was found to be associated with high opioid receptor binding in the right anterior insula. Conversely, a high score of Extraversion, a personality trait characterized by positive affect, was found to be associated with low opioid receptor binding in the left posterior insula. Conclusions: While preliminary, the results of this study suggest that the expression of Neuroticism and Extraversion is related to baseline function of the opioid neurotransmitter system in the insular cortex. These findings may help elucidate the neural mechanisms underlying the expression of personality traits, particularly those implicated in affective processing.

Introduction

Personality refers to a stable pattern of thinking, feeling, and behaving within an individual. In an effort to standardize personality traits, the Five-Factor Model (FFM) categorizes all phenotypical expressions of personality into five higher-order factors: Extraversion, Neuroticism, Openness, Agreeableness, and Conscientiousness. These traits have exhibited reliability as researchers have demonstrated generalizability across cultures and have even found them to be significantly heritable. As a result, the FFM has become a well-represented model of personality dimensions. Though there are several personality inventories that attempt to quantify these traits, the most widely used measurement of the FFM is the NEO Personality Inventory (NEO-PI).
Of the five traits, Neuroticism and Extraversion are most predictive of functional outcomes later in life [7]. Neuroticism refers to a tendency to experience negative affect such as anxiety and dysphoria. Individuals that score high on the measure of Neuroticism are significantly more at risk for developing depression [8]. Conversely, Extraversion refers to a tendency to experience positive affect. Individuals that score high on the measure of Extraversion are generally more optimistic and socially and behaviorally active, and high scores on the measure of Extraversion may serve as a protective factor against depression [9]. Given the relationship between these traits and risk or resilience to psychopathology, it is important to understand the neural correlates of Neuroticism and Extraversion.

Since the advent of neuroimaging over two decades ago, researchers have been able to link individual differences in cognitive and affective processing to neural activation within specific networks of brain regions. Past research has shown that differences in personality traits can also be linked to brain structure and function at rest as measured by structural magnetic resonance imaging (MRI), functional MRI (fMRI), and fluorodeoxyglucose positron emission tomography (FDG-PET) [10–19]. Personality traits have also been shown to influence task-elicited brain function, as demonstrated by imaging studies using emotionally valenced tasks [20–25].

These studies support a biological model of the FFM proposed by DeYoung and Gray [26], wherein Neuroticism and Extraversion are closely related to function within punishment-related corticolimbic and reward-related corticostriatal circuits, respectively. Specifically, it asserts that high trait Neuroticism is linked to abnormal activation in the amygdala, anterior and middle cingulate cortex, medial prefrontal cortex, and hippocampus [27], whereas high trait Extraversion is linked to increased activation in the ventral striatum and orbitofrontal cortex (OFC) [26].

While previous research has examined the relationship between personality traits and global brain function (e.g., glucose metabolism using FDG-PET or blood flow using fMRI), few studies have assessed the role of neurotransmitter systems. Past research has found a link between serotonergic systems and personality traits, which supports the exploration of the monoaminergic transmission as it relates to personality traits [28, 29]. It has been suggested that the opioid system is implicated in the experience of psychic pain along with emotion regulation [30] and may, therefore, be a viable target for the investigation of personality traits associated with affective processing: Neuroticism and Extraversion. In order to address this gap in the literature, the current study aims to explore whether baseline opioid neurotransmission is associated with traits of Neuroticism and Extraversion using [11C]diprenorphine, a radioligand that binds to all opioid receptor types.

As reviewed, the brain regions most commonly associated with Neuroticism and Extraversion were regions of the corticolimbic and corticostriatal circuits. Here, we will focus on the regions most commonly associated with Neuroticism and Extraversion across studies: the insular cortex, OFC, amygdala, and ventral striatum. The literature suggests there is a substantial density of opioid receptors in all four of these regions, which enables us to detect whether opioid receptor binding potential, a proxy of baseline opioid function, is correlated with Neuroticism and Extraversion [31, 32]. We hypothesized that opioid receptor binding potential in these regions would vary as a function of Neuroticism and Extraversion.

### Methods

#### Participants

Twelve subjects (6 males) aged 29–53 years had taken part in a larger parent study [32] and we examined the extant PET and NEO-PI data to complete this study. Participants had a mean age of 36 years (SD = 8.38) and provided informed consent prior to participating in this study, as approved by the Human Research Committee at Massachusetts General Hospital. Participants were healthy volunteers and were without any history of significant head injury, seizure, neurological condition, or current medical or psychiatric condition. Subjects were screened for psychiatric disorders using the Structured Clinical Interview for the Diagnostic Statistical Manual-IV (SCID-DSM-IV) [33]. An advantage to studying this measure in a healthy population is that participants will be free of confounding variables such as comorbid conditions and/or treatments that may affect the endogenous opioid neurotransmitter systems.

#### PET Image Acquisition

The PET scan measuring opioid receptor binding potential at resting state lasted approximately 90 min and was completed at 9:30 a.m. Subjects were positioned at the gantry of the PET camera and the head was aligned relative to the canthomeatal line, utilizing projector laser lines calibrated to the slice positions of the scanner. Head motion was minimized by individually molded thermoplastic masks.

The PET radioligand used was the opioid agonist [11C]diprenorphine (binds to μ, δ, and κ receptors). [11C]diprenorphine was manually injected via a peripheral venous catheter as an intravenous bolus of 15 mCi. Image acquisition began at the moment of injection and continued for 90 min. Images were acquired using a PC-4096 PET camera (Scanditronix AB, Uppsala, Sweden) in 2D mode and reconstructed using a conventional filtered back projec-
tion algorithm with an in-plane resolution of 6.0 mm FWHM. The primary imaging parameters of the PC-4096 camera are in-plane and axial resolution of 6.0 mm FWHM, 15 contiguous slices of 6.5 mm. A rotating pin source containing $^{68}$Ge enabled the measurement of photon attenuation.

**Data Analysis**

The PET images obtained were corrected for movement, realigned, normalized, and smoothed as described in the parent study by Dougherty and colleagues [31]. Binding potential of [11C]diprenorphine was determined using the simplified reference tissue model [34, 35] with the occipital cortex as the reference tissue. Statistical analysis of the PET data was conducted using statistical parametric mapping. Data were analyzed using the SPM8 software package (Wellcome Department of Cognitive Neurology, London, UK).

The continuous measures of Neuroticism and Extraversion of the NEO-PI were each analyzed in a linear statistical model as they correlated to opioid receptor binding potential in the following brain regions selected a priori: insular cortex, OFC, amygdala, and ventral striatum. Voxel-wise analyses restricted to the four regions of interest (defined using the Wake Forest University PickAtlas toolbox) were conducted for each trait at a threshold of $p < 0.05$. Control analyses were conducted to ensure a robust and specific effect of each trait. In each control analysis, age and the alternate personality trait, either Neuroticism or Extraversion, were included as nuisance regressors in the General Linear Model. Exploratory analyses for each trait were conducted as a voxel-wise whole-brain analysis at a threshold of $p < 0.001$. For all analyses, a cluster size threshold of 5 contiguous voxels or greater was used.

**Fig. 1.** Trait correlations of Neuroticism and opioid receptor binding potential in the right anterior insula. 

- **a** Opioid receptor binding potential is positively correlated with Neuroticism scores in the right anterior insula (max. peak: $x = 32, y = 22, z = 6$). Neuroticism was not negatively correlated with opioid receptor binding potential.
- **b** Scatter plot depicting the correlation for illustrative purposes.

**Fig. 2.** Trait correlations of Extraversion and opioid receptor binding potential in the left posterior insula.

- **a** Opioid receptor binding potential is negatively correlated with Extraversion scores in the left posterior insula (max. peak: $x = –34, y = –14, z = 8$). Extraversion was not positively correlated with opioid receptor binding potential.
- **b** Scatter plot depicting the correlation for illustrative purposes.
Results

Participants scored within the normal range for both Neuroticism (mean = 43.17, SD = 12.27) and Extraversion (mean = 53.75, SD = 7.63). Significant correlations were observed between region-specific opioid receptor binding potential and the NEO-PI measures of Neuroticism and Extraversion. Neuroticism was found to be positively correlated with the right anterior insular cortex (max. peak: x = 32, y = 22, z = 6, \( t = 2.28, p = 0.023 \)), whereas Extraversion was found to be negatively correlated with the left posterior insular cortex (max. peak: x = –34, y = –14, z = 8, \( t = 2.51, p = 0.015 \)). Findings held when controlling for age and shared variance between Neuroticism and Extraversion. Neither Neuroticism nor Extraversion was significantly correlated with opioid receptor binding potential in the amygdala, OFC, or ventral striatum (Fig. 1, 2).

Exploratory whole-brain analyses revealed significant correlations between Neuroticism and opioid receptor binding potential in various other brain regions. Neuroticism was positively correlated with left inferior temporal gyrus (\( t = 3.80, p < 0.0001 \)), right mid-frontal gyrus (\( t = 3.53, p < 0.0001 \)), right post-central gyrus (\( t = 3.41, p < 0.0001 \)), and pre-central gyrus (\( t = 3.33, p < 0.0001 \)). No negative correlations between Neuroticism and whole-brain opioid receptor binding potential were detected at the level of \( p < 0.001 \). Exploratory analyses did not detect any correlations between Extraversion and opioid receptor binding potential at the level of \( p < 0.001 \) (see Table 1 for complete results).

Discussion

The objective of the current study was to investigate correlations between the NEO-PI traits and opioid receptor binding potential in the brain. As previously described, opioid receptor binding potential serves as a proxy of opioid receptor availability. \([11C]\)diprenorphine binds to opioid receptors that are not already occupied by endogenous, naturally-occurring opiate peptides. Therefore, higher binding potential of \([11C]\)diprenorphine indicates lower levels of endogenous opiate binding or higher levels of opioid receptor expression.

Based upon previous literature exploring brain function and personality traits, the regions of interest were limited to the insular cortex, OFC, amygdala, and ventral striatum. Trait correlational analyses indicated significant correlations between Neuroticism and Extraversion and opioid receptor binding potential in the insular cortex. Specifically, Neuroticism was positively correlated

| Table 1. Significant correlations between regional opioid receptor binding potential and Neuroticism or Extraversion |
|-----------------|---------|-----------------|-----------------|---------|
| Primary ROI Analyses                                      |
| Neuroticism     | 7       | 2.00            | 32              | 22      | 6     | 0.584 |
| Extraversion    | 29      | 2.16            | –34             | –14     | 8     | –0.621 |
| Exploratory Analyses                                      |
| Neuroticism     | 6       | 3.80            | –44             | –62     | –2    | 0.882 |
|                 | 9       | 3.53            | 20              | 56      | 12    | 0.853 |
|                 | 9       | 3.41            | 66              | –12     | 18    | 0.839 |
|                 | 6       | 3.33            | 54              | –6      | 30    | 0.829 |

Primary region-of-interest (ROI) analyses were completed at a threshold of \( p < 0.05 \), while exploratory analyses were completed at a threshold of \( p < 0.001 \). Pearson’s r values are reported for descriptive purposes. \(^a\) All findings are reported in Montreal Neurological Institute (MNI) format, wherein x indicates distance (in mm) right (+) or left (–), y indicates anterior (+) or posterior (–), and z indicates superior (+) or inferior (–) to the anterior commissure.
with opioid receptor binding potential in the right anterior insula. Extraversion, on the other hand, was negatively correlated with opioid receptor binding potential in the right posterior insula. That is to say, individuals that scored high in trait Neuroticism also had lower levels of endogenous opioid transmission or higher levels of opioid receptor expression in the right anterior insula, whereas those that scored high in trait Extraversion also exhibited high levels of endogenous opioid transmission or lower levels of opioid receptor expression in the left posterior insula. Other brain regions of interest, the OFC, amygdala, and ventral striatum, were not associated with trait levels of Neuroticism and Extraversion. Given that this study examined neurochemical function at rest, the understanding of these results is primarily guided by knowledge of the role of these brain areas as they relate to normal emotional functioning and how the opioid system may impact affective processing.

Opioid systems are primarily involved in pain perception, processing of emotional information, stress responses and reward systems [36]. Both animal and human studies have revealed that the regional release of opioid peptides is a crucial contribution to the suppression of anxiety-driven behaviors [37] and interpretation of aversive stimuli [38]. Additionally, Zubieta and colleagues [30] found that the μ-opioid neurotransmitter system plays a central role in the regulation of emotional processing, particularly internally induced negative affective states. In accordance with the literature, our findings indicate that a high score of Neuroticism could be associated with lower baseline opioid transmission (or higher opioid receptor expression) in the right anterior insula. This is congruent with previous literature implicating the role of the right anterior insula and opioid systems as a mediator of emotional processing [30, 38–41].

The insular cortex is a cortical structure, located within the temporal lobe, which is primarily involved in the affective processing of visceral sensation, such as warmth, pain, or nausea [40]. The insular cortex is organized in a posterior-to-anterior fashion in which sensory input reaches the posterior insula, is integrated in the mid-insula, and emotionally interpreted in the anterior insula [41–43]. The anterior insular cortex, in particular, has been found to modulate many primary emotions such as anger [44], fear [45], disgust [46], and happiness [47]. Relevant to the current study, the anterior insula is responsible for the aversion we feel to threatening stimuli [45, 46] and even social situations [48]. Thus, the anterior insula may play a role in the expression of Neuroticism, the personality trait associated with negative affect. Furthermore, Craig [39] has suggested laterality differences within the insula, stating that the left insula is associated with positive emotions, supporting parasympathetic, energy-enriching emotions, while the right is associated with negative emotions, supporting sympathetic, energy-consuming emotions.

Extraversion, on the other hand, which is a personality trait associated with positive affect, was associated with higher baseline opioid transmission (or lower opioid receptor expression) in the left posterior insula. This is in agreement with previous literature asserting that the left insula mediates the expression of positive emotions [39–41]. Likewise, previous studies support this notion of the availability of opioid peptides suppressing negative emotional states, thereby promoting positive emotions seen in Extraversion [30, 38].

Importantly, these findings, though preliminary, could help elucidate the mechanisms that drive the expression of Neuroticism. Previous research has indicated that increased activation in the insular cortex has been reported in individuals with anxiety disorders and depression during tasks that involve affective processing [49, 50]. With this in mind, it stands to reason that individuals with high trait Neuroticism may exhibit sensitized insular activation and suppressed compensatory opioid transmission, resulting in biased emotional responsivity and increased vulnerability to depression or anxiety. Contrarily, individuals with high trait Extraversion may display less sensitivity to emotional stimuli due, in part, to adequate levels of baseline opioid transmission.

It is noteworthy that three of the four regions implicated in the expression of Neuroticism and Extraversion, the OFC, amygdala, and ventral striatum, did not yield any detectable differences in opioid levels as a function of the traits. In addition, the clusters within the insula cortex identified in the primary region-of-interest analyses did not survive when extending to exploratory voxel-wise analyses to the whole brain at lower statistical threshold. A major limitation of this study is the small sample. With a sample of twelve, it is possible that type II errors occurred and actual differences were not detectable below the p < 0.05 threshold. For this reason, results should be considered informative, yet preliminary, as it is impossible to draw strong conclusions from these data. Another limitation of this study is that the findings in these brain regions, though implicated in FDG-PET studies with glucose metabolism [14], may be modulated by other neurotransmitters such as serotonin or dopamine rather than opioid systems. Additionally, information regarding the subjects’ behaviors immediately prior to study visit ar-
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rival was not collected. In the hours preceding a PET scan, engaging in certain behaviors (e.g., exercising, consuming coffee) can alter brain function. Though information prior to arrival is lacking, pre-scan procedures in the hour preceding the scan was standardized for all subjects, mitigating this limitation. Future studies of this topic should be conducted using a larger sample in order to increase statistical power and improve signal to noise ratio. Additionally, studies examining the opioid transmission as it relates to personality traits should examine this relationship in the context of task-elicited emotional processing.

Conclusion

The results of this study demonstrate that the expression of Neuroticism and Extraversion may be partially modulated by the opioid neurotransmitter system in the insular cortex. These findings contribute to the understanding of personality traits and the underlying mechanisms that impact affective processing. This may provide a foundation upon which future research can investigate the role of the opioid system and personality traits as it relates to vulnerability for psychopathology.

Statement of Ethics

Participants provided informed consent prior to participating in this study, as approved by the Human Research Committee at Massachusetts General Hospital.

Disclosure Statement

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