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Temperament, character and serotonin activity in the human brain: a positron emission tomography study based on a general population cohort

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Background. The psychobiological model of personality by Cloninger and colleagues originally hypothesized that interindividual variability in the temperament dimension ‘harm avoidance’ (HA) is explained by differences in the activity of the brain serotonin system. We assessed brain serotonin transporter (5-HTT) density *in vivo* with positron emission tomography (PET) in healthy individuals with high or low HA scores using an ‘oversampling’ study design.

Method. Subjects consistently in either upper or lower quartiles for the HA trait were selected from a population-based cohort in Finland ($n=2075$) with pre-existing Temperament and Character Inventory (TCI) scores. A total of 22 subjects free of psychiatric and somatic disorders were included in the matched high- and low-HA groups. The main outcome measure was regional 5-HTT binding potential (BP_{ND}) in high- and low-HA groups estimated with PET and [¹¹C]N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine ([¹¹C]MADAM). In secondary analyses, 5-HTT BP_{ND} was correlated with other TCI dimensions.

Results. 5-HTT BP_{ND} did not differ between high- and low-HA groups in the midbrain or any other brain region. This result remained the same even after adjusting for other relevant TCI dimensions. Higher 5-HTT BP_{ND} in the raphe nucleus predicted higher scores in ‘self-directedness’.

Conclusions. This study does not support an association between the temperament dimension HA and serotonin transporter density in healthy subjects. However, we found a link between high serotonin transporter density and high ‘self-directedness’ (ability to adapt and control one’s behaviour to fit situations in accord with chosen goals and values). We suggest that biological factors are more important in explaining variability in character than previously thought.

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Key words: Harm avoidance, healthy volunteers, neuroimaging, personality, positron emission tomography, serotonin, serotonin transporter.

Introduction

Since the launching of the first academic personality theory by Gordon Allport in 1937 (Allport, 1937), personality has been seen as a dynamic organization that determines one’s unique adjustment to the

environment. While the themes of this dynamic organization are not shared by all personality theories, they all suggest that personality is subject to biological and psychological influences. Thus, the personality-determined adaptations are unique to each individual because of differences in heredity and environment.

The most recent personality theory that shares Allport’s concept of personality as an adaptation system is Cloninger’s psychobiological personality concept (Cloninger *et al.* 1993). According to this theory, personality consists of seven dimensions that

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are postulated to cover the structure and development of human personality. The model differentiates between temperament and character traits. Temperament traits are thought to reflect individual differences in automatic responses to emotional stimuli. Character traits reflect differences in personal aims and values and are more influenced by environmental factors such as social learning and mature in a stepwise manner during development (Cloninger *et al.* 1993).

Cloninger proposed a division of temperament into four different dimensions: 'harm avoidance' (HA), 'novelty seeking', 'reward dependence' and 'persistence'. HA is a bias to respond intensely to aversive stimuli and to inhibit behaviour, 'novelty seeking' is a bias in initiation of behaviours, like exploratory activity in response to novelty, 'reward dependence' is a tendency to respond intensely to social approval and 'persistence' means perseverance despite frustration and fatigue (Cloninger, 1987). Temperament is the emotional core of personality and these traits are thought to be genetically homogeneous, moderately and independently heritable and normally distributed in the general population. The first three temperament traits, HA, 'novelty seeking' and 'reward dependence' were also suggested to have their corresponding neurobiological substrates: serotonin, dopamine and noradrenalin, respectively (Cloninger, 1986).

HA has been shown to be a trait that is especially predictive of risk for affective psychopathology (Farmer & Seeley, 2009). It is thought to represent the behavioural inhibition system of the brain (Cloninger, 1986) and by definition high harm-avoidant individuals tend to be cautious, fearful, insecure and pessimistic. From the evolutionary point of view, high HA is advantageous in the face of danger, because it leads to greater care and caution. On the other hand, when danger is unlikely, excessive pessimism and worry are thought to predispose to affective disorders (Cloninger *et al.* 1994, 2006) and this has been demonstrated in a large body of studies (Farmer *et al.* 2003; Cloninger *et al.* 2006; de Winter *et al.* 2007; Wachleski *et al.* 2008; Minaya & Fresán, 2009). The robust associations between HA and anxiety disorders, affective disorders as well as other psychiatric disorders such as schizophrenia are summarized in a recent meta-analysis (Miettunen & Raevuori, 2012).

However, not all individuals that have high HA scores manifest psychiatric disorders. This observation led Cloninger to extend his temperament model with three character dimensions that reflect the maturity and integration of personality, and are accordingly supposed to better reflect an individual's adaptation and social adjustment (Cloninger *et al.* 1993). These three character dimensions are 'self-directedness', 'cooperativeness' and 'self-transcendence' and they

modify the role of temperament in an adult personality. 'Self-directedness' is defined as the extent to which a person identifies himself as an autonomous individual and as the ability to adapt behaviour according to chosen goals and values. 'Self-directedness' is a trait that gives rise to the feelings of personal integrity and self-esteem. 'Cooperativeness' refers to a person's ability to accept and identify with other people. 'Self-transcendence' is a character trait that refers to experiences of spirituality and feelings of unity with the universe (Cloninger *et al.* 1993).

Especially low 'self-directedness' seems to be involved in different forms of psychopathology such as personality disorders (Svrakic *et al.* 1993; Gutierrez *et al.* 2002), depression (Smith *et al.* 2005; Cloninger *et al.* 2006; Minaya & Fresán, 2009) and anxiety-related disorders (Wachleski *et al.* 2008). Considering the associations between personality traits and psychopathology, a greater understanding of their biology might also increase the understanding of the aetiology of emotional disorders.

The relationship between high HA and high activity of the serotonin system was first proposed in 1986 based on the findings in basic biochemical studies and studies on animals. Evidence on humans that led to the hypothesis was the findings that aggression and violent suicidal behaviour are both related to low serotonergic activity and these again are examples of low harm-avoidant behaviour. Also some evidence supported the idea that the serotonin system was related to the trait called 'validity' in Henrik Sjöbring's model for personality, which is the antecedent of HA (Banki & Arato, 1983; Cloninger *et al.* 1994).

Ever since this association was hypothesized it has been the subject of numerous studies, including those using indirect methods to define serotonergic activity such as platelet imipramine-binding tests (Pfohl *et al.* 1990), platelet 5-hydroxytryptamine (5-HT)₂ receptor sensitivity tests (Peirson *et al.* 1999), monoamine challenging tests (Gerra *et al.* 2000), urinary monoamine excretion tests (Curtin *et al.* 1997), cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) assays (Limson *et al.* 1991) and clinical trials with antidepressants (Allgulander *et al.* 1998; Boz *et al.* 2007). In addition to HA, 'self-directedness' has often been correlated with serotonergic markers (Allgulander *et al.* 1998; Peirson *et al.* 1999; Boz *et al.* 2007). Results from these studies should be seen as circumstantial evidence for the hypothesis and inconsistencies remain, as they do in genetic studies on HA and the serotonin system (Lesch *et al.* 1996; Schinka *et al.* 2004; Sen *et al.* 2004; Munafò *et al.* 2009).

In vivo imaging techniques, such as positron emission tomography (PET), are now able to directly measure the serotonergic system in the living human

brain. A total of six published studies have used PET or single photon emission computed tomography to examine the correlation of serotonergic neurotransmission with HA (Rabiner *et al.* 2002; Moresco *et al.* 2002; Borg *et al.* 2003; Van Heeringen *et al.* 2003; Reimold *et al.* 2008; Karlsson *et al.* 2009). Van Heeringen *et al.* (2003) found a negative correlation between HA and 5-HT_{2A} receptor marker [¹²³I]5-I-R91150 binding in nine suicidal subjects. Another study (Moresco *et al.* 2002) also found a negative correlation between 5-HT_{2A} receptor tracer 3-(2-[¹⁸F]fluoroethyl)siperone ([¹⁸F]FESP) and HA in healthy subjects, giving some support for the hypothesis. Finally, three studies examining 5-HT_{1A} receptors with [carbonyl-¹¹C]WAY100635 (Rabiner *et al.* 2002; Borg *et al.* 2003; Karlsson *et al.* 2009) and one examining serotonin transporter 5-HTT with [¹¹C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([¹¹C]DASB) (Reimold *et al.* 2008) in healthy subjects found no correlation between serotonin function and HA.

5-HTT is the main mechanism for terminating synaptic 5-HT transmission (Bengel *et al.* 1998). Studies on 5-HTT knock-out mice and rats (Wellman *et al.* 2007; Kalueff *et al.* 2010) show that a dysregulated serotonin system plays a role in the modulation of both negative emotionality and aggressive behaviour, i.e. the two ends of the HA dimension. Except for the raphe nuclei, 5-HTT is located predominantly in axon terminals of serotonergic neurons (Sur *et al.* 1996), making a 5-HTT tracer an excellent tool to study serotonergic innervation.

The present study is designed to test an association of HA and serotonin function in high- and low-HA subjects specifically selected to be free of psychiatric disorders in order to avoid possible state phenomena associated, e.g. with affective disorders (Reimold *et al.* 2008; Selvaraj *et al.* 2011). A validated tracer [¹¹C]N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine ([¹¹C]MADAM) and a three-dimensional PET technique were used to assess the 5-HTT density (binding potential; BP_{ND}) (Lundberg *et al.* 2005, 2006). To create high- and low-HA subpopulations we used an 'oversampling' method in a large population cohort with pre-existing Temperament and Character Inventory (TCI) scores (Raitakari *et al.* 2008). The idea was to enrich the differences between the groups and hence increase the statistical power to detect any links between 5-HTT density and HA. We expected to detect higher 5-HTT density in the high-HA group. We also investigated the biology (5-HTT density) of character dimensions as postulated by the model and also as recent studies show that genetic factors play a greater role in character development than originally suggested (see Cloninger, 2004).

Method

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 (EC) 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 EC-approved written consents. This study followed the ethical guidelines of the Declaration of Helsinki.

Subjects

The subjects were derived from a population-based, prospective cohort study called The Cardiovascular Risk in Young Finns Study (Akerblom *et al.* 1985). The cohort originally consisted of 3596 randomly selected healthy individuals from six age cohorts (3, 6, 9, 12, 15 and 18 years) at baseline in 1980. This cohort has now been followed up for 29 years, and examined up to eight times during this interval (Raitakari *et al.* 2008). The loss-to-follow-up rate is low in the cohort; at the time of the subject selection (2001), still 68% of the original sample was participating.

Subjects belonging consistently to the highest or lowest quartiles on HA in both follow-ups (in 1997 and 2001) and having complete TCI data available were included (*n* = 2075). For logistic reasons, only subjects living in Turku or Helsinki area and from rural communities in their vicinity were included into this selection. Background information gathered in the cohort study (Raitakari *et al.* 2008) was used to exclude subjects with known chronic somatic diseases, psychiatric illnesses, excess alcohol consumption or body mass index over 35 kg/m² from the initial selection. The subjects were then matched for age (six original age cohorts were combined into three), gender and education (low, intermediate, high). This resulted in a group of 82 matched subjects from which recruiting for this study was made.

From the group of 82 matched subjects, 12 were unobtainable and 34 were excluded based on telephone interview (15 refused, 10 had somatic diseases, seven were regular smokers and two were pregnant). Of the 82 eligible subjects, five were not contacted at all, because the matched groups they would have been representing were already fulfilled by other subjects. A total of 31 subjects were interviewed by a psychiatrist (P.L. or T.M.) using the Structured Clinical Interview for DSM-IV and Hamilton Depression Rating Scale. A total of nine subjects were excluded for fulfilling Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria

Table 1. Characteristics of high- and low-HA groups

	High HA (<i>n</i> =10)	Low HA (<i>n</i> =11)	<i>p</i>
Gender, <i>n</i>			0.835
Male	5	6	
Female	5	5	
Mean age, years (s.d.)	37.6 (5.14)	38.1 (5.43)	0.837
Education, <i>n</i>			0.528
Low	5	4	
High ^a	5	7	
Mean HA score (range)	3.3 (2.97–3.66)	2.0 (1.71–2.23)	<0.001

HA, Harm avoidance; s.d., standard deviation.

^aHigh education refers to graduation from university.

for one or more psychiatric disorders: major depression (*n*=5), panic disorder (*n*=2), social phobia (*n*=1) and alcohol abuse (*n*=1). All the subjects excluded on the basis of psychiatric diagnosis had high HA scores. Somatic health was confirmed prior to PET study with blood and urine tests, electrocardiogram and clinical examination.

The final study group consisted of 22 subjects – 10 subjects in the high-HA group and 12 subjects in the low-HA group. Characteristics of the high- and low-HA groups are presented in Table 1. One low- and one high-HA subject used nicotine products whereas the others did not. None of the volunteers was taking any medications at the time of the study and one low-HA subject was excluded from the final analysis because of considerable movement indicated by the external motion detector during the PET scan resulting in a low-HA group of 11 subjects. All subjects underwent T1- and T2-weighted magnetic resonance (MR) imaging at 1.5 T to rule out structural brain abnormalities and to obtain an anatomical reference for quantification of PET images (T1).

TCI

Temperament and character traits were self-rated by the participants using the Finnish translation of the ninth version of Cloninger's Temperament and Character Inventory (Cloninger *et al.* 1993). The inventory consists of four temperament scales (HA, 'novelty seeking', 'reward dependence' and 'persistence') and three character scales ('self-directedness', 'cooperativeness' and 'self-transcendence'), which were assessed with 40, 35, 24, 8, 44, 42 and 33 items, respectively; 226 items in total. Instead of the original dichotomous true/false format, the items were rated on a five-point Likert scale ranging from totally disagree (1) to totally agree (5). We calculated a mean score for every participant for each of the seven scales

by averaging each participant's answers over all of the items comprising one scale, thus resulting in an average score for each scale that ranged from 1 to 5. The Cronbach α reliabilities for the scales in the total Cardiovascular Risk in Young Finns Study sample were: HA, $\alpha=0.92$; 'novelty seeking', $\alpha=0.85$; 'reward dependence', $\alpha=0.80$; 'persistence', $\alpha=0.64$; 'self-directedness', $\alpha=0.91$; 'cooperativeness', $\alpha=0.91$; and 'self-transcendence', $\alpha=0.91$. The content and construct validity of the measure has been shown to be high in previous studies with Finnish samples (Keltikangas-Jarvinen *et al.* 1999).

Radiochemistry

N-desmethyl-MADAM and MADAM were obtained from PharmaSynth AS (Estonia). High specific radioactivity [¹¹C]methyl iodide was prepared from [¹¹C]methane (Larsen *et al.* 1997; Någren *et al.* 2003).

Preparation of [¹¹C]MADAM

The preparation of [¹¹C]MADAM from [¹¹C]methyl triflate was performed according to a published procedure (Halldin *et al.* 2005) with minor modifications. [¹¹C]methyl triflate, prepared on-line from [¹¹C]methyl iodide, was reacted with 0.4–0.6 mg of *N*-desmethyl-MADAM in 200 μ l acetone. The crude product was purified using high-performance liquid chromatography (HPLC) on a μ Bondapak[®] column (Waters, USA) using 40% acetonitrile in 0.1 M-ammonium formate. After the addition of 0.3 ml of sterile propylene glycol-ethanol (7:3, v/v) the fraction containing the product was evaporated and re-dissolved in 8 ml physiological phosphate buffer (0.1 M, pH 7.4) and filtered through a 0.2 μ m Gelman Acrodisc[®] 4192 sterile filter. The radiochemical purity and the specific radioactivity of the product were determined using HPLC and ultra-violet detection at 242 nm. The volume of the final product solution was calculated by

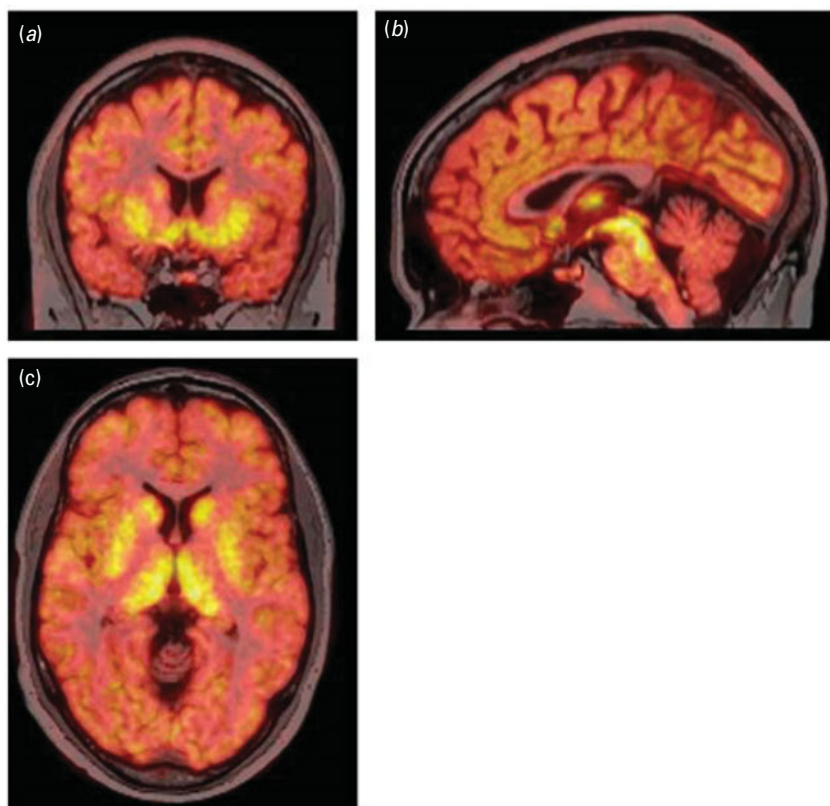


Fig. 1. Uptake of [^{11}C]N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzene ([^{11}C]MADAM) in the human brain showing (a) coronal, (b) sagittal and (c) axial slices (integrated images from 0–75 min). The highest uptake is observed in the midbrain and the lowest in the cerebellum.

weighing the sterile product vessel before and after sterile filtration and division with the density of the sterile solvent.

PET procedures

PET imaging was carried out using a brain-dedicated high-resolution PET scanner (ECAT HRRT; Siemens Medical Solutions, USA) (Rahmim *et al.* 2005). Methods used for attenuation correction, acquiring emission data and reconstruction are described in an earlier report by our group (Hirvonen *et al.* 2008). Head fixation was achieved by using an individually moulded thermoplastic mask. External motion data was acquired using the Polaris Vicra showing movements within the spatial resolution (FWHM) of the scanner.

Serotonin transporter (5-HTT) density was measured using the highly specific [^{11}C]MADAM tracer (Lundberg *et al.* 2005) (see Fig. 1). An intravenous bolus of [^{11}C]MADAM was injected and flushed with saline. The injected dose and mass of [^{11}C]MADAM were 475 (s.d.=70.6) MBq and 0.42 (s.d.=0.19) μg for the high-HA group and 484 (s.d.=33.6) MBq and 0.73 (s.d.=0.50) μg for the

low-HA group. There were no statistically significant differences in injected mass or dose. Emission data was collected in list mode for 75 min as 17 frames of increasing length (3×1 min, 4×3 min and 10×6 min).

Image analysis

To correct for head motion during the scan a frame-to-frame correction was done using external motion data to assess the frames of least motion. These frames were then summed and used as a reference for realignment. The MR images were co-registered to PET images. All realignment and co-registration procedures were performed using Statistical Parametric Mapping software version 2 (SPM2; Friston *et al.* 1995).

Quantification of tracer binding

The *a priori* regions of interest (ROIs) were manually delineated on T1-weighted transaxial MR images that had been co-registered to PET images into 22 different regions using Imadeus software (version 1.4; Forima Inc., Finland). ROIs were drawn onto the dorsal, pregenual and subgenual anterior cingulate cortex, which was defined as suggested by

Drevets *et al.* (2002). In the prefrontal cortex, dorso-lateral and ventrolateral prefrontal cortex, medial frontal cortex, lateral and medial orbital frontal cortex were delineated. ROIs on the dorsal caudate, dorsal putamen and ventral striatum were defined as described (Hirvonen *et al.* 2008). The insular cortex was separated into two parts, anterior and posterior (Cannon *et al.* 2007). ROIs were also drawn onto the thalamus, amygdala, hippocampus, inferior, medial and superior temporal gyrus, supramarginal gyrus, angular gyrus and posterior cingulate cortex and cerebellum. Because specific serotonin-rich areas/nuclei in the midbrain, pons and medulla cannot be differentiated in MR images, the analysis of this region was conducted solely with a voxel-based approach. The term 'midbrain' in this paper refers to a search area including the midbrain, pons and upper medulla unless otherwise indicated.

ROIs were used to calculate regional time-radioactivity curves (TACs) from dynamic PET images. The simplified reference tissue model (Lammertsma & Hume, 1996) was applied to TACs to derive 5-HTT BP_{ND} (Innis *et al.* 2007), which represents the ratio at equilibrium of specific to non-displaceable ligand binding in brain tissue and is linearly related to receptor density. The cerebellum was used as a reference region.

Statistical analysis of ROI-based data

To examine the group difference in [¹¹C]MADAM BP_{ND} we used repeated-measures analysis of variance (ANOVA) with region as a within subject factor and group as a between-subjects factor. Because HA correlated with 'novelty seeking', 'self-directedness' and 'cooperativeness', we also performed an exploratory analysis of covariance to examine whether a group difference could be detected when 'self-directedness', 'cooperativeness' and 'novelty seeking' were controlled for.

To explore the associations of other temperament and character traits with [¹¹C]MADAM BP_{ND}, we combined the two groups into one and in ROI-based data the associations were tested using partial correlation coefficient while controlling for age and gender. Age was selected because of its demonstrated effect on 5-HTT density (Van Dyck *et al.* 2000) and effects on character scores (Cloninger *et al.* 1993). Gender was chosen because it had an effect on 5-HTT binding in our sample as well as in earlier studies (Jovanovic *et al.* 2008).

In this study, a *p* value below 0.05 was considered statistically significant and normality of distribution was confirmed using the Shapiro-Wilk test. All ROI-based statistical analyses were carried out with

version 17 of SPSS statistical software for Windows (release 17.0.0; SPSS Inc., USA).

Voxel-based analysis

Because of the complex anatomy of serotonergic nuclei in the midbrain, this region was analysed separately from the rest of the brain. Thus two voxel-wise analyses were conducted using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) running on Matlab for Windows (version 7.4.0.287; MathWorks, USA). First, a ROI containing the midbrain, pons and medulla [defined with Wake Forest University (WFU) PickAtlas software; http://www.nitrc.org/projects/wfu_pickatlas/] was analysed and then another, confirmatory voxel-wise analysis was carried out on the whole brain excluding the midbrain ROI.

The confirmatory analysis was carried out as previously described (Hirvonen *et al.* 2005). Pre-processing of parametric images and statistical analyses were performed using SPM5. Parametric images were calculated with a simplified reference tissue model applied to all voxels with the cerebellum as a reference region. Images were spatially normalized to Montreal Neurological Institute (MNI) space using summed PET images and a ligand-specific template for [¹¹C]MADAM. Spatially normalized parametric images were smoothed using an 8-mm Gaussian kernel.

Differences between high-HA and low-HA groups were analysed using an independent two-sample *t* test. To test the association of other TCI traits and [¹¹C]MADAM BP_{ND} in the combined group, a multiple regression analysis was performed with age and gender as nuisance variables. In the midbrain ROI analysis false discovery rate (0.05) was used to correct for multiple comparisons. Cluster-level-corrected *p* values <0.05 were considered statistically significant.

Results

[¹¹C]MADAM BP_{ND} in high- and low-HA groups

A ROI-based repeated-measures ANOVA indicated that [¹¹C]MADAM BP_{ND} did not differ in any brain region between the high- and low-HA groups ($F=0.961$, $p=0.408$) (Fig. 2). In addition, there was no significant region \times group interaction in this analysis. A voxel-based analysis confirmed the negative result. Finally, a separate analysis on the midbrain indicated no differences between the high- and low-HA groups. Because of the known intercorrelations between HA and 'novelty seeking', 'cooperativeness' and 'self-directedness', we included also these TCI

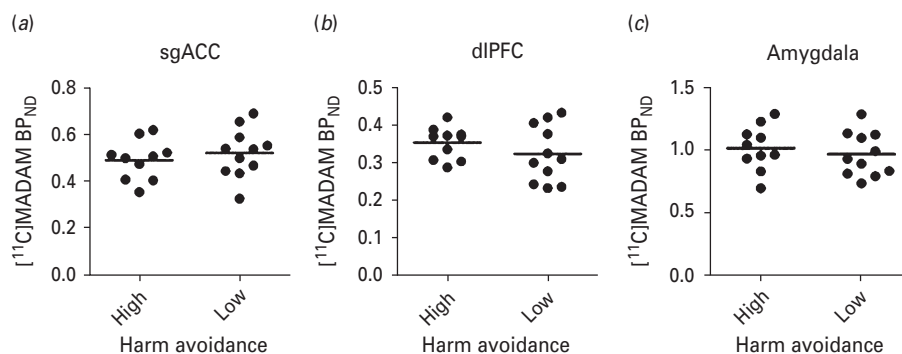


Fig. 2. Examples of [^{11}C]N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine ([^{11}C]MADAM) binding potential (BP_{ND}) in three different brain regions: (a) subgenual anterior cingulate cortex; (b) dorsolateral prefrontal cortex; (c) amygdala. Statistically significant differences were not found in any region ($p > 0.05$).

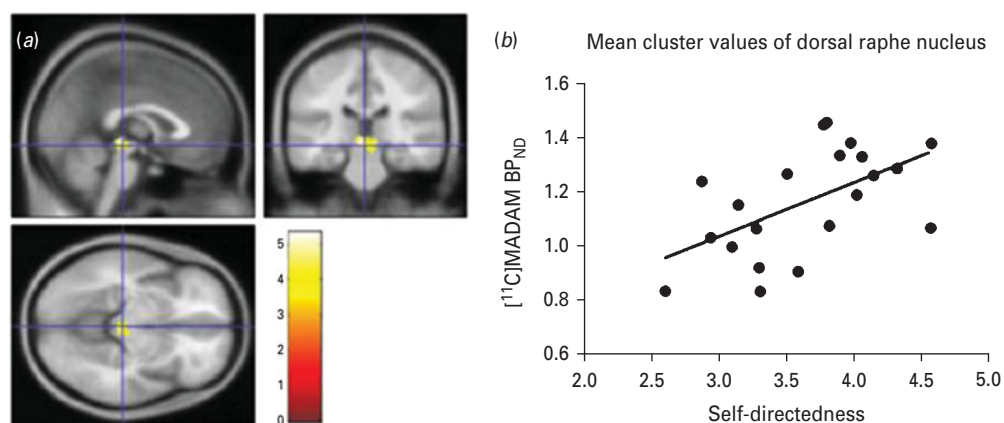


Fig. 3. ‘Self-directedness’ correlates with serotonin transporter (5-HTT) binding potential in the dorsal raphe nucleus ($n = 21$). (a) The results are visualized on an anatomically standardized T1-weighted magnetic resonance image. Cluster-level $p = 0.004$ (corrected for multiple comparisons). Cluster size = 199 voxels. Montreal Neurological Institute (MNI) x, y, z coordinates in millimetres of peak voxel $-4, -26, -4$. (b) Individual mean binding potential (BP_{ND}) values extracted from the cluster using the

dimensions in the statistical model but the results did not change.

Correlations between TCI character dimensions and [^{11}C]MADAM BP_{ND}

Voxel-based analysis restricted to the midbrain revealed a significant positive correlation between ‘self-directedness’ and [^{11}C]MADAM BP_{ND} in a cluster of voxels localized in the dorsal raphe nucleus ($r = 0.555$, $p = 0.004$ after correction for multiple comparisons) (Fig. 3). In contrast, partial correlation analysis of ROI-based data revealed negative correlations between [^{11}C]MADAM BP_{ND} and ‘self-directedness’ as well as between [^{11}C]MADAM BP_{ND} and ‘cooperativeness’ in several brain regions such as the anterior insula and posterior cingulate cortex (Table 2). Nevertheless, these correlations did not survive correction for multiple

comparisons. ‘Self-transcendence’ did not correlate with [^{11}C]MADAM BP_{ND} in any region. A voxel-based analysis was in line with the ROI-based findings.

TCI scores

The mean HA scores were 3.32 (range 2.97–3.66) in the high-HA group and 2.00 (range 1.71–2.23) in the low-HA group ($p < 0.001$). All correlations between TCI dimensions in the current subsample and in the whole cohort are shown in Supplementary Tables S1a and S1b. HA scores showed excellent stability over time, demonstrated by a Pearson correlation of 0.852 between HA scores obtained on the PET study day and those obtained in the year 2001. Age or gender did not affect TCI scores in our sample.

TCI mean character scores in our subsample were as follows: ‘self-directedness’, 3.65 (range 2.60–4.58);

Table 2. 'Self-directedness' and 'cooperativeness' partial correlations with regional [¹¹C]MADAM BP_{ND} (n = 21)^a

Brain regions	'Self-directedness'		'Cooperativeness'	
	r ^b	p ^c	r ^b	p ^c
Cingulate cortex				
Subgenual	-0.203	0.403	-0.224	0.357
Pregenua	-0.339	0.156	-0.424	0.07
Anterior dorsal	-0.362	0.127	-0.271	0.262
Posterior	-0.658	0.002**	-0.444	0.057
Basal ganglia				
Caudate nucleus	-0.177	0.468	-0.327	0.172
Putamen	-0.394	0.095	-0.586	0.008**
Ventral striatum	-0.241	0.32	-0.252	0.298
Thalamus	0.025	0.919	-0.007	0.976
Temporal lobe				
Superior temporal gyrus	-0.196	0.421	-0.358	0.133
Medial temporal gyrus	-0.237	0.328	0.466	0.044*
Inferior temporal gyrus	-0.242	0.318	-0.233	0.338
Anterior insular cortex	-0.614	0.005**	-0.547	0.015*
Posterior insular cortex	-0.369	0.12	-0.387	0.102
Hippocampus	0.423	0.071	0.472	0.041*
Amygdala	-0.208	0.380	-0.115	0.631
Frontal lobe				
Medial prefrontal cortex	-0.508	0.026*	-0.52	0.023*
Medial orbital frontal cortex	-0.451	0.052	-0.42	0.074
Lateral orbital frontal cortex	-0.205	0.386	-0.22	0.352
Dorsolateral prefrontal cortex	-0.425	0.069	-0.41	0.082
Ventrolateral prefrontal cortex	-0.002	0.994	-0.093	0.706

[¹¹C]MADAM, [¹¹C]N,N-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine; BP_{ND}, binding potential.

^a Relevant midbrain results are shown in Fig. 3.

^b Partial correlation coefficient (partial correlation analysis corrected for age and gender).

^c Significance values were not corrected for multiple comparisons.

* $p < 0.05$, ** $p < 0.01$.

'cooperativeness', 3.76 (range 3.15–4.31); 'self-transcendence', 2.37 (range 1.35–3.42). These scores were not statistically different from those observed in the whole cohort ($n = 2075$ in the year 2001), which were as follows: 'self-directedness', 3.70 (range 1.94–4.88); 'cooperativeness', 3.74 (range 1.50–4.84); 'self-transcendence', 2.49 (range 1.18–4.38) and the scores in the subsample were normally distributed. 'Self-directedness', 'cooperativeness' and 'self-transcendence' also showed stability over the two measurement points (1997 and 2001), with Pearson correlation coefficients of 0.926, 0.875 and 0.787, respectively.

[¹¹C]MADAM BP_{ND} in the brain – effect of gender and age

Voxel-based analysis in the midbrain indicated that females had significantly higher [¹¹C]MADAM BP_{ND} in the midbrain ($p < 0.001$, corrected). This same

pattern was seen in several other brain regions but these differences were not statistically significant after correction for multiple comparisons.

We observed a trend towards negative correlations with age and [¹¹C]MADAM BP_{ND}, e.g. in the angular gyrus ($r = -0.471$, $p = 0.031$) and in the posterior insula ($r = -0.433$, $p = 0.05$), but these correlations did not survive correction for multiple comparisons. The failure to detect an age-related decline in [¹¹C]MADAM BP_{ND} is probably due to the small age range (15.8 years) in the subsample.

Discussion

Serotonin transporter and HA in screened healthy subjects

Serotonin is a predominantly inhibitory neurotransmitter in the adult human brain. Outside the raphe nucleus 5-HTTs are located presynaptically in

the serotonergic axon terminals where they critically regulate the amount of serotonin in the synaptic cleft by reuptake. In this study our hypothesis was not supported, i.e. the temperament dimension HA was not associated with 5-HTT density (BP_{ND}) in healthy volunteers. This was the case despite the specific study design to detect differences in the age- and gender-matched high- and low-HA groups. Results did not change after including other modifying TCI personality traits in the model ('novelty seeking', 'self-directedness', 'cooperativeness'). Our result is in line with the study by Reimold *et al.* (2008), which did not detect an association between HA and [^{11}C]DASB BP_{ND} in 19 healthy volunteers. We intentionally excluded subjects with past or current DSM-IV-defined psychiatric disorders in order to avoid effects of, for example, affective disorder diagnosis or its treatment on our results. Excluding subjects with mental disorders from this study limits the generalizability of the results to the healthy population. Exclusion of subjects with mental disorders is a valid approach, as some reports suggest decreased *in vivo* 5-HTT binding in major depression although this remains controversial with possible state-dependent phenomena involved (Bhagwagar *et al.* 2007; Cannon *et al.* 2007; Meyer, 2007; Reimold *et al.* 2008; Selvaraj *et al.* 2011). It is known that high HA predisposes to psychiatric disorders, especially in the mood and anxiety spectrum (see Miettunen & Raevuori, 2012). Our results are useful in the interpretation of serotonin imaging studies in patients with affective disorders and the related state-trait discussion. Future serotonin imaging studies should examine high- and low-HA subjects with and without psychiatric disorders in order to explore the interaction between temperament and, for example, mood and anxiety spectrum diagnosis. Clearly, such a study would also be of high relevance for further testing of Cloninger's psychobiological model of personality and the original hypothesis on the link between serotonin and HA in the general population.

Neither ROI-based data nor voxel-based analysis of parametric BP_{ND} images showed difference between high- and low-HA groups in [^{11}C]MADAM BP_{ND} in any brain region. Power analysis of ROI-based data (at $\alpha=0.05$, $\beta=0.20$) indicated that we can exclude 17% difference in striatum and 16% difference in anterior cingulate cortex in [^{11}C]MADAM BP_{ND} between the groups.

BP_{ND} is a composite measure of affinity and density (Innis *et al.* 2007), which are not separable from the PET procedure used here. Our interpretation of the finding is that HA does not affect 5-HTT density. An acute change in serotonin levels does not affect 5-HTT binding *in vivo* in humans (Praschak-Rieder *et al.* 2005;

Talbot *et al.* 2005). Unchanged 5-HTT level, albeit a key regulator of serotonin drive, does not exclude a change in endogenous 5-HT levels between the two HA groups. Unfortunately, there are currently no established methods of measuring 5-HT levels directly or indirectly in man despite promising new results with a 5-HT_{1B} receptor tracer (Finnema *et al.* 2010). Moreover, our result does not exclude the possibility that HA is linked to the density or function of 5-HT receptors. To our knowledge there are four earlier imaging studies on HA and serotonin receptor density in healthy volunteers (Moresco *et al.* 2002; Rabiner *et al.* 2002; Borg *et al.* 2003; Karlsson *et al.* 2009). Of these studies, three used a 5-HT_{1A} receptor tracer [^{11}C]WAY-100635 (Rabiner *et al.* 2002; Borg *et al.* 2003; Karlsson *et al.* 2009) and none of them found an association between receptor density and HA. Considering that the combined number of healthy subjects in these studies is 96, we think that it is unlikely that HA is related to 5-HT_{1A} receptor density in the healthy population. The fourth study (Moresco *et al.* 2002) using [^{18}F]FESP found a negative correlation between [^{18}F]FESP binding and HA bilaterally in the frontal cortex and in the left parietal cortex. [^{18}F]FESP is a ligand that binds to both 5-HT_{2A} and dopamine D₂ receptors, and is thus not an ideal tracer for imaging the serotonin 5-HT_{2A} receptors.

Interestingly, in an [^{18}F]altanserin PET study on NEO Personality Inventory (NEO-PI) – Revised 'neuroticism', Frokjaer *et al.* (2008) found a positive correlation between 'neuroticism' and 5-HT_{2A} receptor binding in frontolimbic regions. Although HA and 'neuroticism' are not directly comparable, they are highly intercorrelated (De Fruyt *et al.* 2000; Jokela & Keltikangas-Järvinen, 2011) and may both be seen as vulnerability markers for affective disorders. One might thus expect somewhat related biology, not the opposite as seen in the studies by Moresco *et al.* (2002) and Frokjaer *et al.* (2008). It is possible that this controversy simply demonstrates the possible pitfalls of association studies where some neurobiological marker is correlated with numerous psychological traits in a relatively small study sample. 'Neuroticism' is also strongly correlated with 'self-directedness' (De Fruyt *et al.* 2000). Hence the findings by Frokjaer *et al.* (2008) may be in agreement with our results on 'self-directedness'. Overall, our results and the current literature do not support the hypothesized association between HA and 5-HTT or receptor binding in subjects selected for an absence of psychiatric disorders.

As the serotonergic system is intertwined with several other neurotransmitters such as dopamine and γ -amino butyric acid (GABA), the HA trait may be correlated with the balance of a complex

neurotransmitter network instead of just serotonin. There is one study that associates HA with dopamine D₂/D₃ receptor availability in the associative and sensorimotor striatum (Kim *et al.* 2011). In future, neurobiological correlates of human personality should be studied with a multiple neurotransmitter approach as postulated earlier by Cloninger (1986). Such differences in neurotransmitter balances are now widely being searched (Nakamura *et al.* 2010).

Serotonin transporter and character in screened healthy subjects

Our secondary analyses indicated that 'self-directedness' correlates positively with [¹¹C]MADAM BP_{ND} in the raphe nucleus. Negative correlations between 5-HTT BP_{ND} values and 'self-directedness' as well as 'cooperativeness' were seen in multiple brain areas, but these correlations did not survive a conservative correction for multiple comparisons.

'Self-directedness' is related to self-concepts and defined as the extent to which a person identifies himself as an autonomous individual (Cloninger *et al.* 1993) and as the ability to adapt behaviour according to chosen goals and values. The heritability of 'self-directedness' is high and in several studies it may be even higher than that for the four temperament traits (Comings *et al.* 2000; Ando *et al.* 2002, 2004; Gillespie *et al.* 2003; Isen *et al.* 2009). However, little is known about the biology of character dimensions. There is some evidence for a link between serotonin systems and character dimensions. Borg *et al.* (2003) found an association between 'self-transcendence' and 5-HT_{1A} binding, but this has not been confirmed by other studies (Rabiner *et al.* 2002; Karlsson *et al.* 2009). None of the 5-HT_{1A} PET imaging studies found correlations between 5-HT_{1A} and 'self-directedness' or 'cooperativeness'. As far as we know, this is the first *in vivo* imaging study that demonstrates the role of serotonin in 'self-directedness'. We found no statistically significant correlations between [¹¹C]MADAM BP_{ND} and other character dimensions.

Higher 'self-directedness' was robustly associated with higher 5-HTT binding in the dorsal raphe nucleus. Even if the result must be regarded as preliminary, the correlation was found in a relevant brain region, survived correction for multiple comparisons and was found in small volume-corrected and even in a whole-brain SPM analysis. In addition, the distribution of 'self-directedness' scores in the current sample was comparable with that in the larger population sample. Serotonergic neurons projecting to other areas of the brain originate mainly from this region (Hornung, 2003). The firing rate of the serotonergic neurons in the dorsal raphe nucleus is

controlled by autoregulatory 5-HT_{1A} receptors by negative feedback. 5-HTT in the raphe nucleus is located in the somatodendritic part of the neuron in contrast to other brain areas where 5-HTT is found on the presynaptic axon terminals. High levels of 5-HTT in the dorsal raphe nucleus is likely to cause less negative autoregulation via the 5-HT_{1A} receptor and a higher serotonin drive in the terminal areas, e.g. in the orbitofrontal or cingulate cortices. Our interpretation of the finding is that higher 'self-directedness' is related to less negative feedback in the dorsal raphe nucleus and thus with higher serotonergic drive in terminal areas, e.g. in the orbitofrontal and cingulate cortices.

Low levels of serotonin are thought to be essential in the pathophysiology of affective disorders. As noted in the introduction, a low 'self-directedness' score may also predispose to these disorders. Although the results from imaging studies on serotonin and depression are still somewhat inconsistent (for a review, see Meyer, 2007), the latest reports using [¹¹C]DASB report lower 5-HTT binding in the midbrain and higher 5-HTT binding in cortical areas in depressed patients compared with healthy controls (Parsey *et al.* 2006; Cannon *et al.* 2006, 2007; Reimold *et al.* 2008; Selvaraj *et al.* 2011). Our results are consistent with these findings. In fact, in future imaging studies on mood and anxiety disorders, it would be useful to consider the personality traits in the design and analysis in order to differentiate between predisposing factors and factors related to the active disease process itself.

Character scales were first designed as targets of psychotherapeutic interventions (Cloninger *et al.* 1994). However, some evidence indicates that treatment of affective disorders with tricyclic antidepressants and selective serotonin reuptake inhibitors, drugs that increase the levels of synaptic serotonin, also increases 'self-directedness' (Black & Sheline, 1997; Allgulander *et al.* 1998; Agosti & McGrath, 2002; Hirano *et al.* 2002; Joyce *et al.* 2003; Boz *et al.* 2007). One study has even indicated that this increase in 'self-directedness' has also predictive value for changes in depressive symptoms as measured with BDI (Mazza *et al.* 2009). Therefore, character dimensions may modulate the expression of mood states (Farmer *et al.* 2003; Cloninger, 2004; Cloninger *et al.* 2010) and our results may shed light on why both depressive symptoms and 'self-directedness' improve during serotonin-altering psychopharmacological treatment.

Finally, it should be noted that the validity of the distinction between temperament and character traits has been questioned, as factor analyses show a high degree of cross-loading between the traits (Ball *et al.*

1999; Herbst *et al.* 2000; Gana & Trouillet, 2003). In line with these factor analyses, the Pearson correlation coefficient between HA and 'self-directedness' in the whole Young Finns Study cohort was high ($r = -0.63$, see Supplementary Table S1a). De Fruyt *et al.* (2000) reported an equally high Pearson correlation coefficient ($r = -0.63$) between NEO-PI 'neuroticism' and TCI 'self-directedness'. However, even if two traits do correlate and load on the same factor, they may still represent psychologically distinct constructs (Block, 1995). Future studies investigating the role of the serotonin system in human personality should take these limitations in the TCI model into consideration, but also appreciate that the NEO-PI and TCI have high intercorrelations.

Conclusions

We found no support for an association of HA and serotonin transporter density in subjects free of psychiatric disorders as measured with [¹¹C]MADAM and PET. The result has implications in the research for biological factors in affective disorders. Higher serotonin transporter density in the dorsal raphe nucleus predicted higher 'self-directedness' scores. This relationship was robust and warrants further studies of serotonin function, differential aspects of character development and psychopathology.

Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S003329171200164X>.

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Declaration of Interest

None.

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