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The personality trait openness is related to cerebral 5-HTT levels

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ABSTRACT

Potentiation of serotonergic transmission increases cognitive flexibility, but can in other circumstances increase sensitivity to stressful environmental cues. The personality trait *Openness to Experience* reflects and is also associated with an increased risk for mood disorders. We hypothesized that the personality trait has an association with a biomarker of serotonergic transmission, the plasma membrane serotonin transporter (5-HTT). In 50 healthy volunteers, we tested for correlations between scores on the NEO-PI-R scale *Openness to Experience* and its subscales, and cerebral binding of the 5-HTT selective PET radioligand [^{11}C]DASB. Subjects were genotyped for the 5-HTT long/short polymorphism, and for a single nucleotide polymorphism in the long allele, designated L_A/L_G. Midbrain [^{11}C]DASB binding correlated negatively with scores for *Openness to Experience* and its two subscales, *Openness to Actions* and *Openness to Values*. The latter subscore was negatively correlated with [^{11}C]DASB binding in all brain regions in which [^{11}C]DASB binding was quantified. Genetic analysis showed that homozygote L_A carriers had significantly higher [^{11}C]DASB binding in the caudate nucleus, but no significant differences in openness scores. Thus, high scores in personality facets indicative of cognitive flexibility and openness to change are associated with lower [^{11}C]DASB binding. Lower abundance of 5-HTT sites may result in potentiation of serotonergic signaling, which occurs during treatment with SSRIs. We speculate that the set-point of serotonergic signaling in an individual represents a trade-off between flexibility and vulnerability when exposed to environmental stress.

Introduction

In the 60 years since its first chemical isolation (Rapport et al., 1948), serotonin has been implicated as a factor in cognitive flexibility, as well as in mood disorders. Results of studies with behavioral paradigms in humans and other animals have linked serotonin with the processing of affective stimuli (Canli et al., 2008), working memory (Robbins and Roberts, 2007), and synaptic plasticity (Celine et al., 2006). Among healthy human subjects, selective depletion of tryptophan, which reduces serotonin synthesis, led to more rigid behavior (Murphy et al., 2002) and decreased tolerance of the perceived unfair behavior of others (Crockett et al., 2008). Furthermore, reversal learning in rats, which entails flexible re-assignment of behavior in response to environmental cues, is interrupted by lesions of cortical serotonin innervations (Robbins and Roberts, 2007).

Based on these associations between the serotonin system and behavior, we asked if the broad personality dimension *Openness to Experience* (OtExperience) is related to 5-HTT function: OtExperience as measured with the Revised Neuroticism, Extraversion, Openness Personality Inventory (NEO-PI-R) is associated with increased biological response to stress (Oswald et al., 2006) and increased risk of developing winter depression, a classical environment-induced mood disorder (Bagby et al., 1996; Jain et al., 1999). Consistent with the present theme, carriers of the 44-base pair deletion (*S-allele*) in the 5-HTT-linked polymorphic region (5-HTTLPR), which is associated with *lower* 5-HTT mRNA expression (Lesch et al., 1996), have been found to have higher OtExperience scores (Stoltenberg et al., 2002)

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and also to be more at risk to develop seasonal affective disorder (SAD) (Rosenthal et al., 1998; Willeit et al., 2003). On the other hand, OtExperience has been associated with increased cognitive flexibility, more adequate coping strategies for psychiatric disorders among the elderly (Duberstein, 1995), and higher survival rate in somatic disorders (Jonassaint et al., 2007). Due to this duality, OtExperience may be the personality dimension that reflects the net-effects of serotonin on both cognitive flexibility and sensitivity to stressful environmental cues. However, despite this evidence, there has been only a single PET study linking openness (specifically to spiritual experience) and serotonin 1_A receptor availability (Borg et al., 2003).

We used positron emission tomography (PET) in conjunction with genetic analysis of the 5-*HTTLPR* to test for associations between cerebral 5-HTT availability measured *in vivo*, and OtExperience scores from the NEO-PI-R in a population of 50 healthy volunteers. Because recent findings suggest that not only the *S-allele*, but also a single nucleotide polymorphism (SNP) within the 44-base pair insertion of the *L-allele* (L_G) is associated with lower 5-HTT mRNA expression (Nakamura et al., 2000) and lower cerebral 5-HTT binding (Praschak-Rieder et al., 2007; Reimold et al., 2007), we also conducted a genetic analysis of the 5-*HTTLPR* in our sample. Individual scores on the personality test and PET end-point, the 5-HTT binding potential (BP_{ND}) for [^{11}C]DASB, were tested for associations, with the 5-*HTTLPR* carrier status taken into account.

Methods

Subjects

Fifty healthy volunteers were recruited by advertisement for a research protocol approved by the Ethics Committee of Copenhagen and Frederiksberg, DK [(KF) 01-156/04, (KF) 01-124/04, and (KF) 11-283038]. After complete description of the study to the subjects, written informed consent was obtained from 35 males with a mean age of 32 years (SD 15 years), and from 15 females with a mean age of 38 years (SD 18 years). Exclusion criteria for all test persons included a significant medical history, drug abuse or psychiatric disorders. All subjects had a normal neurological examination and their magnetic resonance (MR) brain images were without pathological findings.

PET scans

PET scans were performed with an 18-ring GE-Advance scanner (General Electric, Milwaukee, WI, USA), operating in 3D acquisition mode, and producing 35 image slices with an interslice distance of 4.25 mm. Following a 10 min transmission scan, a dynamic 90 min long emission recording was initiated upon intravenous injection during 12 s of mean 484 (SD 89) MBq (range: 246–601) [^{11}C]DASB with mean specific activity of 32 (SD 16) GBq/μmol (range: 9–82). The emission recording consisted of 36 frames, increasing progressively in duration from 10 s to 10 min. The attenuation and decay corrected recordings were reconstructed by filtered back projection using a 6 mm Hann filter.

MR scans

Structural brain scans were acquired on a Siemens Magnetom Trio 3 T MR scanner with an eight-channel head coil (In vivo, FL, USA). Thirty-five subjects underwent a high-resolution 3D T1-weighted, sagittal, magnetization prepared rapid gradient echo (MPRAGE) scan of the head (MPRAGE1: echo time (TE)/repetition time (TR)/inversion time (TI)=3.93/1540/800 ms; slice resolution=75%; Bandwidth=130 Hz/Px; Echo spacing=9.8 ms) and fifteen subjects underwent a 3D T1-weighted, sagittal, MPRAGE (MPRAGE2: TE/TR/TI=3.04/1550/800 ms; slice resolution=100%; Bandwidth=170 Hz/Px; Echo spacing=7.7 ms). Common to both MPRAGE's was a flip angle of 9°, an FOV of 256 mm, a matrix of 256×256, 1×1×1 mm voxels and 192 slices.

MR/PET co-registration

All time-frames of the attenuation-corrected emission recording were automatically aligned to frame 26 using the AIR algorithm (Woods et al., 1998). In a next step we used a mean PET image, averaging time-frames 10–36 for co-registration to the individual MR image using the AIR algorithm (Woods et al., 1998); the quality of each co-registration was controlled visually.

Volume of interest (VOI) analysis

The VOI were delineated automatically as described in Svarer et al. (2005) in order to identify the volumes in a user-independent fashion. For each of the 10-template VOI sets, a 12-parameter affine transformation and a warping field was calculated between the template MR image and the individual MR image for a subject. Having obtained the MR/PET co-registration for the same individual as described above, the template VOI sets are then transferred to the dynamic PET image space for each subject, using the identified transformation parameters. From the VOI sets, a probability map was created for each subject, and a common VOI set was threshold-generated. These VOI sets were then used for automatic extraction of time activity curves (TAC) for midbrain and volume-weighted (left–right) averages for bilateral thalamus, caudate, putamen and cerebellum for all subjects. The midbrain, the caudate, the putamen and the thalamus were selected as representative brain regions of homogenous, high 5-HTT binding (Houle et al., 2000) since we expected that the 5-*HTTLPR* status would lead to a global effect. The TAC extracted for the cerebellum was used as the reference tissue input for kinetic modeling.

Quantification of non-displaceable tracer uptake

The outcome parameter of the cerebral [^{11}C]DASB binding within a brain region is the non-displaceable binding potential, designated BP_{ND}. The BP_{ND} was calculated for the four VOIs, using the cerebellum input as reference region with non-specific binding. We used a modified reference tissue model designed specifically for quantification of [^{11}C]DASB (MRTM/MRTM2) as described and evaluated by Ichise et al. (2003) using the PKIN tool of the software PMOD version 2.9: A fixed washout constant, designated k2′, was calculated for each individual as an average of k2 in caudate, putamen and thalamus relative to cerebellum using MRTM. Subsequently, k2′ was used as a constrained input parameter for the calculation of BP_{ND} in the four VOIs relative to cerebellum.

Parametric images

For the voxel-based analysis, parametric images representing BP_{ND} for each voxel were calculated for all subjects from the dynamic PET images. Using the PXMOD tool of the PMOD software, we imported the VOI, generated as described above, and re-calculated k2′ relative to cerebellum using MRTM. As described by Ichise et al. (2003), we applied an R1 (tracer delivery to the VOI relative to cerebellum, to some extent reflecting blood flow) threshold of 0.3 to exclude noisy voxels, particularly seen in regions with low tracer clearance. Additionally, we restricted the BP_{ND} outcome to range between 0 and 10. The resulting parametric images were filtered with a 3 mm median filter in their native space. SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) was used to normalize the parametric images to Montreal Neurological Institute (MNI) space using a warping field estimated by normalization of each subject's co-registered MR image. Subsequently, a 12 mm Gaussian filter was applied to all normalized images.

Personality assessment

OtExperience with its facets *Openness to Fantasy*, *Openness to Aesthetics*, *Openness to Feelings*, *Openness to Ideas*, *Openness to Actions* (OtAction), and *Openness to Values* (OtValues) was assessed on the day of the PET scanning with the Danish version of the Revised NEO Personality Inventory (NEO-PI-R). The NEO-PI-R is a well-established and standardized instrument to assess personality traits, using either self-reports or observer ratings. It incorporates the five broad traits of the five-factor model (FFM) of personality and includes six facets or specific traits for each of the five broad factors. Each facet score is derived by adding the scores on eight items in 0–4 Likert format, and the personality trait score is composed by the scores on its six facets. Thus, the possible range of facet scores is 0–32 and the range of trait scores from 0–192. The Danish translation of the NEO-PI-R has been psychometrically evaluated and standardized in a sample of 600 subjects (Costa and McCrae, 1992; Hansen and Mortensen, 2004).

Genotyping

Blood was drawn on the day of the PET-scanning and genomic DNA was purified from the buffy coat by standard methods. The applied procedure for polymerase chain reaction (PCR) is previously described (Klauck et al., 1997). The *5-HTTLPR* long (A/G) polymorphism was detected by MspI restriction enzyme digestion of the PCR products and the generated fragments were resolved by gel electrophoresis. Product sizes for the digest were in line with the literature: L_A=340 bp, L_G=166 bp+B174 bp, S=297 bp (Praschak-Rieder et al., 2007).

Statistics

We used SAS software (SAS Institute Inc.) version 9.1.3 for statistical analysis. To test the correlation between personality and 5-HTT binding, the scores of the NEO-PI-R dimension (trait) OtExperience and its facets were correlated to a left and -right volume-weighted average of BP_{ND} for [^{11}C]DASB in the thalamus, the caudate, the putamen, and the midbrain, with adjustment for age and gender, in a multiple linear regression analysis with OtExperience and its facets as dependent variables and BP_{ND}, genotype, age, and gender as independent variables. To test the correlation between genotype and personality, we used OtExperience and its facets as dependent variables and *5-HTTLPR* genotype, age, and gender as independent variables. We also tested the genotype effect on BP_{ND} for [^{11}C]DASB reported by other groups (Praschak-Rieder et al., 2007; Reimold et al., 2007); for this we used a general linear model with BP_{ND} for [^{11}C]DASB as dependent variable and genotype, age, and gender as independent variables. In addition to the VOI based data we tested the correlation between personality and BP_{ND} for [^{11}C]DASB using a voxel-based analysis with OtExperience and its facets as dependent variables and BP_{ND}, age, and gender, and genotype as independent variables using the Brede Toolbox (http://hendrix.imm.dtu.dk/software/brede/). We analyzed post-hoc for a gene–age interaction effect on personality (with gender as covariate), an association between *Neuroticism* and BP_{ND} for [^{11}C]DASB in the four VOIs (corrected for age and gender), as reported by another group (Takano et al., 2007), and for a correlation between *Neuroticism* and OtExperience and its facets.

For the VOI-based analysis, we report p-values lower than 0.05 as statistically significant. For the voxel based analysis we applied a mask on MNI space including the four VOIs named above. This mask was created by step-wise increasing the BP_{ND} threshold on a mean of all spatially normalized parametric maps until we obtained a distinct, mostly confluent mask encompassing all the target regions as visually identifiable on the overlaid mean of all normalized MR images. For the voxel-based analysis, we report p-values below 0.05 as significant, corrected for multiple comparisons (all voxels within this mask). To this end, we used a permutation test to identify the probability of finding random significance, as described by Nichols and Holmes (2002), applied with 10,000 iterations for each trait or facet.

Results

5-HTT binding versus personality scores

We found a significant negative correlation between 5-HTT binding in the midbrain and OtExperience (r=−0.325, p=0.024), its facets OtAction (r=−0.413, p=0.003), and OtValues (r=−0.371, p=0.009) (Fig. 1). The correlation between 5-HTT binding and OtValues was also significant in the putamen (r=−0.328, p=0.023), the thalamus (r=−0.427, p=0.002) (Fig. 1)), and approaching significance in the caudate nuclei (r=−0.282, p=0.053). These findings

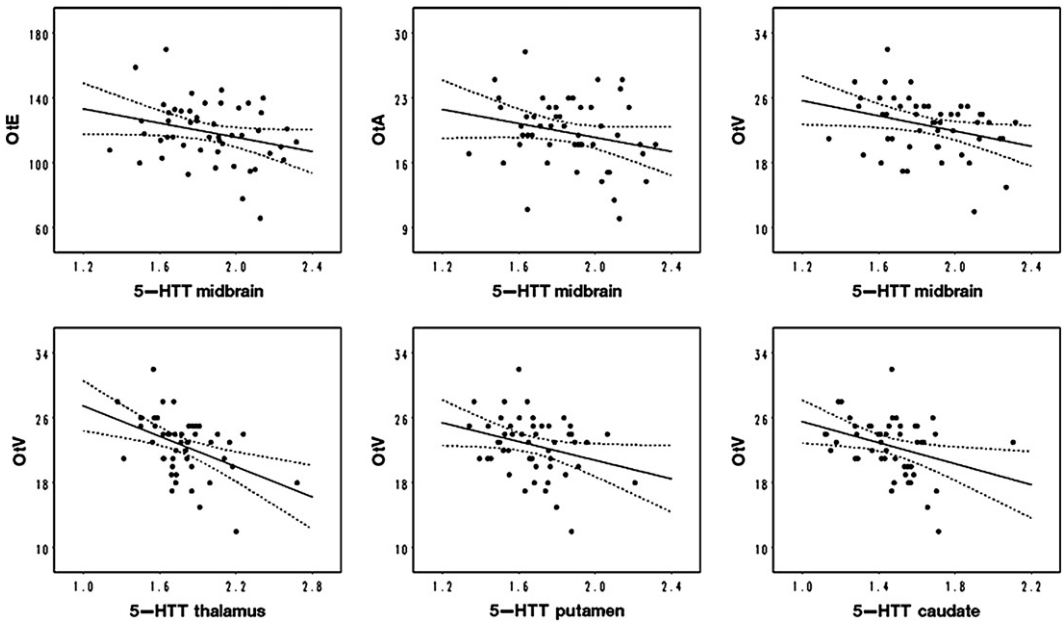

Fig. 1. Correlations between regional specific binding of [^{11}C]DASB and openness, corrected for age and gender, with 95% confidence intervals. The upper three graphs show the correlations in midbrain for OtE, OtA and OtV. The lower three graphs show the correlations between specific binding of [^{11}C]DASB and OtV in thalamus, putamen and caudate.

for OtValues were confirmed by voxel-based analysis for the following coordinates in the MNI space (all p-values corrected for multiple voxels as described above): 14;−24; 4 (1482 voxels, $r=-0.550$, $p=0.004$), 26; −12; −6 (23 voxels, $r=-0.504$, $p=0.023$), 18; −8; −6 (2 voxels, $r=-0.474$, $p=0.050$), 12; 4; 4 (2 voxels, $r=-0.478$, $p=0.043$). We did not find associations between 5-HTT binding and any of the other four openness facets. Further, post-hoc analysis revealed no significant correlation between 5-HTT and the trait *Neuroticism*, or any of its facets, including anxiety and depression. However, in our sample OtValues was inversely correlated with *Neuroticism* ($r=-0.296$, $p=0.033$) and, in particular, its facet anxiety ($r=-0.361$, $p=0.010$).

Gene-effects

Eighteen test persons where homozygote *L-allele* carriers (36%), eleven were homozygote *S-allele* carriers (22%), and twenty-one heterozygotes (41%); these frequencies did not differ significantly (Pearson's Chi^2 test with one degree of freedom) from the frequencies expected according to the Hardy–Weinberg principle or expected according to the observed frequencies in a larger group of 847 Caucasian non-Maori test persons (Caspi et al., 2003). Among the total of eighteen homozygote *L-allele* carriers, fourteen were homozygote L_A-*allele* carriers, and four carried L_AL_G. We found that homozygote L_A-*allele* carriers generally had higher 5-HTT binding than carriers of at least one *S-allele* or one L_G-*allele*, but this difference was only statistically significant in the caudate nuclei ($p=0.042$). We did not find a difference in openness scores between carriers of different alleles of the *5-HTTLPR* polymorphism. However, post-hoc analysis revealed a tendency for a gene–age interaction ($p=0.060$, adjusted for gender) with carriers of L_AL_A becoming less open to values with age, while *S-* or L_G-*allele* carriers retained a high openness to values score with age.

Regional binding and personality facet intercorrelations, age and gender

We found that OtExperience scores correlated significantly with the scores of the facets OtAction ($r=0.586$, $p<0.001$) and OtValues ($r=0.606$, $p<0.001$). 5-HTT binding in the midbrain, the caudate and the putamen was correlated to each other, e.g. 5-HTT binding in the midbrain predicted the 5-HTT binding in the putamen ($r=0.550$, $p<0.001$), in the thalamus ($r=0.502$, $p<0.001$). Men had higher 5-HTT significantly higher binding in the caudate nuclei ($p=0.008$) and significantly lower binding in the midbrain ($p=0.030$), and 5-HTT binding declined with age, statistically significant in the thalamus ($r=0.333$, $p=0.018$). Since the fixed wash-out constant, k2′, has an important influence on BP_{ND} for [^{11}C]DASB, we tested for correlations between k2′ and OtExperience and all openness facets; neither trait nor facets were correlated to k2′ (p, uncorrected for comparisons <1 in all cases). Eight of the participants were smokers, but smoking does not have any impact on BP_{ND} for [^{11}C]DASB (Erritzoe, personal communication).

Discussion

We confirmed our hypothesis that OtExperience is negatively correlated with in vivo cerebral 5-HTT binding. Since OtExperience and its facets OtAction and OtValues showed a negative correlation with the BP_{ND} for [^{11}C]DASB in all these regions, we propose that openness, in particular OtValues, is associated with global scaling in 5-HTT binding, as illustrated in Fig. 2. Furthermore, we replicated, in a group of Europeans, the finding of previous studies that in vivo 5-HTT binding is higher in the caudate nuclei in homozygote L_A-carriers (Praschak-Rieder et al., 2007; Reimold et al., 2007) in the caudate nuclei. We did not replicate the reported association between *5-HTTLPR* genotype and OtExperience (Stoltenberg et al., 2002). Interestingly, a statistical trend suggested that an effect of *5-HTTLPR* on openness was revealed when analyzing age–gene interaction; While carriers of the *S-* or L_G-*allele* remain at the same level of openness over the complete age range, homozygote L_A-*allele* carriers have similar openness scores when younger but become less open to values with age. We suggest that the direct association between *5-HTTLPR* genotype and openness should be reproduced in a larger group of test persons covering a wider age range since (only 6 of our 50 subjects were older than 40 years).

Some consideration regarding the issue of multiple comparisons needs to be done. To test our primary hypothesis, the association between personality and 5-HTT binding, we compared scores of the dimension itself and its six facets and 5-HTT binding in four regions. However, we found overall correlations among the personality scores as well as among the 5-HTT binding in the four VOIs. Therefore, conservative correction for multiple comparisons is inappropriate, and a global association between the dimensions OtAction and OtValues (which both contribute to the score of OtExperience) and the 5-HTT binding in all measured brain regions is likely. In the case of our second positive finding, the gene-effect was found in one out of four regions, with a p-value just reaching significance ($p=0.042$). Since two previous

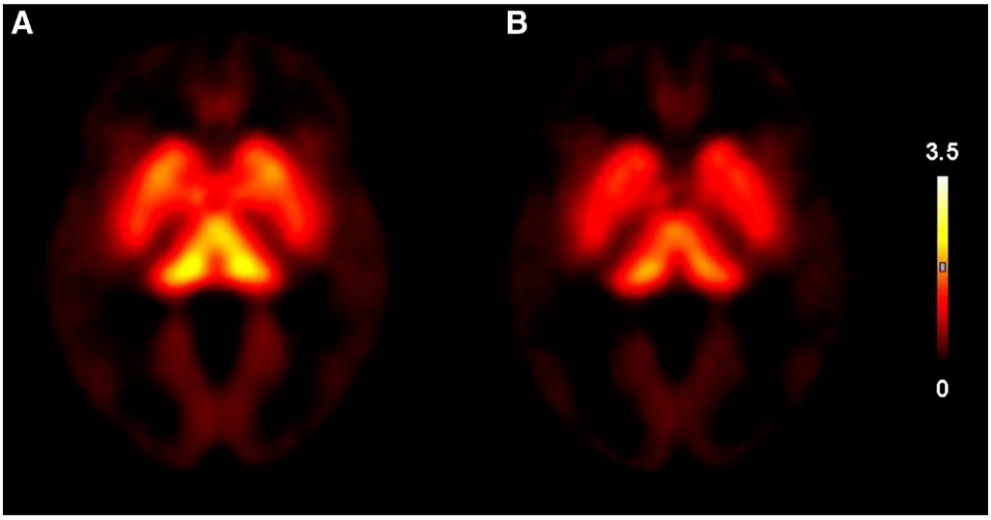

Fig. 2. Averaged parametric maps representing specific binding of [^{11}C]DASB to 5-HTT. Parametric maps (averaged) of (A) the ten subjects with least openness to values and (B) the ten subjects most open to values show a global higher scaling in less open individuals.

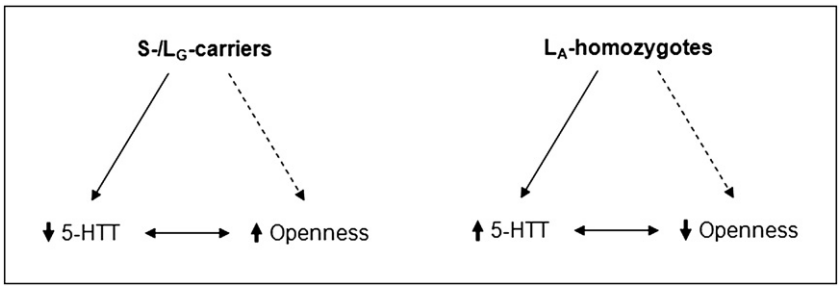

Fig. 3. A suggested model for the association between 5-*HTTLPR* genotype, 5-HTT binding and openness. The bidirectional full connecting arrow represents the negative 5-HTT personality correlation. The one-directional full connection arrow represents the gene effect on 5-HTT binding found by other groups and replicated in our study. The one-directional dashed connecting arrow represents the gene–personality effect as found in one study and only indirectly confirmed in our sample.

studies reported an effect, although in different regions than investigated in our study (i.e. the putamen (Praschak-Rieder et al., 2007) and the midbrain (Reimold et al., 2008)), we propose that 5-HTT binding is determined by a global, but rather subtle, gene-effect, possibly subject to modification by environmental factors.

In vivo imaging studies with PET have emphasized the search for aberrant serotonin markers in the brains of depressed patients. A number of PET studies have measured the abundance of 5-HTT, which clears serotonin from the interstitial space. An important class of antidepressant medications, the SSRIs, blocks this process by binding to the 5-HTT. Results of these PET studies have been inconsistent, showing 5-HTT binding to be elevated (Cannon et al., 2007), decreased in the brains of patients with major depressive disorder (MDD), (Reimold et al., 2008; Oquendo et al., 2007; Parsey et al., 2006) or unchanged (Meyer et al., 2004) in brain of depressed patients. Only one PET study of healthy subjects investigated the relationship between 5-HTT binding and *Neuroticism* scores on the NEO-PI-R and found that high 5-HTT binding was associated with *Neuroticism* (Takano et al., 2007). Conversely, the vast number of genetic studies has associated the *S-allele*, which results in *lower* 5-HTT mRNA expression, to *Neuroticism* (Canli and Lesch, 2007; Lesch et al., 1996).

Our results indicate that OtExperience, primarily driven by the facets OtAction and OtValues, shows a consistent association with the *5-HTTLPR* genotype and cerebral 5-HTT; *S-Allele* carriers had lower 5-HTT binding, and lower 5-HTT binding was found in the more open individuals (Fig. 3). Our suggested model is consistent with the findings in SAD; this mood disorder, which is characterized by winter depression with seasonal deterioration in eating and sleeping patterns, appears by definition only in response to environmental changes. As such, SAD provides an innate model for probing the neurochemical basis of sensitivity to environmental changes. SAD has been consistently linked to both openness to experience (Bagby et al., 1996; Jain et al., 1999) and the *S-allele* (Rosenthal et al., 1998; Willeit et al., 2003). In our sample, we did not find a direct association between *S-/L$_G$-allele* and openness, but rather detected a tendency for an indirect effect, mediated via a gene–age interaction, in our post-hoc analysis. This interaction with age could, if reproducible, be of particular interest, since it indicates that cognitive flexibility might not primarily be higher in carriers of the *S-allele* but remain higher during the process of ageing.

The global association between OtExperience and 5-HTT binding in our study was primarily driven by OtAction and OtValues. While the other four facets (openness to fantasy, openness to aesthetics, openness to feelings, and openness to ideas) represent intellectual openness and curiosity, the two facets OtAction and OtValues reflect an active approach of the individual to try new ways of doing things and re-define their own self-understanding, e.g. values or world-views. In particular, high OtActions reflect the willingness to use a variety of approaches to solve problems and also to try new things such as unusual food as opposed to sticking to the known ways of doing things; high OtValues reflect the readiness to re-think and change one's own political, social, and religious values, as opposed to people with low openness who tend to be conservative and "dogmatic" (Costa and McCrae, 1992). Our findings that OtAction and OtValues correlate with 5-HTT match well with previous views that serotonin contributes to cognitive and behavioral flexibility versus rigidity (Crockett et al., 2008; Murphy et al., 2002; Robbins and Roberts, 2007). Insofar as the personality dimensions of OtAction and OtValues reflect an individual's ability to re-consider and change accustomed ways of thinking and thereby adapt to new circumstances, it is also notable that higher openness is associated with general cognitive ability and more efficient higher intellectual processes (DeYoung et al., 2005). Based on our findings we therefore propose a model that links cognitive flexibility and depression risk in the personality dimension of openness: Lower [^{11}C]DASB BP$_{ND}$, as present in carriers of the *S-* or *L$_G$-allele*, is a marker for slower serotonin re-uptake at the plasma membrane, resulting in higher extracellular serotonin levels leading to a more dynamic neural responsiveness and increased plasticity. This characteristic mode of serotonin transmission would manifest in the realm of personality as higher openness to embark on new ways of living, and an enhanced capacity to re-consider one's self-understanding. But by the same token, this same mechanism also imparts higher sensitivity to stressful environmental cues, as found by population studies, in the manner of a trade-off between benefits of cognitive flexibility and risks of vulnerability.

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