Received: 12 September 2018 | Revised: 13 December 2018 | Accepted: 28 December 2018

DOI: 10.1002/hbm.24511

WILEY

RESEARCH ARTICLE

Trait Openness and serotonin 2A receptors in healthy volunteers: A positron emission tomography study

Dea Siggaard Stenbæk[1,2,3] | Sara Kristiansen[1,2,3] | Daniel Burmester[1,2,3] | Martin Korsbak Madsen[1,2,3] | Vibe Gedsoe Frokjaer[1,2,3] | Gitte Moos Knudsen[1,2,3] | Patrick MacDonald Fisher[1,2,3]

[1]Neurobiology Research Unit, Rigshospitalet, Copenhagen, Denmark

[2]Center for Integrated Molecular Brain Imaging, Rigshospitalet, Copenhagen, Denmark

[3]The Neuroscience Centre, Rigshospitalet, Copenhagen, Denmark

Correspondence
Dea Siggaard Stenbæk, Neurobiology Research Unit Rigshospitalet, Section 6932, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.
Email: dea@nru.dk

Abstract

Recent research found lasting increases in personality trait Openness in healthy individuals and patients after administration of the serotonin 2A receptor (5-HT_{2A}R) agonist psilocybin. However, no studies have investigated whether 5-HT_{2A}R availability as imaged using positron emission tomography (PET) is associated with this trait. In 159 healthy individuals (53 females), the association between 5-HT_{2A}R binding in neocortex imaged with [^{18}F]altanserin or [^{11}C]Cimbi-36 PET and personality trait Openness was investigated using linear regression models. In these models the influence of sex on the association was also investigated. Trait Openness was assessed with the NEO Personality Inventory-Revised. No significant associations between neocortical 5-HT_{2A}R binding and trait Openness were found for [^{18}F]altanserin (p = 0.5) or [^{11}C]Cimbi-36 (p = 0.8). Pooling the data in a combined model did not substantially change our results (p = 0.4). No significant interactions with sex were found (p > 0.35). Our results indicate that differences in 5-HT_{2A}R availability are not related to variations in trait Openness in healthy individuals. Although stimulation of the 5-HT_{2A}R with compounds such as psilocybin may contribute to long-term changes in trait Openness, there is no evidence in favor of an association between 5-HT_{2A}R and trait Openness.

KEYWORDS

[^{11}C]Cimbi-36, [^{18}F]altanserin, 5-HT_{2A}, biomarkers, NEO personality inventory, personality, PET scan, serotonin, trait Openness

1 | INTRODUCTION

Personality trait Openness to experience ("trait Openness") was formulated by Costa and McCrae as part of their 5-factor model of personality (McCrae & Costa, 2006). It pertains to relatively stable individual differences in sensitivity to feeling and esthetic aspects of experience as well as openness to ideas and values both at the level of action and fantasy (McCrae & Costa, 2006; Schwaba & Bleidorn, 2017). Individuals with high scores on this trait tend to be creative (Kandler et al., 2016; Kaufman et al., 2016), keep an open mind as to consider novel opinions and revise ideas and values over the life span (Schwaba, Luhmann, Denissen, Chung, & Bleidorn, 2017). In recent years, trait Openness has attracted researcher's interest because of increases in this trait after intake of serotonergic psychedelics (Carhart-Harris, Kaelen, et al., 2016; Erritzoe et al., 2018; MacLean, Johnson, & Griffiths, 2011), suggesting a link between brain serotonin (5-HT) and trait Openness. A previous positron emission tomography (PET) study from our lab reported a negative correlation between trait Openness and midbrain serotonin transporter (5-HTT) levels in healthy individuals (Kalbitzer et al., 2009), but this could not be replicated by another recent PET study of trait Openness and cerebral 5-HTT levels in healthy individuals (Tuominen et al., 2017). While the 5-HTT is a central feature of serotonergic neurotransmission and a main target for therapeutic drugs, such as selective serotonin reuptake inhibitors, the association between key postsynaptic 5-HT receptors targeted by psychedelics and trait Openness remains to be evaluated.

Psilocybin is a naturally occurring prodrug of psilocin, a serotonergic psychedelic produced by psilocybin mushrooms which shows promise as a novel therapeutic drug (Bogenschutz et al., 2015;

Carhart-Harris, Bolstridge, et al., 2016; Griffiths et al., 2016; Grob et al., 2011; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Moreno, Wiegand, Taitano, & Delgado, 2006; Ross et al., 2016) and is known to induce highly meaningful and, occasionally, mystical-type experiences (Baumeister, Barnes, Giaroli, & Tracy, 2014; Griffiths et al., 2011; Griffiths et al., 2016; Griffiths, Richards, McCann, & Jesse, 2006; Johnson et al., 2014; MacLean et al., 2011; Ross et al., 2016). These psychedelic effects of psilocybin are mediated primarily by its actions as an agonist at the serotonin 2A receptor (5-HT_{2A}R) (Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998). The 5-HT_{2A}R is an excitatory 5-HT receptor in the human brain most highly expressed throughout the cerebral cortex (Beliveau & Ganz, 2017; Varnas, Halldin, & Hall, 2004), and dysfunction of 5-HT_{2A}R is implicated in neuropsychiatric disorders including depression and schizophrenia (Albert, Benkelfat, & Descarries, 2012; Bhagwagar et al., 2006; Lin, Jiang, Kan, & Chu, 2014; Naughton, Mulrooney, & Leonard, 2000; Nikolaus, Muller, & Hautzel, 2016). It is therefore possible that 5-HT_{2A}R-mediated effects of psilocybin and other psychedelics contribute to enduring increases in trait Openness. An even stronger case for a direct coupling between the 5-HT_{2A}R and trait Openness would be to show that individual differences in 5-HT_{2A}R availability in psychedelic-naïve healthy individuals are associated with variation within this trait. However, such an association remains to be empirically tested.

Here, we evaluate the association between 5-HT_{2A}R levels in neocortex and trait Openness in 159 healthy individuals in vivo using either the 5-HT_{2A}R antagonist PET radioligand [^{18}F]altanserin or the 5-HT_{2A}R agonist PET radioligand [^{11}C]Cimbi-36 developed by our lab (Ettrup et al., 2014).

2 | METHODS AND MATERIALS

2.1 | Participants

Data were extracted from the Center for Integrated Molecular Brain Imaging (Cimbi) database for healthy individuals with either a [^{18}F]altanserin or [^{11}C]Cimbi-36 PET scan and NEO Personality Inventory-Revised (NEO PI-R) data (Knudsen et al., 2016). Of the initial 200 healthy individuals identified, we excluded individuals with more than 365 days between their PET scan and NEO PI-R assessment (n = 5), and who had a body mass index of >30, corresponding to obese (n = 36), in reference to an earlier study of personality differences between obese and nonobese individuals in our database (Haahr et al., 2015). Of the remaining 159 individuals (53 females), eight completed both a [^{18}F]altanserin and [^{11}C]Cimbi-36 PET scan for a specific study (Ettrup et al., 2016). Unless otherwise stated, n = 139 [^{18}F]altanserin and n = 28 [^{11}C]Cimbi-36 for the reported analyses.

All individuals were recruited by advertisement for different research protocols approved by the Ethics Committee of Copenhagen and Frederiksberg, Denmark (H-4-2012-105, KF-02-058-99, KF-01-156-04, KF-11-061-03, KF-01-001-02, KF-01-124-04, KF-01-2006-20). Written informed consent was obtained from all individuals after a complete description of the respective study. Although inclusion criteria varied slightly across studies, all individuals included in the current study were healthy and without: (a) primary psychiatric disease, (b) substance or drug abuse, and (c) severe systemic or neurological disease based on self-reported history and physical/neurological examination by a trained clinician. Of participants asked (n = 134), all self-reported being naïve to psychedelic drugs. However, some [^{18}F]altanserin data sets were acquired before this information was systematically collected and is not known (n = 33). A detailed description of the Cimbi database and the PET biomarkers that it contains can be found elsewhere (Beliveau & Ganz, 2017; Knudsen et al., 2016).

2.2 | Measures

2.2.1 | The NEO Personality Inventory-Revised

The Danish version of the NEO PI-R was used to assess personality; this version has previously been normed in a sample of 600 individuals (Skovdahl, Mortensen, & Schiøtz, 2011). The NEO PI-R is a self-report questionnaire comprising 240 items which measures five major traits of personality: Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness, where each trait consists of six subfacets (McCrae & Costa, 2006). The participants rated each item on a 5-point Likert scale from 0 (strongly disagree) to 4 (strongly agree). For the purpose of this study, we used trait Openness and its constituent subfacets: Fantasy, Esthetics, Feelings, Actions, Ideas, and Values. The scores of the items loading on trait Openness were summed to a total raw score, which was used in the analyses. Across all participants, we had two missing item responses for the trait Openness scale (one item response for Openness subscale 1 and one item response for Openness subscale 6), which were substituted with the most neutral response "2" on the 0–4 Likert scale. Internal consistency (measured with Cronbach's alpha, α) for trait Openness was high, α = 0.87.

2.2.2 | Educational attainment

Educational scores were rated on a 5-point Likert scale; 1 (no vocational degree), 2 (<2 years of vocational education), 3 (2–4 years of vocational secondary education), 4 (2–4 years of academic education including a prior high school degree), and 5 (>4 years of academic education including a prior high school degree).

2.2.3 | Magnetic resonance imaging

Magnetic resonance imaging (MRI) scans were acquired for all participants on one of the following scanners: (a) a Siemens 1.5T Vision scanner (Erlangen, DE), (b) a Siemens 3T Magnetom Trio scanner (Erlangen, DE), or (c) a Siemens 3 T Magnetom Verio scanner (Erlangen, DE). A high-resolution T1-weighted structural brain scan (1.5T Vision: TE/TR/TI: 4.40/1140/100 ms, flip angle: 8°, in-plane matrix: 256 × 256, slices: 158, voxel size: 1.2 × 1.2 × 1.1 mm; 3T Trio: TE/TR/TI: 3.04/1550/800 ms, flip angle: 9°, in-plane matrix: 256 × 256, slices: 192, voxel size: 1 × 1 × 1 mm; 3T Verio: TE/TR/TI: 2.32/1900/900 ms, flip angle: 9°, in-plane matrix: 256 × 256, slices: 224, voxel size: 0.9 × 0.9 × 0.9 mm) was acquired for each participant and used for segmentation into gray matter, white matter, and cerebrospinal fluid and delineation of regions of interest (ROIs).

2.2.4 | PET imaging

[^{18}F]altanserin (Lemaire, Cantineau, Guillaume, Plenevaux, & Christiaens, 1991) and [^{11}C]Cimbi-36 (Ettrup et al., 2014) were produced as described earlier and imaging acquisitions parameters have been described previously (Ettrup et al., 2014; Pinborg et al., 2003). Briefly, participants were scanned with either: (a) an High Resolution Research Tomograph (HRRT) scanner (CTI/Siemens, Knoxville, TN) with an approximate in-plane resolution of 2 mm or 2) an 18-ring GE-Advance scanner (GE, Milwaukee, WI) operating in 3D-acquisition mode with an approximate in-plane resolution of 6 mm. [^{18}F]altanserin was administered as a bolus injection followed by continuous infusion to obtain steady state of [^{18}F]altanserin in blood and tissue with a bolus–infusion ratio of 1.75 hr (Pinborg et al., 2003). Following a 10-min transmission scan, a 40-min emission scan was acquired 2 hr after bolus administration and reconstructed into five frames (5 × 8 min). Following a 6-min transmission scan, [^{11}C]Cimbi-36 was administered as a bolus and a dynamic 120-min emission scan was acquired and reconstructed into 45 frames (6 × 10 s, 6 × 20 s, 6 × 60 s, 8 × 120 s, 19 × 300 s). Dynamic PET images acquired on the GE-Advance scanner were reconstructed using filtered back projection and corrected for attenuation, dead time, and scatter using a 6 mm Hann filter. Dynamic PET images acquired on the HRRT scanner were reconstructed using an iterative OP-OSEM3D method with resolution modeling (10 iterations and 16 subsets). Detailed venous and arterial blood sampling procedures for [^{18}F]altanserin and [^{11}C]Cimbi-36 scans, respectively, for assessing plasma radioactivity concentrations and radiometabolites have been described elsewhere (Ettrup et al., 2014; Pinborg et al., 2003).

2.2.5 | Brain image analysis and outcome parameters

To determine single-subject within PET scan motion and realignment the automatic image registration algorithm was used (Woods, Cherry, & Mazziotta, 1992) with PET scans smoothed using a 12 mm (GE-Advance) or a 10 mm (HRRT) within-frame Gaussian filter before alignment. Nonfiltered PET images were resliced using these parameters. [^{18}F]altanserin scans acquired on the GE-Advance scanner were coregistered to high-resolution MR images using a manual method described previously (Pinborg et al., 2003). Otherwise, Statistical Parametric Mapping (SPM) was used to coregister PET and high-resolution MR images and segment high-resolution MR images. Accurate coregistration and segmentation was confirmed visually for all data sets.

We used PVElab to automatically delineate ROIs on the participant's high-resolution T1-weighted MRI scan (Svarer et al., 2005). Mean time-activity curves were extracted from the gray matter voxels within ROIs. We selected a large neocortex ROI because 5-HT$_{2A}$R shows low binding subcortically, is widely expressed throughout neocortex, and displays high interregional correlation across neocortical subregions (Erritzoe et al., 2010). Our neocortex region comprises occipital-, orbitofrontal-, and parietal cortex, pre/post central-, middle/inferior frontal-, middle/inferior temporal-, superior frontal-, and superior temporal gyrus as defined in PVElab.

The primary outcome parameter for [^{18}F]altanserin was the binding potential relative to total plasma concentration (BP_P), a reliable quantification method that effectively accounts for radiolabeled metabolites crossing the blood–brain barrier (Pinborg et al., 2003). BP_P is defined as: $BP_P = (C_T - C_{ND})/C_P = f_P(B_{avail}/K_D)$, where C_T and C_{ND} are the steady-state mean count densities in the ROI and the reference region (cerebellum), respectively; C_P is the steady-state activity of nonmetabolized tracer in plasma; f_P is the free fraction of radiotracer in plasma; B_{avail} is the number of receptor sites available for tracer binding; and K_D is the dissociation constant reflecting affinity of the radiotracer for the receptor (Pinborg et al., 2003). The primary outcome parameter for [^{11}C]Cimbi-36 was the nondisplaceable binding potential (BP_{ND}), a validated and stable quantification for this tracer (Ettrup et al., 2014; Ettrup et al., 2016). BP_{ND} is defined as: $BP_{ND} = (V_T - V_{ND})/V_{ND} = f_{ND}(B_{avail}/K_D)$, where V_T and V_{ND} are the distribution volumes in the ROI and reference region (cerebellum), respectively, from two-tissue compartment modeling with arterial input measurements as previously described (Ettrup et al., 2014). Cerebellum has been previously validated as an appropriate reference region for both [^{18}F]altanserin and [^{11}C]Cimbi-36 (Ettrup et al., 2014; Pinborg et al., 2003).

2.3 | Statistics

The associations between 5-HT$_{2A}$R availability in neocortex and trait Openness were analyzed in two separate ordinary least-squares linear regression models: one for [^{18}F]altanserin and one for [^{11}C]Cimbi-36. We considered scanner-specific [^{18}F]altanserin effects (HRRT vs. GE); however, separate analyses for the two scanners yielded similar effects. Pooled results including both HRRT and GE scans are reported.

Age and sex were included as covariates a priori in both models, based on previous reports from a Danish norm sample of an association with trait Openness (Skovdahl et al., 2011). Education has also been associated with trait Openness (Poropat, 2009), but this information was only available for 91 of the 139 [^{18}F]altanserin scans, and its inclusion did not substantively affect the results, so we report the [^{18}F]altanserin association with trait Openness excluding education as covariate. Body mass index was considered as an additional covariate but was not associated with trait Openness ($p = 0.14$) and therefore excluded from the final model. Subsequently, we pooled the [^{18}F]altanserin and [^{11}C]Cimbi-36 data in a combined model adding radioligand as a covariate together with age and sex. This was done in an effort to increase statistical power with a larger sample size.

We compared the reported trait Openness in our study to the Danish norm sample (mean = 104.8, SD = 18.5) (Skovdahl et al., 2011), using a one-sample t test. p-Values <0.05 were considered statistically significant. For our main results, both the regression coefficient and the standardized regression coefficient are reported in Table 1. Model assumptions (e.g., normality of residuals, QQ-plots) were considered and showed no evidence of model violation. Consistent with a previous study (Moses-Kolko et al., 2011), 5-HT$_{2A}$R was negatively associated with age ($p < 0.001$). However, the variance inflation factor for age and neocortex were ~1.8, indicating that model parameter estimation is unlikely to be affected by collinearity. Statistical analyses were carried out in SPSS (v20.0) and R (v3.3.1) (https://cran.r-project.org/).

TABLE 1 The associations between neocortex 5-HT_{2A}R binding and trait Openness

Predictors	Beta	*SE*	*p*-Value	95% CI	Stand. Beta
Model 1	**[^{18}F]altanserin, *n* = 139**				
Neocortex 2A binding	−2.54	3.75	0.50	−9.95, 4.88	−0.068
Age	−0.43	0.11	0.000078	−0.64, −0.22	−0.40
Sex	−4.32	3.14	0.17	−10.53, 1.89	−0.11
Model 2	**[^{11}C]-Cimbi-36, *n* = 28**				
Neocortex 2A binding	9.03	29.72	0.76	−52.31, 70.37	0.097
Age	1.02	0.26	0.31	−0.99, 3.03	0.26
Sex	−8.81	10.36	0.40	−30.20, 12.57	−0.22
Model 3	**Combined [18F]altanserin and [^{11}C]-Cimbi-36, *n* = 159**				
Neocortex 2A binding	−2.92	3.50	0.40	−9.79, 3.94	−0.07
Age	−0.42	0.10	0.000020	−0.62, −0.23	−0.38
Radioligand	−9.55	4.46	0.032	−18.30, −0.81	−0.19
Sex	−5.24	3.06	0.087	−11.24, 0.77	−0.14

Note. Parameters from the models used to investigate associations between neocortex 5-HT_{2A}R binding and trait Openness, including the combined model with both radioligands, [18F]altanserin and [11C]-Cimbi-36, in Model 3. Combined analyses included 167 observations (eight individuals scanned two times). Sex parameter estimates reflect difference in trait Openness relative to female. SE = standard error, 95% CI = 95% confidence interval, Stand. Beta = standardized regression coefficient.

3 | RESULTS

3.1 | Descriptive data

Table 2 shows descriptive data for the [^{18}F]altanserin and [^{11}C]Cimbi-36 groups. Average age in the [^{18}F]altanserin group was significantly higher than in the [^{11}C]Cimbi-36 group ($p < 0.001$), due to differing age limits associated with specific studies. Reported trait Openness scores did not differ significantly between the [^{18}F]altanserin and [^{11}C]Cimbi-36 groups ($p = 0.62$). Across both groups, reported trait Openness was significantly higher than reported in a Danish norm sample (our sample vs. Danish norm, mean: +10.3 trait Openness units, $p < 0.001$). The median days between 5-HT_{2A}R scans and personality assessments were 0 days (range: 0–358) in the [^{18}F]altanserin group and 6 days (range: 0–60) in the [^{11}C]Cimbi-36 group.

3.2 | 5-HT_{2A}R binding and trait Openness

Table 1 shows the results from our regression models for the [^{18}F]altanserin and [^{11}C]Cimbi-36 group as well as the combined model with pooled data across both groups. Figure 1 shows scatterplots of neocortex 5-HT_{2A}R binding against trait Openness scores for the [^{18}F]altanserin and [^{11}C]Cimbi-36 group. Neither [^{18}F]altanserin neocortex 5-HT_{2A}R BP_P ($p = 0.5$) nor [^{11}C]Cimbi-36 neocortex 5-HT_{2A}R BP_{ND} ($p = 0.8$) were significantly associated with trait Openness. Age was significantly negatively associated with trait Openness in the [^{18}F]altanserin group ($p < 0.001$), whereas this was not the case in the [^{11}C]Cimbi-36 group ($p = 0.3$). Pooling the [^{18}F]altanserin and [^{11}C]Cimbi-36 data in a combined model did not substantially change the observed associations between neocortex 5-HT_{2A}R and trait Openness ($p = 0.4$). Exploratory interaction effects with age and sex did not reveal any condition-specific associations between neocortex and trait Openness ($p > 0.35$).

4 | DISCUSSION

This is the first study to investigate the association between in vivo 5-HT_{2A}R PET binding and personality trait Openness, here in a large sample of 159 healthy individuals. We did not observe any significant associations between 5-HT_{2A}R and trait Openness with either of the two applied PET radioligands ([^{18}F]altanserin or [^{11}C]Cimbi-36) separately or when combined, indicating that the 5-HT_{2A}R is not directly involved in this personality trait.

Although we were not able to detect a relation between trait Openness and 5-HT_{2A}R availability, other in vivo PET 5-HT biomarker studies have been undertaken to examine similar relations. In line with the previously mentioned study from our own lab (Kalbitzer et al., 2009) in which a negative correlation between trait Openness and 5-HTT binding was

TABLE 2 Descriptive information

	[^{18}F]altanserin, *n* = 139			[^{11}C]-Cimbi-36, *n* = 28		
Measures	**Mean ± *SD* or %**	**Median**	**Range, min–max**	**Mean ± *SD* or %**	**Median**	**Range, min–max**
Age in years	38.7 ± 17.4	33.4	18.5–81.7	23.5 ± 5.1	22.8	18.4–46.1
BMI kg/m^2	24.1 ± 2.5	24.1	18.4–29.7	23.7 ± 2.7	23.1	20.6–30.6
Sex (female)	38%			48%		
Education	3.9 ± 1.3	4	1–5	3.8 ± 1.7	5	1–5
Trait Openness	115.5 ± 18.7	114	68–170	113.7 ± 19.7	111	68–160
Injected dose MBq	265.2 ± 55.4	272	155–412	499.9 ± 117.3	563.2	213–603.9
Injected mass	2.7 ± 2.3	2.1	0.2–11	0.8 ± 0.5	0.6	0.1–1.5
Specific activity MBq/μmol	79.8 ± 74.2	58.4	10.3–441.7	378.5 ± 275.5	249.3	95.4–1,033
Neocortex 2A B_P or B_{ND}	1.5 ± 0.5	1.5	0.4–3.7	1.3 ± 0.2	1.3	0.8–1.7
PET scanner (HRRT)	32%			100%		
Days from PET to NEO	11.09 ± 40.28	0	0–314	11.2 ± 14.2	6	0–60

Note. Descriptive information about the study participants. *SD* = standard deviation, BMI = body mass index, MBq = megabecquerel, μmol = micromole, B_P = binding potential, B_{ND} = nondisplaceable binding potential, PET = positron emission tomography, NEO PI-R = NEO Personality Inventory.

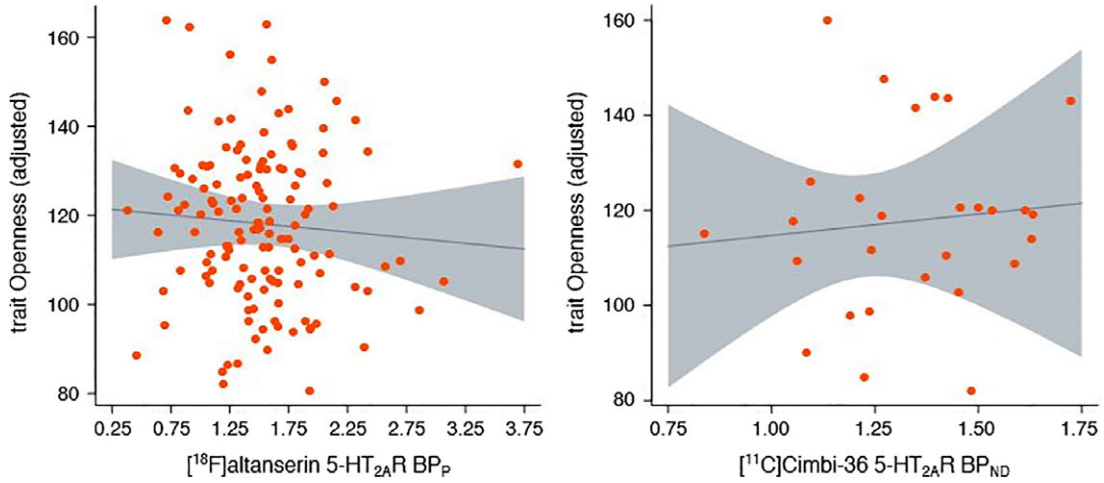

FIGURE 1 Two scatterplots of neocortex 5-HT_{2A}R binding imaged with [^{18}F]altanserin (n = 139) and [^{11}C]Cimbi-36 (n = 28), respectively, against trait Openness scores is shown. Orange dots represent individual measurement points and lines and shading for each line represent slope estimates and 95% confidence intervals. Data shown are adjusted for age and sex [Color figure can be viewed at wileyonlinelibrary.com]

found, other studies reported negative correlations between a similar personality trait Self-transcendence and 5-HTT binding (Kim et al., 2015) and 5-HT_{1A}R levels (Borg, Andree, Soderstrom, & Farde, 2003), respectively. Self-transcendence is a personality trait inherent in Cloninger's Temperament and Character Inventory (TCI) which has some overlap with trait Openness (Cloninger, Svrakic, & Przybeck, 1993; De Fruyt, Van De Wiele, & Van Heeringen, 2000). In line with the findings from the current study, another study found no significant association between 5-HT_{1A}R and trait Self-transcendence (Karlsson, Hirvonen, Salminen, & Hietala, 2011), and two other studies reported nonsignificant associations between trait Openness and 5-HT_4R (Stenbaek et al., 2017) and 5-HT_{1A}R (Tauscher et al., 2001), respectively. Some studies reported significant associations between 5-HT receptor or 5-HTT binding and other personality traits from NEO PI-R and TCI, but none in relation to trait Openness or Self-transcendence (Tauscher et al., 2001; Tuominen et al., 2013; Tuominen et al., 2017). Conversely, other PET studies investigated associations between 5-HT receptor or 5-HTT binding and personality traits from NEO PI-R and TCI, but did not report associations with trait Openness or Self-transcendence (Frokjaer et al., 2008; Frokjaer et al., 2010; Gerretsen et al., 2010; Moresco et al., 2002; Reimold et al., 2008; Soloff, Chiappetta, Mason, Becker, & Price, 2014; Soloff, Price, Mason, Becker, & Meltzer, 2010; Takano et al., 2007), possibly reflecting null findings. A full review of the existing literature on PET biomarkers of the 5-HT system and trait Openness and Self-transcendence can be found in supplementary materials (Table S1, Supporting Information). In reference to these studies, our current study represents the largest to date and does not support an association between 5-HT_{2A}R availability and trait Openness.

Although studies of the 5-HT system with PET and trait Openness reveal no obvious patterns across healthy individuals, classic serotonergic psychedelics do appear to provide novel information about possible change mechanisms in trait Openness and related traits. Observational studies have shown that, compared to controls, long time users of ayahuasca (containing the 5-HT_{2A}R agonist *N*,*N*-dimethyltryptamine) exhibit higher trait Openness (Barbosa et al., 2016) and similar studies revealed higher trait Self-transcendence in ayahuasca users than controls (Bouso et al., 2012; Bouso et al., 2015). Since observational and nonprospective studies are unable to measure changes in personality traits, it is uncertain whether these results reflect an effect of psychedelics or that individuals with specific trait profiles are more prone to seek out psychedelics (in either experimental or recreational settings). Recent experimental studies in healthy individuals have reported increases in trait Openness measured 2 weeks after administration of the serotonin psychedelic lysergic acid diethylamide (Carhart-Harris, Kaelen, et al., 2016), and enduring increases in trait Openness 1 year and 3 months after administration of psilocybin in healthy individuals (MacLean et al., 2011) and patients with treatment-resistant depression (Erritzoe et al., 2018), respectively. Intriguingly, it has also been reported that change in trait Openness was predicted by the occurrence of psilocybin-induced mystical experiences, whereas baseline measures of Openness were unable to predict whether a mystical experience would occur (Griffiths et al., 2011). Considering that the occurrence of mystical experiences is positively related to psilocybin dose (Griffiths et al., 2011), our findings suggest a limited association between 5-HT_{2A}R and trait Openness at baseline, whereas the malleability of trait Openness may nevertheless be related to the capacity for 5-HT_{2A}R modulation by serotonergic psychedelics (e.g., 5-HT_{2A}R baseline levels). Future studies evaluating 5-HT_{2A}R-mediated mechanisms of changes in personality after intake of psilocybin (or other serotonergic psychedelics) would shed light on this link.

4.1 | Methodological considerations

A major strength of the current study is its sample size. It is the largest PET study to examine the association between an imaging marker of 5-HT signaling and trait Openness. It is also the first to study the association between 5-HT_{2A}R and trait Openness. However, some limitations of the study should be considered. First, with our sample size of 159 participants, we have sufficient statistical power (β = 0.8) to detect effect sizes of $r \geq 0.2$ (small/medium and greater). Although we are powered to detect in the higher end of small to medium effect sizes, we are underpowered to detect smaller effects. Our standardized regression

coefficient (−0.07, 95% CI: −0.27, 0.13) is such that even a statistically significant association of this kind may be of limited practical relevance. Second, study exclusion criteria including family or personal history of psychiatric disorders may have caused us to miss a potential association between 5-HT_{2A}R and trait Openness in more vulnerable populations. Third, self-report biases, for example, censorship, social desirability biases, or systematic manipulation of answers on items (Domino, 2006), are inherent problems with applied psychometric tools such as the NEO PI-R and may have biased associations with 5-HT_{2A}R binding. However, studies of the correlation between self-report scores and ratings by spouse on the NEO PI-R supports the reliability of the self-reported personality traits (McCrae & Costa, 2006).

In summary, we applied PET imaging to study 5-HT_{2A}R availability as a possible molecular marker associated with trait Openness in a large sample of 159 healthy individuals with no current or prior psychiatric history. No significant association was observed, suggesting that there is no evidence in favor of an association between 5-HT_{2A}R and trait Openness.

ACKNOWLEDGMENTS

The authors would like to thank B. Dall, G. Thomsen, S. Larsen, A. Dyssegaard, and L. Freyr for their assistance with the data collection. The authors would also like to acknowledge and thank The John and Birthe Meyer Foundation for the donation of the Cyclotron and PET scanner.

CONFLICT OF INTERESTS

All authors declare no conflict of interests.

ORCID

Dea Siggaard Stenbæk https://orcid.org/0000-0002-5439-4637

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How to cite this article: Stenbæk DS, Kristiansen S, Burmester D, et al. Trait Openness and serotonin 2A receptors in healthy volunteers: A positron emission tomography study. *Hum Brain Mapp*. 2019;40:2117–2124. https://doi.org/10.1002/hbm.24511