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Temperament trait Harm Avoidance associates with μ-opioid receptor availability in frontal cortex: A PET study using [^{11}C]carfentanil

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ABSTRACT

Harm Avoidance is a temperament trait that associates with sensitivity to aversive and non-rewarding stimuli, higher anticipated threat and negative emotions during stress as well as a higher risk for affective disorders. The neurobiological correlates of interindividual differences in Harm Avoidance are largely unknown. We hypothesized that variability in Harm Avoidance trait would be explained by differences in the activity of μ-opioid system as the opioid system is known to regulate affective states and stress sensitivity.
Brain μ-opioid receptor availability was measured in 22 healthy subjects using positron emission tomography and [^{11}C]carfentanil, a selective μ-opioid receptor agonist. The subjects were selected from a large Finish population-based cohort (N = 2075) on the basis of their pre-existing Temperament and Character Scores. Subjects scoring consistently in the upper (10) and lower (12) quartiles for the Harm Avoidance trait were studied. High Harm Avoidance score associated with high μ-opioid receptor availability (i.e. lower endogenous μ-opioid drive) in anterior cingulate cortex, ventromedial and dorsolateral prefrontal cortices and anterior insular cortex. These associations were driven by two subscales of Harm Avoidance; Shyness with Strangers and Fatigability and Asthenia.
In conclusion, higher Harm Avoidance score in healthy subjects is associated with higher μ-opioid availability in regions involved in the regulation of anxiety as well as in the control of emotions, affective component of pain and interoceptive awareness. The results have relevance in the research of vulnerability factors for affective disorders.

Introduction

Cloninger's biosocial model of personality defines personality as the combination of heritable, neurobiologically explained temperament reflecting behavioral conditioning, and character traits that reflect both neurobiological mechanisms and sociocultural learning. Temperamental dimensions that refer to heritable variation in automatic responses to environmental stimuli, are as follows: Harm Avoidance (HA), Novelty Seeking, Reward Dependence and Persistence. The character dimensions are Self-directedness, Cooperativeness, and Self-transcendence, and they reflect differences in higher cognitive functions underlying a person's self- concept, goals and values (Cloninger et al., 1993). These domains construct a dynamic system that regulates the development of psychological functions and explain personality as an adaptive system (Cloninger et al., 1997).

The model defines HA as sensitivity to aversive and novel stimuli that evoke negative emotions such as Anticipatory Worry, fear and anxiety (Cloninger, 1986). A person who has a high HA score tends to be cautious, fearful, shy and easily fatigued (Cloninger et al., 1994). These descriptions also reflect the four subscales of HA: 'Anticipatory Worry', 'Fear of Uncertainty', 'Shyness with Strangers' and 'Asthenia and Fatigability'. A large number of studies summarized in a recent meta-analysis have demonstrated a relationship between high HA and mood- and anxiety disorders (Miettunen and Raevuori, 2011). That is, persons suffering from these disorders have in average higher scores in HA.

Personality traits have been suggested to be predisposing factors to psychiatric illnesses (Zubin and Spring, 1977). This view is supported by prospective studies that have found personality traits such neuroticism and HA to be predictive of future mood- and anxiety

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symptoms or disorders (Cloninger et al., 2006; Elovainio et al., 2004; Gil and Caspi, 2006; Kendler et al., 2006). Even tough association between human personality and psychiatric illnesses is likely to be more complex, there is heuristic value in considering certain personality traits as vulnerability factors as it provides a unique way to study the neurobiology of risk for psychiatric disorders in healthy population.

Cloninger's (1986) original hypothesis proposed that differences in the activity of brain serotonin system would explain differences in HA, but direct evidence on this is inconsistent (Borg et al., 2003; Karlsson et al., 2009; Moresco et al., 2002; Rabiner et al., 2002; Reimold et al., 2008). Moreover, we did not find support for the original hypothesis in a PET study with [^{11}C]MADAM, a serotonin transporter tracer (Tuominen et al. unpublished data). It is therefore plausible to search for new neurotransmitters or neurotransmitter interactions that could explain interindividual differences in HA trait.

In this study, we test our hypothesis that high HA associates with low μ-opioid drive. We have shown in earlier studies that higher HA score predicts higher anticipated threat before a stressful task (Ravaja et al., 2006) and more negative emotions during a stressful situation (Heponiemi et al., 2005). Others (Zubieta et al., 2001, 2003) have shown that negative emotional states are related to the activity μ-opioid system in humans. μ-opioids have shown to suppress stress induced anxiety in primates (Kalin et al., 1988) and μ-opioids have well documented anxiolytic like actions in rodents (Asakawa et al., 1998; Bilkei-Gorzo et al., 2008; Fichna et al., 2007). Thus opioids may regulate adaptation to novel and emotionally salient stimuli, which is the core feature of HA. We expected that higher HA scores are related to higher μ-opioid receptor availability in brain regions that are relevant for fear and anxiety (see Etkin, 2010). We address this hypothesis using positron emission tomography (PET) and μ-opioid receptor tracer [^{11}C]carfentanil in subjects preselected to have either high or low scores in HA in two subsequent measures.

Materials and methods

This study is a part of a larger 'Neurobiology of Personality' project at the University of Turku and University of Helsinki, Finland. The current study protocol was approved by the Joint Ethical Committee of the University of Turku and the Turku University Central Hospital. After having received all the relevant information in written form from the investigators, all study subjects gave Ethical Committee-approved written consents. This study followed the ethical guidelines of the Declaration of Helsinki.

Subjects

Subjects were derived from a population-based, still ongoing prospective cohort study called "The Cardiovascular Risk in Young Finns Study" started in 1980 (see Raitakari et al., 2008). During the follow-up Temperament and Character Inventory (TCI; (Cloninger et al., 1994)) was administered in year 1997 and in year 2001.

Subjects that had complete TCIs from both years (N = 2075) and belonged to either upper or lower quartile in HA score in both years were identified. For logistical reason, only subjects living in Turku or Helsinki and rural areas in their vicinity were included into this selection. Next, subjects with known chronic somatic diseases, psychiatric illnesses, excess alcohol consumption or BMI over 35 were excluded based on data gathered along the cohort study. Subjects in lower and upper quartiles were then matched for age, sex, and education, which resulted in a group of 82 matched subjects.

Of the 82 subjects, 12 were unattainable, 34 were excluded based on telephone interview (15 refused, 10 had somatic diseases, 7 were regular smokers and 2 were pregnant) and 5 were not contacted at all, because the matched groups they would have been representing were already fulfilled by others. 31 subjects were SCID interviewed by a psychiatrist (P.L. & T.M.). As a result, nine subjects were excluded for fulfilling diagnostic criteria for one or more psychiatric disorders (5 major depressive disorders, 2 panic disorders, one diagnosis of social anxiety disorder and one diagnosis of alcohol abuse). All the subjects excluded on the basis of psychiatric diagnosis were scoring high on Harm Avoidance. Finally, prior to PET study urine drug analyses were performed and somatic health of the subjects was confirmed with laboratory tests and medical examination.

The final study group consisted of 22 subjects, 10 subjects in high and 12 subjects in low Harm Avoidance groups (Table 1). None of the subjects were taking any medications at the time of the study, but one subject in both groups was using nicotine products. All subjects underwent magnetic resonance imaging (MRI) at 1.5 T to rule out structural brain abnormalities and to obtain an anatomical reference for quantification of PET images.

TCI

Temperament and character dimensions were measured with Finnish translation of the ninth version of TCI. Instead of the original true –false response format we used a 5-point Likert scale. Mean value of responses to questions in each dimension was used in statistical analysis.

Preparation of [^{11}C]carfentanil

The precursor carfentanil carboxylic acid and carfentanil were obtained from ABX advanced biochemical compounds, Radeberg, Germany. [^{11}C]Methane was produced at the Accelerator Laboratory of Åbo Akademi with a 103-cm isochronous Efremov cyclotron using the 14 N(p,α)11C reaction. High specific radioactivity [^{11}C] methyl iodide was prepared from [^{11}C]methane (Larsen et al., 1997; Någren et al., 2003). The preparation of [^{11}C]carfentanil from [^{11}C] methyl triflate was performed according to a published procedure (Ingman et al., 2005) with minor modifications. [^{11}C]Methyl triflate, prepared on-line from [^{11}C]methyl iodide, was reacted with .3–.4 mg of carfentanil carboxylic acid and 3.75–5.0 μl .2 M tetrabutylammonium hydroxide (aq) in 150–200 μl acetone. The crude product was purified using HPLC on a μBondapak® column (Waters, Milford, MA) using 35% acetonitrile in 10 mM phosphoric acid. After addition of .3 ml of sterile propylene glycol/ethanol (7:3 v/v) the fraction containing the product was evaporated and re-dissolved in 9 ml physiologic phosphate buffer (.1 M, pH 7.4) and 1.5 ml of sterile propylene glycol/ethanol (7:3 v/v) and filtered through a .2 μm Gelman Acrodisc® 4192 sterile filter. The radiochemical purity and the specific radioactivity of the product were determined using HPLC and UV-detection at 210 nm. The volume of the final product solution was calculated by weighing the sterile product vessel before

Table 1
Characteristics of high and low HA groups.

Mean values and standard deviations are shown for age and BP_{ND} values. For Harm Avoidance mean value and range is shown. High education refers to graduation from university. Anterior (dorsal) cingulate cortex is shown here as an example (see Table 2), BP_{ND} = Binding potential.

	High HA (N = 10)	Low HA (N = 12)	p value
Male/female	5/5	6/6	.696
Age	37.6 ± 5.14	38.0 ± 5.19	.868
Education (low/high)	5/5	4/8	.429
Harm Avoidance score	3.32 (2.97–3.66)	1.95 (1.37–2.23)	<.001
Anterior cingulate [^{11}C]carfentanil BP_{ND}	1.23 ± .32	1.04 ± .18	.049