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Brain serotonin transporter is associated with cognitive-affective biases in healthy individuals

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Abstract

Cognitive affective biases describe the tendency to process negative information or positive information over the other. These biases can be modulated by changing extracellular serotonin (5-HT) levels in the brain, for example, by pharmacologically blocking and downregulating the 5-HT transporter (5-HTT), which remediates negative affective bias. This suggests that higher levels of 5-HTT are linked to a priority of negative information over positive, but this link remains to be tested in vivo in healthy individuals. We, therefore, evaluated the association between 5-HTT levels, as measured with [11C] DASB positron emission tomography (PET), and affective biases, hypothesising that higher 5-HTT levels are associated with a more negative bias. We included 98 healthy individuals with measures of [11C]DASB binding potential (BP_{ND}) and affective biases using The Emotional Faces Identification Task by subtracting the per cent hit rate for happy from that of sad faces ($EFIT_{AB}$). We evaluated the association between [11C] DASB BP_{ND} and $EFIT_{AB}$ in a linear latent variable model, with the latent variable ($5\text{-}HTT_{LV}$) modelled from [11C]DASB BP_{ND} in the fronto-striatal and fronto-limbic networks implicated in affective cognition. We observed an inverse association between $5\text{-}HTT_{LV}$ and $EFIT_{AB}$ ($\beta = -8\%$ $EFIT_{AB}$ per unit $5\text{-}HTT_{LV}$, CI $= -14\%$ to -3%, $p = .002$). These findings show that higher 5-HTT levels are linked to a more negative bias in healthy individuals. High 5-HTT supposedly leads to high clearance of 5-HT, and thus, a negative bias could result from low extracellular 5-HT. Future studies must reveal if a similar inverse association exists in individuals with affective disorders.

KEYWORDS
attentional bias, cognition, emotions, healthy volunteers, latent variable modelling, mood disorders, positron emission tomography, serotonin, serotonin transporter

1 | INTRODUCTION

Affective cognition describes the interplay between emotion and cognition in humans. A well—documented aspect of affective cognition

that is important for mental health is cognitive-affective biases, which describe the tendency to process negative information or positive information over the other (Elliott et al., 2011). Simply phrased, do you see the glass as half-full or half-empty? Affective biases distribute

along a valence continuum ranging from extremely positively biased cognition (processing positive over negative information) to extreme negatively biased cognition (processing negative over positive information). Healthy individuals generally display a neutral or a slightly positive bias (Dam et al., 2020; Korn et al., 2014), while individuals with depression generally display a negative bias (Dam et al., 2020; Miskowiak & Carvalho, 2015). During a depressive episode, individuals tend to exhibit negative biases across domains of cognitive processes, including attention, perception, reward processing and memory, reliably demonstrated using cognitive tests (Leppänen, 2006; Miskowiak & Carvalho, 2015; Roiser et al., 2012). In tests of attention to and perception of basic emotions with faces, individuals with depression consistently allocate more attention to and more accurately recognise sad faces compared to happy faces (Bourke et al., 2010; Dalili et al., 2015) and miscategorise neutral faces as sad (Leppänen et al., 2004). In memory tests, they preferentially recall more negative words than positive words (Matt et al., 1992). Although healthy nondepressed individuals generally show neutral or positive affective biases, a subset display negative biases (Pool et al., 2016; Dam et al., 2020) indicating an increased risk of developing depression (van Oostrom et al., 2013). Negative biases in how one views the self, the world and the future seem to predispose, trigger and maintain depressive episodes (Beck, 2008; Clasen et al., 2013; Hammen, 2018; Roiser et al., 2012), while positive biases may be protective against developing depressive episodes (Korn et al., 2014). Therefore, it is important to understand what might drive these affective biases to better inform preventive and treatment initiatives for depression.

It is well established that we can alter affective biases by changing the level of extracellular serotonin (5-HT) in the brain. A commonly used research method to reduce brain 5-HT is through dietary depletion of the 5-HT precursor tryptophan, which acutely elicits negative biases in healthy individuals (Firk & Markus, 2008; Robinson et al., 2012; Rogers et al., 2003) including those remitted from depression (Booij et al., 2005; Hayward et al., 2005; Munafò et al., 2006) generally without affecting mood. Conversely, boosting brain 5-HT with dietary tryptophan elicits a positive bias in healthy individuals (Meyer et al., 2003; Murphy et al., 2006). Brain 5-HT can be modulated more directly by pharmacologically targeting the 5-HT transporter (5-HTT), a protein located on 5-HT neurons in the midbrain and projection sites throughout the brain. The 5-HTT is the primary mechanism by which 5-HT is cleared from the extracellular space and hence critically involved in controlling the duration and magnitude of 5-HT signalling (Charnay & Léger, 2010). Blocking the 5-HTT pharmacologically with a *Selective Serotonin Reuptake Inhibitor* (SSRI), the first-line pharmacological treatment for depression, leads to increased extracellular 5-HT acutely in several brain areas (Bel & Artigas, 1992; Fritze et al., 2017), which is followed by gradual downregulation of 5-HTT levels over time resulting in a further increase in extracellular 5-HT (Benmansour et al., 2002). SSRIs remediate negative biases by inducing a cognitive shift towards positive information observed in healthy individuals (Browning et al., 2006; Harmer et al., 2003; Harmer et al., 2004) and individuals with depression (Bhagwagar et al., 2004), suggesting a link between 5-HTT levels and affective

biases. However, whether 5-HTT levels are associated with affective biases in healthy individuals not stimulated by dietary or pharmacological supplements remain unknown.

Imaging 5-HTT levels in the living human brain is possible using positron emission tomography (PET) with the radioligand [^{11}C]DASB. Quantifying brain 5-HTT levels using PET enables us to evaluate its direct association with affective biases. As 5-HTT levels are proposed to be a surrogate marker of extracellular 5-HT concentrations (Paterson et al., 2010), associating brain 5-HTT to affective biases further allows us to infer how effective biases may relate to extracellular 5-HT concentrations. From previous studies, we know that 5-HT modulates fronto-striatal (Eshel & Roiser, 2010) and fronto-limbic circuits (Robinson et al., 2013), both key neural circuits involved in affective bias processing (Godlewska & Harmer, 2020; Roiser et al., 2012). Mapping the association between affective biases and 5-HTT levels in fronto-striatal and fronto-limbic regions will enable us to understand the underlying neurobiology of affective biases better.

This study evaluates the association between brain 5-HTT levels in fronto-striatal and fronto-limbic regions and cognitive affective in emotion recognition biases in 98 healthy individuals. We hypothesise that 5-HTT levels are inversely associated with affective biases so that higher 5-HTT in fronto-striatal and fronto-limbic is associated with a more negative bias.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

We included data from 98 healthy individuals with a [11C]DASB PET scan and a measure of affective biases using *the Emotional Face Identification Task* (EFIT). Data were pooled across four studies stored in the Cimbi database at the Neurobiology Research Unit, Rigshospitalet (Knudsen et al., 2016), collected between 2010 and 2012. Part of the data have been published elsewhere (Hjordt et al., 2017; Mc Mahon et al., 2016; Mc Mahon et al., 2018). While all participants were without primary psychiatric disease at the time of testing and scanning, 19 participants were in their remitted phase of a seasonal affective disorder (SAD). These participants remitted from SAD were included to assess a more representative sample of the healthy population, which naturally also includes healthy individuals at-risk for depression. They had not received psychotropic drugs or bright light therapy as a treatment in the past year, and a trained psychiatrist had assessed them during the summer and excluded the presence of psychiatric disease at the time of cognitive testing and the PET scan (described in detail elsewhere (Mc Mahon et al., 2016)). All participants were recruited through advertisement and gave their written informed consent to participate as described in the respective study protocols, all approved by *The Ethics Committee of the capital region, Copenhagen, Denmark* (protocol numbers for H-12010091, H-22010108, H-12010085, H-42011103). Although inclusion criteria varied slightly across studies, all participants were healthy and without (1) primary psychiatric illness (besides participants remitted from SAD), (2) past or

current substance or drug abuse, and (3) neurological or severe systemic disease, based on both a general somatic and a neurological examination, together with a self-reported medical history. Educational attainment scores for all participants were measured using a five-point Likert scale from 1 (no vocational degree) to 5 (>4 years of higher learning at the university level). We assessed their intelligence quotient (IQ) with the *Reynolds Intellectual Screening Test* (Reynolds & Kamphaus, 2011). Depression scores for all participants were measured with the major depression inventory (MDI) with a range from 0 to 50, where >21 indicates a depressed mood (Bech et al., 2015). Trait neuroticism was measured using the Danish version of the NEO Personality Inventory-Revised (NEO-PI-R) (Costa Jr. & McCrae, 2002), reported as nonstandardised raw scores. A saliva sample was collected for genotyping of the serotonin transporter-linked polymorphic region (5-HTTLPR) using a previously described method (Fisher et al., 2015).

2.2 | Outcome measures

2.2.1 | The emotional faces identification task

EFIT is the most widely used cognitive test to assess affective biases in emotion recognition. The test validly measures the ability to correctly identify facial emotions, including happiness, anger, fear, sadness, disgust, and neutrality (Hjordt et al., 2017; Young et al., 1997). A total of 172 facial images with emotional expressions are presented on a black computer screen at different intensities, from minimum to maximum emotional valence (morphed with neutral facial expressions). Subjects are instructed to identify the presented facial emotion with a mouse as fast and accurate as possible. The primary outcomes are the hit rate for each emotion, calculated as the percentage of correctly identified emotions. The affective bias is calculated by subtracting the per cent hit rate for sad faces from the per cent hit rate for happy faces so that a score above zero indicates a positive affective bias while a score less than zero indicates a negative affective bias. This is a standard method to calculate affective biases (Bland et al., 2016; Dam et al., 2019) found to be particularly sensitive for depression (Dam et al., 2020), which is related to 5-HTT functioning (Gryglewski et al., 2014). As we were only interested in affective biases, we did not attend to hit rates of other emotions than happy and sad.

2.2.2 | Neuroimaging

Magnetic resonance imaging

A high-resolution T1-weighted structural brain scan was acquired for each participant and used to segment and delineate brain regions. Participants were scanned on one of two magnetic resonance imaging (MRI) scanners, a Siemens Magnetom Trio 3 T scanner ($n = 38$) or a Siemens Verio 3T scanner (Siemens, Erlangen, Germany) ($n = 60$).

[11C]DASB PET imaging

Using [11C]DASB to measure 5-HTT binding is advantageous as it binds to 5-HTT with high affinity and high selectivity, with a good

ratio of specific binding relative to free and nonspecific binding while showing reliable measurement in multiple brain regions (Wilson et al., 2002). We quantified [11C]DASB as the ratio at the equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in the brain tissue (BP_{ND}) (Ginovart et al., 2001). All participants were scanned using a Siemens ECAT high-resolution research tomography (HRRT) scanner operating in 3D-acquisition mode with an approximate in-plane resolution of 2 mm (Olesen et al., 2009). Following a transmission scan of 6 min, an intravenous bolus of [11C]DASB was injected over 20 s. Post-injection, the imaging protocol consisted of a dynamic 90-min emission scan acquired over 36 frames (6 × 10 s, 3 × 20 s, 6 × 30 s, 5 × 60 s, 5 × 120 s, 8 × 300 s, 3 × 600 s). The dynamic PET images were reconstructed using an iterative OP-OSEM 3D method with resolution modelling (10 iterations and 16 subsets).

Brain image analysis and outcome parameters

Preprocessing the PET data at the subject level included an in-scan automatic image registration algorithm to determine motion and realignment (Woods et al., 1992). PET scans were smoothed using a 10-mm within-frame Gaussian filter before alignment. Subsequently, we estimated rigid translation/rotation parameters aligning each PET frame to a single-PET frame with sufficient structural information using the scaled least-squares cost function (frame 26: 20–25 min post-injection). Nonfiltered PET images were resliced using these parameters. Co-registration of high-resolution MR and PET images was performed using SPM, based on the mean of frames 10–26, corresponding to a flow-weighted image. Accurate co-registration was confirmed by visual inspection across all planes.

From the participants' structural MRI scans, brain regions were automatically delineated using Pvelab (Svarer et al., 2005). Time-activity curves were determined, reflecting the mean of grey-matter voxels within each region. We did not apply partial volume correction, as the participants were generally young (mean age: 25.5 ± 6.2 years, range: 18–45 years). Kinetic modelling of regional time-activity curves determined our primary outcome, the regional BP_{ND}, in PMOD (Zurich, Switzerland), using the multilinear reference tissue model 2, a modified reference tissue model, validated for quantifying [11C]DASB (Ichise et al., 2016). Here, a fixed k2′ was estimated for each individual using putamen, caudate, and thalamus as the high-binding regions, while cerebellar grey matter without vermis was used as the reference region.

2.3 | Statistical analyses

We examined the associations between 5-HTT BP_{ND} and affective biases in emotion recognition assessed with the EFIT using a linear latent variable model (LVM) with the lava-package version 1.6.10 in R version 4.1.2 (see Appendix S1 for further detail) (Holst & Budtz-Jørgensen, 2012). The LVM enables us to model the large correlation in 5-HTT BP_{ND} across brain regions (Erritzoe et al., 2010) into a single

latent variable, 5-HTT$_{LV}$. Here, we modelled 5-HTT$_{LV}$ from brain regions with a good signal-to-noise ratio involved in affective bias processing, including regions in the fronto-striatal circuit (Eshel & Roiser, 2010) (i.e., frontal cortex, putamen, and caudate) and fronto-limbic circuit (Robinson et al., 2013) (i.e., frontal cortex, anterior cingulate cortex [ACC], and amygdala). The frontal cortex was arbitrarily selected as a reference region for the LVM, so 5-HTT$_{LV}$ values were expressed in 5-HTT frontal cortex units. To display a more meaningful effect of 5-HTT$_{LV}$ on the affective bias, we multiplied the regional 5-HTT BP$_{ND}$ outcomes by 10 prior to modelling 5-HTT$_{LV}$. The effect of 5-HTT$_{LV}$ on the affective bias is thus reported as a 0.1 increase in 5-HTT$_{LV}$ throughout the manuscript. Within the LVM, each regional [11C]DASB BP$_{ND}$ was separately adjusted for sex, age, BMI, IQ, trait neuroticism, number of daylight minutes at PET-scan, weight-adjusted injected masse of [^{11}C]DASB, MR-scanner type, the 5-HTTLPR (i.e., alleles LL, SS, and SL) and group (i.e., healthy individuals with or without remitted SAD), which are variables that may influence 5-HTT BP$_{ND}$ (Mc Mahon et al., 2016; Spies et al., 2015; Tuominen et al., 2017). Although the brain-derived neurotrophic factor has been found to impact 5-HTT BP$_{ND}$ (Fisher et al., 2017) it was not included as a covariate as the data was not available for all participants. All one-parameter extensions of the LVM were considered based on score tests of improvement in model fit. If the smallest false discovery rate (FDR)-adjusted p-value was below 0.05, the corresponding parameter was added to the model. The procedure was repeated until no additional parameter was found relevant. Possible extensions included additional covariance parameters but not nonlinear or interaction effects for the mean structure. To visualise the association between 5-HTT$_{LV}$ and EFIT, we computed the estimated 5-HTT$_{LV}$ value for each individual based on their regional 5-HTT BP$_{ND}$. In addition to the LVM, we used a post hoc region-specific statistical approach to verify our LVM results, namely univariate multiple linear regression models, to test the associations between affective biases and 5-HTT BP$_{ND}$ in the five brain regions of interest together with 5-HTT in the midbrain and whole brain (i.e., 5-HTT BP$_{ND}$ in occipital-, orbitofrontal-, parietal-, and sensory-motor cortex, anterior-, and posterior cingulate cortex, entorhinal cortex, middle inferior frontal-, and middle inferior temporal gyri, superior frontal- and superior temporal gyri, insula, caudate, putamen, hippocampus, amygdala, and thalamus). These analyses are presented in Table 2.

To examine whether a potential association between 5-HTT levels and affective biases was group dependent, and thus, whether pooling the two groups could be justified, we carried out group-wise sensitivity analyses. For healthy individuals without a history of depression (n = 79), we evaluated the association between 5-HTT$_{LV}$ BP$_{ND}$ and affective biases using the same LVM as in the primary analysis. For healthy individuals in the remitted period of their SAD, due to the smaller group size (n = 19) and lack of convergence in the LVM, we evaluate the association between frontal cortex 5-HTT BP$_{ND}$, our reference region, and affective biases in a linear regression model. All additional models included the same covariates as in the LVM, except for the MR scanner in the model for healthy individuals in the remitted period of their SAD, as all were scanned on the same

MR. Model assumptions (e.g., normality of residuals, QQ-plots and influential cases) were considered and showed no evidence of model violations.

P-values <.05 (two-sided) were considered statistically significant. For the post hoc analyses, we also presented FDR-corrected values. Results are reported with parameter estimates (e.g., r for the Pearson

TABLE 1 Descriptive information for the 98 healthy individuals in the study

Categorical variables	Number	Percentage
Healthy Individuals with/without SAD	19/79	19%/81%
Female/male	74/24	76%/24%
5-HTTLPR genotype LL/LS /S	35/37/26	36%/38%/26%

Continuous variables	Mean ± SD	Median [Min ; Max]
Age in years	25.5 ± 6.2	22.9 [18.4; 45.3]
IQ	107.7 ± 7.6	108 [93; 126]
Body mass index	23.3 ± 3.1	22.9 [17.7; 32.9]
Neuroticism	82.5 ± 20.7	82.5 [38; 148]
MDI	5.3 ± 3.2	5 [0; 15]
Daylight minutes	778 ± 231	808 [428; 1052]
Injected DASB mass pr kg	0.027 ± 0.031	0.013 [0.004; 0.158]

DASB BPND in brain regions	Mean ± SD	Median [Min; Max]
Frontal cortex BPND	0.41 ± 0.07	0.41 [0.23; 0.58]
ACC BPND	0.63 ± 0.09	0.61 [0.43; 0.95]
Caudate BPND	1.92 ± 0.31	1.92 [1.33; 3.07]
Putamen BPND	2.26 ± 0.33	2.22 [1.63; 3.43]
Amygdala BPND	1.86 ± 0.31	1.82 [1.28; 3.04]
Midbrain BPND	2.09 ± 0.26	2.07 [1.33; 2.71]
Whole-brain BPND	0.51 ± 0.07	0.50 [0.34; 0.73]

The emotional face identification task	Mean ± SD	Median [Min; Max]
Happy face, % hit rate	85% ± 8%	88% [58%; 100%]
Sad face, % hit rate	72% ± 13%	75% [32%; 94%]
Affective bias	13% ± 15%	13% [−22%; 46%]

Note: Outcomes: Affective bias is calculated as happy minus sad hit rate in the emotional face identification task (EFIT) and DASB BPND is displayed as raw data (not multiplied by 10).
Abbreviations: ACC, anterior cingulate cortex; BPND, binding potential nondisplaceable, IQ, intelligence quotient; MDI, major depression inventory; SAD, seasonal affective disorder.

correlation coefficient) and a 95% confidence interval (CI) for the estimates.

3 | RESULTS

3.1 | Baseline characteristics

The study population's demographics, psychometrics, PET parameters, and cognitive test outcomes are reported in Table 1. MDI scores confirmed the absence of depression by cut-off > 21 in the study population (Bech et al., 2015) (score range = 0–15), and the mean IQ was slightly higher compared to the average of 100 in the general population (mean IQ ± SD = 107.7 ± 7.6). The time between [^{11}C]DASB PET scan and EFIT was a maximum of 1 week for 81 participants and up to 1 month for 14 participants and up to 147 days for the remaining three participants (median days between PET scan and EFIT for all participants = 0 days).

3.2 | 5-HTT BP$_{ND}$ intercorrelation across brain regions

Figure 1 visualises *the distribution of 5-HTT BP$_{ND}$ in a representative healthy individual* from our sample. High 5-HTT BP$_{ND}$ intercorrelation between brain regions was confirmed by correlation analyses

(i.e., Pearson's *r*: frontal cortex and ACC = 0.9, caudate = 0.5, putamen = 0.5, amygdala = 0.5; ACC and caudate = 0.5, putamen = 0.5, amygdala = 0.5; caudate and putamen = 0.7, amygdala = 0.5), and the midbrain 5-HTT BP$_{ND}$ was also highly correlated with the regions of interest (i.e., *r*: frontal cortex = 0.5, caudate = 0.3, putamen = 0.4, ACC = 0.5, amygdala = 0.4) and likewise for whole-brain 5-HTT BP$_{ND}$ (i.e., *r*: with frontal cortex = 0.9, ACC = 0.8, caudate = 0.6, putamen = 0.6, amygdala = 0.6).

3.3 | The association between 5-HTT BP$_{ND}$ and cognitive-affective biases

An LVM structure of 5-HTT BP$_{ND}$ was supported by the strong loading of regional 5-HTT BP$_{ND}$ onto the latent variable, 5-HTT$_{LV}$ (loadings from all regions: point estimate range = 1.6–3.7, *p* < .001), as presented in Figure 2. Tests of improvement in model fit with a FDR of *p* < .05 supported adding one covariance between caudate and putamen, which had no impact on the estimate or *p*-value for the association between 5-HTT$_{LV}$ and affective bias.

Within our LVM, 5-HTT$_{LV}$ BP$_{ND}$ was inversely associated with affective bias in emotion recognition as measured with EFIT; each 0.1 increase in 5-HTT$_{LV}$ BP$_{ND}$ was associated with an 8% decrease in affective bias, that is, a more negative bias (CI = −14% to −3%, *p* = .002), see Figure 3. In line with the results from the LVM, univariate region-specific analyses showed a significant inverse association
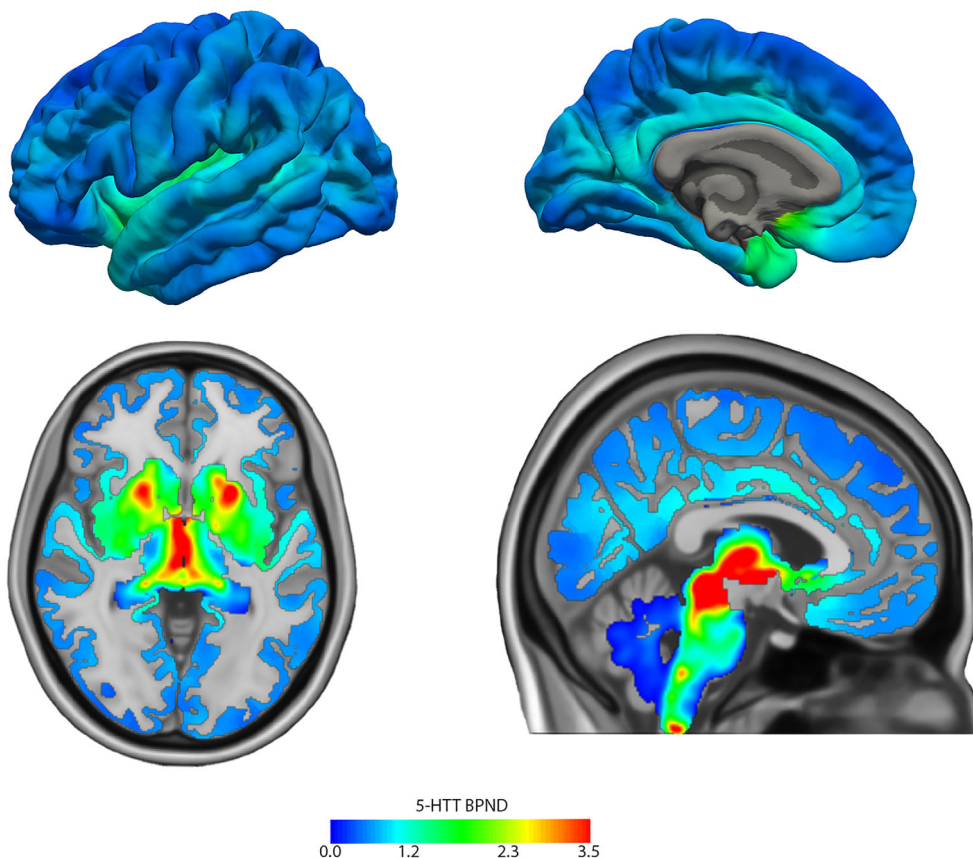

FIGURE 1 The distribution of 5-HTT BPND in a representative healthy individual from the study sample. Cortical values are presented on the standard FreeSurfer surface (fsaverage, left hemisphere; lateral view, upper left and medial view, upper right) and subcortical values are presented in the standard MNI152 space (transverse view, bottom left, and sagittal view, bottom right)
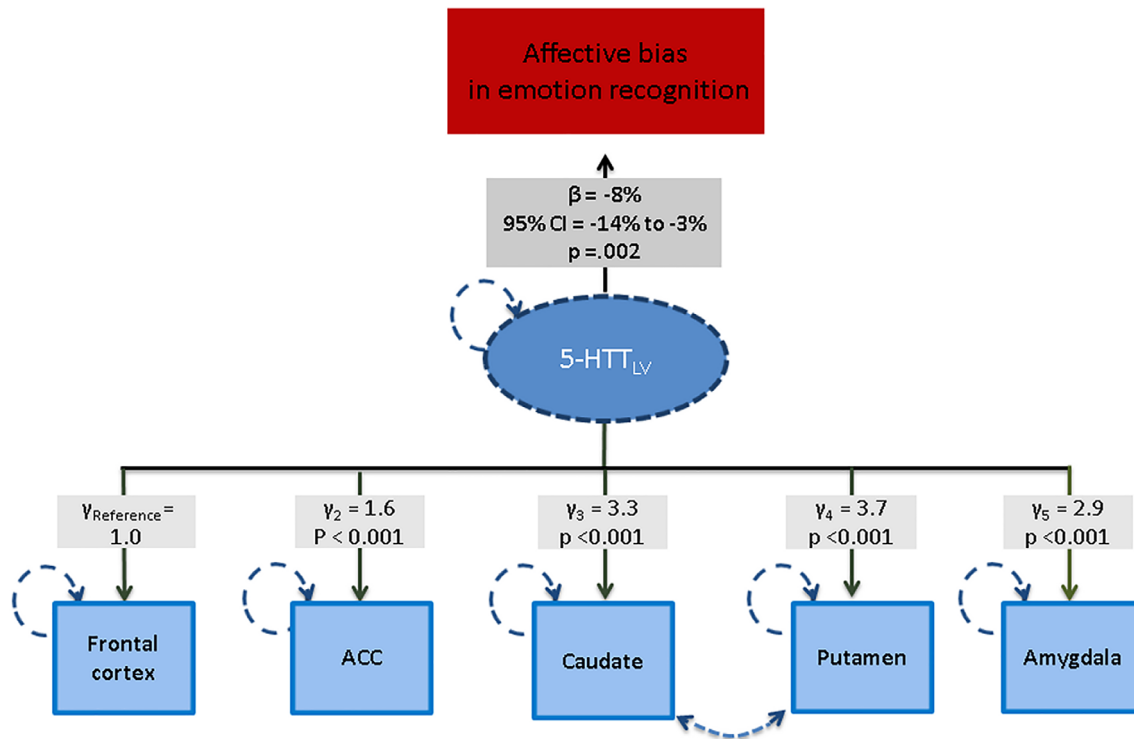
FIGURE 2 An illustration of the latent variable model (LVM). The red box represents the dependent variable affective bias in emotion recognition. The five brain regions of interest in the bottom blue boxes represents measured regional [11C]DASB BPND values used to define the latent variable (5-HTTLV), which is represented in the blue oval. The effect of 5-HTTLV on affective bias is displayed as increase of 0.1 in 5-HTTLV. The hatched lines between caudate and putamen illustrates partial correlation included as covariance parameter. Circular blue hatched lines reflect variables estimated with error. Each regional [11C]DASB BPND was separately adjusted for sex, age, BMI, IQ, trait neuroticism, number of daylight minutes at PET-scan, weight-adjusted injected masse of [11C]DASB, MR-scanner type, the 5-HTTLPR (i.e., alleles LL, SS and SL) and group (i.e. healthy individuals with or without remitted SAD) (not illustrated). β, point estimate for the regression coefficient of emotional face identification task (EFIT). γ, point estimate for the loadings onto 5-HTTLV. ACC, anterior cingulate cortex

FIGURE 3 A plot of the estimated latent variable in units of [11C]DASB PET (i.e., 5-HTTLV) by observed affective bias in per cent measured with the emotional identification task. The effect of 5-HTTLV on affective bias is displayed as an increase of 0.1 in 5-HTTLV. The red line corresponds to the estimated association between 5-HTTLV and affective biases (i.e., beta coefficient = 8%) adjusted for covariates including sex, age, BMI, IQ, neuroticism, number of daylight minutes at PET-scan, weight-adjusted injected masse of [11C]DASB, MR-scanner type, the 5-HTTLPR and group (i.e., healthy individuals with or without a seasonal affective disorder (SAD)
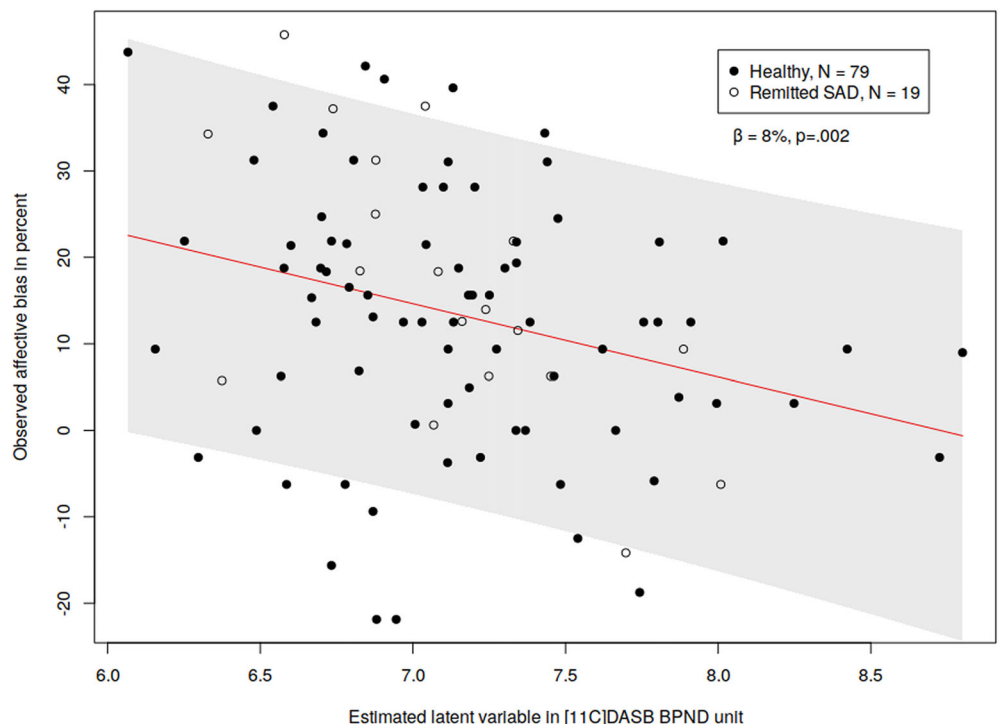
Affective bias in emotion recognition

Brain region	Estimate (%)	SE B (%)	P	FDR	95% CI	
Frontal cortex	−6.7	2.4	0.007	0.031	−11.6	−1.9
ACC	−4.1	1.6	0.013	0.031	−7.3	−0.9
Caudate	−1.1	0.5	0.047	0.054	−2.1	0.0
Putamen	−1.1	0.5	0.028	0.043	−2.1	−0.1
Amygdala	−0.1	0.5	0.874	0.874	−1.1	1.1
Midbrain	−1.4	6.4	0.031	0.043	−2.7	−0.1
Whole-brain	−6.1	2.3	0.012	0.031	−10.5	−1.3

TABLE 2 The association between serotonin transporter binding and affective bias using univariate multiple linear regression models with the covariates sex, age, BMI, IQ, trait neuroticism, number of daylight minutes at PET-scan, weight-adjusted injected masse of [11C]DASB, MR-scanner type, the 5-HTTLPR (i.e., alleles LL, SS, and SL) and group (i.e., healthy individuals with or without remitted SAD)

Note: Affective bias in emoting recognition as measured with the emotional face identification task (EFIT) ($n = 98$) is reported in percent. The effect of regional 5-HTT BPND on affective bias is displayed as increase of 0.1 in 5-HTT BPND. Estimate is the unstandardised beta.
Abbreviations: ACC, anterior cingulate cortex, FDR, 5% false discovery rate correction; SE B, standard error for unstandardised beta; P, unadjusted significance level; 95% CI, 95% confidence interval.

between affective biases and 5-HTT BP_{ND} across the fronto-striatal and fronto-limbic regions of interests (i.e., frontal cortex, caudate, putamen, and ACC), and as well as 5-HTT BP_{ND} in the midbrain and the whole brain, whose FDR adjusted *p*-values were below 5% except for the caudate. However, we did not find a significant association between affective biases and 5-HTT BP_{ND} in the amygdala (see Table 2 for region-specific posthoc analyses and Figure S1 for visualisations).

For healthy individuals without a history of depression, the sensitivity analysis showed a significant inverse association between 5-HTT$_{LV}$ and affective biases ($n = 79$, $\beta = -7\%$, CI $= -13\%$ to -6%, $p = .03$). Likewise, for healthy individuals with a remitted SAD, the sensitivity analysis showed a significant inverse association between frontal cortex 5-HTT BP_{ND} and affective biases ($n = 19$, $\beta = -16\%$, CI $= -22\%$ to -11%, $p < .001$). The estimated associations in both groups had a similar statistical significance level indicating that the result from the primary analysis was not an artefact of pooling the groups.

4 | DISCUSSION

This is the first study to investigate the association between in vivo brain 5-HTT levels and affective biases in a large sample of healthy individuals. Consistent with our hypothesis, we find that individuals with higher 5-HTT levels, as indexed by PET [^{11}C]DASB BP_{ND}, are relatively better at recognising sad faces than happy faces: For every 0.1 increase in [^{11}C]DASB BP_{ND} there was an 8% more negative bias. Consistent with previous studies, the healthy individuals in our study distributed along the continuum of affective biases, ranging from positive to negative biases (Dam et al., 2020). Critically, we demonstrate that this affective bias continuum (positive to negative) can be coupled to in vivo brain 5-HTT levels, a key marker of 5-HT brain signalling.

Only one previous study has investigated the association between 5-HTT levels, and affective bias carried out in a sample of

20 medication-free individuals with depression and 20 matched healthy individuals (Meyer et al., 2004). In line with our results, the study found that higher 5-HTT levels were correlated with more negatively biassed self-reported attitudes in individuals with current depression; however, no association was found in healthy individuals (Meyer et al., 2004). The latter negative finding could be ascribed to lack of power as the study's sample size was considerably smaller than ours and thus perhaps not big enough to detect an association. Furthermore, the study used a self-reported measure of negatively biassed attitudes, exclusively capturing the negative side of the affective bias continuum. Measuring the full continuum of affective biases represents a major strength of our study of healthy individuals, especially given previous observations that healthy individuals display an average positive affective bias (Dam et al., 2020). A further strength of our study is the use of a standardised cognitive test which is not subject to response bias to the same extent as self-reported affective bias. We separately examined healthy individuals without a history of depression and healthy individuals in the remitted phase of SAD. We found a significant inverse association between 5-HTT levels and affective biases in both groups. Notably, in individuals in the remitted phase of SAD, the effect of 5-HTT on affective biases was relatively larger and with minimal overlap in confidence interval across the groups. Although different statistical models were used, this could indicate greater importance of 5-HT on cognitive-affective processing in individuals with a vulnerability to depression, a finding consistent with the hypothesis that 5-HT is involved in vulnerability to depression (Frokjaer et al., 2009). Whether a stronger association between 5-HTT and affective biases is a risk-marker for depression and whether it ultimately influences the severity of the depressive state should be investigated in longitudinal clinical studies. Taken together, our results of an inverse association between 5-HTT levels and affective biases apply to healthy populations with and without a history of depression, and since a similar association was found in a depressed population (Meyer et al., 2004), the link between 5-HTT and affective biases seems to be independent of psychiatric risk profile and current mood.

It has been proposed that 5-HTT, here indexed with [^{11}C]DASB BP$_{ND}$, could serve as a surrogate marker of extracellular 5-HT concentrations (Paterson et al., 2010), but it remains debated how 5-HTT and 5-HT are related. One model proposes that low 5-HT concentrations lead to 5-HTT downregulation (Milak et al., 2005; Rothman et al., 2003), while high 5-HT concentrations restrict 5-HTT internalisation leading to higher 5-HTT density (Steiner et al., 2008). An opposing model suggests that high 5-HTT levels lead to increased clearance of extracellular 5-HT (Mathews et al., 2004), and that high 5-HTT levels may therefore be a marker of low extracellular 5-HT concentrations. This remains open to debate, but some evidence favours the latter model as boosting 5-HT concentrations decreases 5-HTT availability in the brain of rats (Fritze et al., 2017; Lundquist et al., 2007), cats (Ginovart et al., 2003) and nonhuman primates (Lundquist et al., 2007; Yamamoto et al., 2007). Accordingly, we find that higher 5-HTT levels are related to a more negative bias in emotion recognition, consistent with the hypothesis that lower 5-HT concentration is involved in increased attention to and processing of threat-related stimuli and negative information (Godlewska & Harmer, 2020). In further support of this hypothesis, behavioural studies report that depleting 5-HT leads to negative biases (Booij et al., 2005; Firk & Markus, 2008; Hayward et al., 2005; Munafò et al., 2006; Robinson et al., 2012; Rogers et al., 2003), while boosting the 5-HT lead to positive biases in humans (Bhagwagar et al., 2004; Browning et al., 2006; Harmer et al., 2003; Murphy et al., 2006), and rodents (Bari et al., 2010; Stuart et al., 2013). Another model of how 5-HTT is regulated proposes that 5-HTT levels may reflect an early-life wiring of 5-HT brain architecture more broadly, as 5-HTT sits on both serotonergic neurons and projections throughout the brain (Gaspar et al., 2003). This is consistent with findings of an association between early-life wiring of 5-HT and later affective cognition and risk of depression (Ansorge et al., 2004). Importantly, these different models of how 5-HTT is regulated may not exclude one another but complement each other. Future mechanistic studies will help elucidate the dynamics of how 5-HTT and 5-HT interact in the human brain. While much is still unresolved, we hope that understanding how different aspects of 5-HT signalling are involved in affective cognition may ultimately lead to novel preventive initiatives and treatment strategies urgently needed for individuals with depression or at high risk of depression.

4.1 | Methodological considerations

This is the first PET study to examine the association between an imaging marker of 5-HT signalling and affective biases in healthy individuals in a large sample. Considering our sample, a small proportion had a history of depression ($n = 19$) who were included to examine a more representative sample of the general healthy population with natural variations in vulnerability to depression. Sensitivity analyses revealed that the inverse relation between 5-HTT and affective biases was present in healthy individuals with and without a history of depression, which we believe justifies pooling the groups. We did not have an equal sex distribution in our sample, as 74% were women; however, the sex distribution is comparable to that of depressed populations where the majority are women (Dam et al., 2020), allowing for comparing our results to future studies exploring affective biases in depression. This study was conducted with a North European sample of younger age, limiting our results' generalisability to other populations. It remains to be investigated whether our results can be replicated in more diverse populations.

5 | CONCLUSION

In healthy individuals, we found that 5-HTT levels in the fronto-striatal and fronto-limbic brain regions are inversely associated with affective biases in emotion recognition. This finding bolsters the previously reported association between 5-HT and affective biases using a key in vivo marker of serotonin signalling. Although the relationship between 5-HTT levels and 5-HT signalling remains debated, our finding could reflect that negative biases result from excessive clearance of extracellular 5-HT. Whether excessive 5-HT clearance underlies the negative bias typically observed in individuals with affective disorders should be investigated in large depressed populations.

CONFLICT OF INTEREST

Vibe G. Frokjaer declares that she serves as a lecturer for Sage Therapeutics and Lundbeck Pharma A/S. Gitte M. Knudsen served as a consultant and lecturer for Sage Therapeutics/Biogen and Sanos. All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Cimbi database. Restrictions apply to the availability of these data, which were used under license for this study. Data are available in the Cimbi database managed by Peter S. Jensen with the permission of Cimbi Steering Group.

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