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Discordant peripheral levels of brain-derived neurotrophic factor and serotonin are associated with enhanced emotional intelligence in men

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Abstract

Emotional intelligence (EI), a normally-distributed, multi-faceted construct, encompasses the abilities to perceive, understand, regulate, and use emotions adaptively. As low EI is a risk factor for mood disturbance, there is clinical value in mapping its biological contributions. Although the neurochemistry and neurogenetics of mood disorders, particularly with respect to brain-derived neurotrophic factor (BDNF) and serotonin (5-HT), are well studied, the relationship between these neurotransmitters and facets of emotion processing across the full EI continuum is unknown. In this study we tested for associations between peripheral levels of BDNF and 5-HT, as well as behaviorally relevant BDNF and 5-HT interactions, and dimensions of EI in 74 healthy adults. Urinary neurotransmitter levels adjusted for creatinine concentration were determined via enzyme-linked immunosorbent assay, and performance-based EI was measured with the Mayer-Salovey-Caruso Emotional Intelligence Test Version 2.0. Results found that BDNF and 5-HT levels were uncorrelated and that neither alone predicted EI. However, in men there was a BDNF x 5-HT interaction such that those with discordant combinations of neurotransmitter levels (high 5-HT/low BDNF; low 5-HT/high BDNF) demonstrated superior ability to understand complex emotional meanings, transitions, and situations, an effect that was not confounded by general cognitive intelligence. No interactions were present in women. These results suggest that an interaction between BDNF and 5-HT systems contributes to EI in healthy men, although the precise physiological nature of this interaction and its consequences for brain structure and function in emotion processing pathways require further study.
Keywords: brain-derived neurotrophic factor, serotonin, peripheral biomarker, emotional intelligence, emotional processing.

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Introduction

Depression and anxiety have been associated with abnormal levels of *in vivo* brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) (Dell'Osso et al., 2010; Pandey & Dwivedi, 2009), and there is evidence of genetic variation underlying atypical BDNF and 5-HT expression in people with mood disorders (Elzinga et al., 2011; Petersen et al., 2012). Aligned with this, studies have reported aberrant grey matter density (Frodl et al., 2008; Wagner et al., 2011) and volume (Eker et al., 2010; Inoue et al., 2010) in brain regions along BDNF and 5-HT pathways as well as impaired functional connectivity among these regions during resting state (Jang et al., 2012) and during emotion processing tasks (Mukherjee et al., 2011). Although there is a sizable body of literature that documents the separate roles of BDNF and 5-HT in mood disturbance, research is beginning to look for evidence of behaviorally meaningful interactions between the two systems in relation to affective processing. Such interaction is plausible because BDNF and 5-HT are known to co-regulate each other, acting in concert to control neurogenesis and synaptic plasticity (Martinowich & Lu, 2008).

Much of the research on the emotion dysregulation correlates of BDNF/5-HT interaction in humans has focused on epistatic relationships among genes that regulate BDNF and 5-HT, specifically on a handful of polymorphisms. Results of these studies are mixed, with some indicating that a genetic combination that codes for low BDNF and low 5-HT confers risk for mood pathology (Anttila et al., 2007; Kim et al., 2012) and some indicating that low BDNF and high 5-HT constitutes an at-risk profile (Dougherty, Klein, Congdon, Canli, & Hayden, 2010; Egan et al., 2003; Kaufman et al., 2006; Kim et al., 2008). Yet other studies suggest that a genetic predisposition to low BDNF can actually be protective against mood disturbance in the context of high levels of synaptic 5-HT (Pezawas et al., 2008a; Schumacher et al., 2005; Strauss et al., 2005; Hünnerkopf, Strobel, Gutknecht, Brocke, & Lesch,

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2007). Although the cumulative data on directionality of genotypic effects are highly inconsistent, these findings nevertheless raise the possibility that the BDNF and 5-HT systems interact to influence emotional reactivity to stress, rendering certain individuals of increased susceptibility for affective dysfunction.

Studies that simultaneously examine BDNF and 5-HT as they relate to normal variation in emotion processing are scarce and, to our knowledge, there is no research that explores how BDNF and 5-HT levels interactively predict patterns of emotional intelligence (EI). EI refers to a set of mental abilities, normally distributed in the general population, that are involved in emotional information processing. Given that mood disturbance is often associated with poor EI (Lizeretti, Extremera, & Rodríguez, 2012) and given that EI training can improve psychiatric symptoms (Jahangard et al., 2012), there is considerable clinical utility in characterizing its neurochemical contributions. The present study addresses this gap in the literature by measuring *in vivo* levels of peripheral BDNF and 5-HT in conjunction with a performance-based EI battery in healthy adults. As the first study of this kind, we specifically chose a nonclinical sample to ensure a wide representation of EI abilities. In light of reported sex differences in circulating levels of BDNF (Komulainen et al., 2008) and 5-HT (Cosgrove, Mazure, & Staley, 2007), we included men and women in the cohort in order to take sex into account during analysis. In recognition of the multi-faceted nature of EI we adopted the Mayer–Salovey–Caruso Emotional Intelligence Test Version 2.0 (MSCEIT V2.0; Mayer, Salovey, & Caruso, 2002) as our primary index of EI as it deconstructs EI into four skill-based branches: the ability to perceive emotion, the ability to understand emotions, the ability to use emotions to facilitate thought, and the ability to manage emotions adaptively.

Although much of the literature concerning BDNF and 5-HT epistasis in human emotion processing utilizes a neurogenetic approach, genotyping data do not perfectly represent *in vivo* physiological neurochemistry. Because a multitude of genes affects circulating levels, it is not surprising that BDNF- and 5-HT-related polymorphisms are weak predictors of neurotransmitter concentration (Luykx et al., 2013; Terracciano et al., 2010; Trajkovska et al., 2007; Yoshimura et al., 2011). As an alternative approach, we assessed BDNF and 5-HT levels via enzyme-linked immunosorbent assay (ELISA) in urine, choosing urine over other peripheral sources (e.g., plasma) due to the non-invasive nature of fluid collection. Urinary BDNF and 5-HT concentrations, when adjusted for level of overall hydration via creatinine normalization (Cone et al., 2009), are good proxy measures of central BDNF and 5-HT for several reasons. BDNF crosses the blood–brain barrier bi-directionally (Pan, Banks, Fasold, Bluth, & Kastin, 1998), and there is evidence that the brain is the primary source for peripheral BDNF (Rasmussen et al., 2009). Once in the periphery, BDNF is first stored in blood platelets (Lommatzsch et al., 1999; Ziegenhorn et al., 2007), then released into circulation upon agonist stimulation (Fujimura et al., 2002), and eventually filtered from the blood by nephrons in the kidney for excretion in urine (for review of mechanisms, see Marc, Ailts, Campeau, Bull, & Olson, 2011). The findings that peripheral and central BDNF concentrations correlate strongly in animal models (Klein et al., 2011) and that peripheral BDNF concentration is associated with cortical integrity in humans (Lang, Hellweg, Seifert, Schubert, & Gallinat, 2007) further suggest that peripheral concentration is a good biomarker for central BDNF concentration. Moreover, two recent studies documenting the viability of urinary ELISA for the detection of human BDNF (Collins & Koven, 2014; Koven & Collins, in press) highlights the viability of urinary BDNF level as a peripheral biomarker of central BDNF activity. 5-HT crosses the blood-brain barrier uni-directionally and bi-directionally in different locations of the capillary cell membrane (Wakayama, Ohtsuki, Takanaga, Hosoya, & Terasaki, 2002) via the serotonin transporter and is shuttled from the peripheral bloodstream to the kidneys by active transport mechanisms (Marc et al., 2011). Animal models indicate a strong positive correlation between central 5-HT activity and urinary 5-HT levels (Lynn-Bullock, Welshhans, Pallas, & Katz, 2004), and data from Nichkova and colleagues (2012) confirm that variations in urinary 5-HT, assessed via ELISA, track central nervous system changes in humans.

The overarching goal of the study was to determine if an interaction between peripheral BDNF and 5-HT concentration predicted EI ability in a nonclinical cohort. Given neurogenetic data indicating epistasis between BDNF- and 5-HT-related polymorphisms in emotional dysfunction, we expected a similar interaction to exist in the context of normative EI.

Methods

Participants

The sample included 74 right-handed, young adults (29 men, 45 women; mean age = 19.0 ± 1.3 years) who participated in the study for partial college course credit. To ensure a healthy sample, individuals were excluded if they endorsed a history of current psychiatric illness, neurological disorder (e.g., epilepsy, traumatic brain injury, learning disorder), or significant systemic medical illness. Participants were also excluded for conditions known to alter BDNF and 5-HT levels, including recent use of psychotropic medications (Tamaji et al., 2012) and medical conditions of the bladder (Antunes-Lopes, Carvalho-Barros, Cruz, Cruz, & Martins-Silva, 2011). Women were excluded if they were menstruating in order to prevent the introduction of blood-borne neurotransmitters into the urine sample. Seventy percent of the sample reported their ethnicity as White, 17.6% as Asian, 9.6% as Latino, and 2.8% as Black. The protocol was consistent with ethical guidelines of the Declaration of Helsinki and was approved by the local Institutional Review Board.

Procedure

The protocol included provision of written informed consent and urine capture, as well as completion of a health and demographics questionnaire, a performance-based EI test, and an abbreviated adult intelligence test. To control for diurnal cycles of peptides in peripheral fluids (Pluchino et al., 2009), all data were collected between 10:00 and 12:00 hours. Urine was collected following a mid-stream capture protocol in 120 mL sterile cups and stored at -80°C.

Assessment

BDNF urinalysis involved acidification, extraction, and ELISA. Acidification and extraction steps, which maximize detection of BDNF in biological fluids, followed procedures described by Collins and Koven (2014). The BDNF ELISA was completed with a commercially available kit from Abcam (Cambridge, MA, USA), which has a sensitivity range of 0.066 – 16 ng/ml BDNF and no cross-reactivity with over 40 different cytokines. Absorbance level of each sample was measured using a BioTek Synergy HT microplate reader (Winooski, VT, USA) at 450 nm, with concentration calculated according to a standard curve. Intra- and inter-CV were 10.8% and 14.6%, respectively.

Unlike BDNF, 5-HT is more easily detectible in human urine, eliminating the need for preliminary acidification and extraction. The 5-HT ELISA was completed with a commercially available kit from Alpco Diagnostics (Salem, MA, USA), which has a sensitivity range of 5 – 860 ng/mL 5-HT. As the 5-HT ELISA uses a highly specific antibody, there is negligible cross-reactivity with other urinary compounds; the highest cross-reactivity is with tryptamine at 0.19%. Absorbance level of each sample was measured at 450 nm, and concentration was calculated according to a standard curve. Intra- and inter-CV were 7.5% and 12.8%, respectively.

Although the neurotransmitter foci for this study were BDNF and 5-HT, urinary creatinine (Cr) was also assessed in order to index, and control for, varying hydration levels. Cr assessment was completed with a commercially available kit from Cayman (Ann Arbor, MI, USA), which has a dynamic sensitivity of 0 – 15 mg/dL Cr. Absorbance level per sample was measured at 500 nm, with concentration calculated according to a standard curve. Intra- and inter-CV were 3.2% and 5.0%, respectively.

The MSCEIT V2.0 is a 141-item performance-based EI test battery with a hierarchical structure. The web-based MSCEIT was used and data scored by Multi-Health Systems (North Tonawanda, NY, USA) using consensus-based norms—as is recommended for most applications of the MSCEIT (Mayer et al., 2002). Performance across the eight subtests (Faces; Pictures; Sensations; Facilitation; Blends; Changes; Emotion Management; Emotional Relations) can be calculated at the level of four branch scores (Perceiving Emotions; Facilitating Thought; Understanding Emotions; Managing Emotions), two area scores (Experiential EI; Strategic EI), and one superordinate score (MSCEIT total). For a description of each variable, see Table 1. All variables were normed with respect to age and sex and are reported as standard scores ($M = 100$; $SD = 15$). Higher values indicate higher EI. The full-scale reliability of the MSCEIT, as normed by consensus scoring, is .93, with area reliabilities of .90 (Experiential EI) and .88 (Strategic EI) and branch score reliabilities ranging from .79 to .91. The MSCEIT has shown high test-retest reliability at the branch, area, and total scale levels (Brackett & Mayer, 2003).

Although not of direct interest to this study, we included the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) in the protocol given concerns that differences in EI may be attributable to cognitive intelligence (Fiori & Antonakis, 2011). With the WASI, a full scale intelligence quotient (FIQ) can be generated from two subtests: Vocabulary, which assesses crystallized verbal knowledge, and Matrix Reasoning, which assesses nonverbal reasoning ability. Subtest raw scores are converted to *T*-scores ($M = 50$, $SD = 10$), and the FSIQ is reported as a standard score; in each instance, higher scores reflect better performance (Wechsler, 1999).

Statistical analysis

Analyses were computed using SPSS software version 21.0 for Windows (Armonk, NY, USA). 5-HT and BDNF concentrations were standardized based on Cr concentration, resulting in a single value per participant that reflected the ratio of BDNF to Cr (BDNF/Cr) and 5-HT to Cr (5-HT/Cr), respectively, in units of μmol/mol. Normality of data was checked using Kolmogorov–Smirnov Goodness of Fit tests.

One-way analyses of variance (ANOVA) were used to determine if the BDNF/Cr and 5-HT/Cr ratios differed by sex. Given confirmation of sex differences, all subsequent analyses were conducted separately but analogously for men and women. Two-tailed Pearson correlations were conducted to determine if IQ and EI were correlated. Additional Pearson correlations were conducted to measure the strength of association between BDNF/Cr and 5-HT/Cr ratios. Confirming independence among neurotransmitter concentration values, participants were then divided into high and low BDNF/Cr as well as high and low 5-HT/Cr groups via median split, following Kuepper et al. (2010) who similarly examined interactive effects between peripheral neurotransmitters/hormones, in order to determine if the two neurotransmitters interacted to predict EI performance. Following the hierarchical structure of the test, MSCEIT data were subjected to multivariate analysis of variance (MANOVA) with two independent factors (factor 1: high versus low BDNF/Cr; factor 2: high versus low 5-HT/Cr), beginning with the two area scores as dependent measures and then probing downward into the relevant branch

if/when significance was achieved. In accordance with recommendations by Mayer and colleagues (2002), we chose not to analyze MSCEIT data at the subtest level given concerns that subtest scores are less reliable than superordinate scores.

Results

Descriptive statistics are shown in Table 1. Superordinate MSCEIT variables and WASI variables were normally distributed, with performances by men and women falling within the average range or higher on each test. This level of performance is consistent with the sample being drawn from a population of normal, healthy adults. 5-HT/Cr levels for four participants were determined to be outliers and therefore excluded from further analysis. Of the remaining sample, 5-HT/Cr values were normally distributed. Although a direct comparison of 5-HT/Cr values across studies is difficult due to methodological differences in collection and assay, the mean concentration of the present sample is between, and therefore consistent with, the means documented by two other studies, one that reported 5-HT/Cr levels based on 24-hr urine collection and quantified by automated mass spectrometric analysis

Table 1. Descriptive statistics for all variables for men (n = 26) and women (n = 43).

Variables	M ± SD_{men}	M ± SD_{women}	Description
Biological			
$BDNF_{sqrt}$/Cr (µmol/mol)	28.0±26.1	39.1±23.9	square root transformed urinary concentration of BDNF, adjusted for Cr
5-HT/Cr (µmol/mol)	66.2±41.1	108.7±64.5	urinary concentration of 5-HT, adjusted for Cr
Cognitive Intelligence			
WASI FIQ	118.9±11.1	114.0±11.5	a global index of intellectual functioning
WASI Vocabulary	63.7±8.5	62.1±8.1	the respondent defines words of different levels of difficulty
WASI Matrix Reasoning	57.1±5.5	53.8±7.0	the respondent chooses a figure that completes a visuospatial pattern
Emotional Intelligence			
MSCEIT total score	108.0±15.2	105.4±14.6	a global index of overall performance-based EI
Experiential EI	106.4±14.3	104.3±14.6	indexes the ability to perceive emotional information, to relate it to other sensations, and to use it to facilitate thought
a. Perceiving Emotions	107.5±18.8	101.5±12.1	indicates the degree to which the respondent can identify emotions in external stimuli
1. Faces	116.4±20.3	109.2±23.5	the respondent identifies the feeling states of others based on photographs of subtle facial expressions
2. Pictures	109.0±13.0	108.7±13.1	the respondent identifies emotions associated with complex environmental landscapes and designs
b. Facilitating Thought	108.9±16.3	106.3±16.4	indicates the degree to which the respondent uses emotions to improve thinking and facilitate problem-solving
3. Sensations	105.2±16.9	99.1±11.8	the respondent compares different emotions to different sensations, such as color, temperature, and light
4. Facilitation	108.1±13.5	108.9±15.8	the respondent judges which mood best accompanies and promotes certain cognitive behaviors
Strategic EI	116.8±20.3	109.5±13.8	indexes the ability to understand emotion information and to use it strategically for planning and self-management
c. Understanding Emotions	126.1±21.1	122.0±24.7	indicates how well the respondent understands complex emotional meanings, emotional transitions, and emotional situations
5. Blends	111.2±12.2	109.0±14.7	presents multiple choice questions that require the respondent to deconstruct emotional blends into their emotional constituents
6. Changes	131.1±17.0	128.2±15.6	presents multiple choice questions that ask the respondent how emotions transition from one to another over time
d. Managing Emotions	103.4±14.6	99.8±9.9	indicates how well the respondent manages emotions in self and others to achieve positive outcomes
7. Emotion Management	103.6±19.6	100.2±10.0	the respondent identifies the most effective action for a fictional character to take in order to achieve a specified emotional outcome
8. Emotional Relations	106.0±17.1	103.0±12.8	the respondent identifies which action would be the most effective to use to manage the feelings of another individual

BDNF = brain-derived neurotrophic factor; Cr = creatinine; WASI = Wechsler Abbreviated Scale of Intelligence; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test Version 2.0; EI = emotional intelligence. Reporting of MSCEIT scores follows a hierarchical structure, with one superordinate total score, two area scores (italics), four branch scores (a, b, c, d), and eight subtests (numbered 1-8). MSCEIT variables and WASI FIQ are reported as standard scores, with population M of 100 and SD of 15. According to clinical practice, the interpretation of standard score ranges is as follows (Flanagan & Caltabiano, 2004): <69 = very deficient; 70-79 = deficient; 80-84 = below average; 85-89 = low average; 90-110 = average; 111-115 = high average; 116-120 = above average; 121-130 = superior; >131 = very superior. WASI subtest scores are reported as T-scores, with population M of 50 and SD of 10, with interpretation as follows (Wechsler, 1999): <32 = very low; 33-37 = low; 38-42 = below average; 43-47 = low average; 48-52 = average; 53-57 = high average; 58-62 = above average; 63-67 = high; >68 = very high.

(de Jong, Wilkens, de Vries, & Kema, 2010) and one that analyzed 5-HT/Cr in urine spot samples with ELISA (Nichkova et al., 2012). With regard to BDNF/Cr, concentration levels were initially skewed, corroborating findings in other studies of peripheral sources of BDNF (Trajkovska et al., 2007; Ziegenhorn et al., 2007), but were subsequently normalized with square root transformation ($BDNF_{sqrt}$/Cr).

ANOVA revealed that, relative to men, women had significantly higher 5-HT/Cr levels, $F(1,67) = 9.03$, $p = .004$, and marginally higher $BDNF_{sqrt}$/Cr levels, $F(1,67) = 3.27$, $p = .08$. In order to explore these sex effects, we conducted the remaining analyses separately but analogously across subgroups of men and women.

Among men and women, none of the WASI scores (FIQ, Vocabulary *t*-score, Matrix Reasoning *t*-score) correlated with the two MSCEIT area scores (coefficients ranging from .04 to .35, all p = ns). Given that IQ and EI at the superordinate level were not confounded, IQ was dropped from subsequent analyses.

Among men, $BDNF_{sqrt}$/Cr and 5-HT/Cr were uncorrelated, $r(26) = -.13$, p = ns. At the level of MSCEIT area scores, MANOVA indicated no main effects for 5-HT/Cr or $BDNF_{sqrt}$/Cr but a marginal interaction between the two, Wilks' $\lambda = .80$, $F(2,21) = 2.60$, $p = .09$. Tests of between-subjects effects showed that the interaction effect was present for Strategic EI, $F(1,22) = 5.03$, $p = .04$, but not for Experiential EI, $F(1,22) = 1.57$, p = ns.

In order to localize the effects more specifically within Strategic EI, a second MANOVA was conducted with the same grouping factors but with Understanding Emotions and Managing Emotions as dependent variables. The full model showed no main effects but a marginally significant neurotransmitter interaction effect, Wilks' $\lambda = .77$, $F(2,21) = 3.06$, $p = .07$, with tests of between-subjects effects indicating that the interaction was significant for Understanding Emotions, $F(1,22) = 6.24$, $p = .02$, but weaker for Managing Emotions, $F(1,22) = 3.01$, $p = .09$. As shown in Figure 1, simple effects tests revealed that men with the high BDNF/low 5-HT combination outperformed men with the low BDNF/low 5-HT combination by a 20-point margin in Understanding Emotions, $F(1,22) = 3.37$, $p = .08$. Additionally, men with the low BDNF/high 5-HT combination outperformed men with the low BDNF/low 5-HT combination by nearly a 30-point margin in Understanding Emotions, $F(1,22) = 6.12$, $p = .02$,

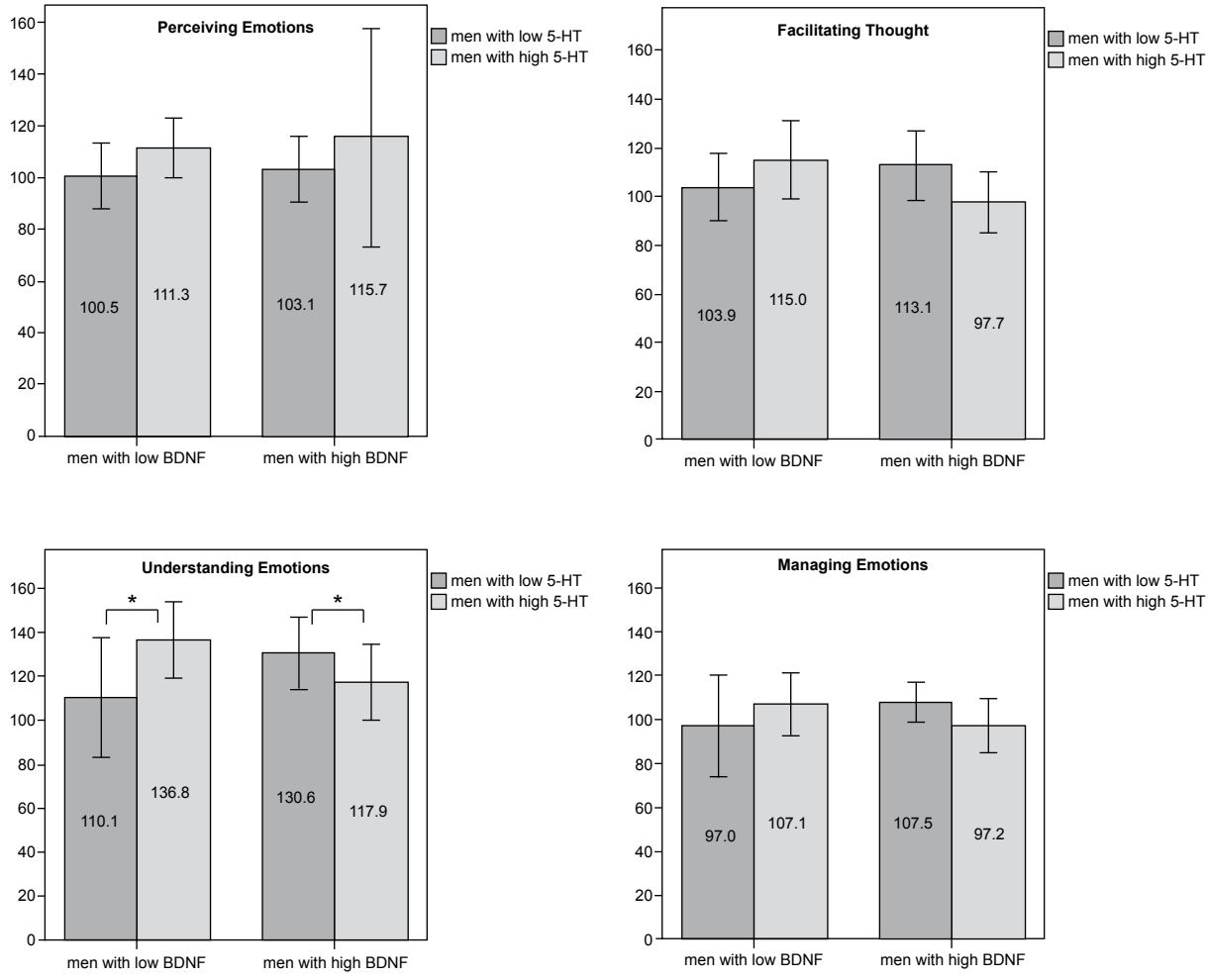

Figure 1.

a finding that remained significant after Bonferroni correction (α = .05/2). Both groups of men with discrepant neurotransmitter levels (i.e., high BDNF/low 5-HT and the low BDNF/high 5-HT) performed nearly equally well in this particular EI branch, with mean scores falling within the very superior performance range. There was no significant difference in Understanding Emotions score between high BDNF/low 5-HT men and high BDNF/high 5-HT men or between low BDNF/high 5-HT men and high BDNF/high 5-HT men.

Among women, $BDNF_{sqrt}$/Cr and 5-HT/Cr were uncorrelated, $r(43) = -.12$, p = ns. At the level of MSCEIT area scores, MANOVA revealed no main effects for $BDNF_{sqrt}$/Cr or 5-HT/Cr and no interaction effect. Given null results at this level of analysis, no additional MANOVAs were conducted on MSCEIT branch scores in women.

Discussion

This study reports an interaction effect in healthy adult men between peripheral levels of BDNF and 5-HT as a predictor of performance in one domain of EI, as measured by the MSCEIT. This domain, Emotional Understanding, reflects the capacity to analyze emotions, to appreciate how, when, and why emotions change over time, and to predict the behavioral and social outcomes of various emotional states. This relationship was not confounded by cognitive intelligence, as we detected no relationship between Experiential EI and Strategic EI from the MSCEIT and any WASI score. The nature of the interaction is such that men with discordant combinations of neurotransmitter levels (high 5-HT/low BDNF; low 5-HT/high BDNF) demonstrated emotional understanding skill in the very superior performance range. Because our study is of correlational design, we cannot determine the direction of causality. Although the logical inference is that discordance between BDNF and 5-HT confers a particular strength in this domain of EI because there is indirect support for this in the neurogenetic literature, it is nonetheless possible that emotional understanding competency itself prompts discordant neurotransmitter levels.

Data concerning the neurochemistry of EI are scarce in the literature. While there are no reports relating EI to BDNF, a handful of studies have explored the association between EI and 5-HT activity. Using a genotyping approach, Kim and colleagues (2011) found that men with a genetic likelihood of increased synaptic 5-HT concentration had significantly lower scores on the Trait Meta Mood Scale, particularly for the subscale that measures attention to one's emotions, than men with a profile indicative of decreased 5-HT activity. In a different study, Lo et al. (2010) found that male schizophrenic patients with a genotypic predisposition to increased 5-HT activity performed worse in the emotion management domain of the MSCEIT than men with a predisposition to decreased 5-HT activity. Taken together, these studies suggest that elevated 5-HT levels are associated with worse EI, or, conversely, that low levels of 5-HT are related to better EI.

In our study we found no main effect of peripheral 5-HT levels on MSCEIT performance and, therefore, we cannot directly link our findings with those described above. Interestingly, however, we did find that high 5-HT level predicts high emotional understanding in conjunction with low BDNF level, an interaction that is explainable with consideration of how these neurotransmitters are believed to regulate social cognition. In a model proposed by Homberg and Lesch (2011), high levels of 5-HT increase sensitivity to motivationally relevant stimuli via hyper-reactivity and/or hyperactivity in the amygdala and areas of the prefrontal cortex. When environmental conditions are stable, this hypervigilance results in maladaptive, excessive emotionality. Compounding this is the functional uncoupling between the anterior cingulate cortex and amygdala in individuals genetically predisposed to having higher 5-HT synaptic concentration (Pezawas et al., 2005), which could lead to a loss of control over one's emotions through disinhibition (Pezawas et al., 2008a). From this perspective, elevated 5-HT would not confer exceptional EI unless through modulation by another neurotransmitter system in a way that mitigates these effects.

Structural and functional outcomes of BDNF activity, then, become important to consider. Several studies highlight what appear to be adverse consequences of low levels of BDNF. It is known, for example, that individuals with a genetic predisposition to diminished BDNF secretion have reduced hippocampal volume (Bueller et al., 2006) and neuronal integrity (Egan et al., 2003), which may explain the behavioral findings of diminished episodic memory (Egan et al., 2003), poor associative learning of aversive cues (Hajcak et al., 2009), and impaired fear recognition (Mukherjee et al., 2011) in similarly genotyped individuals. Mukherjee and colleagues (2011) argue that the decreased neural plasticity associated with low BDNF level reduces capacity for emotional memory retrieval, which consequently weakens contextualization of new, incoming emotional information. Such consequences of low BDNF, however, may ultimately be quite adaptive vis-à-vis high levels of 5-HT and its associated hypervigilance, emotionality, and poor self-regulation. This neuroprotective view of low BDNF is consistent with the report by Pezawas and colleagues (2008a,b) that low BDNF availability reduces the impact of excessive 5-HT on emotional reactivity, thus leading to increased stress resilience.

We also found that the combination of low 5-HT and high BDNF level was associated with superior emotional understanding. Although this pattern of result has not previously been reported in the literature, it can be explained according to the theoretical model above, specifically that the improved emotional memory encoding and heightened contextualization of emotional stimuli associated with higher BDNF (Choi, Gourley,

& Ressler, 2012) balances the diminished emotionality associated with low 5-HT. What this emerging model cannot easily explain, however, is the specificity of the BDNF x 5-HT interaction effect within EI. With a modest sample size subdivided further by sex, it is possible that we lacked sufficient statistical power to find effects in the other MSCEIT branches. Although there was a similar neurotransmitter interaction effect in the Managing Emotions branch, it was weak and non-significant. Taken together, however, the data suggest that a BDNF x 5-HT interaction is important for Strategic EI but not necessarily for Experiential EI. As research has already shown discrete facets of EI to have unique cognitive (Koven & Thomas, 2010) and neuroanatomical (Koven, Roth, Garlinghouse, Flashman, & Saykin, 2011) correlates, it is quite possible that the other MSCEIT branches have distinct neurochemical signatures beyond the scope of what we assessed in this study. There is evidence, for example, to show that performance differences in the Experiential EI domain are governed in part by endogenous oxytocin levels (Koven & Max, 2014) such that higher oxytocin facilitates extra-personal emotion recognition and the channeling of emotions to enhance social proficiency. Subsequent research that explores the contributions of multiple neurotransmitters to EI, while remaining sensitive to its multifaceted nature and the need to control for relevant confounds, can help elucidate the nature and limits of neurochemical interaction.

The other aspect of our data that this model cannot explain is why the interaction effect was present in men but not in women. The fact that we found a sex-specific effect is not entirely surprising because sexual dimorphism is widely reported in the literature on mood disorder prevalence and treatment efficacy (Gorman, 2006) as well as trait and ability EI (Petrides & Furnham, 2000). With regard to neurochemistry specifically, it is known, for example, that the *BDNF* Val66Met polymorphism (Shalev et al., 2009) and several 5-HT-related polymorphisms (Stoltenberg, Christ, & Highland, 2012) affect depression and stress resilience differently in men than women. As to the specific mechanism by which to explain these sex differences, there is accumulating evidence that reproductive hormones can interact with BDNF and 5-HT systems in multiple ways, each with potential consequences for affective functioning. For example, BDNF concentration in women follows an estrous cycle (Pluchino et al., 2009), and *BDNF* gene expression is known to increase and decrease in the presence of estrogen and progesterone, respectively (Begliuomini et al., 2007; Bimonte-Nelson, Nelson, & Granholm, 2004). In animal models, the severity of depressive- and anxiety-like behavior in mice with reduced *BDNF* bioavailability co-varies with estrous fluctuation in reproductive hormones (Bath et al., 2012), as does control of hippocampal functioning (Spencera, Waters, Milner, Lee, & McEwen, 2010). Furthermore, estradiol has been shown to modulate 5-HT synthesis and degradation (Smith, Henderson, Abell, & Bethea, 2004), transport (Benmansour, Piotrowski, Altamirano, & Frazer, 2009), type 2A receptor density (Kugaya et al., 2003), and type 1A autoreceptor sensitivity (Henderson & Bethea, 2008), and these estrogen-serotonin interactions are known to have functional consequences for mood and cognition (Amin, Canli, & Epperson, 2005). Moreover, significant early environmental stress is known to influence the impact of ovarian hormones on brain development and neurotransmitter-relevant gene expression (Epperson & Bale, 2012), both of which can have lasting behavioral effects into adulthood. As we did not measure levels of ovarian steroids or query our participants about childhood trauma history, we are unable to assess their relevance as modulators of EI ability in women. Future research into the specificity of interactions among 5-HT, BDNF, and sex hormones may help explain sex differences in endophenotypes of relevance to EI.

The discussion above needs to be considered in the context of the study's limitations. First, only one of the post-hoc findings remained significant after Bonferroni correction, which is likely due to limited statistical power associated with the small sample size. Second, as our sample included healthy adults exclusively, we do not know whether BDNF and 5-HT interact in a similar fashion in patients with mood disorders. Furthermore, EI is known to change over the course of adulthood (Kafetsios, 2004) and because our study primarily used young adults, we do not know whether such an interaction is present in older adults. Future studies with larger and more diverse samples are needed to determine the generalizability of our effects across cohorts.

In addition to being the first study to report evidence of an *in vivo* interaction between BDNF and 5-HT systems with respect to EI, this study also confirms the utility of urinalysis for the detection of peripheral biomarkers of affective processing (Dingle, Oei, & Young, 2010; Nichkova et al., 2012). Many neurotransmitters and/or their metabolites are detectible in urine (for review, see Marc et al., 2011), making this methodology especially appropriate for examining interactions among neurotransmitter systems. Furthermore, urine capture is painless, non-invasive, and inexpensive, which is an advantage over other peripheral sources of BDNF (e.g., serum, plasma, and platelets). This is also the first known study to examine urinary BDNF specifically as a correlate to EI ability. Although the results reported here support the viability of urinary BDNF as a central nervous system biomarker, the precise relationship between neurotrophins in the brain and those excreted in urine is not fully established in the literature.

In summary, our results show an interaction effect between peripheral levels of BDNF and 5-HT on a performance-based measure of EI in healthy men. Specifically, men with discordant levels of urinary neurotransmitters (high 5-HT/low BDNF; low 5-HT/high BDNF) demonstrated superior ability to understand complex emotional meanings, emotional

transitions, and emotional situations, an effect that was not confounded by general cognitive intelligence. This result suggests an interaction between BDNF and 5-HT systems that is useful to achieve EI competency in emotional understanding. Such an interaction may reflect an advantage that comes with balancing neural activation that, on the one hand, enhances emotional memory encoding and contextualization of emotional stimuli (associated with BDNF activity) and on the other hand, increases tonic sensitivity to motivationally relevant, environmental cues (associated with 5-HT activity).

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