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REGULAR RESEARCH ARTICLE

Neuroticism Associates with Cerebral in Vivo Serotonin Transporter Binding Differently in Males and Females

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Abstract

Background: Neuroticism is a major risk factor for affective disorders. This personality trait has been hypothesized to associate with synaptic availability of the serotonin transporter, which critically controls serotonergic tone in the brain. However, earlier studies linking neuroticism and serotonin transporter have failed to produce converging findings. Because sex affects both the serotonergic system and the risk that neuroticism poses to the individual, sex may modify

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Significance Statement

Neurobiological underpinnings of the personality trait neuroticism are still not well understood. Here, using a large sample, we show that higher neuroticism associates with higher thalamic serotonin transporter binding in males, whereas in females, higher neuroticism associates with lower thalamic serotonin transporter binding. The finding helps to elucidate the brain-level molecular mechanisms predisposing to affective disorders. The study also provides clues into the neural mechanisms of sex differences in many psychiatric illnesses.

the association between neuroticism and serotonin transporter, but this question has not been investigated by previous studies.

Methods: Here, we combined data from 4 different positron emission tomography imaging centers to address whether neuroticism is related to serotonin transporter binding in vivo. The data set included serotonin transporter binding potential values from the thalamus and striatum and personality scores from 91 healthy males and 56 healthy females. We specifically tested if the association between neuroticism and serotonin transporter is different in females and males.

Results: We found that neuroticism and thalamic serotonin transporter binding potentials were associated in both males and females, but with opposite directionality. Higher neuroticism associated with higher serotonin transporter binding potential in males (standardized beta 0.292, $P = .008$), whereas in females, higher neuroticism associated with lower serotonin transporter binding potential (standardized beta -0.288, $P = .014$).

Conclusions: The finding is in agreement with recent studies showing that the serotonergic system is involved in affective disorders differently in males and females and suggests that contribution of thalamic serotonin transporter to the risk of affective disorders depends on sex.

Keywords: neuroticism, sex, serotonin, serotonin transporter, PET

Introduction

Women have higher incidence of major depressive disorder (MDD) and subclinical depressive symptoms than men (Lindeman et al., 2000). The neurotransmitter mechanisms that might contribute to this difference are still not well understood. On average women score higher in neuroticism, which is a personality trait that reflects the propensity for experiencing negatively valenced emotional states. By definition, individuals on the higher end of the neuroticism spectrum are more prone to feel negative emotions such as sadness and anxiousness and also have more difficulties when trying to cope with stress (Costa and McCrae, 1992*a*). Higher neuroticism scores also increase the risk for developing MDD (Kendler et al., 2006) and anxiety disorders (Hettema et al., 2006). Thus, sex differences in manifesting this trait may contribute to the sex difference in the incidence of MDD. Moreover, high neuroticism also increases the risk for MDD more so in women than in men (Kendler and Gardner, 2014), which suggests that sex impacts the mechanism through which neuroticism confers greater risk for affective disorders.

The sex difference in the incidence of MDD putatively is mediated at least partly by the effects of sex hormones, because the MDD incidence is higher in women only after puberty (Wade et al., 2002). Further, sex hormones affect the serotonin system in multiple ways (Barth et al., 2015), which may be one mechanism conveying the effects of sex on the incidence of affective disorder. Serotonergic function has a well-documented role in the pathophysiology of MDD and the mechanisms of antidepressant pharmacotherapy (Cannon et al., 2007; Meyer, 2007; Sharp and Cowen, 2011). The synaptic serotonin levels are crucially controlled by the serotonin transporter (5-HTT). Thus, the 5-HTT has been viewed as a promising target in the search for the neural underpinnings of neuroticism. Investigating the central 5-HTT in neuroticism may elucidate the neurobiological mechanisms of the greater susceptibility for developing MDD and thereby illuminate the etiology of affective disorders (Marcus et al., 2008).

Despite initially promising findings, human studies linking 5-HTT and neuroticism have been inconsistent, and the role of 5-HTT in neuroticism has remained elusive. The S-allele in the 5-HTT gene-linked promoter region (5-HTTLPR) was initially found to be associated with higher neuroticism (Lesch et al., 1996). However, subsequently several negative findings have been published, and the latest meta-analyses have yielded inconclusive results, mainly due to the large heterogeneity in the results across studies (Munafo et al., 2009; Minelli et al., 2011). Intriguingly, recent evidence converges to suggest that sex may modulate the effects of 5-HTTLPR polymorphism on phenotype (Gressier et al., 2016). That is, in females, the S-allele seems to associate more with depression and negative affect, whereas in males it associates more with aggressive and externalizing traits.

So far, 3 published positron emission tomography (PET) studies have investigated whether neuroticism associates with in vivo 5-HTT binding. Takano and colleagues (Takano et al., 2007) found a positive association between neuroticism and thalamic 5-HTT binding, Klaver et al. (Klaver et al., 2007) a negative relationship, while Kalbitzer and colleagues (Kalbitzer et al., 2009) did not detect any significant relationship between these 2 measures. On explanation may be that single site PET studies often lack power due to too-small sample sizes. Moreover, the first study included only males, whereas the latter ones included both males and females. To date, no study has directly investigated whether sex modulates the effect of neuroticism on 5-HTT binding. If such a sex effect exists, it might also explain inconsistencies in the literature and elucidate the neurobiological basis for the greater incidence of MDD in women and the tendency for women to manifest a partly distinct symptom profile than men during major depressive episodes (Martin et al., 2013).

In the present study, we sought to resolve these conflicts in previous PET imaging studies regarding the association between 5-HTT and neuroticism. We combined data from 4 different imaging centers that have measured the 5-factor model personality questionnaire and 5-HTT binding using PET with a selective 5-HTT radiotracer. Importantly, the combined data set was large enough to allow us to test whether sex modulates the association between neuroticism on 5-HTT binding. Because previous studies have found correlations between other personality traits and 5-HTT (Kalbitzer et al., 2009), we also explored these associations in this data set.

Methods

Study Design

The study sample comprises 147 healthy subjects (91 males and 56 females) from 4 independent imaging centers (Table 1). The imaging centers were: the National Institute of Radiological Sciences, Chiba, Japan (NIRS), the Neurobiology Research Unit, Copenhagen University Hospital Rigshospitalet, Denmark (NRU), the National Institute of Mental Health, Bethesda, Maryland, USA (NIMH), and the Turku PET Centre, Turku, Finland (TPC). NIRS, NRU, and NIMH have previously published these data (Klaver et al., 2007; Takano et al., 2007; Kalbitzer et al., 2009; Erritzoe et al., 2010). In addition, unpublished data from 31 subjects were collected at the TPC, following the same methods described in Tuominen et al. (Tuominen et al., 2012). The protocols of the original studies were approved by local ethics committees, and subjects gave informed consent accepted by those committees. The study at the NIRS was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan; the study at the NRU was approved by the Ethics Committee of Copenhagen and Frederiksberg, Denmark; the study at the NIMH was approved by the Institutional Review Board at the National Institute of Mental Health, Bethesda, MD; and the study at the TPC was approved by the by the Joint Ethical Committee of the University of Turku and the Turku University Central Hospital, Turku, Finland. At the NIHM and Turku PET Centre, subjects were interviewed using the Structured Clinical Interview for DSM-IV, whereas at the NIRS and NRU the subjects underwent an unstructured interview. At all study sites, exclusion criteria included lifetime psychiatric illness and present substance abuse. At the TPC, serotonin transporter binding was measured using [^{11}C]MADAM (Lundberg et al., 2005) and personality traits using NEO-FFI (Costa and McCrae, 1992*b*), whereas other centers used [^{11}C]DASB (Houle et al., 2000) and NEO-PI-R scale (Costa and McCrae, 1992*a*). To account for the different number of items in the NEO-PI-R and NEO-FFI, we calculated a mean neuroticism score for each individual by dividing the raw score by the number of items in the neuroticism scale. Thus, neuroticism scores ranged from 0 to 4 (each item is rated from 0 to 4). The PET data were collected with Siemens ECAT47 at the NIRS, with HRRT scanner (Siemens) at the TPC, and with GE-Advance scanner (General Electric) at the NRU and NIHM. The data were modeled at the TPC using the simplified reference tissue model (Lammertsma and Hume, 1996) and at other centers using the multi-linear reference tissue model 2 (Ichise et al., 2003) with cerebellar gray matter as the reference region. These models allow the estimation of the nondisplaceable binding potential (BP_{ND}; Innis et al., 2007), which equals $f_{ND}\ B_{avail}/K_D$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, B_{avail} is concentration of available receptors, and K_D is radioligand equilibrium dissociation constant. BP_{ND} is directly proportional to the density of 5-HTTs and therefore can be used as an index of their density. All the imaging data included into the present study were preprocessed and modeled at the respective center with the primary study in mind. The current analyses were performed using only the regional BP_{ND} values that were available. Voxel-wise BP_{ND} maps were not available.

At the NRU, regions-of-interest (ROIs) were delineated automatically (Svarer et al., 2005), whereas in other centers ROIs were delineated manually onto individual PET scans using the co-registered T1-weighted MRI scan. All 4 centers had delineated thalamus as an ROI, but otherwise the centers used different ROIs (supplementary Table 1). At the NIRS, the striatum was delineated as one ROI, whereas in the other 3 centers this ROI was divided into caudate and putamen. Because serotonin transporter binding in the caudate and putamen is highly correlated (Tuominen et al., 2014) and we did not have the sizes of each individual's ROIs, we computed an arithmetic mean of BP_{ND}s in the caudate and putamen and used that as an estimate of striatal BP_{ND} for the data from 3 centers that had delineated these regions separately. No other region in the brain was consistently defined by all the centers, and therefore the statistical analyses were confined to these 2 regions: the thalamus and striatum.

Statistical Methods

To better assess the effects of sex and age on the association between neuroticism and 5-HTT BP_{ND}s, individual data points were included into the statistical model instead of carrying out

Table 1. Details of the Data Collected at Each Center

						Serotonin transporter BP_{ND}	
Center	N (M/F)	Age	Neuroticism[a]	Questionnaire	Tracer	Thalamus	Striatum
NIRS[1]	31 (31/0)	23.6 ± 2.8	2.1 ± 0.46	NEO-PI-R	[^{11}C]DASB	1.8 ± 0.29	1.3 ± 0.16
NRU[2]	57 (37/20)	35.1 ± 18.0	1.5 ± 0.40	NEO-PI-R	[^{11}C]DASB	1.8 ± 0.25	1.6 ± 0.18[b]
NIMH[3]	28 (8/20)	36.3 ± 9.1	1.9 ± 0.14	NEO-PI-R	[^{11}C]DASB	1.7 ± 0.23	1.3 ± 0.17[b]
TPC[4]	31 (15/16)	39.1 ± 5.1	1.2 ± 0.76	NEO-FFI	[^{11}C]MADAM	1.4 ± 0.15	1.1 ± 0.16[b]

Values are presented as mean ± SD.

[a]Neuroticism score ranges from 0 to 4 (each item is rated from 0 to 4) and was calculated by dividing the raw score by the number of items in the questionnaire.

[b]Arithmetic mean of nondisplaceable binding potential (BP_{ND}s) in the caudatus and putamen. 1, National Institute of Radiological Sciences, Chiba, Japan; 2, Neurobiology Research Unit, Copenhagen University Hospital Rigshospitalet, Denmark; 3, National Institute of Mental Health, Bethesda, MD; 4, Turku PET Centre, Turku, Finland.

a meta-analysis. Multiple linear regression analyses using the individual data were performed for the 2 brain regions (thalamus and striatum) separately. The 5-HTT BP_{ND} was used as the dependent variable, and the neuroticism*sex interaction term, neuroticism, sex, and age as independent variables. The different centers were coded as dummy variables and included as covariate in all statistical models. The interaction term was created by multiplying sex and neuroticism values. We predicted that the interaction term would significantly associate with 5-HTT BP_{ND}. To explore if data from a single center dominated the effect, we also carried out this analysis 4 other times, leaving one center at the time out from the analysis. To obtain estimates of standardized beta coefficients for males and females separately, multiple regression analyses were performed separately for both sexes with the 5-HTT BP_{ND} as the dependent variable, and neuroticism, age, and centers as independent variables.

To illustrate the results in the thalamus, a partial regression plot (Larsen and McCleary 1972) between neuroticism scores and the thalamic 5-HTT BP_{ND} values was created. First, we computed residuals for both sexes by regressing the 5-HTT BP_{ND} against the age and centers while omitting neuroticism scores from the model. Second, we computed residuals for both sexes by regressing neuroticism against the age and centers while omitting 5-HTT BP_{ND} values from the model. The resulting residual vectors can be understood as mean centered neuroticism scores corrected for the age and centers, and mean centered 5-HTT BP_{ND} values corrected for the age and center respectively. Finally, the residual vectors for both sexes from the above 2 regression analyses were plotted against each other.

Because previous studies have reported associations between other personality traits and serotonin transporter BP_{ND} (Kalbitzer et al., 2009), we also performed exploratory multiple linear regression analyses for the other 4 personality traits included in the inventory: extraversion, agreeableness, openness to experience, and conscientiousness. Despite some reports of associations between these personality traits and the serotonin system, there are no compelling theoretical reasons to assume that these personality traits are associated with the serotonin system. Thus, these analyses were considered as exploratory. In a similar manner, the model included 5-HTT BP_{ND} as the dependent variable, and personality trait, sex, age, and the centers as independent variables. As we did not have a priori hypothesis about sex interaction for other personality traits, the interaction term was not included into the analyses.

Results

Neuroticism and 5-HTT in the Thalamus

A statistically significant multiple linear regression was found using the thalamic BP_{ND} values as the dependent variable and neuroticism, neuroticism * sex, sex, age, and centers as independent variables ($F_{(7,139)}$ = 14.566, P < .001, R^2 = .394). The 5-HTT BP_{ND} in the thalamus was significantly associated with the neuroticism*sex interaction term (t = 2.749, standardized β = 0.963, P = .007) and with the age term (t = -2.542, standardized β = -.288, P = .014). The multiple linear regression analyses for each sex separately using the thalamic BP_{ND} values as the dependent variable and neuroticism, age, and centers as independent variables were also significant (males: $F_{(5,85)}$=11.385, P < .001, R^2 = .366; females: $F_{(4,51)}$=13.011, P<.001, R^2=.466). In males, neuroticism was a significant positive predictor of thalamic 5-HTT BP_{ND} (t = 2.707, standardized β = .292, P=.008), whereas in females, neuroticism was a significant negative predictor and a negative association (t = -2.542, standardized β = -.288, P= .014). As illustrated in the partial regression plot (Figure 1), higher neuroticism scores in males were associated with higher 5-HTT BP_{ND} values in the thalamus, whereas higher neuroticism scores in females were associated with lower BP_{ND} values in the same region. Results from excluding one center at a time from the analyses are shown in supplementary Material and supplementary Figure 1.

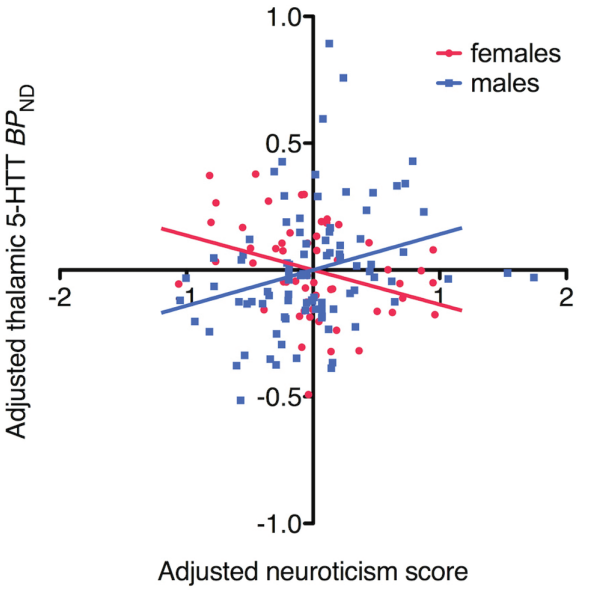

Figure 1. Partial regression plot illustrates the associations between neuroticism score and the thalamic serotonin transporter binding potential (5-HTT BP_{ND}) in males and females. Adjusted neuroticism scores are the residuals when regressing the neuroticism scores against age and center while omitting 5-HTT BP_{ND} values. Adjusted thalamic 5-HTT BP_{ND} values are the residuals when regressing BP_{ND} values against age and center while omitting neuroticism scores. Thus, the adjusted scores can be viewed as mean centered neuroticism scores and BP_{ND} values that have been corrected for age and study center.

Neuroticism and 5-HTT in the Striatum

The multiple linear regression model using the striatum BP_{ND} as the dependent variable and neuroticism, neuroticism * sex, sex, age, and centers as independent variables was statistically significant ($F_{(7,139)}$ = 20.022, P < .001, R^2 = .477). However, no significant main effect of neuroticism or sex by neuroticism interaction was observed on the striatal 5-HTT BP_{ND}.

Extraversion, Agreeableness, Openness to Experience, and Conscientiousness and 5-HTT

Multiple regression analyses, using the other 4 personality traits (extraversion, agreeableness, openness to experience, and conscientiousness) were also carried out. However, in the resulting regressions models, none of these other personality traits were statistically significant predictors of the 5-HTT BP_{ND} in the thalamus or striatum (all P > .05).

Conclusions

The present study is the largest PET study to date that has examined the in vivo molecular brain biology basis of personality. The multi-site approach allowed us for the first time to show

that neuroticism and 5-HTT are linked in a sex-dependent manner. More specifically, in males, higher neuroticism scores associated with higher thalamic 5-HTT binding, whereas in females, high neuroticism scores associated with lower 5-HTT binding in the thalamus. In contrast, other personality traits described by the 5-factor model were not significantly associated with 5-HTT binding.

The interpretation between the magnitude of 5-HTT binding and intrasynaptic 5-HT levels is complex. Under some experimental conditions, higher 5-HTT binding correlates with decreased serotonin metabolite concentrations in the cerebrospinal fluid (Heinz et al., 1998, 2002). Nevertheless, the cell surface expression of 5-HTT sites generally parallels serotonin levels, as the cell surface expression of 5-HTT sites rapidly responds to changing serotonin concentrations (Blakely et al., 1998). Furthermore, the extent to which 5-HTT binding simply reflects the number of serotonergic afferents to projection areas is unknown. Thus, our data may not support simplistic hypotheses regarding the relationship between neuroticism ratings and synaptic serotonin levels per se.

An increasing body of literature supports the involvement of the cerebral serotonin system in neuroticism. Frokjaer and colleagues (Frokjaer et al., 2008) showed that higher neuroticism scores associate with higher 5-HT_{2A} receptor binding in the frontolimbic regions (n = 83). More recently, we found that both cortical and subcortical 5-HT_{1A} receptor binding is lower in subjects who have higher neuroticism scores (Hirvonen et al., 2015) (n = 34). Decreased 5-HT_{1A} and increased 5-HT_{2A} receptor binding in subjects with high neuroticism could result as compensatory changes to low serotonin levels (Hirvonen et al., 2015), which in turn have been linked to negative emotionality and depressive mood. For instance, low serotonin levels are associated with a negative emotional processing bias including an increase in the responsiveness to punishment (Cools et al., 2008; Fisher et al., 2015) and, in susceptible subjects, depressive symptoms (Benkelfat et al., 1994). In summary, the literature suggests that lower synaptic serotonin levels underlie higher neuroticism scores. Given the present results, we speculate that sex also affects the association between neuroticism and other constituents of the serotonin system. In this sample, we did not find a difference in 5-HTT BP_{ND} in the thalamus or striatum between males and females, but there is some evidence that healthy women have higher 5-HT_{1A} binding (Parsey et al., 2002) and lower serotonin synthesis rate (Nishizawa et al., 1997; Sakai et al., 2006) than males. Whether neuroticism correlates with serotonin synthesis rate or 5-HT_{1A} binding in a sex-dependent manner is currently unknown. Such an interaction could potentially have opposing effects with the present finding on the intrasynaptic serotonin levels and could help explain why 5-HTT binding associates with neuroticism differently in men and women. Despite that the exact molecular interpretation of our finding remains elusive, it clearly demonstrates that the underlying neurobiology of neuroticism is at least, to some extent, different between the sexes.

We found that neuroticism was associated with 5-HTT binding in a sex-dependent manner in the thalamus but not in the striatum. The mediodorsal and periventricular nuclei of the thalamus form part of the extended medial prefrontal network, which is centrally involved in MDD (Price and Drevets, 2010). Within that network, these thalamic nuclei putatively process, gate, and relay information from subcortical structures to the prefrontal cortex. Disrupting thalamic function by lesion leads to higher acute and chronic stress responses (Bhatnagar et al., 2002; Spencer et al., 2004), demonstrating its role in stress regulation. In MDD patients, thalamic metabolism is increased (Price and Drevets, 2010; Su et al., 2014), but whether the thalamic 5-HTT binding is different in MDD patients has remained elusive. Previous PET studies have found both increased and decreased 5-HTT binding in the thalamus in MDD patients (Savitz and Drevets, 2013). Similarly, the literature is mixed on whether MDD associates with increases or decreases in 5-HT1a and 5-HT2a receptors (Shrestha et al., 2012; Savitz and Drevets, 2013).

Unfortunately, psychiatric imaging studies have rarely taken into account the possible modifying effects of sex. The few studies that have done so suggest that there may be important sex differences in the neurobiology of affective disorders. Recent data has shown that patients with seasonal affective disorder have upregulated cerebral 5-HTT in the winter, whereas individuals that are resilient to the disorder have downregulated 5-HTT (Mc Mahon et al., 2016). This result was mostly driven by the female participants. The sex-specific differences may also apply to other parts of the serotonin system. Serotonin synthesis capacity may be higher in female MDD patients than in male patients (Frey et al., 2010). On the other hand, one study reported that male MDD patients have elevated 5-HT_{1A} receptor levels but females do not (Kaufman et al., 2015). A similar sex difference has been shown in patients with panic disorder: male patients have higher 5-HTT levels than male controls, whereas 5-HTT binding did not significantly differ between female patients and female controls (Maron et al., 2011; Cannon et al., 2013). Our results support putative sex differences in the neurobiology of affective disorders. Because neuroticism is a major risk factor for affective disorders, our results further suggest that sex differences are critical in the brain architecture of risk for MDD. Indeed, even the 5-HTTLPR polymorphism may affect males and females differently. Gressier and colleagues (Gressier et al., 2016) showed that females suffering from MDD more often had the S-allele, whereas males with MDD more often had the L-allele. The S-allele leads to a lower number of 5-HTT proteins, which is detected as lower binding in PET studies (Willeit and Praschak-Rieder, 2010). Neuroticism can be viewed as an intermediary endophenotype between genetic predisposition and an affective disorder. The present study further demonstrates this endophenotype has different neurobiological correlates of risk for affective disorders in males and females.

Limitations

Results from this study should be appraised in the context of a number of limitations. First, women experience more subclinical depressive symptoms compared with men (Lindeman et al., 2000). Especially in a cross-sectional setting, it is difficult to disentangle high neuroticism personality from subclinical depression. Thus, it is possible that the negative association in females is partially mediated by subclinical depressive symptoms rather than associated with neuroticism personality trait per se. Second, we did not measure the phase of the menstrual cycle in females nor did we have sex steroid hormone levels available for the females. Although sex steroid hormones affect the 5-HT_{2A} receptor density (Moses et al., 2000; Kugaya et al., 2003; Moses-Kolko et al., 2003) and high-dose sex steroid hormones also affect the 5-HTT binding (Kranz et al., 2015), differences in the phase of the menstrual cycle are unlikely to contribute to the finding in females as the phase does not affect 5-HTT binding (Jovanovic et al., 2009; Frokjaer et al., 2015).

Another limitation is that individual body mass index (BMI) values were not available, and therefore we did not adjust the regressions for BMI. Erritzoe and colleagues showed an inverse association between BMI and 5-HTT binding (Erritzoe et al.,

2010). Because higher neuroticism typically associates with higher BMI (Vainik et al., 2013), spurious variations in BMI could not explain the positive association seen in males, but such variations could potentially contribute to the negative association seen in females. Finally, the amount of daylight has an effect on 5-HTT BP_{ND} (Praschak-Rieder et al., 2008), and this effect may depend on 5-HTTLPR status (Kalbitzer et al., 2010), which in itself has a moderate effect on 5-HTT BP_{ND} (Savitz and Drevets, 2013). In the present study, neither 5-HTTLPR status nor seasonal variations were controlled for.

Combining data from 4 independent centers also inherently introduces methodological discrepancies. In this study, a number of potentially confounding methodological differences were present between centers. First, neuroticism was measured using NEO-PI-R in all centers except one, where a shorter version of the NEO-PI, called NEO-FFI, was used. Because correlation between NEO-PI-R and NEO-FFI neuroticism scores ranges between 0.89 and 0.92 (Costa and McCrae, 1992*b*), differences between these instruments are unlikely to affect the results. Second, different centers used different PET scanners, which may have affected the 5-HTT BP_{ND} estimates. Further, the ROI's were delineated differently across the centers. The thalamus and striatum are easily distinguishable from the PET and T1-weighted MRI and are therefore easy to delineate. However, as the 5-HTT BP_{ND} is not uniform even within these structures, differences in the delineation procedures may have introduced some error variance into the BP_{ND} estimates. Moreover, 5-HTT binding was measured with 2 different tracers, [^{11}C]MADAM and [^{11}C]DASB. Both tracers bind specifically to the 5-HTT (Emond et al., 2002; Wilson et al., 2002), and the rank values and test-retest variability of different regions are highly comparable (Kim et al., 2006; Lundberg et al., 2006). There are no published head-to-head comparisons between the 2 tracers, but [^{11}C]MADAM seems to give somewhat lower BP_{ND} values, at least in the regions included. However, systematically lower 5-HTT binding values in a single sample are unlikely to affect the overall finding, because centers effects were statistically adjusted for. Additionally, we tested whether our finding would remain the same if the centers would be excluded, one at a time, from the analysis. These analyses showed that excluding the study that used [^{11}C]MADAM made the neuroticism by sex interaction an even more significant predictor of the 5-HTT BP_{ND} in the model. Surprisingly, after excluding the NRU sample, the interaction effect was no more statistically significant. This may be simply due to the fact that the NRU sample is the largest sample, and excluding it reduced the power of our analysis. Nonetheless, these analyses highlight the importance of large data sets to discover associations between behavior and brain neurotransmitter systems. Finally, in our study we did not look for associations beyond thalamus and striatum, as no other regions were consistently delineated by all the centers. Moreover, the delineation methods were likely to be more variable across the centers for other regions compared with the thalamus and striatum, which are easily distinguishable from the PET and T1-weighted MRI. Therefore, this combined data set cannot assess if the difference in the neuroticism by sex interaction in the 5-HTT BP_{ND} extends beyond the thalamus and striatum. Future studies must elucidate if the results extend to other brain regions.

In summary, we found that in males, neuroticism associates positively with 5-HTT binding in the thalamus, whereas in females the association was negative. Our results bridge the gap between genetic studies and clinical PET imaging studies that both have shown evidence for sex differences in how the serotonin system is involved in the pathophysiology of affective disorders. This finding underscores the importance of taking sex into account when studying normal brain function. Better understanding of sex effects will hopefully facilitate better understanding of the etiology of psychiatric disorders. Since many published single-site PET studies lack power due to too-small sample sizes, the approach to combine many data sets applied here should be encouraged in the molecular imaging field. In summary, our results suggest that thalamic 5-HTT could contribute differently to the risk of affective disorders in males and females. Future studies need to elucidate if similar sex differences exist in other constituents of the serotonin system.

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Statement of Interest

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