Lateralization of the serotonin-1A receptor distribution in language areas revealed by PET

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Lateralization is a well described aspect of the human brain. A plethora of morphological, cytological and functional studies describes hemispheric asymmetry in auditory and language areas. However, no study has reported cortical lateralization in the healthy human brain in vivo on the level of neurotransmitter receptors and in relation to functional organization so far. In this study, we assessed the distribution of the main inhibitory serotonergic receptor (the 5-HT1A receptor) and analyzed its regional binding with regard to hemisphere, sex and plasma levels of sex steroid hormones (testosterone, estradiol, progesterone). We quantified the 5-HT1A receptor binding potential by positron emission tomography (PET) using the highly selective and specific radioligand [carbonyl-11C]WAY-100635 and measured hormone levels in thirty-four (16 females, 18 males) healthy right-handed subjects. The obtained data were analyzed in an automated region of interest (ROI) based approach investigating 14 auditory, language and limbic areas. We found significantly higher 5-HT1A receptor binding in the superior and middle frontal gyri of the right hemisphere, the triangular and orbital parts of the inferior frontal gyrus, the supramarginal gyrus, the superior gyrus of the temporal pole and the middle temporal gyrus. Regions of the primary and secondary auditory cortex (Heschl’s gyrus and superior temporal gyrus) and the Rolandic operculum displayed significantly higher receptor binding in the left hemisphere. 5-HT1A receptor binding was 1.8–2.9% higher in right frontal ROIs and 2–3.6% higher in left primary and secondary auditory regions. There was no hemispheric difference in 5-HT1A receptor binding in the hippocampus, amygdala, and insula. Post-hoc testing suggested that lateralization of 5-HT1A receptor binding differed between the sexes in the triangular part of the inferior frontal gyrus. For the first time, this PET study shows lateralization of the main inhibitory receptor of the serotonergic system in functionally asymmetric organized regions of the healthy human brain in vivo.

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However, the connection between sex hormones and language lateralization is much discussed (Friederici et al., 2008; Gadea et al., 2003) and remains a question for further investigation.

Compared to the multitude of studies describing brain asymmetry on either anatomical or functional principles there is a remarkable lack of data for neurochemical hemispheric differences. Only few previous studies have investigated lateralization effects in the serotonin receptor binding. An asymmetry of temporal areas has been observed previously in patients with complex partial seizures, with a lower [18F] FCWAY binding in the ipsilateral inferior mesial and lateral temporal cortices. Control subjects, however, showed no lateralization in these regions (Tozcek et al., 2003). For the 5-HT2A receptor, data published by Trichard et al. (1998) suggested a lateralization of the 5-HT2A receptor binding potential to the left hemisphere though no definite conclusions can be drawn from this study, as the authors did not compare the binding potential values in both hemispheres statistically. To the best of our knowledge, only striatal dopamine D2/3 receptors have been described to exhibit a different hemispheric distribution in the healthy human brain (Larisch et al., 1998).

Asymmetric organization in language areas also seems to be mirrored in the lateralization of modular neurotransmitter systems as the serotonergic system. The influential role of serotonin on auditory processing is supported by studies using loudness dependence of auditory evoked potentials (LDAEP). Here, a close relationship between the level of serotonergic neurotransmission and the difference of amplitudes in auditory event-related potentials was demonstrated (Hegerl et al., 2001). In healthy subjects, left-hemispheric dominance for language is re-demonstrated (Hegerl et al., 2001). In healthy subjects, left-hemispheric dominance for language is reflected by right ear advantage for speech stimuli. Alterations of this lateralization and magnitude of LDAEP have been shown to be associated with depression (Pine et al., 2000) and social anxiety disorder (Bruder et al., 2004a), i.e. disorders that are both linked to dysfunctions of serotonergic neurotransmission (Kasper et al., 2005; Lanzenberger et al., 2007) and have been found to relate to (Bruder et al., 2001) and even predict (Bruder et al., 2004b; Gallinat et al., 2000; Linka et al., 2004) treatment response to SSRIs. These studies suggest a hemispheric distribution of serotonin receptors and reuptake sites that relates to the hemispheric differences in anatomy and function.

The main inhibitory serotonergic receptor subtype, the serotonin-1A (5-HT1A) receptor, is of high interest for psychiatric research due to its modulatory effects on emotion and its involvement in the pathogenesis of psychiatric disorders (Drevets et al., 2007; Kasper et al., 2002; Lanzenberger et al., 2007). Since there is a significant relationship between regional brain activation and expression of the 5-HT1A receptor as shown by our group (Gerstl et al., 2008) and others (Savic et al., 2004), we would expect that the lateralized functional organization of language areas is mirrored by the 5-HT1A receptor distribution pattern. Sex differences in 5-HT1A binding have been suggested (Jovanovic et al., 2008), though not confirmed (Stein et al., 2008), and the expression of the 5-HT1A receptor seems to be modulated by circulating sex steroid hormones (Bethea et al., 1998; Zhang et al., 1999).

We therefore investigated lateralization in the 5-HT1A receptor distribution and its relationship to sex and circulating sex hormones. We hypothesized that (1) the 5-HT1A receptor binding potential is lateralized to the dominant hemisphere in language areas (2) sex differences can be found in the receptor binding potential of lateralized brain regions of interest and (3) that plasma levels of testosterone correlate with the magnitude of 5-HT1A receptor binding in regions of interest more lateralized in the male brain when compared to the female brain.

Methods

Subjects

A total of 36 healthy subjects (mean age=26.2 years, SD=4.9), 18 men and 18 women, matched for age and socio-economic status, were enrolled in this PET study. Participants were recruited from the community via advertisements and gave written informed consent at the screening visit. The included subjects also participated in measurements published elsewhere (Spindelegger et al., 2008; Stein et al., 2008). Each participant underwent a general physical and neurological examination including an electrocardiogram and routine blood screening for assessment of physical health. Handedness was assessed using a modified version of the Edinburgh Inventory (Oldfield, 1971). Two female subjects had to be excluded, since their handedness scores indicated them as left-handed which has been described as an influencing factor for language dominance (Knecht et al., 2000).

Bioactive hormone plasma levels for 17β-estradiol, testosterone and progesterone were assessed at the day of the PET scan by taking blood samples from the cubital vein. Since the menstrual cycle phase might influence regional 5-HT1A receptor binding (Jovanovic et al., 2006), all female volunteers were measured in the follicular phase, i.e. within the first 3 to 10 days of the menstrual cycle, which was verified by plasma levels of progesterone and 17β-estradiol. Additionally, only women without intake of oral contraceptives or hormone treatment were included. Hormone analyses were performed at the Clinical Institute for Medical and Chemical Laboratory Diagnostics at the Medical University of Vienna (MUW). Assays were performed using the E170 Module (Roche E170 Modular Analytical System®). Electrochemiluminescence (ECLA) was used for quantification of total progesterone, estradiol, and testosterone in plasma. The lower limit of sensitivity was 0.02 ng/ml and the interassay coefficient of variation was 4–8% for testosterone, 0.2 ng/L and 4–7% for progesterone, and 10 pg/ml and 4–8% for estradiol, respectively (see http://www.kimcl.at). Pregnancy was excluded in female participants using an hCG urine test (ACON Laboratories, Inc., USA) at the screening visit and before each PET scan. Participants were screened for psychiatric disorders with the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) performed by an experienced psychiatrist. Subjects with chronic medication, hormonal treatment, pregnancy or a history of drug abuse were excluded. The study was approved by the ethics committee at the Medical University of Vienna. All subjects received reimbursement for participation.

PET scanning

Positron emission tomography scans were conducted with a GE Advance PET scanner (General Electric Medical Systems, Milwaukee, Wisconsin) at the Department of Nuclear Medicine, Medical University of Vienna as described previously (Lanzenberger et al., 2007; Spindelegger et al., 2008). Briefly, the head of each subject was placed in the scanner parallel to the orbitomeatal line using a laser beam system and correct positioning was checked with a scout scan in order to cover the cerebellum in the field of view (FOV). To assure a stable head position during scan time a polyurethane cushion and straps covering forehead and chin were used. Tissue attenuation was measured in a five-minute transmission scan in 2D mode with a retractable 60Ge ring source. The 3D dynamic scans started simultaneously with intravenous bolus injection of [carbonyl-11C]WAY-100635 in phosphate buffered saline (pH 7.4). Thirty time frames covering the total acquisition time of 90 min were acquired, 15 frames of 1 min and 15 frames of 5 min duration. Scatter and attenuation correction were applied and PET data were reconstructed by means of an iterative filtered back-projection algorithm (FORE-ITER) resulting in 35 contiguous slices (matrix 128 × 128) with a spatial resolution of 4.36 mm full-width at half maximum (FWHM) at the center of the FOV.

Radiochemistry

The highly specific radioligand [carbonyl-11C]WAY-100635, an antagonist at the 5-HT1A receptor, was synthesized at the Department
of Nuclear Medicine, Medical University of Vienna following the optimized multistep synthesis procedure developed by Wadsak et al. (2007). The synthesis procedure comprised cyclotron \[^{11}C\]CO\(_2\) isotope generation, purification by high-performance liquid chromatography (HPLC) and solid phase extraction. The mean injected tracer radioactivity was 5.61±0.79 MBq (mean±SD) per kilogram body weight (HPLC) and solid phase extraction. The mean injected tracer radiochemical purity of 97.87±0.01% (mean±SD).

Region of interest (ROI) analysis of regional binding

Manual delineation on individual magnetic resonance imaging scans in ROI-based approaches is often biased by the variability between raters and side differences in ROI size, whereby direct interhemispheric comparability is compromised. Consequently, we chose to delineate ROIs by generating a standardized ROI template based on the 5-HT\(_{1A}\) receptor distribution map itself and on the Anatomical Automated Labelling (AAL, Tzourio-Mazoyer et al., 2002) atlas fitting the MNI (Montreal Neurologic Institute) standard brain of the Statistical Parametric Mapping (SPM5) software package. Using PMOD 2.95 (Mikolajczyk et al., 1998) individual PET summation (PET\(_{\text{AD}}\)) images were generated by adding up all 30 time frames. These were normalized to the MNI space by applying a non-linear iterative algorithm. Calculating the average from the mean of individual PET scans and its mirrored equivalent resulted in a symmetric average 5-HT\(_{1A}\) receptor distribution map. By projecting and adapting the anatomical borders provided by the Anatomical Automated Labelling (AAL) atlas to this 5-HT\(_{1A}\) receptor distribution map, a symmetric ROI template was designed.

Supplementary material to the symmetric 5-HT\(_{1A}\) receptor binding potential map can be found on the website http://www.meduniwien.ac.at/neuroimaging/mf54_downloads.html.

The ROI template covered 14 brain areas, namely the superior frontal gyrus, the middle frontal gyrus, the orbital, triangular and opercular parts of the inferior frontal gyrus, the Rolandoic operculum, the Heschl’s gyrus, the supramarginal gyrus, the superior and middle temporal gyrus, the superior gyrus of the temporal pole, the insula, the hippocampus, the amygdala and the cerebellum as reference regions. The regions of interest are displayed on triplanar and surface views in Fig. 1. All ROIs including the cerebellum were delineated symmetrically, i.e. the ROIs were generated on a symmetric average 5-HT\(_{1A}\) receptor distribution map with exactly the same size and location on both hemispheres. The cerebellum was delineated as two separated regions of interest, one for each hemisphere, with a fixed volume of 4.5 cm\(^3\) as described by Parsey et al. (2005). The cerebellar ROIs were placed on PET signal intensities representing cerebellar grey matter (excluding vermis and venous sinus).

Quantification of 5-HT\(_{1A}\) receptor binding

For quantification of the 5-HT\(_{1A}\) receptor binding potential, individual dynamic PET scans were normalized to the ROI template in MNI space using deformation matrices obtained by normalizing PET\(_{\text{AD}}\) images to the created 5-HT\(_{1A}\) receptor distribution map as described above. Regional BP\(_{\text{ND}}\) values were then calculated by applying the Simplified Reference Tissue Model (SRTM2), a two-tissue compartment model (Wu and Carson, 2002), to each of the 14 regions of the symmetric ROI template by means of the kinetic modelling tool of PMOD 2.95. Due to its low specific binding of \[^{11}C\]WAY-100635, the cerebellum was defined as reference region (Burnet et al., 1997; Hall et al., 1997). The 5-HT\(_{1A}\) receptor potential values (BP\(_{\text{ND}}\) – following the guidelines published by Innis et al. (2007)) for each ROI were determined from mean region-specific and decay-corrected time activity curves using a custom-made software implemented in Matlab 7.4 (MathWorks, Nantick, Massachusetts).

Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, Illinois). All tests were two-tailed and the threshold of significance was set at \(p\leq0.05\). For each ROI a lateralization quotient (LQ) was calculated to characterize the hemispheric asymmetry of the 5-HT\(_{1A}\) receptor BP\(_{\text{ND}}\), providing a value between −100 and +100. Negative values indicate higher BP\(_{\text{ND}}\) on the left side, positive values higher receptor binding on the right side. The LQ was calculated as follows:

![Fig. 1](image.png)
LQ = 100 *[ (BPND [ROI right] - BPND [ROI left]) / (BPND [ROI right] + BPND [ROI left])]. The LQ equals approximately one-half the percent difference of regional 5-HT1A receptor BPND between hemispheres. In order to control for normal distribution and equality of variance, the Kolmogorov–Smirnov test and the Levene's test were applied. Possible effects of age or radiochemical parameters, namely injected radioactivity, radiochemical purity, weight of WAY-100634, weight of unlabelled WAY-100635 and specific radioactivity of the radioligand, on the regional 5-HT1A receptor BPND were controlled for by calculating Spearman's and Pearson's product moment correlation coefficients, respectively. Variables without correlations to receptor binding or receptor laterality were excluded from further analyses. The possible bias of age and handedness scores on the region-specific LQ was excluded in the same way. Due to the narrow age range within the study population we expected no significant effect of age on the 5-HT1A receptor binding and therefore no subsequent analyses were performed.

To assess hemispheric differences in receptor binding, a repeated-measures analysis of variance (ANOVA) was applied with the 5-HT1A receptor binding in each ROI as dependent variable, hemisphere and region as within-subject factor, and sex as between-subject factor. Obtained region-specific significance values were corrected for type I error using the Bonferroni adjustment for multiple comparisons. Furthermore, an analysis of sex differences in LQ values was done using a multivariate analysis of variance (MANOVA) with regional LQ values (14 levels) as dependent variables and sex as fixed factor, followed by independent-samples t-tests for each region. The Bonferroni corrected significance level was set at \( p \leq 0.00357 \). Regions that displayed sex differences in 5-HT1A receptor binding were furthermore tested for a linear correlation between hormone levels and regional LQ values. The correlation method was adapted to the distribution (i.e., parametric or non-parametric) of hormone data and was calculated for the whole study population as well as for the male and female subgroup.

Results

Hemispheric lateralization analysis of 5-HT1A receptor binding

There was no correlation between radiochemical variables, age and handedness scores and regional receptor binding or LQ values, therefore these parameters were dropped from further analyses. The repeated-measures ANOVA showed a highly significant main effect for hemisphere on the regional 5-HT1A receptor BPND (Pillai's trace=0.82, \( F_{1,33}=6.27, p=0.00017 \)). However, there was no hemisphere * gender effect (Pillai's trace=0.47, \( F_{14,39}=1.19, p=0.35 \)). Post-hoc univariate tests for hemispheric differences of 5-HT1A receptor BPND in each ROI were significant in 5 of 14 regions following adjustment for multiple comparisons (\( p \leq 0.00357 \)). Results are shown in Table 1. The hemispheric dominance of receptor binding is reflected by the LQ mean values given in Table 1 and Fig. 2.

After Bonferroni correction for multiple comparisons (\( p \)-level set at \( p \leq 0.00357 \)), significant lateralization of the BPND values was found in the superior (\( F_{1,33}=10.14, p=0.0032 \)) and middle frontal gyrus (\( F_{1,33}=22.52, p=0.00004 \)), the triangular part of the inferior frontal gyrus (\( F_{1,33}=14.13, p=0.00068 \)), the superior temporal gyrus (\( F_{1,33}=9.93, p=0.0035 \)) and the Rolandic operculum (\( F_{1,33}=7.97, p=0.0014 \)). All of the above mentioned regions lateralized to the right hemisphere, except for the superior temporal gyrus and the Rolandic operculum. Also the Heschl's gyrus (\( F_{1,33}=7.12, p=0.011 \)) showed lateralization to the left hemisphere, though this effect did not withstand the Bonferroni correction.

Sex and lateralization quotient values

The MANOVA assessing sex differences in LQ values showed no significant main effect for sex on the regional 5-HT1A receptor BPND lateralization (Pillai's trace=0.48, \( F_{14,20}=1.39, p=0.247 \)). However, exploratory t-tests revealed a significant sex difference in the triangular part of the inferior frontal gyrus (\( t_{1,33}=-3.22, p=0.0029 \)), that survived the Bonferroni correction. Comparison of the mean LQ values in females and males revealed a higher lateralization of receptor binding to the right hemisphere in females than in males (Fig. 3); t-tests in the remaining regions were all non-significant indicating a sex-dependent and region-specific lateralization in the triangular part of the inferior frontal gyrus.

Sex hormones and lateralization quotient values

Our analyses for linear associations between hormone levels and LQ values were focused on the triangular part of the inferior frontal gyrus exclusively, due to the lack of sex differences in the lateralization of 5-HT1A receptor binding in any other region examined. Here, Spearman's correlation coefficient confirmed a significant negative correlation between LQ values and bioactive testosterone levels (\( r=-0.45, p=0.007 \)), when analyzing the whole study population. Subsequent correlation analyses in the separate male (\( r=0.05, p=0.843 \)) and female (\( r=0.117, p=0.666 \)) group did

### Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Right BPND Mean ± SEM</th>
<th>Left BPND Mean ± SEM</th>
<th>Lateralization (LQ) Mean ± SEM</th>
<th>ANOVA (BPND) ( F_{1,33} )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior frontal gyrus</td>
<td>3.32±0.12</td>
<td>3.26±0.12</td>
<td>0.91±0.27</td>
<td>10.14</td>
<td>0.0032</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>3.53±0.13</td>
<td>3.44±0.13</td>
<td>1.33±0.25</td>
<td>22.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior frontal gyrus, orbital part</td>
<td>3.62±0.13</td>
<td>3.53±0.13</td>
<td>1.22±0.39</td>
<td>9.39</td>
<td>0.0044</td>
</tr>
<tr>
<td>Inferior frontal gyrus, triangular part</td>
<td>3.28±0.12</td>
<td>3.18±0.11</td>
<td>1.41±0.43</td>
<td>14.13</td>
<td>0.0007</td>
</tr>
<tr>
<td>Inferior frontal gyrus, opercular part</td>
<td>3.61±0.13</td>
<td>3.58±0.13</td>
<td>0.39±0.47</td>
<td>0.59</td>
<td>0.4480</td>
</tr>
<tr>
<td>Insula</td>
<td>4.95±0.18</td>
<td>4.93±0.17</td>
<td>0.10±0.38</td>
<td>0.28</td>
<td>0.6005</td>
</tr>
<tr>
<td>Rolandic operculum</td>
<td>4.30±0.15</td>
<td>4.45±0.16</td>
<td>-1.59±0.45</td>
<td>12.16</td>
<td>0.0014</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>3.99±0.15</td>
<td>3.90±0.15</td>
<td>1.22±0.42</td>
<td>7.97</td>
<td>0.0081</td>
</tr>
<tr>
<td>Heschl's gyrus</td>
<td>4.06±0.16</td>
<td>4.20±0.15</td>
<td>-1.82±0.60</td>
<td>7.12</td>
<td>0.0118</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>4.11±0.15</td>
<td>4.20±0.15</td>
<td>-1.01±0.34</td>
<td>6.55</td>
<td>0.0035</td>
</tr>
<tr>
<td>Temporal pole, superior gyrus</td>
<td>5.02±0.19</td>
<td>4.92±0.19</td>
<td>0.99±0.35</td>
<td>9.93</td>
<td>0.0154</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>4.48±0.16</td>
<td>4.41±0.16</td>
<td>0.99±0.35</td>
<td>6.25</td>
<td>0.0178</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>4.83±0.25</td>
<td>4.85±0.25</td>
<td>-0.74±1.41</td>
<td>0.03</td>
<td>0.8640</td>
</tr>
<tr>
<td>Amygdala</td>
<td>4.21±0.17</td>
<td>4.24±0.18</td>
<td>-0.37±0.79</td>
<td>0.21</td>
<td>0.6520</td>
</tr>
</tbody>
</table>

The listed LQ values equal approximately one-half the percent difference of regional 5-HT1A receptor BPND and \( p \)- and \( F \)-values for univariate tests of the repeated-measures ANOVA are given in the right column, significant \( p \)-values surviving the adjustment for multiple comparisons (\( p \leq 0.00357 \)) are bolded (\( n=34 \)).
not reflect the overall effect and showed no significant correlations. As expected, the analyses of the 13 remaining regions showed no significant correlation with the testosterone plasma level ($p > 0.05$) either. There was also no significant correlation between the LQ of 5-HT$_{1A}$ receptor binding in frontal areas and estradiol or progesterone levels.

**Fig. 2.** Regional lateralization of the serotonin-1A (5-HT$_{1A}$) receptor binding potential. Bars display mean values of the lateralization quotient, calculated from regional receptor binding potential values. Error bars indicate the standard error of mean (SEM), $n=34$. Significant differences ($p<0.00357$) in receptor binding between hemispheres according to post-hoc univariate tests are marked with an asterisk.

**Fig. 3.** Regional lateralization of serotonin-1A (5-HT$_{1A}$) binding potential values split by gender. Bars display mean values of the lateralization quotient. Asterisk indicates significant difference (post hoc t-test, $t_{135} = -3.32, p=0.003$). Error bars give the standard error of mean (SEM), $n_{female}=14, n_{male}=16$. 

**Brain Regions Of Interest**
- Superior Frontal Gyrus
- Middle Frontal Gyrus
- Inferior Frontal Gyrus, Orbital Part
- Inferior Frontal Gyrus, Triangular Part
- Inferior Frontal Gyrus, Opercular Part
- Insula
- Rolandic Operculum
- Heschl’s Gyrus
- Supramarginal Gyrus
- Superior Temporal Gyrus
- Temporal Pole, Superior Gyrus
- Middle Temporal Gyrus
- Hippocampus
- Amygdala
Discussion

To the best of our knowledge, this is the first PET study demonstrating a significant lateralization of the serotonergic system in functionally asymmetric organized regions of the healthy human brain. Supporting our first hypothesis, the hemispheric lateralization in 5-HT_{1A} receptor binding was found in several auditory and language areas. Regions representing the primary and secondary auditory cortex (i.e. Heschl's gyrus and superior temporal gyrus) showed a left-hemispheric dominance of the 5-HT_{1A} receptor binding. Also, receptor binding in the left Rolandic operculum was higher on the left than on the right side. This effect is clearly distinct from receptor lateralization in neighbouring cortical regions since all of them displayed trends (p > 0.05) towards right-hemispheric dominance (Fig. 2). The left Heschl's gyrus and superior temporal gyrus were shown activated during early auditory processing of language (Zatorre et al., 2002) and are different in cytoarchitecture to their right-hemispheric counterparts, with higher numbers of functional minicolumns in the left hemisphere. Therefore, higher left-hemispheric receptor binding may either indicate a specific influential role of the 5-HT_{1A} receptor on early auditory processing of language cues, or might reflect the higher number of functional units encompassed by the ROI. In addition, the area-specific lateralization of Heschl's gyrus and superior temporal gyrus to the left side in contrast to neighbouring areas which tend to lateralize to the right side makes artefacts associated with limitations of spatial normalization procedures less probable.

All remaining regions with significant receptor lateralization exhibited higher 5-HT_{1A} receptor binding in the right hemisphere. This is of special interest in the light of hemisphere-specific models of emotion processing and the influence of serotonergic modulation on mood disorders. The “right-hemisphere hypothesis” states that the right side of the brain is specialized for the perception, expression and experience of emotion, regardless of valence. This model originates from observations made in patients with right-hemispheric lesions showing difficulties to express emotion or to recognize and discriminate facial affect (Adolphs et al., 1996). But also studies using intracarotid sodium amytal injection (Ahern et al., 1991) and neuroimaging techniques (Buchanan et al., 2000; Sato et al., 2004) emphasize the role of the right hemisphere in perception of emotion. The right frontal lobe and especially its inferior aspect represent important communicative functions (Nishitani et al., 2005). Unlike the left hemisphere with the extensively-described Broca area that is predominantly involved in naming (Salmelin et al., 1994), semantic (Amunts et al., 2004) and syntactic (Friederici and Kotz, 2003) functions, the right sided counterpart serves more emotion-related functions such as processing of emotional prosody (Meyer et al., 2002; Mitchell et al., 2003) and assessment of facial emotion (Nakamura et al., 1999). Processing of prosodic information also activates inferior parietal and middle temporal regions (Johnstone et al., 2006; Mitchell et al., 2003). Activation patterns associated with perception of emotional prosody seem to be distributed within the inferior frontal gyrus, basal parietal structures and the middle temporal gyrus of the right hemisphere (Mitchell et al., 2003), while the perception of facial emotion activates the right frontal cortex (Nomura et al., 2003). Although some studies (Buchanan et al., 2000; Wildgruber et al., 2004) propose prosodic information to be processed bilaterally in inferior frontal regions, the dominance of the right hemisphere is regarded as a common feature of emotional communication.

In our study, the superior and middle frontal gyrus, the orbital and triangular parts of the inferior frontal gyrus, the superior and middle temporal gyrus and the supramarginal gyrus showed significantly higher receptor binding in the right hemisphere, although only the significance levels in the superior and middle frontal gyrus and the triangular part of the inferior frontal gyrus withstood Bonferroni correction. This hemispheric asymmetry of 5-HT_{1A} receptor binding in frontal, temporal and inferior parietal regions might indicate a right-lateralized modulation of the serotonergic inhibition. Considering the modulatory role of this receptor on emotion processing, as suggested by studies assessing alterations of receptor binding in affective disorders (Drevets et al., 2007; Lanzenberger et al., 2007), the right-hemispheric lateralization is consistent with hemisphere-specific models of emotion processing.

The 5-HT_{1A} receptor binding in limbic areas is extensively described in studies investigating the role of this receptor in depression and anxiety disorders. The lack of significant hemispheric differences in the hippocampus and amygdala goes in line with those prior findings since receptor lateralization in both areas has never been described in healthy brains. However, PET studies in epilepsy using the same or a derivative of the used radioligand reported side differences in patients (Savic et al., 2004; Tozcek et al., 2003). Furthermore, hemi-parkinsonism is associated with lateralization of the dopaminergic system mainly demonstrated in the striatum. But these asymmetries are based on pathological states including regional deletions and death of neurons expressing the 5-HT_{1A} receptor.

The second hypothesis of this PET study was a lateralization difference in 5-HT_{1A} receptor binding between men and women. Using [carbon-11]CWAY-100635, the 5-HT_{1A} receptor binding potential has been reported to be both different (Parsey et al., 2002; Jovanovic et al., 2008) and similar in men and women (Meltzer et al., 2001; Stein et al., 2008). However, none of these studies investigated a possible lateralization of the receptor distribution. In the present study, in agreement with Meltzer et al. (2001) and Stein et al. (2008), we found no general effect of sex. However, exploratory t-tests revealed a highly significant lateralization in the triangular part of the inferior frontal gyrus, with higher 5-HT_{1A} receptor binding in the right vs. left hemisphere in females compared to males. As mentioned before, the triangular part of the inferior frontal gyrus processes perception and production of emotional prosody. Females usually outperform males in emotional language tasks (e.g., Scholten et al., 2008) and suffer stronger impairment to the recognition of prosody by frontal lesions (Rymarczyk and Grabowska, 2007). Wildgruber et al. proposed sex differences in the processing of emotional intonation in several regions (Wildgruber et al., 2002), and Schirmer et al. described different functioning of the inferior frontal gyrus between sexes in a congruous vs. incongruous emotional prosody task but could not provide evidence for sex differences of prosodic function in the right inferior frontal gyrus (Schirmer et al., 2004). Although we found no direct evidence from functional studies towards sex differences in the right inferior frontal gyrus, our findings might reflect a sex-specific influence of the serotonin system on emotional prosody via the 5-HT_{1A} receptor. Our analyses were not able to detect correlates of receptor binding to the morphological sex differences in the Heschl’s gyrus found by Rademacher et al. (2001), who described atypical asymmetry (i.e. to the right side) to be more likely in females. Also the higher degree of anatomical (Good et al., 2001) and functional lateralization (Shaw et al., 1995) of language found in males was not mirrored by the 5-HT_{1A} receptor distribution in the present study. To summarize, sex differences of the lateralization in 5-HT_{1A} receptor binding were restricted to the triangular part of the inferior frontal gyrus.

The third hypothesis of this study investigated the relationship between lateralization in 5-HT_{1A} receptor binding and sex steroid hormones. Testosterone is regarded as an important factor for cerebral asymmetry in several developmental models (Geschwind and Galaburda, 1985c; Wintelson and Nowakowski, 1991) and might modulate sex differences in hemispheric lateralization of the serotonergic system. The correlation analysis testing this hypothesis was restricted to the triangular part of the inferior frontal gyrus according to preceding t-tests showing sex differences in LVQ values.
only in this region. The analysis of the whole study group revealed a significant negative correlation between plasma levels of bioactive testosterone and the 5-HT1A receptor lateralization. Subsequent analyses restricted to the male or female subgroup in this region did not reveal any correlation of LQ values with testosterone. The remaining regions were used as control regions and showed, as we suspected, no significant correlation. Furthermore, we found no effects of estradiol and progesterone on the LQ of 5-HT1A receptor binding. However, we can exclude possible effects of the menstrual cycle on receptor binding as suggested by Jovanovic et al. (2006) as we have controlled for cycle phase on the day of the PET measurement using plasma levels of 17β-estradiol and progesterone. To summarize, we were not able to confirm theories linking testosterone to cerebral lateralization in language on the level of the 5-HT1A Receptor binding.

To conclude, this PET study in thirty-four healthy subjects shows a significant lateralization in the 5-HT1A receptor distribution in the superior and middle frontal gyrus, the triangular part of the inferior frontal gyrus, the superior temporal gyrus and the Rolandic operculum. There was a significant difference in lateralization between men and women in the triangular part of the inferior frontal gyrus. These results provide evidence for a relationship between serotonergic organization and language representation in lateralized brain functions.

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