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Higher trait neuroticism is associated with greater fatty acid amide hydrolase binding in borderline and antisocial personality disorders

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Borderline personality disorder (BPD) and antisocial personality disorder (ASPD) are the two most frequently diagnosed and researched DSM-5 personality disorders, and both are characterized by high levels of trait neuroticism. Fatty acid amide hydrolase (FAAH), an enzyme of the endocannabinoid system (ECS), has been linked to regulation of mood through modulation of anandamide, an endocannabinoid. We hypothesized that prefrontal cortex (PFC) FAAH binding would relate to trait neuroticism in personality disorders. Thirty-one individuals with personality disorders (20 with BPD and 11 with ASPD) completed the investigation. All participants completed the revised NEO Personality Inventory, which yields standardized scores (e.g., *T* scores) for the traits of neuroticism, openness, conscientiousness, agreeableness, and extraversion. All participants were medication free and were not utilizing illicit substances as determined by drug urinalysis. Additionally, none of the participants had a comorbid major depressive episode, bipolar disorder, psychotic disorder, or substance use disorder. Each participant underwent one [¹¹C]CURB PET scan. Consistent with our hypothesis, neuroticism was positively correlated with PFC FAAH binding ($r = 0.42$, $p = 0.021$), controlling for genotype. Neuroticism was also positively correlated with dorsal putamen FAAH binding ($r = 0.53$, $p = 0.0024$), controlling for genotype. Elevated brain FAAH is an endophenotype for high neuroticism in BPD and ASPD. Novel pharmacological therapeutics that inhibit FAAH could emerge as potential new treatments for BPD and ASPD with high neuroticism.

Neuroticism is one of the Big Five dimensional domains of personality that encompasses individual differences in negative emotional responding to frustration, threat, or loss^{1–4}. It is operationally defined by items, which, in aggregate, reflect anger, sadness, irritability, self-consciousness, vulnerability, worry, and hostility that correlate well with one another in factor analyses^{1–3}. Although neuroticism is associated with manifestations of psychological illness, such as mood and anxiety disorders; adverse physical health outcomes; and poorer quality of life¹, comparably less is known about its neurochemical substrate, especially in common mental disorders. This gap in the literature hinders development of new therapeutics that could serve to mitigate the effects of high neuroticism.

Borderline personality disorder (BPD) is a debilitating illness characterized by severe emotional dysregulation, tumultuous interpersonal relationships, and self-harming and suicidal behavior⁵. According to meta-analytic review, BPD is the personality disorder most strongly associated with neuroticism^{6,7}. Additionally, longitudinal analysis points to robust associations between BPD symptomatology and neuroticism⁸. Antisocial personality disorder (ASPD) is another common condition that shares clinical similarities with BPD. Expression of neuroticism positively correlates with ASPD, especially with symptoms of anger and impulsivity⁹, although meta-analysis shows smaller effect sizes for ASPD and neuroticism than with BPD and the latter⁶. Clinically, a significant positive relationship exists between neuroticism in childhood or adolescence and adult antisocial behavior¹⁰. ASPD

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and BPD are highly comorbid¹¹. Higher neuroticism scores are seen in ASPD with comorbid BPD, especially among individuals with substance use disorders¹².

Advances in the study of endocannabinoid signaling pathways have furthered our understanding of the neurochemistry of myriad psychiatric disorders (for review, see¹³). The brain endocannabinoid system (ECS) is comprised of two main G protein-coupled cannabinoid receptors, cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R) and two principal endogenous cannabinoids (e.g., endocannabinoids), *N*-arachidonyl ethanolamide (anandamide or AEA) and 2-arachidonylglycerol (2-AG). Other endocannabinoid-related signaling lipids, such as the *N*-acyl ethanolamides, *N*-palmitoylethanolamine and *N*-oleoylethanolamine, are also known to exist but are less well-studied¹⁴. In a distinctive signalling pathway, AEA and 2-AG are synthesized on demand in the post-synaptic neuron and released as required into the synaptic cleft and bind, in retrograde fashion, to pre-synaptic CB1R and CB2R located on axon terminals on the pre-synaptic neuron¹⁵. To terminate endocannabinoid signalling, fatty acid amide hydrolase (FAAH), an integral membrane serine hydrolase, degrades AEA in the post-synaptic neuron, while 2-AG is metabolized by the enzyme monoacylglycerol lipase in the pre-synaptic neuron¹⁵. CB1Rs are promiscuous in the central nervous system (CNS) with high levels in the cerebral cortex, hippocampus, amygdala, striatum, and substantia nigra, and they play functional roles in regulating mood, stress, and anxiety^{16,17}. FAAH is also widely distributed in the CNS, including the cerebral cortex, hippocampal formation, amygdala, and cerebellum with its regional distribution correlated with the density of CB1Rs^{18–21}. Therefore, enzymatic regulation of AEA by FAAH is able to indirectly control CB1R signaling and ostensibly modulate cognitive processes underlying mood and anxiety symptoms²².

Using [¹¹C]CURB positron emission tomography (PET), we reported that FAAH expression was elevated in the prefrontal cortex (PFC) of BPD and that PFC FAAH density correlated with measures of anger/hostility²³. Conversely, we also found utilizing [¹¹C]CURB PET that amygdala FAAH expression was lower in the amygdala of ASPD and that impulsive behaviors were negatively associated with FAAH density in other brain regions studied²⁴. These findings have enhanced our knowledge about the pathophysiology of BPD and ASPD and their symptom clusters, yet an unanswered question remains how FAAH expression may relate to personality traits such as neuroticism. There is precedent for investigating FAAH and neuroticism in other psychological disorders. For example, individuals with posttraumatic stress disorder and comorbid alcohol dependence who were wildtype for the *FAAH* gene displayed increased subjective anxiety responses to a stress challenge versus subjects with a single nucleotide polymorphism of the *FAAH* gene conferring lower levels of brain in vivo FAAH expression who reported decreased anxiety for the same stress paradigm²⁵. Importantly, all analyses in this study controlled for trait neuroticism. Based on these findings, we aimed to investigate FAAH brain expression in a combined sample of BPD and ASPD participants. The most consistent finding from structural magnetic resonance imaging (sMRI) studies of trait neuroticism has been structural alterations of the PFC and its subdivisions among individuals with higher neuroticism^{26–31}. Therefore, we focused on the PFC and hypothesized that trait neuroticism in BPD and ASPD would be associated with greater PFC FAAH binding, although we also explored other brain regions to test this association. It should also be noted that the association between ASPD and neuroticism is weaker than for ASPD and agreeableness³². Since the ECS may also be related to agreeableness³³, and AEA-mediated signaling at CB1R, driven by oxytocin, appears to control social reward³⁴, we also investigated whether the agreeableness dimension would be associated with FAAH binding in the PFC and other brain regions.

Results

Participants' clinical and demographic information is reported in Table 1. Information on comorbid conditions is presented in Table 2.

Partial correlation between PFC [¹¹C]CURB λ_{k_3} and neuroticism. We found a significant partial correlation between PFC [¹¹C]CURB λ_{k_3} and trait neuroticism, controlling for genotype ($r=0.42$, $p=0.021$). When we log-transformed our data, we found that the significant correlation persisted ($p=0.021$). PFC [¹¹C]CURB λ_{k_3} was also significantly correlated with neuroticism facets anxiety ($r=0.42$, $p=0.023$) and self-consciousness ($r=0.37$, $p=0.047$), controlling for genotype, although these results were uncorrected for multiple comparisons. Figure 1 depicts the residuals of PFC [¹¹C]CURB λ_{k_3} after regressing PFC [¹¹C]CURB λ_{k_3} onto genotype by the residuals of neuroticism after regressing neuroticism onto genotype.

Partial correlations between secondary regions of interest (ROIs) [¹¹C]CURB λ_{k_3} values and neuroticism. When we tested the relationship between [¹¹C]CURB λ_{k_3} and neuroticism in the secondary ROIs, only the relationship between dorsal putamen [¹¹C]CURB λ_{k_3} and neuroticism remained significant, after controlling for genotype and correcting for multiple comparisons ($r=0.53$, $p=0.0024$). Dorsal putamen [¹¹C]CURB λ_{k_3} was also positively correlated with neuroticism facets anxiety ($r=0.47$, $p=0.0092$), depression ($r=0.39$, $p=0.034$), and self-consciousness ($r=0.46$, $p=0.012$). These latter correlations were uncorrected for multiple comparisons. Statistics for the secondary ROIs are presented in Table 3. Figure 2 presents the residuals of dorsal putamen [¹¹C]CURB λ_{k_3} after regressing dorsal putamen [¹¹C]CURB λ_{k_3} onto genotype by the residuals of neuroticism after regressing neuroticism onto genotype.

Partial correlations between PFC [¹¹C]CURB λ_{k_3} and trait neuroticism among individuals with comorbid conditions. One of the challenges of interpreting the relationship between trait neuroticism and PFC [¹¹C]CURB λ_{k_3} is whether this finding is driven by comorbid conditions such as major depressive disorder (MDD) or anxiety disorders. For example, 61% of the sample had comorbid MDD, although none of the participants had a current major depressive episode. Similarly, 65% of the sample had a current anxiety disorder. When we examined the relationship between PFC [¹¹C]CURB λ_{k_3} and neuroticism among the participants with MDD,

Age	30.8 ± 9.6 years
Sex	18 female; 13 male
Ethnicity	20 Caucasian; 6 Asian; 2 Black; 2 Hispanic; 1 Aboriginal
Education	14.3 ± 2.3 years
Full scale IQ	100.7 ± 14.8
BMI	25.6 ± 5.2
Neuroticism <i>T</i> score	73.5 ± 7.9
Anxiety <i>T</i> score	63.5 ± 11.1
Anger <i>T</i> score	73.2 ± 7.1
Depression <i>T</i> score	71.0 ± 9.5
Self-consciousness <i>T</i> score	68.5 ± 9.9
Impulsivity <i>T</i> score	63.5 ± 11.3
Vulnerability <i>T</i> score	70.4 ± 11.0
Extraversion <i>T</i> Score	44.1 ± 12.7
Openness <i>T</i> score	55.3 ± 11.1
Agreeableness <i>T</i> score	32.0 ± 10.5
Conscientiousness <i>T</i> score	34.8 ± 13.0
Specific activity of radiotracer	3778.3 ± 1296.4 mCi/μmol
Mass injected of radiotracer	9.5 ± 0.72 mCi

Table 1. Demographic and clinical characteristics.

we did not find a significant relationship ($r=0.30$, $p=0.23$). However, we did detect a trend association between PFC [^{11}C]CURB λ_3 and trait neuroticism among those with current anxiety disorders ($r=0.40$, $p=0.092$).

Partial correlations between PFC [^{11}C]CURB λ_3 and other Big Five dimensional domains of personality. PFC [^{11}C]CURB λ_3 was not significantly correlated with *T* scores of the extraversion, openness, agreeableness, or conscientiousness domains (p -values ranged from 0.37 to 0.92).

Partial correlations between secondary ROIs [^{11}C]CURB λ_3 values and agreeableness. When we tested the relationship between [^{11}C]CURB λ_3 and agreeableness in the secondary ROIs, none of the correlations were significant (p -values ranged from 0.13 to 0.99).

Discussion

This study investigated the relationship between brain FAAH binding and neuroticism in a sample of ASPD and BPD participants. Consistent with our main hypothesis, we found that PFC [^{11}C]CURB λ_3 correlated positively with trait neuroticism. Exploratory analyses determined that PFC FAAH binding was linked to greater anxiety and self-consciousness. A second main finding was that dorsal putamen [^{11}C]CURB λ_3 similarly correlated positively with neuroticism. In terms of facet-level associations, dorsal putamen FAAH binding was positively associated with anxiety, depression, and self-consciousness. These findings have relevance for understanding the neurochemistry of personality traits in BPD and ASPD and offer tentative guidance for testing FAAH inhibitors in personality-disordered individuals scoring high in neuroticism.

There are very few studies that have explored *in vivo* measures of personality functioning in ASPD or BPD and none to our knowledge that have specifically assayed components of the ECS, apart from one functional MRI study of healthy individuals that found no relationship between neuroticism and amygdala [^{11}C]CURB λ_3 ³⁵. Here, we focused on the relationship between FAAH binding and neuroticism in personality disorders. Our findings comport well with the animal literature linking pharmacological inhibition or genetic deletion of FAAH to the rescue of depressive and anxious phenotypes³⁶. According to this model, decreased FAAH activity increases brain AEA levels and stimulates anxiolytic-like responses in a CB1R-dependent manner³⁷. In support of this view, CB1R activation in the prefrontal cortex, ventral hippocampus, and periaqueductal grey elicits anxiolytic-like effects^{38,39}. Because maladaptive behavioral and neuroendocrine reactions to protracted stress contribute to manifestation of depressive-like behaviors⁴⁰, it is thought that facilitation of AEA signaling may counter these effects by enhancing adaptive stress coping behaviors⁴¹ and diminishing neuroendocrine responses to psychological stressors⁴². Overall, this research suggests that augmentation of AEA-CB1R signaling through inhibition of FAAH activity may be an effective strategy for alleviating depressive and anxious symptomatology. By contrast, dampened AEA-CB1R circuitry through increased FAAH expression may contribute to increased levels of neuroticism, including trait anxiety and depression, which was observed in our sample of ASPD and BPD participants.

Bolstered by sMRI data revealing alterations of the PFC in trait neuroticism^{26–31}, we similarly detected elevated PFC [^{11}C]CURB λ_3 as a function of increased neuroticism in ASPD and BPD. The PFC, which broadly plays a role in affective processing and emotion regulation⁴³, has been previously identified as an important locus for

Comorbid diagnoses in sample	BPD + ASPD participants
	<i>n</i> = 31
Major depressive disorder (%)	61.3
Dysthymic disorder (%)	0
Panic disorder (%)	9.7
Agoraphobia (%)	6.5
Specific phobia (%)	6.5
Social phobia (%)	16.1
Generalized anxiety disorder (%)	35.5
Obsessive compulsive disorder (%)	6.5
Posttraumatic stress disorder (%)	22.6
Previous alcohol use disorder (%)	25.8
Previous cannabis use disorder (%)	9.7
Previous opioid use disorder (%)	3.2
Previous sedative/hypnotic use disorder (%)	3.2
Previous stimulant use disorder (%)	3.2
Previous hallucinogen use disorder (%)	3.2
Previous polysubstance dependence (%)	3.2
Somatization disorder (%)	0
Pain disorder (%)	0
Undifferentiated somatoform disorder (%)	0
Hypochondriasis (%)	0
Body dysmorphic disorder (%)	0
Anorexia nervosa (%)	0
Bulimia nervosa (%)	0
Eating disorder not otherwise specified (%)	0
Paranoid personality disorder (%)	16.1
Schizoid personality disorder (%)	3.2
Schizotypal personality disorder (%)	0
Histrionic personality disorder (%)	0
Narcissistic personality disorder (%)	0
Avoidant personality disorder (%)	25.8
Obsessive compulsive personality disorder (%)	12.9
Dependent personality disorder (%)	9.7

Table 2. Comorbid psychiatric conditions.

expression of facets of neuroticism in BPD. For example, Soloff and colleagues reported that trait impulsivity, one facet of neuroticism, was related to decreased serotonin-2A receptor (5-HT_{2A}R) binding potential using [¹⁸F] altanserin PET in the medial frontal cortex among female BPD participants⁴⁴. Studies have also examined the association of PFC 5-HT_{2R} binding with trait neuroticism in healthy cohorts, with some findings showing contradictory findings that could be a reflection of differences in the neural substrates between clinical and healthy populations. One investigation found a positive correlation between frontolimbic 5-HT_{2A}R and neuroticism in healthy volunteers that was mainly driven by the anxiety and vulnerability facets⁴⁵. In another PET study of healthy participants using the radiotracer [¹¹C]WAY-100635, trait anxiety was inversely correlated with 5-HT_{1A}R binding in the dorsolateral PFC (DLPFC)⁴⁶. A similar negative correlation was observed between DLPFC [¹¹C]WAY-100635 binding potential and trait neuroticism in another sample of healthy subjects⁴⁷. Since prominent linkages between the ECS and serotonergic system have been described⁴⁸, we suggest that the positive association of PFC [¹¹C]CURB λ_3 with neuroticism may be partially explained by interactions of the ECS with serotonergic signaling pathways. This line of reasoning is supported by preclinical evidence showing that basal serotonergic tone is higher in the frontal cortex of FAAH knockout mice following potassium-induced depolarization⁴⁹ and that downregulation of 5-HT_{2A}R and 5-HT_{2C}R occurs in the PFC⁴⁸, perhaps as a result of higher endogenous levels of 5-HT. These neurochemical changes were paralleled by anxiolytic-like effects. Other reports have signaled that pharmacological inhibition of FAAH leads to increased brain-derived neurotrophic factor and neurogenesis in other brain regions functionally linked to the PFC⁵⁰. In light of this evidence, we propose that increased PFC FAAH could lead to decreased endogenous 5-HT tone in affected regions that predisposes to greater expression of neuroticism. Dual radiotracer PET experiments that simultaneously measured PFC [¹¹C]CURB λ_3 and 5-HT_{1A}R or 5-HT_{2A}R binding potential could shed light on this question.

The association between dorsal striatum [¹¹C]CURB λ_3 and neuroticism may provide a mechanism to understand impaired decision-making in personality disorders. While the involvement of the dorsal striatum in control of motor movement has been well-established, evidence further implicates the dorsal striatum and its

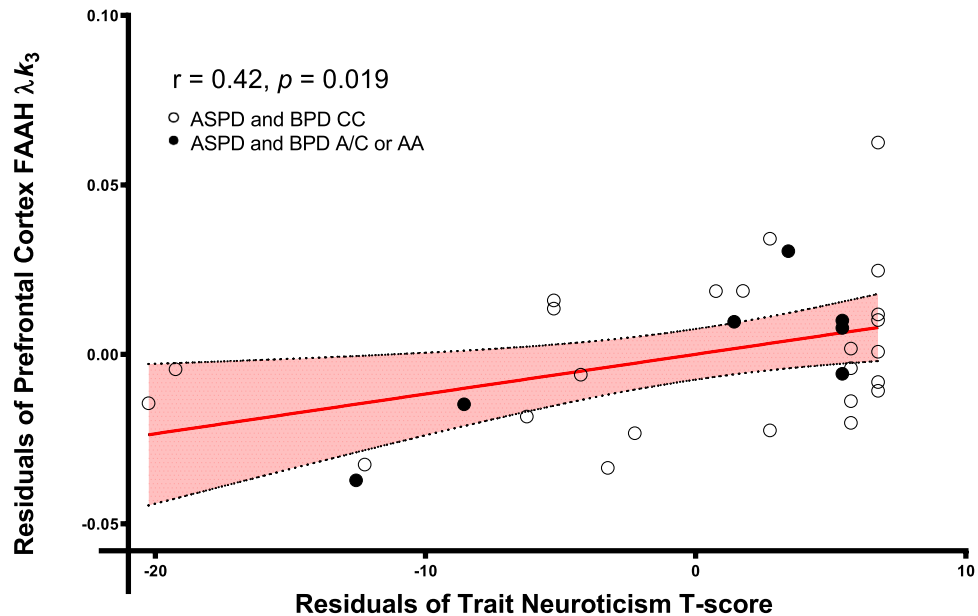


Figure 1. Prefrontal cortex fatty acid amide hydrolase λ_3 is correlated with trait neuroticism (T score) controlling for genotype in antisocial and borderline personality disorders.

Region	r	p -value
Anterior cingulate cortex	0.42	0.023
Temporal cortex	0.43	0.019
Hippocampus	0.40	0.030
Insula	0.48	0.0080
Thalamus	0.42	0.020
Ventral striatum	0.45	0.013
Dorsal caudate	0.45	0.013
Dorsal putamen	0.53	0.0024
Amygdala	0.46	0.010
Cerebellum	0.34	0.065

Table 3. Partial correlations between trait neuroticism and secondary regions of interest, controlling for genotype.

corticostriatal network in action selection and initiation⁵¹. Poor decision making has been demonstrated in ASPD and BPD⁵², and poor decision making has been linked to increased neuroticism in some samples⁵³. Therefore, ASPD and BPD with high neuroticism may be poor decision makers. Additionally, some sMRI investigations have also shown connections between trait neuroticism and functional alterations of the striatum⁵⁴. Preclinical research indicates that receptors involved with striatal synaptic plasticity are crucial for striatal-based learning⁵⁵. One investigation determined that striatal CB1R receptor deletion impaired habit learning⁵⁶. Preclinical models further demonstrated that FAAH inhibition can preserve the structural integrity of the striatum and prevent neuronal loss following an excitotoxic lesion⁵⁷. These results indicate a role for endocannabinoids in habit learning⁵⁵ and suggest that higher FAAH binding associated with greater neuroticism may produce deficits resulting in impaired decision making in ASPD and BPD.

When we examined the relationship between PFC [¹¹C]CURB λ_3 and neuroticism in individuals who had comorbid MDD, we did not find a significant correlation. However, a trend association emerged for the relationship between PFC [¹¹C]CURB λ_3 and neuroticism among participants with current anxiety disorders, which aligns with our other finding of a significant correlation between facet anxiety, but not facet depression, and PFC [¹¹C]CURB λ_3 . Thus, the association between PFC FAAH binding and neuroticism may be more driven by facet-level anxiety. These results coincide with clinical observations that FAAH inhibitors have shown some benefit for treatment of anxiety disorders⁵⁸.

Several limitations of the present study must be acknowledged. First, we combined ASPD and BPD participants to investigate them as a single group. We justified collapsing ASPD and BPD into a single group, because the conditions are both Cluster B personality disorders, both are highly comorbid with one another¹¹, and both show high levels of neuroticism. In fact, there was no difference in trait levels of neuroticism between the ASPD

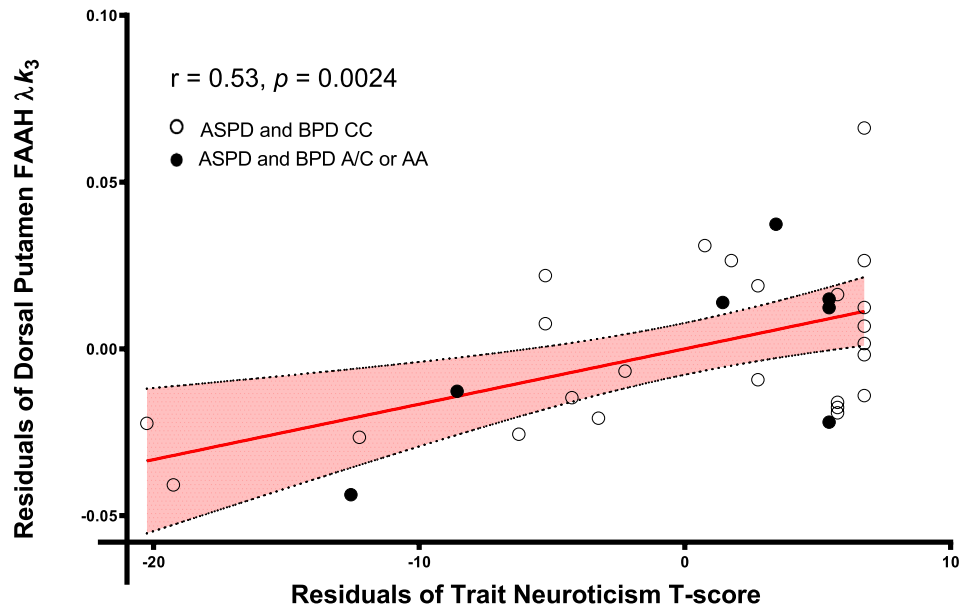


Figure 2. Dorsal putamen fatty acid amide hydrolase λk_3 is correlated with trait neuroticism (T score) controlling for genotype in antisocial and borderline personality disorders.

and BPD groups (ASPD = 71.4 ± 6.9 , BPD = 74.8 ± 8.3 ; $t = -1.1$, $df = 29$, $p = 0.26$), which suggests that neuroticism levels did not relate to gender in this sample. There is also precedent for studying Cluster B personality disorders as a single group in biological studies^{59,60}. Finally, using standardized T scores of neuroticism for all of the correlational analyses allowed for some comparison across genders. Collapsing ASPD and BPD into one group did enable us to increase the study power. Still, our investigation was likely underpowered to detect effects for the secondary ROIs; all regions showed correlations between [^{11}C]CURB λk_3 and neuroticism in the expected direction but did not survive correction for multiple comparisons. Second, as this study was cross-sectional, the design cannot inform on whether PFC [^{11}C]CURB λk_3 is stable to changes in trait neuroticism over time. Third, we did not sample for serum levels of endocannabinoids, such as AEA and the endocannabinoid-related signaling lipids N -palmitoylethanolamine and N -oleoylethanolamine that may be correlated with in vivo brain levels of FAAH expression. While measuring serum endocannabinoids could provide peripheral markers of FAAH expression, no clear-cut relationship has been demonstrated between peripheral and central FAAH biomarkers⁶¹. A fourth limitation is that none of our BPD or ASPD participants had an active substance use disorder. We purposely excluded individuals with active substance use disorders to avoid confounds of psychoactive substances on the central marker of interest. However, individuals with BPD or ASPD are noted to have elevated rates of active substance use disorders, perhaps upwards of 70% in some samples⁶². Thus, our results may not be generalizable to the larger, more common, group of BPD and ASPD individuals with comorbid substance use disorders. Finally, since [^{11}C]CURB is an irreversible tracer, λk_3 is a proxy measure of FAAH availability, as absolute quantification is not possible.

In summary, we have confirmed previous results of high neuroticism in ASPD and BPD and report that PFC and dorsal caudate [^{11}C]CURB λk_3 are positively correlated with trait neuroticism. With the investigation of FAAH inhibitors for anxiety disorders and anxious endophenotypes, our data support the careful testing of these pharmacological agents in personality disorders with high neuroticism. Establishing an evidence base for novel therapeutics in personality disorders would represent a positive step forward, as authorized pharmacological treatments for ASPD and BPD are currently lacking.

Methods

All participants provided written informed consent after all study components were fully explained to them. The Research Ethics Board of the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, Canada, approved all procedures of this investigation. All methods were performed in accordance with the relevant guidelines and regulations.

Participants. Thirty one participants completed this investigation: 20 patients with BPD and 11 participants with ASPD. We have previously reported neuroimaging data on a subset of these participants. However, the research questions and analyses for the present investigation were different from those of the previous studies^{23,24}. BPD participants were primarily female ($n = 18$), while all ASPD subjects were male. All diagnoses were verified according to results from the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)⁶³ and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)⁶⁴ by trained raters. Additionally,

BPD and ASPD diagnoses were reviewed and confirmed by a forensic psychiatrist experienced in the assessment and treatment of personality disorders (NJK).

BPD. BPD participants were recruited from the community and the BPD Clinic at CAMH. Exclusion criteria for the BPD participants included a current major depressive episode (MDE); history of mania, hypomania, or psychotic illness; and diagnosis of substance abuse or dependence in the past 12 months as confirmed by the SCID-I. The use of psychotropic medications or herbs in the past three months was also exclusionary. For all participants in this study, neurological illness; head trauma; positive drug screen for drugs of abuse, including cannabis, on scan and assessment days; and contraindications to safe magnetic resonance imaging (MRI) scanning also precluded participation. All BPD participants screened negative for drugs of abuse on all assessment days and MRI and PET scanning days. The urine drug screen utilized was Rapid Response™, Drugs of Abuse Test Panel (BTNX Inc., Markham, Ontario, Canada) that tests for the presence of opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, amphetamines, tetrahydrocannabinol, and methadone.

ASPD. ASPD participants were recruited from the local Toronto community and correctional centers. Exclusion criteria for the ASPD participants included a current major depressive episode (MDE); history of mania, hypomania, or psychotic illness; and diagnosis of substance abuse or dependence in the past 12 months as confirmed by the SCID-I. None of the participants had used psychotropic drugs or herbs in the previous three months. All ASPD participants screened negative for drugs of abuse on all assessment days and MRI and PET scanning days using the same drug assay as for the BPD participants.

All study participants were asked to refrain from using alcohol the night before and the day of PET scanning.

Image acquisition and analysis. Each participant completed one [¹¹C]CURB PET scan at the CAMH Brain Health Imaging Centre utilizing a three-dimensional HRRT brain tomograph (CPS/Siemens, Knoxville, TN, USA). We have previously reported on the radiosynthesis of [¹¹C]CURB⁶⁵. Participants lay on their backs for the duration of the scan and wore a thermoplastic mask to reduce movement. A transmission scan was conducted followed by injection of 370 ± 40 MBq (10 ± 1 mCi) of [¹¹C]CURB⁶⁶. Brain radioactivity was calculated during sequential frames of increasing duration, and the total scan time was 60 min. Next, PET images were re-constructed using a filtered back-projection algorithm with a HANN filter at Nyquist cutoff frequency⁶⁷. Arterial samples were continuously sampled for the first 22.5 min with an automatic blood sampling system (Model PBS-101, Veenstra Instruments, Joure, The Netherlands) after [¹¹C]CURB injection. Whole blood and plasma radioactivity (1500 relative centrifugal force, 5 min) was counted using a Packard Cobra II or Wizard 2480 γ -counter (Packard Instrument Co., Meridian, CT, USA) cross-calibrated with the PET system. The concentration of parent radioligand and its metabolites was measured in each manual sample (except for the one at 15 min) as previously reported⁶⁵. Blood-to-plasma radioactivity ratios were fit using a biexponential function and parent plasma fraction utilizing a Hill function. A dispersion- and metabolite-corrected arterial plasma input function was generated as previously described⁶⁵.

A single standard proton-density weighted brain MRI scan was acquired for each participant (TE = 17, TR = 6000, FOV = 22 cm, matrix = 256 × 256, slice thickness = 2 mm; number of excitations = 2) on a Discovery MR750 3 T MRI scanner (General Electric, Milwaukee, WI, USA) for ROI delineation. ROIs were generated automatically using in-house software (ROMI) as previously reported⁶⁸. Time-activity curves were acquired over 60 min. in each of the ROIs and analyzed by a two-tissue compartment model with irreversible binding to the second component. FAAH binding was quantified using the composite parameter λk_3 ($\lambda = K_1/k_2$)⁶⁵.

FAAH polymorphism genotyping. A single nucleotide polymorphism of the *FAAH* gene (rs324420) encompasses transversion of a cytosine residue to the nucleoside adenosine (C385A) that influences the kinetics of [¹¹C]CURB. C/A and A/A genotypes show lower production of in vivo brain FAAH expression compared to those with the C/C genotype⁶⁹. For all study participants, the *FAAH* rs324420 variant was genotyped in accordance with the manufacturer's directions for a TaqMan SNP Genotyping assay (ID C_1897306_10; Life Technologies, Burlington, Canada) on a ViiA7 instrument (Life Technologies, Burlington, Canada) using 20 ng total genomic DNA template, Perfecta FastMix II (Quantabio, Beverly, MA, USA), in a total reaction volume of 10 μ L.

Instruments. BPD and ASPD participants completed the 240-item revised NEO Personality Inventory (NEO PI-R)⁷⁰, which was used to assess the Big Five personality dimensions. Scores for the facets underlying neuroticism (e.g., anxiety, angry hostility, depression, self-consciousness, impulsiveness, and vulnerability) were also calculated. Each facet was a sum of eight items, and the neuroticism personality trait was the sum of the facet scores (some items were reverse coded). Participants rated the NEO PI-R items on a scale ranging from (0) strongly disagree to (4) strongly agree. The NEO PI-R domain and facet scales generally have large and mostly acceptable estimates of internal reliability and retest reliability in addition to strong convergent and discriminant validity⁷¹. To correct for gender and age, raw scores were converted to *T* scores using published normative data⁷¹. Standardized scores < 45 *T* are in the low range, scores between 45 and 55 *T* are in the average range, and scores > 55 *T* are in the high range⁷¹.

Statistical analysis. Our first model calculated partial correlations between PFC FAAH binding and NEO-PI-R neuroticism scores controlling for *FAAH* genotype with a *p*-value < 0.05 indicating significance. We also conducted exploratory analyses between PFC FAAH expression and NEO-PI-R neuroticism facet scores controlling for *FAAH* genotype with a *p*-value < 0.05 indicating significance.

Our secondary model tested the whole brain, including anterior cingulate cortex, temporal cortex, hippocampus, insula, thalamus, ventral striatum, dorsal caudate, dorsal putamen, amygdala, and cerebellum. Partial correlations were computed between each ROI and NEO-PI-R neuroticism score, controlling for *FAAH* genotype. Bonferroni correction was applied (0.05/10 ROIs = 0.005) to correct for multiple comparisons.

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Author contributions

N.J.K., I.B., and R.M.B. conceived and designed the study idea. N.J.K. participated in data collection. N.J.K. wrote the first draft of the manuscript. N.J.K., I.B., and R.M.B. critically reviewed the manuscript. All authors contributed to and approved the final version of the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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