CHAPTER SEVEN
ROLE AND DISTRIBUTION OF SEROTONIN TYPE 2A RECEPTORS IN ALZHEIMER’S DISEASE
ROLE OF SEROTONIN AND SEROTONIN TYPE 2A RECEPTORS IN ALZHEIMER’S DISEASE

INTRODUCTION
Serotonin or 5-hydroxytryptamine (5-HT) is widely distributed in the whole brain and each receptor subtype has a specific regional distribution. It plays a role in a great variety of behaviours such as activity rhythms, food intake, sexual behaviour and emotional states. Serotonin type 2A (5-HT$_{2A}$, formerly called 5-HT$_2$) receptors, with a mainly cortical distribution, have been implicated in several largely ‘neuroexcitating’ brain functions, such as appetite control, thermoregulation and sleep and play an important role in the pathophysiology of mood and anxiety disorders, schizophrenia, ageing and also Alzheimer’s disease (AD). The following part explains the potential role of serotonin and serotonin type 2A receptors in Alzheimer’s disease.

ROLE OF SEROTONIN AND SEROTONIN TYPE 2A RECEPTORS IN COGNITIVE BEHAVIOUR
Alzheimer’s disease is typically characterised by a progressive memory impairment, predominantly a loss of short-term memory [5]. The 5-HT receptor is involved in various cognitive functions, especially learning, (working) memory and attentional processes [1]. These functions are not independent from each other or from other behavioural levels. For example, there are some connections between anxiety and memory, or between memory and attentional processes so 5-HT may modulate learning and memory by both direct and indirect ways [4]. Concerning the receptor subtypes, evidence exists that 5-HT$_{2A/2C}$ agonists prevent memory impairment and facilitate learning (consolidation) in situations involving a high cognitive demand [4,7]. The 5-HT$_{2A}$ receptor is thought to mediate also attentional rather than memory processes and acts by stimulating phospholipase C [3]. Finally, several interactions exist between the serotonergic and other neurotransmitter systems involved in memory. One of these interactions, especially for spatial memory, is the interaction between and modulation of the cholinergic system where 5-HT regulates the central cholinergic activity by modulating hippocampal and neocortical acetylcholine release, this through substance P interneurons. Also, the serotonergic role in learning and memory is made possible by interacting with the glutamatergic, dopaminergic or GABAergic systems [6].

ROLE OF SEROTONIN AND SEROTONIN TYPE 2A RECEPTORS IN NON-COGNITIVE BEHAVIOUR
Probably the most important role of the serotonin receptor lies in the non-cognitive aspects of Alzheimer’s disease. Indeed, serotonin plays an important role in a great variety of behaviours such as food intake, activity rhythms, sexual behaviour and emotional states. After all, in many cases these non-cognitive features of AD are the main reason for hospitalisation and cause the greatest distress to caregivers. For example, 5-HT$_{2A}$ receptor polymorphisms have been associated with both visual and auditory hallucinations and prominent psychotic symptoms [8,11].

ROLE OF SEROTONIN AND SEROTONIN TYPE 2A RECEPTORS IN AMYLOID FORMATION
Alzheimer’s disease amyloid consists of amyloid β-peptides (Aβ) derived from the larger precursor amyloid precursor protein (APP). Non-amyloidogenic APP processing involves regulated cleavage within the Aβ domain followed by secretion of the ectodomain (APPs). Both the synthesis of the
Amyloid precursor protein (APP) and its processing (i.e. to amyloidogenic Aβ peptides, soluble non-amyloidogenic APPs, and other APP fragments) are regulated by neurotransmitters. As such APP secretion is influenced by norepinephrine, prostaglandins, and muscarinic acetylcholine receptors [9]. However, the 5-HT$_{2A}$ receptor has been suggested to regulate in a dose-dependent way APPs secretion, which could eventually lead to the formation of amyloidogenic derivatives [12].

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5-HT has also a role in natural immunity in general, and more specifically in the superoxide production, phagocytosis, and the optimal accessory cell function of macrophages for natural killer and T-cells, which could eventually influence the removal of amyloid plaques [10]. Finally, the cerebral availability of plasma tryptophan, the precursor of 5-HT, decreases with activation of the immune system, the latter believed to be upregulated in AD [2]
REFERENCES


ABSTRACT

Serotonin (5-HT) and more specifically the 5-HT_{2A} receptor is involved in cognitive and non-cognitive behavior and plays an important role in Alzheimer’s disease (AD). The objective was to assess the 5-HT_{2A} binding potential (BP) in healthy volunteers and AD with SPECT and 123I-5-I-R91150, a selective radio-iodinated 5-HT_{2A} receptor antagonist. Twenty-six controls and 9 AD patients were included. A semiquantitative analysis with normalization on cerebellar uptake provided estimates of BP for 26 cortical regions of interest. An age-related decline of neocortical BP was found (11.6 % per decade). Compared to age-matched controls, a generally decreased neocortical BP in AD was found with a significant regional reduction in the orbitofrontal, prefrontal, lateral frontal, cingulate, sensorimotor, parietal inferior, and occipital region. These results are in line with previous postmortem, in vitro, and PET findings. The age-related decline highlights the necessity for matched advanced age study samples. The fact that the 5-HT_{2A} receptor is differentially affected in AD patients has implications for both the etiological basis and therapeutic management of AD.
INTRODUCTION
Approximately 90% of the total body amount of serotonin (5-HT) acts in the gastrointestinal system. Only 1-2% is present in the central nervous system where 5-HT receptors are generally involved in sleep, pain, behavior, learning, and memory [5,10]. More specifically, serotonin type 2A (5-HT_{2A}) receptors have been implicated in several brain functions, such as appetite control, sexuality, thermoregulation, and sustained attention and play an important role in the pathophysiology of mood, depressive, anxiety, and psychotic disorders, schizophrenia, ageing and also Alzheimer’s disease [2,5,9,18,30,31,42].

Alzheimer’s disease (AD), the most common form of dementia, is typically characterized by progressive impairment of recent memory. However, in the course of AD, other cognitive dysfunctions, behavioral and psychiatric symptoms emerge and become at least equally important [21]. The role of the 5-HT_{2A} receptor in AD is manifold. Firstly, the 5-HT_{2A} receptor has been suggested to play a role in the amyloid precursor protein secretion. Since this is linked to the β-amyloid fibrillogenesis, this could eventually lead to the subsequent formation of amyloid plaques, typically seen in AD [24,25,35,36]. Secondly, several genetic associations between 5-HT_{2A} receptor polymorphisms and the AD symptomatology e.g. visual or auditory hallucinations have been reported [23,34]. Thirdly, 5-HT has a role in natural immunity in general, and more specifically in the superoxide production, phagocytosis, and the optimal accessory cell function of macrophages for natural killer and T-cells, which could eventually influence the removal of amyloid plaques [32]. Moreover, the cerebral availability of plasma tryptophan, the precursor of 5-HT, decreases with activation of the immune system, the latter believed to be upregulated in AD [1,8]. Finally, a decrease in serotonergic cells in the central nervous system could eventually lead to a disturbance of functional interactions between the serotonergic on one hand and the cholinergic or dopaminergic system on the other hand [16,19,40,44].

$^{123}$I radiolabeled R91150 is a radio-iodinated 5-HT_{2A} receptor antagonist with high affinity ($K_D = 0.11 \pm 0.01$ nM). The selectivity of this ligand for 5-HT_{2A} receptors as compared to other neurotransmitter receptor binding sites such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2C}, 5-HT_{3}, dopamine D_{2}, α_{1} and α_{2} adrenoreceptors and histamine H_{1} receptors, is at least a factor of 50. $^{123}$I-5-I-R91150 binding is saturable and displaceable with the known 5-HT_{2A} receptor antagonist ketanserin and proved suitable for the imaging of 5-HT_{2A} receptors with single photon emission computed tomography (SPECT) in the human brain [11].

The objectives of the present study were, firstly, to study the age and gender effect of the 5-HT_{2A} receptor binding potential in a large group of healthy subjects (n=26) with an age range of 22 to 85 years and, secondly, to determine whether there are abnormalities in the 5-HT_{2A} receptor binding potential in AD patients compared to age-matched healthy controls, and if so, whether these abnormalities are correlated with cognitive defects or depressive symptomatology.
Role and distribution of serotonin type 2A receptors in Alzheimer’s disease

METHODS

PATIENTS

The study was approved by the medical ethics committee of the Ghent University Hospital and all patients gave informed (proxy-)consent. Nine AD patients (two males, mean age 81 ± 6 yrs, range 73-88 yrs) according to the NINCDS-ADRDA criteria were included with the diagnosis made by a board-certified neurologist [27]. The diagnosis was supported by the fact that there was evidence of cerebral atrophy on computed tomography or magnetic resonance imaging in all AD patients and by the fact that structural imaging did not reveal any brain disease causing dementia other than Alzheimer’s disease. The control group consisted of 26 healthy subjects (11 males; mean age 51 ± 24 yrs; range 22-85 yrs). For the comparison with the AD patient group, only the oldest age group was used consisting of 9 healthy subjects (3 males; mean age 77 ± 5 yrs, range 70-85 yrs). These two groups did neither differ significantly concerning age (Mann-Whitney U test, p = 0.16) or sex (Pearson Chi-Square test, p = 0.6).

METHODS

$^{123}$I-5-I-R91150 SPECT

Radionuclide synthesis and injection

Na$^{123}$I was purchased from Bristol-Myers Squib Pharma Belgium N.V. formerly Dupont Pharmaceuticals Ltd. (Brussels, Belgium). R91150 (4-amino-N-[1-[3-(4-fluorophenoxy)propyl][4-methyl-4-piperidinyl] 5-iodo-2-methoxybenzamide) is an original product of Janssen Pharmaceutica (Beerse, Belgium). $^{123}$I-5-I-R91150 was synthesized by electrophilic substitution on the 5-position of the methoxybenzamide group of R91150, followed by purification with high-performance liquid chromatography. The specific activity of the labeled compound was 370 GBq/µmol while the radiochemical purity of the final product yielded more than 99%. Thyroid was blocked with Lugol's solution for all subjects (5% iodine and 10% potassium iodide; one-day protocol of 20 drops one hr before radioligand injection). The administered dose was 185 MBq.

Image acquisition and reconstruction

All subjects were scanned on a triple-headed gamma camera (Toshiba GCA9300A, Dutoit Medical, Wijnegem, Belgium) equipped with low-energy super-high-resolution lead fan-beam collimators (measured resolution 8.1 mm) and $^{153}$Gd transmission rod sources allowing transmission scanning prior to emission scanning, enabling image coregistration [46]. Since previously published work with sequential dynamic brain scans has shown that the cortico-cerebellar ratio reaches pseudo-equilibrium between 90 and 110 min postinjection and remains stable thereafter for up to 4 h, acquisition was started between 110 and 140 min after tracer injection [11]. Emission images were acquired in a 128x128 matrix with 90 projections during 40 min consisting of 4 sequential frames of 10 min in order to omit frames when the subject was unable to complete the whole imaging session (at least two frames required for high enough count statistics). After triple-energy window scatter correction and uniform attenuation correction ($\mu$=0.09 cm$^{-1}$), images were processed by means of filtered backprojection and a post-reconstruction Butterworth filter of order 8 and a cut-off frequency of 0.08 cycles/cm [47].
Estimation of binding potential

After image registration into Talairach space, a volume of interest (VOI) analysis was performed making use of a predefined in-house modified VOI-map sampling the whole brain and consisting of 26 cortical, 6 subcortical, 2 cerebellar, and one pons 3D-volumes of interest (Brass, Nuclear Diagnostics, Hägersted, Sweden) [46]. Every registration with the subsequent VOI analysis was carefully checked for errors. In two subjects, a manual adjustment was necessary where the lower cerebellar slices were not completely imaged due to subject positioning on the camera (at least five cerebellar slices had to be visualized for final inclusion). The binding potential for a specific region was defined as the activity per volume element in that specific region divided through the activity per volume element in the cerebellum (void of 5-HT2A receptors), expressed as a percentage. The neocortical binding potential was defined as the unweighted average of the binding potential of frontal, temporal, parietal, and occipital regions. For the comparison of AD patients to healthy controls, the binding potential values for symmetrical regions were summed to achieve improved statistics in the relatively small sample under study. An asymmetry index (AI) was calculated, defined as $AI = (R-L)/(R+L)^2*200$ (%).

Psychiatric and neuropsychological testing

All AD patients, except one, underwent a screening for depressive symptomatology by means of the geriatric depression scale (GDS), a reliable and validated self-rating 30 items depression screening scale for elderly populations with scores ranging from 0 to 30 with a cut-off of 9 for mild and 19 for severe depression [50,51]. Also, AD patients underwent a Mini-Mental State Examination (MMSE), a method for grading the cognitive state consisting of a series of short subtests designed to elicit information about orientation, registration, attention and calculation ability, recall, language, and praxis. It has a total score ranging from 0 to 30 with 30 representing perfect performance, with a generally accepted cut-off of 27 for the exclusion of mental impairment and 23 to 24 for the diagnosis of dementia [17,20]. Finally all AD patients underwent a screening battery for cognitive impairment (Amsterdam dementia screening test, ADS6) containing the following subtests: picture recognition (n=8), orientation (n=8), drawing alternating sequences (n=8), verbal fluency (n=8), copying geometric figures (n=7), and free recall (n=7) [14]. Not every (sub)test could be performed in all patients due to non-compliance.

Statistical analysis

Data were analyzed by means of SPSS v10.0 for Windows (Chicago, IL, USA). For normality testing, a Kolmogorov-Smirnov test statistic was applied. For differences between groups, a two-tailed independent samples t test or a Mann-Whitney U test was applied when appropriate. A p-value lower than 0.05 was considered as significant. Data are given as means ± one standard deviation.
RESULTS

Age, sex, GDS, MMSE-score, and cognitive deficits of the AD patients are presented in Table 1.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>GDS</th>
<th>MMSE</th>
<th>Most prominent cognitive defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>memory</td>
</tr>
<tr>
<td>88</td>
<td>F</td>
<td>2</td>
<td>9</td>
<td>memory, orientation, attention, visuoconstruction</td>
</tr>
<tr>
<td>76</td>
<td>F</td>
<td>9</td>
<td>15</td>
<td>(visual) memory, orientation</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>9</td>
<td>21</td>
<td>(visual) memory</td>
</tr>
<tr>
<td>73</td>
<td>F</td>
<td>7</td>
<td>25</td>
<td>verbal memory and attention, visuospatial aspect, orientation</td>
</tr>
<tr>
<td>86</td>
<td>M</td>
<td>9</td>
<td>9</td>
<td>orientation, visuoconstruction, memory, word fluency, learning</td>
</tr>
<tr>
<td>85</td>
<td>F</td>
<td>15</td>
<td>20</td>
<td>memory, understanding, orientation</td>
</tr>
<tr>
<td>85</td>
<td>M</td>
<td>3</td>
<td>25</td>
<td>orientation, memory</td>
</tr>
<tr>
<td>74</td>
<td>F</td>
<td>19</td>
<td>17</td>
<td>visuoconstruction, language, visual memory</td>
</tr>
</tbody>
</table>

Table 1 Demographic variables of the AD patient group

$^{123}$I-5-I-R91150 SPECT uptake values

THE DISTRIBUTION OF RADIOLOGAND UPTAKE IN HEALTHY CONTROLS

The distribution of radioligand uptake throughout the brain as measured in 26 healthy volunteers is shown in figure 1. Relative regional specific uptakes compared to the cerebellum varied between 174 for the occipital cortex and 160 for the sensorimotor area. As for asymmetries in radioligand uptake, two statistically significant asymmetries were found consisting of a 2% asymmetry in frontal uptake in favor of the right side ($p = 0.003$) with the greatest difference in the prefrontal cortex (3%; $p = 0.001$) and another 3% asymmetry in favor of the left side for the temporal cortex ($p = 0.002$), with the greatest difference in the temporal superior cortex (5%; $p < 0.001$).
Role and distribution of serotonin type 2A receptors in Alzheimer’s disease

**NEOCORTICAL BINDING POTENTIAL IN HEALTHY VOLUNTEERS AND RELATION WITH AGE AND GENDER**

There was no statistically significant difference in radioligand uptake according to sex for any volume of interest. Concerning the age effect, the average neocortical binding potential varied between 217 at 23 years and 119 at 73 years. There was a significant age-related decline of neocortical binding potential (linear regression analysis: $R^2 = 0.87$, $p < 0.001$) resulting in an average decline of $11.6 \pm 0.9$ % per decade (figure 2). When only subjects over 60 years old were included, no significant age-related decline was present ($n = 13; R^2 = 0.1$, $p = 0.3$). Moreover, when only subjects over 70 years old were included ($n = 8$), the receptor binding potential as measured with $^{123}$I-5-I-R91150 SPECT seemed to increase visually, however, this did not reach statistical significance ($p = 0.4$). The distribution of radioligand uptake throughout the brain compared between the 13 youngest (up to 52 years old) and the 13 oldest subjects (from 62 years on) is shown in figure 3. The highest age-related decline was reached in the posterior cingulate with a decrease of $14.2$ % per decade ($R^2 = 0.78$, $p < 0.001$) while the lowest age-related decline was found in the left and the right mesotemporal region with a mean decrease of $7.6$ % per decade ($R^2 = 0.8$, $p < 0.001$). There was no statistically significant asymmetry change according to age for any region.
Figure 2. Age-related decline of the 5-HT$_{2A}$ receptor neocortical binding potential as measured with $^{123}$I-5-I-R91150 SPECT.

Figure 3. The distribution of radioligand uptake throughout the brain compared between the 13 youngest and the 13 oldest subjects (22-52 versus 62-85 yrs). LF = left frontal; RF = right frontal; LSMA = left sensorimotor; RSMA = right sensorimotor; LT = left temporal; RT = right temporal; LP = left parietal; RP = right parietal; LO = left occipital; RO = right occipital; AC = anterior cingulate; PC = posterior cingulate
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Grouped mean uptake values for AD patients and age-matched controls are displayed in figure 4.

![Figure 4. Grouped mean uptake values ± SD for AD patients and age-matched controls.](image)

A generally decreased neocortical binding potential was found in the AD patient group \((p = 0.02)\). Mean regional uptake values for AD patients and controls are shown in Table 2.

<table>
<thead>
<tr>
<th>Region</th>
<th>AD patients</th>
<th>age-matched controls</th>
<th>p-value, uncorrected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UV</td>
<td>SD</td>
<td>UV</td>
</tr>
<tr>
<td>Orbitofrontal</td>
<td>117.6</td>
<td>21.5</td>
<td>139</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>107.7</td>
<td>18.6</td>
<td>126.7</td>
</tr>
<tr>
<td>Lateral frontal</td>
<td>116.8</td>
<td>15.1</td>
<td>135.2</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>110.4</td>
<td>25.3</td>
<td>128.2</td>
</tr>
<tr>
<td>Cingulate gyri</td>
<td>117.3</td>
<td>25.4</td>
<td>137.7</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>114.9</td>
<td>14.9</td>
<td>134.5</td>
</tr>
<tr>
<td>Temporal anterior</td>
<td>112.3</td>
<td>24.8</td>
<td>128.7</td>
</tr>
<tr>
<td>Temporal superior</td>
<td>125.5</td>
<td>26.4</td>
<td>142.4</td>
</tr>
<tr>
<td>Temporal medial inferior</td>
<td>129.4</td>
<td>22.9</td>
<td>144.3</td>
</tr>
<tr>
<td>Mesotemporal</td>
<td>100.6</td>
<td>17.9</td>
<td>113.3</td>
</tr>
<tr>
<td>Parietal inferior</td>
<td>121.6</td>
<td>17.3</td>
<td>141.8</td>
</tr>
<tr>
<td>Parietal superior</td>
<td>108.0</td>
<td>33.3</td>
<td>136.3</td>
</tr>
<tr>
<td>Occipital</td>
<td>129.5</td>
<td>19.3</td>
<td>141.2</td>
</tr>
</tbody>
</table>

*statistically significant p-values

Table 2. \(^{123}I\)-5-I-R91150 regional uptake values (UV) and standard deviation (SD) for AD patients compared to age-matched controls.
Role and distribution of serotonin type 2A receptors in Alzheimer’s disease

For the individual regions, a statistically significant decreased binding potential in AD patients compared to controls was found in the orbitofrontal, prefrontal, lateral frontal, cingulate, sensorimotor, parietal inferior, and occipital region ($p_{uncorrected} < 0.05$). After Bonferroni correction for multiple comparisons, only the difference in radioligand uptake for the sensorimotor region yielded significance ($p = 0.05$).

Concerning asymmetries, a statistically significant asymmetry was found for the mesotemporal region in favor of the left side ($p = 0.02$). However, individually neither the left or right mesotemporal area differed significantly from age-matched controls concerning radioligand uptake.

Figure 5 shows the radioligand uptake values for AD patients and age-matched controls for the right sensorimotor and left orbitofrontal region. Figure 6 shows a representative slice of an age-matched healthy volunteer and an AD patient with the specific radioligand uptake decreases in the lateral frontal, sensorimotor, and posterior cingulate region.

![Boxplot](image1.png)

**Figure 5.** Boxplots of the $^{125}$I-5-I-R91150 uptake values for AD patients and age-matched controls for the right sensorimotor (upper) and the left orbitofrontal (lower) region.
Neuropsychological testing and correlation with the $^{123}$I-5-I-R91150 uptake values

The mean Mini-Mental State Examination score (MMSE) yielded $18 \pm 6$ (range 9-25). The mean score on the geriatric depression scale (GDS) was $9.1 \pm 6$ (range 2-19), where, according to the cut-offs used, two mildly and no severely depressed patients were included. No effect of depression score on regional or neocortical binding potential was present within the AD patient group. A significant positive correlation was found between the $^{123}$I-5-I-R91150 uptake value in the left orbitofrontal region and the global cognitive deficit as assessed with the MMSE-score (Spearman’s $\rho$ correlation coefficient of 0.7; $p < 0.05$). No correlation was found between $^{123}$I-5-I-R91150 uptake values for any region and global or subscores on the ADS6 cognitive screening battery.
DISCUSSION
The present findings concerning age dependency of 5-HT
receptor density are in agreement with previous ex
vivo distribution studies demonstrating a general decrease in cortical 5-HT and more
specifically 5-HT receptor density [39]. This decline is also consistent with clinical observations of age-
related changes in behaviors such as sleep or executive functioning, known to be linked to serotoninergic
function [15,33]. Moreover, peak minus baseline prolactin responses to fenfluramine (a serotonin-
releasing agent) were shown to be negatively correlated with age [26]. Concerning the regional age-
dependent decreases in 5-HT receptor density, a very recent study with \[^{18}F\]altanserin found the highest
age-related decline in the cingulate region while the lowest decline was found in the hippocampus, which
is in concordance with the regional age-related decreases found in the present study [43].

This decrease in 5-HT receptor density gradually declines, reaching a minimum between the 5th and the
6th decade [45]. As for in vivo imaging studies, several studies confirmed this linear decrease in cortical 5-
HT receptor binding in the living human brain with a more rapid decline in the first half of adult life,
directly reflecting the loss of specific 5-HT receptors with age [7,41,49]. Moreover, one study used the
same radioligand as in the present study in a healthy control group up to 60 years old [4]. Also, it was
previously shown that the effect of atrophy is relatively small compared to the large change in 5-HT receptor
binding in healthy aging [29]. The present study extends these previously published data since healthy
subjects up to an age of 85 years were included where no significant age-related effect from the
age of 60 on could be demonstrated. On the contrary, the receptor density seemed to slightly increase
again from the age of 70, however, this did not reach statistical significance. This phenomenon of a
parabolic relationship between aging and 5-HT receptor density with an upswing from the age of 60 has
also been reported previously for the prefrontal cortex and the hippocampal dentate using \[^{1}H\]ketanserin
autoradiography [22]. Concerning gender, our data could not show any significant gender difference in
radioligand uptake for any brain region. Up till now only one PET study with \[^{18}F\]altanserin, a 5-HT receptor
antagonist, has reported a gender difference in cortical 5-HT receptor uptake in healthy
subjects with a higher binding capacity in men in general with the greatest differences in the frontal and
cingulate cortices [6].

Concerning the present findings about radioligand uptake in the AD patient group, our results are in line
with previously published ex vivo data. Indeed, most postmortem studies showed, in addition to mostly
frontal deficits, also deficits in cingulate and parietal 5-HT binding sites [37]. However, an important
issue concerning post-mortem studies is that some of these results, due to the nature of many of these
studies, are potentially biased, firstly towards Alzheimer’s disease of end-stage severity and secondly by
post mortem delay. However, also two previously published PET studies with \[^{18}F\]setoporone and
\[^{18}F\]altanserin showed this specific decrease in 5-HT receptor density for AD patients, with the greatest
deficits in frontal, cingulate, and temporal regions [7,28]. Interestingly, the reduction in radioligand uptake
in the sensorimotor cortex, in fact the only statistically significant difference compared to age-matched
controls proof against formal Bonferroni correction, is somewhat unexpected but in line with recently published PET results using $[^{18}F]$altanser in [28]. Hypothetically, this could be related to a reduction in planned motor behavior and a reduction in sensory processing. Both aspects have been described in literature and are often observed in clinically demented patients [38,48].

Since binding potential may reflect changes in receptor density ($B_{\text{max}}$) as well as receptor affinity ($K_D$), abnormalities in either or both measures may contribute to the finding of a difference or, alternatively, a lack of difference in regional binding potential between different study groups. However, most postmortem binding assays and saturation binding experiments of 5-HT$_{2A}$ receptor ligands in AD brains have shown abnormal $B_{\text{max}}$ values and normal $K_D$ values [12,13]. Therefore, it is likely that the low specific binding potential for several brain regions found in the present study is the result of a corresponding loss of 5-HT$_{2A}$ receptors. This is similar to what has already been reported for most neurotransmitter changes in AD for e.g. the nicotinic, 5-HT$_{1}$, glutamate, NMDA, somatostatin or neuropeptide Y receptor sites [37].

Concerning the dynamic content of the measured receptor data, static scans were acquired and no full kinetic modelling of the receptor binding potential was measured. As mentioned already, pseudo-equilibrium conditions were assumed and the relative measure of neocortical to (nearly receptor-free) cerebellar activity was taken as a measure of the binding index, as has been shown in previous literature both by our group as well as others [3,4,11]. Under pseudo-equilibrium circumstances, the delivery phase of the tracer (initial flow) is not a determinant of the binding index anymore and therefore, regional estimates of perfusion need not to be correlated directly to the 5-HT$_{2A}$ binding data.

No effect of depression score on global or regional binding potential was present within the AD patient group, although the low number of depressed subjects precluded a definitive examination of the 5-HT$_{2A}$ receptor status in AD patients with concommitant depression. This is however in agreement with a previous PET study where no significant abnormalities in 5-HT$_{2A}$ receptor binding potential as measured with $[^{18}F]$altanser were observed in 11 patients with late-life depression according to DSM-IV and Hamilton depression scale criteria. Moreover, no effect of depression on neither global nor regional binding potential was present within the AD patient group (3 out of 11 with concurrent depression) [28]. These findings are consistent with the hypothesis that the 5-HT$_{2A}$ receptor is differentially affected in late-life depression and AD, a finding that has implications for the etiological basis of mood and cognitive features of neuropsychiatric disorders of late life.

In conclusion, the results of the present study agree with and extend previous postmortem, in vitro and PET/SPECT in vivo findings. The age-related decline in 5-HT$_{2A}$ receptor binding potential with a tendency towards a slight upswing towards later life highlights the necessity for age-matched controls in (clinical and) imaging studies and the need for larger study samples at advanced age. Moreover, it stresses the
etiological and potential therapeutic implications concerning mood changes and psychotropic drug dosing for older age groups. The fact that the 5-HT$_{2A}$ receptor is differentially affected in AD patients compared to age-matched controls has implications for both the etiological basis and the therapeutic management of AD.
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