

# Aggression is Related to Frontal Serotonin-1A Receptor Distribution as Revealed by PET in Healthy Subjects

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**Abstract:** *Objectives:* Various studies indicate that serotonin regulates impulsivity and the inhibitory control of aggression. Aggression is also known to be modified by sex hormones, which exert influence on serotonergic neurotransmission. The present study aimed to elucidate potential interactions between human aggression, the inhibitory serotonergic 5-HT<sub>1A</sub> receptor, and sex hormones. *Experimental Design:* Thirty-three healthy volunteers (16 women, aged 26.24 ± 5.5 yr) completed a validated questionnaire incorporating five dimensions of aggression. Subsequently, all subjects underwent positron emission tomography with the radioligand [carbonyl-<sup>11</sup>C]WAY-100635 to quantify 5-HT<sub>1A</sub> binding potentials (BP<sub>NDS</sub>) in the prefrontal cortex, limbic areas, and midbrain. Also, plasma levels of testosterone, 17β-estradiol and sex hormone-binding globulin (SHBG) were measured. Relations between aggression scores, regional 5-HT<sub>1A</sub> BP<sub>NDS</sub>, and hormone levels were analyzed using correlations, multivariate analyses of variance, and linear regressions. *Principal Observations:* Statistical analyses revealed higher 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in subjects exhibiting higher aggression scores in prefrontal (all  $P < 0.041$ ) and anterior cingulate cortices ( $P = 0.016$ ). More aggressive subjects were also characterized by lower SHBG levels ( $P = 0.015$ ). Moreover, higher SHBG levels were associated with lower 5-HT<sub>1A</sub> BP<sub>NDS</sub> in frontal ( $P = 0.048$ ) and cingulate cortices (all  $P < 0.013$ ) and in the amygdala ( $P = 0.03$ ). *Conclusions:* The present study provides first-time evidence for a specific interrelation between the 5-HT<sub>1A</sub> receptor distribution, sex hormones, and aggression in humans. Our findings point to a reduced down-stream control due to higher amounts or activities of frontal 5-HT<sub>1A</sub> receptors in more aggressive subjects, which is presumably modulated by sex hormones. *Hum Brain Mapp* 30:2558–2570, 2009. © 2008 Wiley-Liss, Inc.

**Key words:** positron emission tomography; serotonergic 1A receptor; serotonin; aggression; sex hormones; prefrontal cortex

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## INTRODUCTION

The serotonergic system has been implicated in the regulation of impulsivity and aggressive behavior [reviewed in Ferrari et al., 2005; Nelson and Trainor, 2007]. On the one hand, reduced serotonin (5-HT) levels have been frequently linked to higher levels of aggression in rodents, nonhuman primates, and humans [Brown et al., 1979; Chiavegatto et al., 2001; Kantak et al., 1980; Mehlman et al., 1994; Valzelli et al., 1981]. Moreover, selective serotonin reuptake inhibitors (SSRIs) have been shown to exhibit both antidepressant and aggression-lowering effects [Coccaro and Kavoussi, 1997; Kasper and Olié, 2002; New et al., 2004; Pinna et al., 2003; Reist et al., 2003]. On the other hand, antidepressants that block the degradation of serotonin and other amines including norepinephrine by inhibiting monoamine-oxidase A (MAO-A), turned out to increase aggression in rodents [Datla and Bhattacharya, 1990; Florvall et al., 1978]. This is in line with highly aggressive behaviors of MAO-A knockout mice [Cases et al., 1995], and behavioral anomalies of persons exhibiting a MAO-A point mutation [Brunner et al., 1993].

Aggressive behavior might thus depend on a more complex involvement of serotonin-mediated neurotransmission, particularly when considering area-specific effects [de Boer and Koolhaas, 2005; Miczek et al., 2007]. In the cortex, antagonists at the excitatory 5-HT<sub>2</sub> receptor reduced aggression in mice [Sakaue et al., 2002; White et al., 1991], whereas agonists at the inhibitory 5-HT<sub>1A</sub> and/or 5-HT<sub>1B</sub> receptors decreased aggressive behavior probably via presynaptic autoreceptors in the raphe nuclei (RN) in rodents [Bannai et al., 2007; De Almeida and Lucion, 1997; de Boer et al., 2000; Miczek et al., 1998]. Rats that were bred on low aggression showed a higher 5-HT<sub>1A</sub> receptor expression in the midbrain [Popova et al., 2005], yet a decrease in 5-HT<sub>1A</sub> receptor mRNA in the frontal cortex [Popova et al., 2007].

In humans, 5-HT<sub>2</sub> receptor antagonists also decreased aggressive behavior [Cherek and Lane, 2001]. Parsey et al. [2002] found negative correlations between life-time history of aggression and the inhibitory 5-HT<sub>1A</sub> receptor binding potentials in the RN, but surprisingly also in frontal areas, using positron emission tomography (PET) and the radioligand [<sup>11</sup>C]WAY-100635 in 25 healthy humans. Conversely, pointing to a rather enhanced inhibition of prefrontal areas in aggression due to serotonergic neurotransmission, patients suffering from impulsive personality disorder exhibited a lower prefrontal glucose metabolism after a serotonin releasing challenge compared to controls [Siever et al., 1999; Soloff et al., 2003].

Other factors that might have contributed to these partly conflicting findings are aggression-related actions of sex hormones [reviewed in Archer, 2006; Soma et al., 2008], because the impact of both serotonin and sex hormones on aggression appeared to be interrelated [Birger et al., 2003; Higley et al., 1996]. Moreover, interventional studies in rodents suggested that sex hormones modulate aggressive

behavior via the serotonergic system, specifically via 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors [Cologer-Clifford et al., 1997; Ricci et al., 2006; Simon et al., 1998]. Recent imaging studies in the living human brain revealed activations of the prefrontal cortex and limbic areas in aggression-related processing [reviewed in Bufkin and Luttrell, 2005]. These activations were more persistent after administration of sex hormones [Hermans et al., 2008], however, a direct involvement of 5-HT<sub>1A</sub> receptor-mediated neurotransmission has to be shown in humans.

Taken together, previous studies gave rise to the hypothesis that serotonin modulates aggressive behavior partially via the inhibitory 5-HT<sub>1A</sub> receptor in selective brain areas such as the prefrontal cortex. Further, both aggression and the 5-HT<sub>1A</sub> receptor distribution are suggested to be influenced by the amount of sex hormones. To test these assumptions, we wanted to elucidate whether aggressive traits, measured by sensitive neuropsychological testings, are associated with the regional distribution of pre- and postsynaptic 5-HT<sub>1A</sub> receptors in specific prefrontal, limbic, and midbrain areas using *in vivo* PET. We also measured plasma levels of sex hormones to investigate the assumed regulatory influence of sex hormones on aggression, and on the regional 5-HT<sub>1A</sub> receptor distribution.

## METHODS

### Subjects

Thirty-six healthy young subjects (18 women and 18 men, aged 26.17 yr ± 5.3 SD) in a narrow age range and with similar educational levels (≥12 yr of education) were recruited via advertisement at the Medical University of Vienna, Austria. All subjects underwent a medical examination at the screening visit including medical history, electrocardiogram, and routine laboratory tests. Exclusion criteria were history of severe disease, any psychiatric or neurological disorder, and drug abuse. One woman and one man had to be excluded after PET-scanning from further analysis because the respective integral of the time activity curve in the reference region was an outlier [mean ± 2 SD, Bantick et al., 2004; Rabiner et al., 2002]. Further, one woman had to be excluded because of failure to complete the questionnaire, leaving 33 subjects (aged 26.24 yr ± 5.5 SD) for statistical analysis. PET- and aggression-data acquisition and analyses were done by investigators blinded to the study question. All females were measured in the follicular phase to exclude potential effects of menstrual cycle phase on the 5-HT<sub>1A</sub>-receptor distribution [Betha et al., 2002; Flügge et al., 1999; Parsey et al., 2002], which in healthy women appeared to be rather minor and restricted to the RN [Jovanovic et al., 2006]. Demographic details and hormone plasma levels are given in Table I. All subjects provided written informed consent and received reimbursement after participation. The study was approved by the Ethics Committee of the Medical University of Vienna.

**TABLE I. Demographic parameters and hormone plasma levels of subjects included in the analyses ( $n = 33$ )**

	Mean $\pm$ SD	Minimum	Maximum
Age, yr	26.24 $\pm$ 5.5	20	47
Body mass index, kg/m <sup>2</sup>	23.13 $\pm$ 3.3	16.9	36.3
Sex-hormone binding globulin (SHBG), ng/l	48.04 $\pm$ 27.5	12.3	131.4
Testosterone in males (bioavailable), $\mu$ g/l	3.12 $\pm$ 1.2	1.7	6.8
Testosterone in females (bioavailable), $\mu$ g/l	0.12 $\pm$ 0.05	0.04	0.24
17 $\beta$ -estradiol in males (bioavailable), ng/l	19.77 $\pm$ 5.8	12	30
17 $\beta$ -estradiol in females (bioavailable), ng/l	27.81 $\pm$ 15.4	12	59

### Aggression Score

Aggression-related personality traits and the disposition to aggressive behavior were assessed by the validated Questionnaire for Measuring Factors of Aggression [German, Hampel and Selg, 1975] on the day of the PET measurements. This test, frequently used in similar studies [Gietl et al., 2007; Rujescu et al., 2008], comprises in line with the Buss and Durkee Hostility Inventory [Buss and Durkee, 1957] 77 items on five dimensions of aggression including (1) spontaneous verbal or physical aggression towards others, (2) reactive aggression, attacks in response to an event, (3) impulsiveness with the qualities rage and anger, (4) self-aggression including depressive symptoms and self-harm, and (5) inhibition of aggressive thoughts, acts, and impulsivity. The sum of the first three subscores (1–3) gives a total aggression score without self-aggressive behaviors. In addition, several items were included to test whether subjects answer straightforward (frankness). As main outcome measures, test evaluation resulted in one total score and five subscores for the five aggression-related dimensions with a higher score indicating higher ratings on spontaneous aggression, reactive aggression, impulsiveness, self-aggression, and inhibition of aggression, respectively. No significant differences (independent  $t$  tests/Mann-Whitney tests) or correlations (Pearson/Spearman) between age or sex and aggression scores were found ( $P > 0.05$ ).

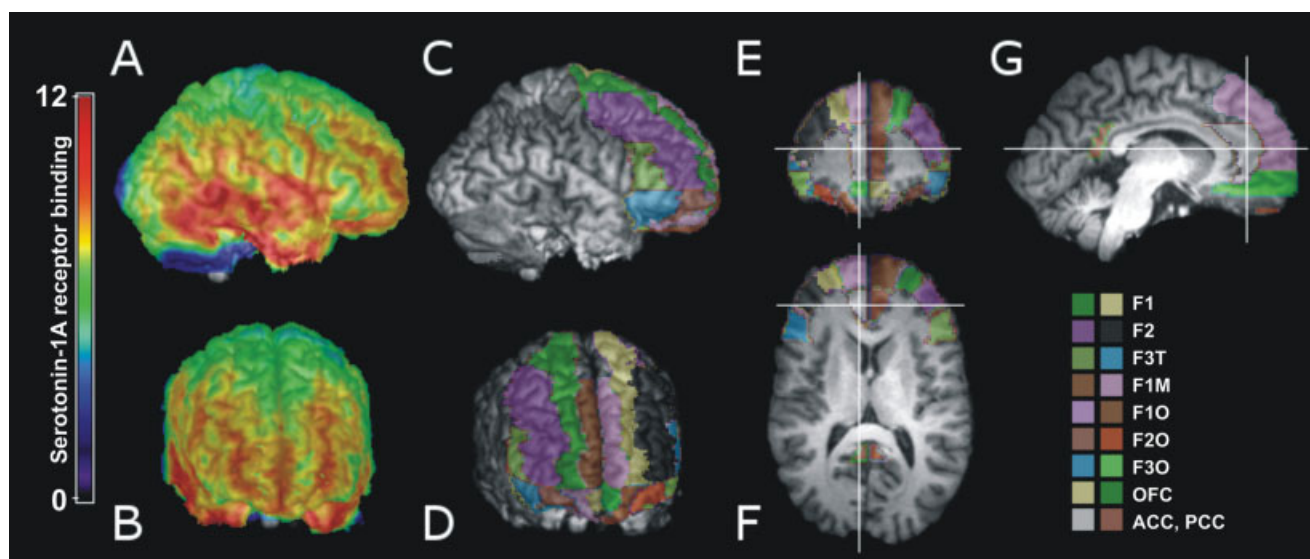
In our study-sample of healthy individuals with a high educational level and social status (most subjects were students of medicine), nearly all subjects exhibited a generally low level of aggression. Therefore, aggression scores were non-normally distributed and hardly continuous over a large range. Because this might conflict with linear regression theory [Zou et al., 2003], we considered to use as secondary outcome measures a dichotomous division of aggression scores. Therefore, two group percentiles (“higher” vs. “lower” aggression) were separated on the basis of median values. Given that  $n = 33$ , separating two percentiles was rated as best approach.

### Positron Emission Tomography (PET)

All subjects underwent PET in an advance high-resolution full-ring scanner (General Electric Medical Systems, Milwaukee, WI) with the selective radioligand [carbonyl-<sup>11</sup>C]WAY-100635 to measure the distribution of the 5-HT<sub>1A</sub> receptor subtype in selected brain regions of interest (ROIs) as previously described by our group [Gerstl et al., 2008; Lanzenberger et al., 2007; Spindelegger et al., in press; Stein et al., in press]. The radiotracer was prepared in a fully automated PET synthesizer (GE Healthcare, Uppsala, Sweden) as published by our group in detail [Wadsak et al., 2007]. Heads were fixed and adjusted in parallel to the orbitomeatal line with the neocortex and full cerebellum in the field of view. Image acquisition included a two-dimensional 5-min transmission scan for correction of tissue attenuation using a retractable <sup>68</sup>Ge ring source before dynamic three-dimensional scans lasting 90 min. Measurements started with a bolus injection of [carbonyl-<sup>11</sup>C]WAY-100635 in phosphate-buffered saline (mean injected activity: 5.54 MBq/kg body weight  $\pm$  0.9 SD; mean specific activity: 136 GBq/ $\mu$ mol  $\pm$  118 SD; mean radiochemical purity: 97.7%  $\pm$  1.3 SD; mean weight of WAY-100635: 2.05  $\mu$ g  $\pm$  4 SD; mean weight of unlabeled WAY-100635: 3.6  $\mu$ g  $\pm$  4.7 SD). Dynamic scans were obtained 15 times each 1 min followed by 15 times each 5 min, resulting in 30 consecutive time frames. Thereof 35 contiguous brain slices (matrix 128  $\times$  128, thickness 4.25 mm) were reconstructed using an iterative filtered back-projection algorithm (FORE-ITER) with a spatial resolution of 4.36-mm full-width at half maximum at the center of the field of view.

### Magnetic Resonance Imaging

Structural magnetic resonance imaging (MRI) was performed with a 3 Tesla whole-body MEDSPEC S300 MR-scanner (Bruker BioSpin, Ettlingen, Germany) using a magnetization-prepared rapid gradient-echo (MPRAGE, T1 weighted) sequence (128 slices, 256  $\times$  256 matrix, slice



**Figure 1.**

Exemplary parametric 5-HT<sub>1A</sub> receptor binding potential map (**A, B**) and automated delineation of regions of interest (ROIs, **C–G**) drawn on an individual coregistered magnetic resonance image. F1, superior frontal cortex; F2, middle frontal cortex; F3T, triangular part of the inferior frontal cortex; F1M, medial part of the superior frontal cortex; F1O, orbital part of the superior frontal cortex; F2O, orbital part of the middle frontal cortex; F3O, orbital part of the inferior frontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

thickness 1.56 mm, voxel size 0.78 × 0.86 mm). Coregistration between high-resolution MR and PET images (Fig. 1) was done using SPM5 (The Wellcome Department of Imaging Neuroscience, University College London; [www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)).

### Kinetic Modeling and ROI Analysis

As outcome measure of the 5-HT<sub>1A</sub> receptor distribution, the regional 5-HT<sub>1A</sub> receptor binding potential [BP<sub>ND</sub>; Innis et al., 2007] was calculated using the kinetic modeling tool implemented in PMOD 2.95 [PMOD Technologies, Zurich, Switzerland; see Mikolajczyk et al., 1998]. Dynamic PET scans were spatially normalized to a tracer-specific template in MNI stereotactic space corresponding to a ROI-template based on automated anatomical labeling [Tzourio-Mazoyer et al., 2002]. Using the 30 time-frames of the dynamic PET data, decay-corrected time activity curves were obtained within thirteen relevant ROIs. Quantification of the 5-HT<sub>1A</sub> receptor distribution was carried out by use of the Simplified Reference Tissue Model 2 [Lammertsma and Hume, 1996; Wu and Carson, 2002] with the cerebellum as reference region due to a very low 5-HT<sub>1A</sub> receptor density in this area [Burnet et al., 1997; Hall et al., 1997]. On the basis of previous imaging studies on aggression [Bufkin and Luttrell, 2005] and 5-HT<sub>1A</sub> receptor density analyses [Rabiner et al., 2002; Varnäs et al., 2004], the following (bilateral) ROIs were selected including on the postsynaptic side the dorsolateral, ventromedial,

and orbital prefrontal cortex as well as limbic areas (Fig. 1): (1) superior frontal cortex (F1), (2) middle frontal cortex (F2), (3) triangular part of the inferior frontal cortex (F3T), (4) medial part of the superior frontal cortex (F1M), (5) orbital part of the superior frontal cortex (F1O), (6) orbital part of the middle frontal cortex (F2O), (7) orbital part of the inferior frontal cortex (F3O), (8) medial orbital part of the superior frontal cortex (OFC), (9) anterior cingulate cortex (ACC), (10) posterior cingulate cortex (PCC), (11) amygdala (AMY), and (12) caput hippocampi (all characterized by rather high 5-HT<sub>1A</sub> BP<sub>ND</sub>s). On the presynaptic side, (13) the RN were delineated. In addition, (14) the cerebellum served as reference region. Right and left ROIs were combined to improve signal-to-noise ratio.

### Hormone Measurements

In the mornings before PET scans, blood samples were collected to perform standard screenings (e.g., control of self-reported cycle phase in women). In addition, plasma levels of 17β-estradiol, testosterone, and the sex hormone-binding globulin (SHBG) were assessed to check for potential interactions with the 5-HT<sub>1A</sub> receptor distribution and aggression scores [Bethea et al., 2002; Cologer-Clifford et al., 1997; Higley et al., 1996; Ricci et al., 2006; Rubinow et al., 1998; Simon et al., 1998]. SHBG is a glycoprotein that binds to and is indirectly regulated by sex hormones. SHBG also determines the amount of circulating testosterone and estrogen and can be regarded as an integrative



**TABLE 2. Aggression scores between groups according to the Questionnaire for Measuring Factors of Aggression (Hampel and Selg, 1975)**

	Mean $\pm$ SD			<i>P</i> <sup>a</sup> (1 vs. 2)
	Group 1 (low ratings)	Group 2 (high ratings)	Total	
Total aggression (1-3), maximum = 45	3.56 $\pm$ 2.1	10.27 $\pm$ 5	6.58 $\pm$ 5	<0.0001
Women/men/all	10/8/18	6/9/15	17/16/33	NS
Spontaneous (1), maximum = 19	0.78 $\pm$ 0.9	2.8 $\pm$ 1.4	1.7 $\pm$ 1.5	<0.0001
Reactive (2), maximum = 13	0.78 $\pm$ 0.9	2.73 $\pm$ 2.8	1.67 $\pm$ 2.2	0.005
Impulsiveness (3), maximum = 13	1.94 $\pm$ 1.6	4.73 $\pm$ 2	3.21 $\pm$ 2.3	0.0001
Frankness, maximum = 10	5.4 $\pm$ 2.6	6.7 $\pm$ 2.1	6 $\pm$ 2.4	NS
Self-aggression (4), maximum = 13	0.33 $\pm$ 0.5	4.83 $\pm$ 3	1.97 $\pm$ 2.8	<0.0001
Women/men/all	10/11/21	6/6/12	17/16/33	NS
Frankness, maximum = 10	5.43 $\pm$ 2.7	7 $\pm$ 1.5	6 $\pm$ 2.4	NS
Inhibition of aggression (5), maximum = 10	2.72 $\pm$ 1.3	6.18 $\pm$ 1	4.5 $\pm$ 2.1	<0.0001
Women/men/all	7/9/16	9/8/17	17/16/33	NS
Frankness maximum = 10	5.75 $\pm$ 2.5	6.24 $\pm$ 2.4	6 $\pm$ 2.4	NS

<sup>a</sup> Two independent sample tests (Mann-Whitney).

marker for the availability of sex hormones. For analyses, bioavailable amounts of 17 $\beta$ -estradiol and testosterone were used. Therefore, values of free 17 $\beta$ -estradiol and testosterone can be estimated by division by 24.6 and 23.4, respectively [Vermeulen et al., 1999]. Details of hormonal plasma levels are given in Table I.

### Statistical Analysis

To detect potential interactions between serotonergic neurotransmission and different dimensions of aggression, raw aggression scores were compared with regional 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> using bivariate Spearman correlation coefficients (two tailed) and a Bonferroni adjustment for multiple comparisons. Secondary, due to non-normal distributions, aggression scores were divided a priori into two groups each (higher vs. lower ratings) based on median values (Table II). Therewith, multivariate analyses of variance (MANOVA) with regional 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> as dependent variables (13 levels) and either one of the aggression subscores (total aggression or self-aggression or inhibition of aggression) as main factor (each two levels) were calculated. To adjust for potential confounding variables, radiochemical parameters (injected activity, specific activity, radiochemical purity, and weight of precursor WAY-100635), sex, and age [Jovanovic et al., 2008; Parsey et al., 2002] were included into the model. Radiochemical parameters revealed no significant associations and were therefore excluded from further analyses. Subsequently, independent *t* tests were performed to assess regional BP<sub>ND</sub> differences between groups.

To test whether aggression scores were associated with sex hormones, bivariate correlations were conducted with plasma levels of SHBG (pooled), 17 $\beta$ -estradiol (sex specific), and testosterone (sex specific) using Spearman correlation coefficients (two tailed) and a Bonferroni adjustment for multiple comparisons. Secondary, dichotomous aggres-

sion score groups were compared with sex hormones using independent *t* tests (two tailed) and the dependent variables SHBG (pooled), 17 $\beta$ -estradiol (sex specific), and testosterone (sex specific), corrected by a Bonferroni adjustment for multiple comparisons.

Regional 5-HT<sub>1A</sub> BP<sub>NDS</sub> were related to sex hormones by linear regression models (forward inclusion) with regional 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> as dependent variables and levels of SHBG, or 17 $\beta$ -estradiol, or testosterone, as fixed factors. Age and sex were entered into the model to adjust for potential confounding. Regarding 17 $\beta$ -estradiol and testosterone, analyses were performed for women and men separately.

Normal distribution, equality of covariance matrices, and homogeneity of variances considering 5-HT<sub>1A</sub> receptor BP<sub>ND</sub> and sex hormone data were assumed according to the Kolmogorov-Smirnov test (*P* > 0.05), the Box's test (*P* > 0.05), and the Levene's test (*P* > 0.05). Statistical analyses were performed using SPSS 12 (SPSS, Chicago, IL).

## RESULTS

### Correlations Between Aggression Scores and 5-HT<sub>1A</sub>

Significant correlations that survived the Bonferroni correction for multiple comparisons (*P* < 0.0038) were observed between total aggression scores and regional BP<sub>NDS</sub> in the ACC (*r* = 0.512, *P* = 0.002). Significant correlations did not reach the Bonferroni threshold in the superior (*r* = 0.47, *P* = 0.006) and middle (*r* = 0.46, *P* = 0.008) frontal cortices, in the triangular (*r* = 0.39, *P* = 0.024) and orbital (*r* = 0.49, *P* = 0.004) parts of the inferior frontal cortex, in the medial part of the superior (*r* = 0.42, *P* = 0.016) and in the orbital part of the middle (*r* = 0.37, *P* = 0.032) frontal cortices as well as in the orbitofrontal cortex (*r* = 0.44, *P* = 0.01).

**TABLE 3. Statistics of Spearman correlations between aggression subscores and regional 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub>**

	Total aggression score			
	Spontaneous aggression		Impulsiveness	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Superior frontal cortex	0.41	0.018	0.59	0.0003
Middle frontal cortex	0.33	0.063	0.41	0.018
Triangular part of the inferior frontal cortex	0.35	0.047	0.58	0.0004
Medial part of the superior frontal cortex	0.32	0.068	0.53	0.0016
Orbital part of the superior frontal cortex	0.36	0.04	0.58	0.0004
Orbital part of the middle frontal cortex	0.29	0.1	0.48	0.0047
Orbital part of the inferior frontal cortex	0.35	0.048	0.6	0.0002
Orbitofrontal cortex	0.32	0.066	0.55	0.0009
Anterior cingulate cortex	0.25	0.16	0.4	0.023
Posterior cingulate cortex	0.08	0.65	0.22	0.22
Amygdala	0.32	0.07	0.56	0.0007
Hippocampus	0.09	0.61	0.17	0.34
Raphe nuclei	0.03	0.86	0.05	0.78

Even more robust Bonferroni-corrected correlations were found when separating the individual components “spontaneous aggression” and “impulsiveness” from the total aggression score (Table III for *r* and *P* values; Fig. 2 for examples). The component “reactive aggression” as well as scores on self-aggression and inhibition of aggression showed no correlations in any ROI (all *P* > 0.05, data not shown).

#### Aggression Score Subgroups and 5-HT<sub>1A</sub>

Secondary, MANOVA detected significant effects of total aggression score subgroups (Pillai’s trace = 0.68,  $F_{(13, 19)} = 3.1$ , *P* = 0.013) and self-aggression score subgroups (Pillai’s trace = 0.64,  $F_{(13, 19)} = 2.63$ , *P* = 0.027) on the regional 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub>. No significant interactions were found between other aggression scores subgroups or potentially confounding variables (radiochemical parameters, age, sex) and regional 5-HT<sub>1A</sub> BP<sub>NDS</sub> (*P* > 0.05).

Considering total aggression, subsequent *t* tests revealed significant mean differences between groups (high vs. low ratings) in the following ROIs (Fig. 3A): superior (F1, *r* = 0.38, *P* = 0.029) and middle (F2, *r* = 0.38, *P* = 0.033) frontal cortices, medial part of the superior frontal cortex (F1M, *r* = 0.37, *P* = 0.033), orbital part of the middle (F2O, *r* = 0.36, *P* = 0.041) and inferior (F3O, *r* = 0.45, *P* = 0.009) frontal cortices, orbitofrontal cortex (OFC, *r* = 0.41, *P* = 0.017), and ACC (*r* = 0.42, *P* = 0.016). In these areas on average, a 13.25% higher mean 5-HT<sub>1A</sub> receptor BP<sub>ND</sub> corresponded to the more aggressive subgroup. No group-differences were found in the other ROIs including the hippocampus. Note that mean 5-HT<sub>1A</sub> receptor BP<sub>ND</sub> in the RN contrasted to those in frontal areas, namely that the high-aggressive subgroup exhibited a lower mean 5-HT<sub>1A</sub> receptor BP<sub>ND</sub>, however, without statistical significance.

Regarding self-aggression, post hoc independent *t* tests failed to reach significance in any region (*P* > 0.05), yet a

somewhat similar trend, meaning higher mean 5-HT<sub>1A</sub> BP<sub>NDS</sub> in the more (self-)aggressive subgroup, can be seen (Fig. 3B). Rather opposite associations, i.e., lower regional 5-HT<sub>1A</sub> BP<sub>NDS</sub> in the high-rating subgroup, were observed when evaluating inhibition of aggression (Fig. 3C), however, data did not reach the level of significance in MANOVA.

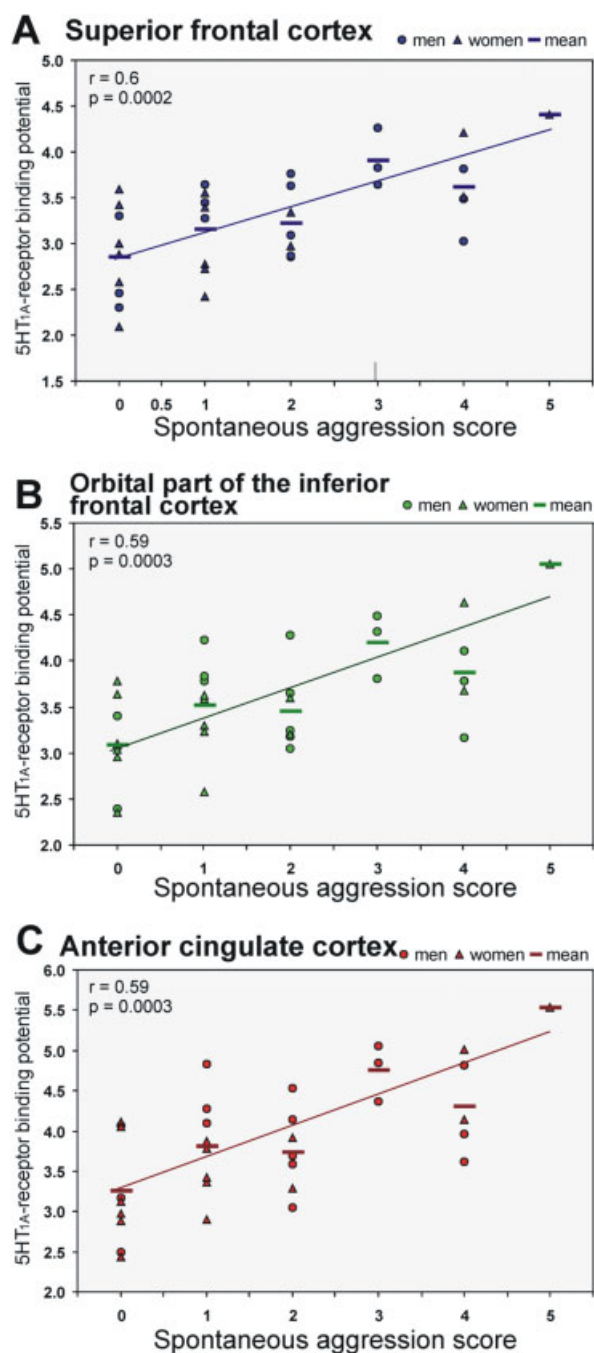
#### Correlations Between Aggression Scores and Sex Hormones

Correlation analyses revealed inverse associations between inhibition of aggression scores and SHBG levels, which withstood the Bonferroni correction for multiple comparisons (*r* = -0.43, *P* = 0.012). Without correction, significant inverse correlations were observed between the “spontaneous aggression” component of the total aggression score and SHBG (*r* = -0.36, *P* = 0.039). The other components did not correlate with SHBG levels (*P* > 0.05). Strong Bonferroni-corrected positive correlations were found in men comparing inhibition of aggression with 17β-estradiol (*r* = 0.73, *P* = 0.001) and testosterone (*r* = 0.58, *P* = 0.016). No further correlations were seen.

#### Aggression Score Subgroups and Sex Hormones

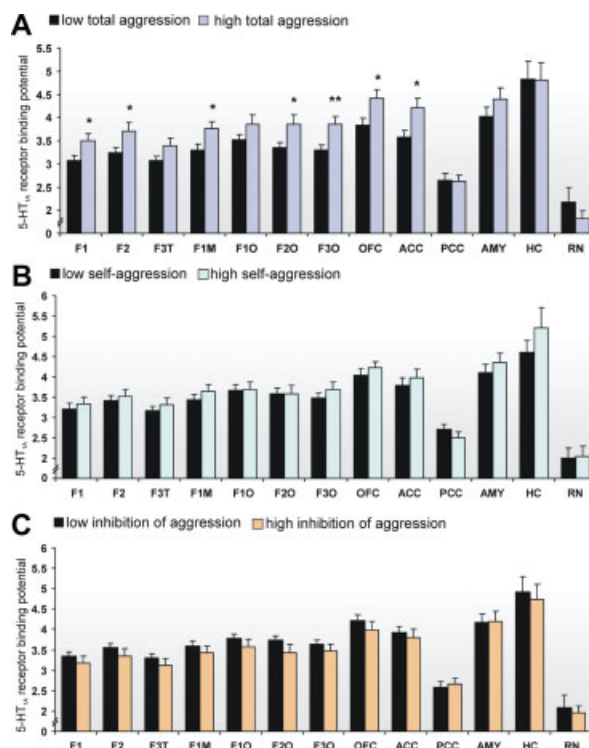
Secondary, independent *t* tests revealed a significantly lower mean plasma SHBG level in subjects exhibiting higher scores on the “spontaneous aggression” component of the total aggression score, which withstood the Bonferroni correction (*t* = 2.59, *P* = 0.015, Fig. 4). A similar trend was seen between the “reactive aggression” component groups of the total aggression score (*t* = 1.99, *P* = 0.058, Fig. 4). No differences were found between other aggression score subgroups (*P* > 0.05).

Mean plasma levels of 17β-estradiol (*t* = -2.35, *P* = 0.002, Bonferroni-corrected) and testosterone (*t* = -3.85, *P* = 0.033,



**Figure 2.**

Correlations between the 5-HT<sub>1A</sub> receptor binding potential and the “spontaneous aggression” component of the total aggression score in the frontal superior cortex (F1, **A**), in the orbital part of the frontal inferior cortex (F3O, **B**), and in the anterior cingulate cortex (ACC, **C**). Lines give regression fit, *r* and *P* values according to Spearman correlation coefficients triangles = women, circles = men, bars = means; *n* = 33. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]



**Figure 3.**

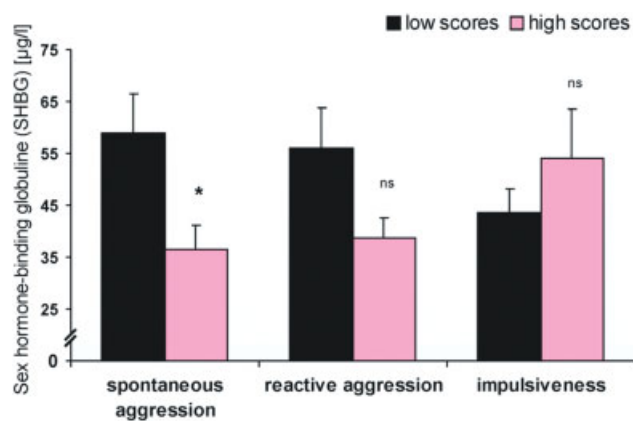
Regional 5-HT<sub>1A</sub> receptor binding potentials in high- vs. low-aggression subgroups. (**A**) total aggression score, (**B**) self-aggression score, (**C**) inhibition of aggression score. Asterisks indicate levels of significance according to independent *t* tests (\**P* < 0.05; \*\**P* < 0.01). Bars display means, error bars give standard error (SE), *n* = 33. AMY, amygdalae; HC, hippocampus; RN, raphe nuclei; further abbreviations explained in the legend of Figure 1. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

uncorrected) were significantly higher in men exhibiting higher scores of inhibition of aggression. In women, a significantly higher mean testosterone level was seen in the subgroup with higher scores on “spontaneous aggression” as component of the total aggression score ( $t = -2.39$ ,  $P = 0.031$ , uncorrected). No other effects were observed ( $P > 0.05$ ).

### Sex Hormones and 5-HT<sub>1A</sub>

Linear regression analyses revealed significant inverse associations of SHBG and the 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in the orbital part of the inferior frontal cortex ( $\beta = -0.35$ ,  $t = -2.06$ ,  $P = 0.048$ ), in the ACC ( $\beta = -0.43$ ,  $t = -2.65$ ,  $P = 0.013$ ) and PCC ( $\beta = -0.54$ ,  $t = -3.53$ ,  $P = 0.001$ ; Fig. 5), as well as in the AMY ( $\beta = -0.38$ ,  $t = -2.28$ ,  $P = 0.03$ ). Similar trends were seen in the other prefrontal cortices ( $P < 0.1$ ) but not in the hippocampus and RN ( $P > 0.1$ ).

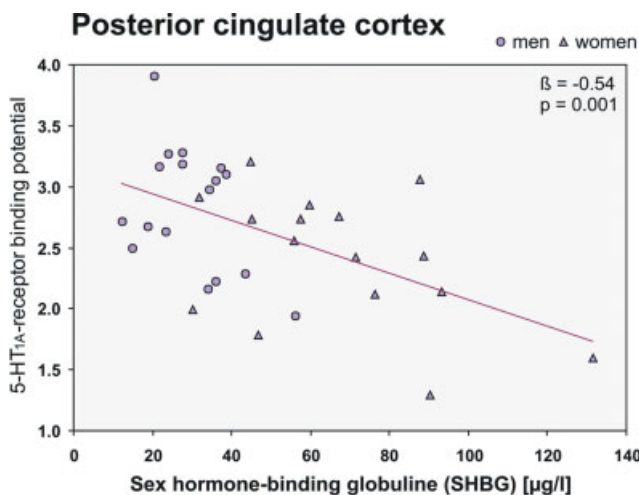
In the RN, 17 $\beta$ -estradiol levels were significantly associated with the 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in women ( $\beta = 0.54$ ,  $t = 3.45$ ,  $P = 0.002$ ). Testosterone levels were found to be



**Figure 4.**

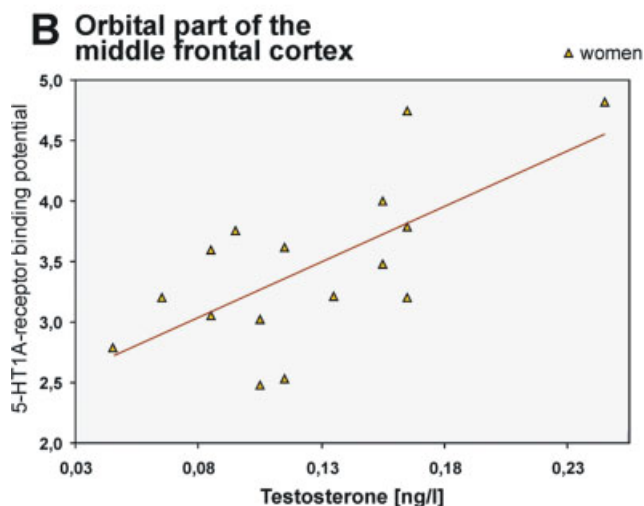
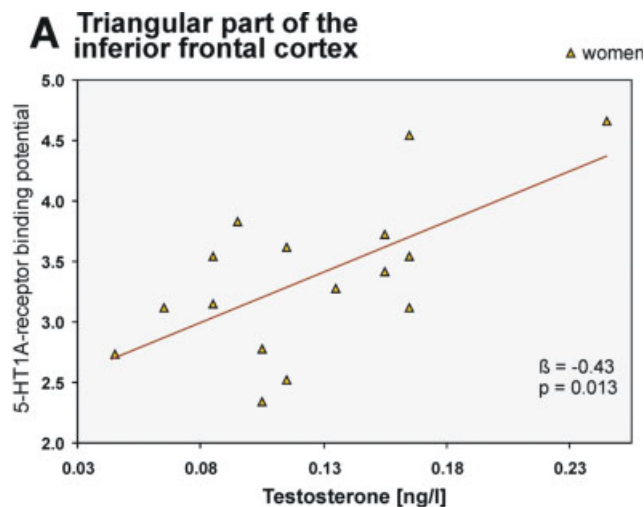
Plasma levels of sex hormone-binding globulin in high- vs. low-aggression subgroups in the components of the total aggression score (“spontaneous aggression,” “reactive aggression,” and “impulsiveness”). Asterisks indicate levels of significance according to *t* tests (\**P* < 0.05). Bars display means, error bars give standard error of the median (SE), *n* = 33. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

significantly related to 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in frontal areas in women, namely in the superior ( $\beta = 0.61$ ,  $t = 2.91$ ,  $P = 0.012$ ) and middle frontal cortices ( $\beta = 0.64$ ,  $t = 3.09$ ,  $P = 0.008$ ), in the triangular ( $\beta = 0.65$ ,  $t = 3.24$ ,  $P = 0.006$ , Fig. 6A) and orbital parts of the inferior cortex ( $\beta = 0.59$ ,  $t = 2.72$ ,  $P = 0.017$ ), in the medial part of the superior ( $\beta = 0.61$ ,  $t = 2.9$ ,  $P = 0.012$ ) and orbital part of the



**Figure 5.**

Inverse association between plasma levels of sex hormone-binding globulin (SHBG) and the 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in the posterior cingulate cortex. Line gives regression fit,  $\beta$  and *P* values according to linear regression, triangles = women, circles = men; *n* = 33. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]



**Figure 6.**

Association between plasma levels of testosterone and the 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in women in the triangular part of the inferior frontal (A) and in the orbital part of the middle frontal cortices (B). Lines give regression fit,  $\beta$  and *P* values according to linear regressions; *n* = 16. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

middle frontal cortex ( $\beta = 0.68$ ,  $t = 3.46$ ,  $P = 0.004$ , Fig. 6B), in the orbitofrontal cortex ( $\beta = 0.59$ ,  $t = 2.53$ ,  $P = 0.024$ ), as well as in the ACC ( $\beta = 0.63$ ,  $t = 3.06$ ,  $P = 0.008$ ). In men, testosterone was significantly associated only in the PCC ( $\beta = 0.49$ ,  $t = 2.15$ ,  $P = 0.049$ ). In this area, a similar trend was also seen in women ( $P = 0.09$ ). No further associations were found ( $P > 0.05$ ).

## DISCUSSION

This study demonstrates for the first time a selective interrelation between the 5-HT<sub>1A</sub> receptor distribution, sex



hormones, and aggression scores in humans, as previously hypothesized [Birger et al., 2003; Davidson et al., 2000]. Using PET and the radioligand [ $^{11}\text{C}$ ]WAY-100635 in 33 healthy subjects, we found higher total aggression scores in subjects exhibiting a higher density or affinity of postsynaptic 5-HT<sub>1A</sub> receptors in the dorsolateral and ventromedial prefrontal cortex, in the orbitofrontal cortex, and in the ACC. Moreover, a higher rating on the “spontaneous aggression” component of the total aggression score was characterized by lower SHBG levels. Third, higher SHBG plasma levels corresponded to lower postsynaptic 5-HT<sub>1A</sub> receptor affinities or densities in the prefrontal cortex and even more pronounced in the ACC and PCC and in the AMY. In women only, strong correlations were also found regarding levels of testosterone and frontal areas.

### Aggression and Frontal Serotonin

It is well established that the outcome variable “binding potential” ( $= B_{\text{Max}}/K_D$ ) measured with PET and the radioligand [ $^{11}\text{C}$ ]WAY-100635 stands for the density or affinity of the 5-HT<sub>1A</sub> receptor in the respective area [detailed in a consensus statement, Innis et al., 2007; Pike et al., 1996]. Thus, our findings point to a higher density or affinity of inhibitory 5-HT<sub>1A</sub> receptors in frontal areas in subjects exhibiting higher aggression scores. As a consequence, it seems likely that higher aggression goes along with an increased inhibition or hypofunction of prefrontal and anterior cingulate cortices during serotonergic neurotransmission. Considering the suggested crucial role of higher-order cortices like the prefrontal cortex in the control of impulsive affective states [Davidson et al., 2000], this might result in intensified emotional behaviors. For example, lesions of the prefrontal cortex due to stroke [Chan et al., 2006] or war injuries [Grafman et al., 1996] have been reported to increase aggressive behavior in humans. Further support for this hypothesis arose from PET studies ascribing prefronto-limbic circuits an essential role in allowing or inhibiting aggressive behaviors. In patients with impulsive personality disorder, a drastically reduced glucose metabolism was found in the prefrontal and anterior cingulate cortices after administration of the serotonin-releaser fenfluramine compared to controls, thus suggesting an impaired (pre)frontal activation by serotonin [Siever et al., 1999; Soloff et al., 2003]. A study including 41 murderers likewise observed prefrontal hypo- and subcortical hyperactivation using PET [Raine et al., 1997, 1998]. When trying to reduce pathologic aggressive behavior, treatments with SSRIs have commonly shown to be potent agents [New et al., 2004]. This provided further evidence of a positive association between aggression and the postsynaptic 5-HT<sub>1A</sub> receptor, because SSRI treatment in anxiety patients were found to reduce 5-HT<sub>1A</sub> receptor densities or affinities in the posterior and subgenual part of the ACC and hippocampus and as trend also in the orbitofrontal cortex according to a recent study of our group [Spindellegger et al., in press]. It seems therefore likely that a loss

of inhibitory prefrontal control over limbic centers, due to 5-HT<sub>1A</sub>-mediated neurotransmission, might induce exaggerated affective responses including enhanced aggressive behavior [Davidson et al., 2000].

### Pre- and Postsynaptic 5-HT<sub>1A</sub> Receptors

The current results, namely a higher 5-HT<sub>1A</sub> receptor distribution in the prefrontal and anterior cingulate cortices in subjects with higher aggression scores, are in line with a recent animal study using polymerase chain reaction in genetically defined aggressive rats [Popova et al., 2007]. However, they contradict a previous PET study investigating 25 human subjects [Parsey et al., 2002]. We observed an inverse correlation between aggression and the 5-HT<sub>1A</sub> receptor BP<sub>ND</sub> in the ventromedial prefrontal, orbitofrontal, and anterior cingulate cortices, but also in the AMY and RN using also the selective radiotracer [ $^{11}\text{C}$ ]WAY-100635 [Parsey et al., 2002]. Note that in the current study, we observed a congruent pattern in the RN, which might have failed to reach significance due to partial volume effects. A similar negative 5-HT<sub>1A</sub> correlation in the RN was also claimed by other studies in rodents [Popova, 2006]. However, in addition to the relatively smaller number of subjects, Parsey et al. [2002] used a questionnaire designed to measure life-time history of aggressive events, which might not reflect the same separated dimensions of aggression as measured by the sensitive questionnaire used in our study [Hampel and Selg, 1975]. Moreover, the age range was quite large and statistical results were considerably weaker than ours. Similar limitations may also explain the negative findings of Rabiner et al. [2002], who correlated the 5-HT<sub>1A</sub> receptor distribution with global scores of personality questionnaires in a database of 61 healthy, exclusively male subjects but did not find any significant associations.

Our findings are in line with studies suggesting a different role of pre- and postsynaptic 5-HT<sub>1A</sub> receptors in mediating aggression-related serotonergic neurotransmission [de Boer and Koolhaas, 2005; Miczek et al., 2007]. It was found that certain high-affinity 5-HT<sub>1A</sub> receptor agents, such as ipsapirone and S-15535, exert antiaggressive effects most likely via a selective agonistic action at somatodendritic autoreceptors in the RN, but no or a rather antagonistic action on postsynaptic 5-HT<sub>1A</sub> receptors in central target areas as measured in rodents [de Boer et al., 1999; Millan et al., 1994; Scott et al., 1994]. Thus, corresponding to our results, a functionally distinct role of presynaptic [i.e., in the RN, Hoyer et al., 2002] and postsynaptic [i.e., in neocortical areas, Hoyer et al., 2002] 5-HT<sub>1A</sub> receptors should be assumed in consistency with the literature.

### Aggression, Serotonin, and Sex Hormones

Considering sex hormones, we found higher aggression scores to be significantly associated with lower SHBG levels. Moreover, we observed inverse associations between plasma

levels of SHBG and the 5-HT<sub>1A</sub> receptor density or affinity in frontal and limbic areas. Because SHBG determines the amount of circulating testosterone and estrogen, it should display reciprocal associations compared to testosterone and 17 $\beta$ -estradiol. We observed such an inverse relationship regarding testosterone and aggression as well as testosterone and 5-HT<sub>1A</sub> in women. This on the one hand further underlines the well-documented modulatory role of sex steroid hormones in aggression. For example, levels of both estrogens and testosterone have been shown to control maternal aggression, whereas primarily testosterone exerts regulatory influence on intermale aggression in rats [reviewed in Albert et al., 1992; Lonstein and Gammie, 2002]. Because higher testosterone levels are also associated with more aggressive behaviors in mammals including humans [reviewed in Archer, 2006], our positive relationship between levels of bioavailable sex hormones, particularly testosterone, and aggression scores in men are quite as expected.

On the other hand, our study provides first evidence for the putative link between serotonin and sex hormones in the modulation of human aggressive behavior [Birger et al., 2003]. It was frequently suggested that aggression-related actions of sex hormones are at least in part mediated by serotonergic neurotransmission [Cosgrove et al., 2007; Rubi-now et al., 1998]. Beside a variety of studies on sexual dimorphisms in the serotonergic system [Cosgrove et al., 2007], several studies in rodents and primates have investigated how sex-steroids modulate serotonergic transmission. Regarding the 5-HT<sub>1A</sub> receptor, it has been suggested in both rodents [Flügge et al., 1999] and humans [Spindelegger et al., 2008] that fluctuating levels of sex hormones during the menstrual cycle are accompanied by changing 5-HT<sub>1A</sub> receptor distributions. Moreover, as shown in nonhuman primates, a long-term administration of estrogen leads to down-regulating of both pre- and postsynaptic 5-HT<sub>1A</sub> receptor affinity or density [Lu and Bethea, 2002; Pecins-Thompson and Bethea, 1999]. This regulatory effect of estrogen might be reflected by our results, since we observed a significant positive correlation between 17 $\beta$ -estradiol levels and the 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub> in the RN in women. Here, specific transcription factors might be implemented in the underlying molecular machinery, which was first demonstrated experimentally in nonhuman primates for MAO. According to Zhang et al. [2006] and Gundlah et al. [2002], ovarian steroids have been found to activate MAO gene expression via estrogen receptors. Taken together, extensive interrelation between sex hormones and serotonergic neurotransmission might play a crucial role in modulating aggressive behavior. Interestingly, androgenic and estrogenic metabolites of testosterone were found to distinctively modulate 5-HT<sub>1A</sub> and <sub>B</sub> receptor agonist effects in the control of aggressive behavior in mice and hamsters in the lateral septum and medial preoptic area [Cologer-Clifford et al., 1996; Simon et al., 1998]. This is in line with our findings in humans when considering selective, area-specific associations between aggression, sex hormones, and the 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub>.

## Strengths and Limitations

As a limitation of our study, the subject population primarily consisted of medical students which might have affected the generalizability of results. In addition, aggressive behavior was not assessed in an experimental setting but in a self-reported, yet detailed and validated questionnaire that was designed to differentiate between distinct dimensions of aggression. However, the sensitive acquisition of aggression-related items resulted in statistically robust data. Further strengths of our study lie in the large and balanced sample size including both sexes, the advanced PET imaging with [<sup>11</sup>C]WAY-100635, as well as adjustment for potential confounders and sensitive hormone measures.

## CONCLUSION AND OUTLOOK

Our study provides good evidence that aggressive behavior is closely associated with and presumably controlled by serotonergic neurotransmission in humans, particularly via postsynaptic 5-HT<sub>1A</sub> receptors in frontal areas. These interactions might be further modulated by a specific regulatory effect of sex hormones on the serotonergic system, because plasma hormone levels were related to both aggression and 5-HT<sub>1A</sub> receptor BP<sub>NDS</sub>. Future prospective trials should now examine the proposed underlying mechanisms. Specifically, it should be clarified how sex hormones might up- or down-regulate serotonergic receptors, transporters, and signalling with regard to aggressive behavior.

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