Serotonin2A receptor binding potential in people with aggressive and violent behaviour

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Objective: Indexes of brain serotonin2A (5-HT2A) density have never been investigated in a sample of humans with violent aggressive behaviour unbiased by medication use or current axis I psychiatric disorders. The objective of this study was to investigate prefrontal cortex 5-HT2A binding potential (BPND), an index of 5-HT2A density, in an unbiased sample of people with violent aggressive behaviour. Methods: We used [18F] setoperone positron emission tomography to measure 5-HT2A BPND in the dorsolateral prefrontal cortex (primarily sampling Brodmann area 9) in 16 participants with violent aggressive behaviour and 16 healthy control participants. Results: In people with violent aggressive behaviours, the slope of 5-HT2A BPND decline in the dorsolateral prefrontal cortex is 44% less than in healthy control participants (analysis of variance group by age interaction, p = 0.004). Prefrontal cortex 5-HT2A BPND was significantly lower in participants with more severe impulsivity and aggression (multiple linear regression with age and Barratt Impulsivity Scale [BIS] as predictor variables and regional 5-HT2A BPND as dependent variable; effect of BIS, dorsolateral prefrontal cortex: F1,13 = 7.95, p = 0.014). Conclusion: Lower prefrontal 5-HT2A BPND is related to violent aggression. Lower 5-HT2A BPND occurs at a younger age, when violent behaviour is more frequent, and is more prominent when impulsivity and aggression are more severe.

Introduction

Both neuroimaging and neuropsychological studies suggest that abnormal functioning of structures regulating emotional responses, such as the prefrontal cortex, amygdala and anterior cingulate cortex, increase the risk of developing aggressive violent behaviour. A prevailing theory regarding the role of serotonin in the neurobiology of violence is that...
people with impulsive and/or aggressive violent behaviour have lifelong lower extracellular serotonin levels throughout the brain that are functionally relevant in the prefrontal cortex, leading to behavioural disinhibition.\textsuperscript{12,13,17} The main reason for this belief is that the metabolite of serotonin, 5-hydroxyindolacetic acid (5-HIAA), is often low in the cerebrospinal fluid of people with impulsive and aggressive behaviour.\textsuperscript{17,22} Cerebrospinal fluid (CSF) 5-HIAA has an indirect relation to brain serotonin, so there may be explanations for this finding other than globally low serotonin levels in the brain. For example, low CSF 5-HIAA may be caused by low serotonin metabolism, and this latter abnormality has also been implicated in violent behaviour. Therefore, additional investigations are important to corroborate this hypothesis with respect to low extracellular brain serotonin in people with violent behaviour. Investigations of 5-HT\textsubscript{2A} receptors in people exhibiting violent behaviour may have important implications because 5-HT\textsubscript{2A} density has an inverse relation to extracellular serotonin levels such that increased 5-HT\textsubscript{2A} density may occur during chronic 5-HT depletion.\textsuperscript{9,12}

Arora and Meltzer\textsuperscript{15} reported a relation between suicide using a violent method and elevated frontal cortex 5-HT\textsubscript{2A} receptor density. In a subsequent review, Mann and colleagues\textsuperscript{14} observed that investigations of suicide completers that report increased prefrontal cortex 5-HT\textsubscript{2A} receptor density\textsuperscript{13,15–18} typically report more violent methods of suicide. A recent psychological autopsy study reported greater aggression and impulsivity in people who die by violent suicide.\textsuperscript{19} Thus it is possible that these early postmortem human studies of violent suicide support a link between aggression and elevated prefrontal cortex 5-HT\textsubscript{2A} receptor binding.

Serotonin\textsubscript{1a} and 5-HT transporter (5-HTT) receptors and tryptophan uptake have been investigated in people with borderline personality disorder\textsuperscript{20–22} A study also exists of brain 5-HTT binding in people with aggression and a history of methamphetamine abuse.\textsuperscript{23,24} However, there has never been a study specifically investigating whether prefrontal 5-HT\textsubscript{2A} binding is elevated in people with violent aggressive behaviour that addresses biases of other syndromes and diagnoses. The most definitive study to date of aggression and 5-HT\textsubscript{2A} receptors in humans focused on people who died by suicide.\textsuperscript{25} However, in this study, current major depressive disorder was present in the majority of participants who died by suicide (23/37), and current medication use was present in about one-half of the participants who died by suicide (17/37). Both current antidepressant use and being in a major depressive episode are known to influence indices of 5-HT\textsubscript{2A} receptor density in humans.\textsuperscript{8,26–29} Therefore, it is not clear whether a relation between 5-HT\textsubscript{2A} receptors and aggression exists after biases such as current major depressive episodes and antidepressant use have been addressed.

The main hypothesis of this study was that prefrontal 5-HT\textsubscript{2A} receptor binding potential (BP\textsubscript{ND}), as measured with \textsuperscript{18}F setoperone positron emission tomography (PET), would be elevated in people who have violent angry behaviours towards others. This hypothesis is based on the more general model of lowered extracellular serotonin throughout the prefrontal cortex in people with violent behaviour.\textsuperscript{7,27} In such a model, 5-HT\textsubscript{2A} receptors would be expected to be upregulated secondary to chronically lowered extracellular serotonin levels.\textsuperscript{6,27} The second hypothesis was that the subset of people with the most severe impulsivity would have the most elevated prefrontal 5-HT\textsubscript{2A} BP\textsubscript{ND}. The 5-HT\textsubscript{2A} BP\textsubscript{ND}, an index of 5-HT\textsubscript{2A} receptor density, can be measured with \textsuperscript{18}F setoperone PET.\textsuperscript{29,30} To address biases of medication use and active axis I disorders, enrolment criteria excluded psychotropic medication use within the previous 6 months and required remission of axis I symptoms for at least 3 months, with the exception of full remission from alcohol abuse, for which a 1-month cut-off was applied. The prefrontal cortex region (focusing on Brodmann area 9) was chosen because this is the region where most of the investigations of suicide completers report elevated 5-HT\textsubscript{2A} receptor density.\textsuperscript{13,15–18} If violent angry behaviours are associated with increased prefrontal cortex 5-HT\textsubscript{2A} receptor density, then prefrontal cortex 5-HT\textsubscript{2A} BP\textsubscript{ND}, an index that reflects 5-HT\textsubscript{2A} density, should be increased.

Setoperone shows high selectivity for 5-HT\textsubscript{2A} receptors in human cortex, as discussed previously.\textsuperscript{28,29} In the present paper, abnormalities of 5-HT\textsubscript{2A} receptors in brain cortex are viewed as reflecting abnormalities of 5-HT\textsubscript{2A} receptors in cortex because available evidence suggests that the density of the other 2 subtypes is very low. In cortex, messenger ribonucleic acid of 5-HT\textsubscript{2A} receptors is extremely low,\textsuperscript{28} and binding to 5-HT\textsubscript{2C} receptors suggests a very low density of these receptors.\textsuperscript{29}

\section*{Methods}

\subsection*{Participants}

This study was approved by the Centre for Addiction and Mental Health Ethical Review Committee at the University of Toronto. We recruited 16 healthy individuals (mean age 29.06, standard deviation [SD] 6.17 yr; 9 men, 7 women) and 16 individuals with histories of violent behaviour, anger dyscontrol and aggression (mean age 29.31, SD 6.26 yr; 10 men, 6 women). The participants ranged in age from 19 to 39 years. All had been free of psychotropic medication for at least 6 months, had no history of neurotoxin use and had good medical health.

Healthy participants were age-matched to within 3 years of violent participants. We screened healthy participants to rule out axis I disorders, using the Structured Clinical Interview for the fourth edition of the \textit{Diagnostic and Statistical Manual of Mental Disorders} (DSM-IV).\textsuperscript{31} In a structured interview, we also asked healthy individuals questions about suicide attempts, impulsive behaviour, anger dyscontrol problems, alcohol intake and substance abuse to rule out these behaviours.

The 16 participants with anger management and aggression problems were recruited from either the Anger Management Clinic or an advertisement at the Centre for Addiction...
and Mental Health. The main inclusion criteria were age 18–40 years, good medical health, consistent report over 3 different interviews of repeated, serious, violent behaviour toward others that could not be accounted for by either substance abuse or an axis I disorder (except for intermittent explosive disorder, which was not exclusionary). Table 1 describes the behaviours in terms of frequency and examples of severity. Given the comorbidity of axis I mood and anxiety disorders in patients with aggressive behaviour, patients with a history of major depressive disorder or other axis I illnesses were not excluded provided there was a clear history of violent aggressive behaviour outside the episode of the axis I illness and that the axis I illness was in remission. The exception to this was bipolar disorder I and II, which were both exclusionary.

Participants with histories of violent behaviour received the following screening instruments so that we would have detailed clinical information: the Structured Clinical Interview for DSM-IV for axis I disorders,35 the Structured Clinical Interview for DSM-IV for axis II disorders36 and the Structured Clinical Interview for DSM-IV for axis II disorders36 and the Scale for Suicidal Ideation.37 The Barratt Impulsiveness Scale, version 11 (BIS)39 were chosen as the primary quantitative measure of impulsivity, and the BDHI measures a subset of obsessive–compulsive disorder. Urine drug screening was with a history of major depressive disorder or other axis I illness and that the axis I illness was in remission. The first 3 of these participants were also in the group who had histories of alcohol abuse. Four participants had current suicidal ideation, and 2 participants had a history of attempting suicide. In addition to having either antisocial personality disorder and/or conduct disorder, 5 participants also met criteria for a different axis II disorder: 2 for paranoid personality disorder, 1 for borderline personality disorder, 1 for histrionic personality disorder and 1 for obsessive–compulsive disorder. Urine drug screening was done for all participants with a history of violence. All patients received common blood tests to rule out medical causes of disturbed mood (thyroid function, electrolytes and complete blood cell count).

### Image acquisition and analysis

An intravenous bolus of 185 MBq of [18F] setoperone29,31 was injected. PET images were obtained with a GEMS 2048–15B camera (intrinsinc in-plane resolution, full width at half maximum 5.5 mm; Scanditronix Medical, General Electric); [18F] setoperone had high radiochemical purity (> 99%) and high specific activity (44, SD 39 GBq/μmol at the time of injection). Images were obtained in five 1-minute frames, followed by seventeen 5-minute frames. The images were corrected for attenuation with the use of a 68Ge transmission scan and were reconstructed by filtered back projection (Hanning filter).

The kinetics of [18F] setoperone can be described with a 3-tissue compartment model in regions with specific binding and a 2-tissue compartment model in the reference region.30,31 The kinetics of [18F] setoperone are fast in humans, with peak uptake in regions of specific binding, typically between 10 and 20 minutes. Traditionally, reference tissue methods have been suitable for [18F] setoperone, and this has previously been partially discussed.20,28,32 For 3 reasons, we used the simplified reference tissue model, version 2 (SRTM).29 It is sensitive to the age-related decline in 5-HT2A BP

### Table 1: Description of violent behaviours

<table>
<thead>
<tr>
<th>Type of aggressive behaviour</th>
<th>No. of participants with behaviour</th>
<th>Frequency of behaviour, no. (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assault with blunt objects</td>
<td>15</td>
<td>16.07 (15.59)*</td>
</tr>
<tr>
<td>e.g., baseball bat, lead pipe, table legs, metal poles, bricks, “pistol-whipping”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assault with sharp objects</td>
<td>10</td>
<td>5.50 (5.74)*</td>
</tr>
<tr>
<td>e.g., stabbing with knife or screwdriver, slicing with broken glass, threaten with knife</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical fights and assaults without a weapon</td>
<td>16</td>
<td>303.44 (467.24)*†</td>
</tr>
<tr>
<td>e.g., fists, kicking, head-butting, biting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angry outbursts leading to property destruction</td>
<td>14</td>
<td>15.21 (7.3)*</td>
</tr>
<tr>
<td>e.g., smashing windows, damaging vehicles using blunt objects, beating holes through walls, slashing tires, setting fire, destruction of miscellaneous household items</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angry outbursts without property destruction or assault</td>
<td>16</td>
<td>50.88 (46.45)‡</td>
</tr>
<tr>
<td>e.g., yelling, screaming, threatening body gestures, hitting and throwing objects that did not break</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.  *Frequency is described as mean number (SD) of lifetime events. †All participants reported at least 20 lifetime events. ‡Frequency is described as current mean number (SD) of monthly events. Current number of monthly outbursts ranged from 1 to 140.
the selection of regions of interest (ROIs). However, we applied several criteria based on related investigations. Because a subset of suicide victims may have violent behaviour, our highest priority was to review studies of suicide victims and choose regions reported to have elevations in 5-HT, receptor binding. Consequently, the primary ROI was a bilateral region of the middle frontal gyrus that mainly sampled Brodmann area 9. Our second criterion was to select regions in which abnormal function was found to be associated with impulsive, aggressive behaviours; this led us to select the orbitofrontal cortex (Brodmann areas 47 and part of 11). The third criterion was to choose regions sampled in our other published studies of 5-HT 2A receptor binding in major depressive disorder and borderline personality disorder so that measures would be consistent across different patient samples. Therefore, we included the posterior medial temporal gyrus (Brodmann areas 20 and 21) and anterior cingulate (Brodmann areas 24 and part of 32) regions.

We found these ROIs by using a semiautomated method verified by visual assessment with reference to a coregistered magnetic resonance imaging scan (General Electric Signa 1.5T scanner, spin-echo sequence proton density weighted image; x, y, z voxel dimensions 0.78, 0.78 and 3 mm, respectively). The reference tissue was a sampling of posterior cerebellar cortex that omitted the vermis and the white matter and avoided venous sinuses and occipital cortex by 6 mm. These methods have been previously described in more detail.

Statistical analysis

The primary hypothesized ROI was the dorsolateral prefrontal cortex; however, we undertook similar analyses for each cortex region. The main analyses focused on prefrontal cortex 5-HT 2A BPND and violent aggressive behaviour. First, we compared the age-related decline in regional cortex 5-HT 2A BPND in participants exhibiting violent behaviour with that in control participants. Using an analysis of covariance (ANCOVA) with age as a covariate, we examined the interaction between age and group. We then compared regional cortex 5-HT 2A BPND between groups, applying the Johnson–Neyman technique. Finally, we assessed the association between regional cortex 5-HT 2A BPND and severity of impulsivity and aggression by applying an ANCOVA with 5-HT 2A BPND as the dependent variable and age and BIS score as predictor variables.

Results

We obtained similar results in each region regardless of whether we used the SRTM2 method or the Logan method. For regional 5-HT 2A BPND values in the sampled participants, the correlation coefficient between the 2 methods was between 0.92 and 0.99 for every region. For each analysis, we present the results obtained with the SRTM2 method and then comment on whether the results are similar to those obtained with the Logan method.

Relation of violent aggressive behaviour and age to cortex 5-HT 2A BPND

Serotonin 2A BPND declined linearly with age in both groups. However, there was a considerably slower rate of decline in cortex 5-HT 2A BPND in the group with violent aggression, compared with the control group (dorsolateral prefrontal cortex: –0.046/yr in the violent group; –0.081/yr in the control group; 44% difference) (Fig. 1 and Table 2). This differential age effect was statistically significant (ANCOVA interaction between age and group, F 1,28 = 9.86, p = 0.004). Similar results were found in other regions, where the difference in age-related 5-HT 2A BPND decline ranged from 44% to 53% (ANCOVA interaction between age and group, F 1,28 = 4.24–13.52, p = 0.049–0.001 (Fig. 1 and Table 2). Even after the application of a partial volume correction method, the age-dependent difference in prefrontal 5-HT 2A BPND remained significant (ANCOVA interaction between age and group, F 1,28 = 8.70, p = 0.006). We expected some reduction in the level of significance because partial volume correction methods tend to increase variance.

Moreover, for this specific sample, it did not seem necessary to apply partial volume correction because there was no significant between-group difference in whole prefrontal cortex ROI volume (tobs = –0.66, p = 0.52, 2% difference).

A recent report found that cortex 5-HT 2A BPND was elevated in individuals with a history of recurrent major depressive episodes (MDE). In the present study, there were 4 participants in the violent group who had histories of a single MDE only. Although it is possible that participants with a single previous MDE are different from those with multiple previous MDEs, we performed a subanalysis excluding the 4 participants with a history of MDE. Excluding these 4 participants from the violent group did not alter the rates of age-related decline in 5-HT 2A BPND (the slopes remained similar). Moreover, the differences in the slope of the age-related decline between this subgroup of violent participants and the healthy control group were similarly significant for every region (differences ranged from 41% to 63%, F 1,28 = 5.57–17.12, p = 0.03–0.0004).

Comparison of regional 5-HT 2A BPND between groups

Because the slopes of the age-related decline were different, we applied the Johnson–Neyman technique to consider the differences between groups with respect to age. For almost all the analyses of all regions, cortex 5-HT 2A BPND was significantly lower in the group with violent behaviour than in control participants at age 19 years, similar to that in control participants at age 29 years and significantly higher than in control participants at age 39 years (see Table 3). The exception was the analysis for the rostral anterior cingulate region when the SRTM2 method was used.

Relation between impulsivity, aggression and cortex 5-HT 2A BPND

Our primary quantitative measures of impulsive behaviour...
were the BIS\textsuperscript{39} and the BDHI.\textsuperscript{39} In this sample, the total values of these 2 measures were highly intercorrelated (Pearson correlation coefficient, $r = 0.66, p = 0.006$). Cortex 5-HT\textsubscript{2A} BP\textsubscript{ND} scores were strongly associated with BIS scores such that lower 5-HT\textsubscript{2A} BP\textsubscript{ND} was associated with more severe impulsivity (Fig. 2). Multilinear regression using age and BIS score as predictor variables and regional 5-HT\textsubscript{2A} BP\textsubscript{ND} as the dependent variable, the effect of BIS was as follows: dorsolateral prefrontal cortex, $F_{1,13} = 7.95, p = 0.014$; orbitofrontal cortex, $F_{1,13} = 7.48, p = 0.017$; rostral anterior cingulate cortex, $F_{1,13} = 8.34, p = 0.013$; posteromedial temporal cortex, $F_{1,13} = 5.43, p = 0.037$. We obtained similar results for all analyses with the Logan method.\textsuperscript{42} Even after we applied a partial volume correction method,\textsuperscript{45} the correlation between the BIS scores and prefrontal 5-HT\textsubscript{2A} BP\textsubscript{ND} remained. There was no significant correlation between prefrontal cortex ROI volume and BIS score or between BIS scores and age.

Post hoc analyses showed a trend between the BIS score\textsuperscript{38} and the Scale for Suicidal Ideation\textsuperscript{37} ($r = 0.46, p = 0.07$) and a significant correlation between the BDHI\textsuperscript{39} and the Scale for Suicidal Ideation\textsuperscript{37} ($r = 0.57, p = 0.02$).

**Discussion**

This study is the first prospectively designed investigation of 5-HT\textsubscript{2A} receptors in people with violent aggressive be-
haviour toward others wherein the participants do not have major biasing influences on 5-HT₂A receptors, such as medication use or active axis I psychiatric illnesses. We did not find an elevation in prefrontal cortex 5-HT₂A BPND at all ages. Instead, we found that cortex 5-HT₂A BPND is different in this group, being lower around age 20 years and higher at ages 35–40 years, compared with control participants. We also found a strong relation between severity of impulsive behaviour and cortex 5-HT₂A BPND in that 5-HT₂A BPND is lower when impulsive behaviours are more severe. These findings have important implications for the neurochemical model of human aggressive behaviour, for our understanding of whether 5-HT₂A receptor abnormalities are specific to diagnosis or suicide and for the practice of reducing violent behaviour with selective serotonin reuptake inhibitors (SSRIs).

We interpret lower prefrontal cortex 5-HT₂A BPND to be related to violent aggressive behaviour because lower 5-HT₂A BPND correlated with greater severity of impulsivity and aggression. In addition, lower 5-HT₂A BPND tended to occur at younger ages, which became evident when we evaluated the subject data at age 19 years. The comparison between violent and nonviolent groups is dependent on the age chosen, and we felt that the result at age 19 years was most relevant for this comparison because repeated impulsive and violent behaviour typically starts in the teenage years and almost always starts before the midtwenties. For this interpretation, we applied the traditional strategies in neurologic and psychiatric illness research to understand the connection between brain pathology and symptoms: observed brain abnormalities are considered in relation to the symptoms that start or are highly prevalent at the time of the abnormality. A lower prefrontal cortex 5-HT₂A BPND in the violent aggressive group was opposite to the hypothesis;

<p>| Table 2: Serotonin₂A receptor BPND decline per year of life in participants with violent behaviour and in nonviolent healthy control participants |
|-------------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Brain region sampled</th>
<th>Brodmann areas</th>
<th>5-HT₂A BPND decline per year of life; Group; mean (SD)</th>
<th>% difference in 5-HT₂A BPND decline*</th>
<th>ANCOVA† interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>9, parts of 8, 10 and 46</td>
<td>Control 5-HT₂A BPND</td>
<td>44 9.86 0.004</td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>47, part of 11</td>
<td>Violent 5-HT₂A BPND</td>
<td>53 13.52 0.001</td>
<td></td>
</tr>
<tr>
<td>Rostral anterior cingulate cortex</td>
<td>24, part of 32</td>
<td>Control 5-HT₂A BPND</td>
<td>47 4.24 0.049</td>
<td></td>
</tr>
<tr>
<td>Posterior medial temporal cortex</td>
<td>20, 21</td>
<td>Violent 5-HT₂A BPND</td>
<td>48 10.54 0.003</td>
<td></td>
</tr>
</tbody>
</table>

5-HT₂A = serotonin₂A; ANCOVA = analysis of covariance; BPND = binding potential; SD = standard deviation.
* (Slope of 5-HT₂A BPND decline in healthy control participants – slope of 5-HT₂A BPND decline in participants with violent behaviour)/slope of 5-HT₂A BPND change in healthy-control participants.
† ANCOVA with age as a covariate, reporting significance of interaction between age and group.

| Table 3: Differences in serotonin₂A receptor binding potential (5-HT₂A BPND) between participants with violent behaviour and nonviolent healthy individuals considering age* |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Method; region                     | Group           | Least-squared means (and p value) for each age | Region of non-significance, age† | Age-group interaction |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Dorsolateral prefrontal cortex      | Healthy 2.48 (0.014) 1.67 (0.96) 0.86 (0.010) 23.5, 33.9 9.86 0.004 | | | |
|                                    | Aggressive 2.12 (0.008) 1.67 (0.63) 0.81 (0.002) 23.7, 31.9 13.5 0.001 | | | |
| Orbitofrontal cortex                | Healthy 2.43 (0.008) 1.62 (0.63) 0.81 (0.002) 23.7, 31.9 13.5 0.001 | | | |
|                                    | Aggressive 2.03 (0.130) 1.65 (0.72) 0.84 (0.056) 0, 42.5 4.24 0.049 | | | |
| Rostral anterior cingulate cortex   | Healthy 2.56 (0.033) 1.79 (0.29) 0.98 (0.032) 26.9, 37.4 10.5 0.003 | | | |
|                                    | Aggressive 2.14 (0.003) 1.72 (0.29) 0.98 (0.032) 26.9, 37.4 10.5 0.003 | | | |
| Posterior medial temporal cortex    | Healthy 2.60 (0.009) 1.79 (0.29) 0.98 (0.032) 26.9, 37.4 10.5 0.003 | | | |
|                                    | Aggressive 2.14 (0.003) 1.72 (0.29) 0.98 (0.032) 26.9, 37.4 10.5 0.003 | | | |

* The Johnson–Neyman procedure was applied to identify regions of nonsignificance and regions of significance between groups, based on age.
† The numbers in this column refer to an age window for which the results are not significant. Results are significant outside the age window.

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however, it is consistent with a recent set of studies demonstrating that mice whose prefrontal cortex 5-HT$_{2A}$ receptors have been removed show decreased avoidance of risk-laden behaviours.\textsuperscript{48}

Earlier investigations in humans often report lower CSF 5-HIAA in people with aggressive behaviour.\textsuperscript{5-7} Lower CSF 5-HIAA can support several neurochemical models of aggression, including low brain 5-HT (both intracellular and extracellular), reduced 5-HT conversion to 5-HIAA\textsuperscript{8} and general loss of neurons.\textsuperscript{49-51} The results of the present study could be interpreted as being unsupportive of the first model. Cortex 5-HT$_{2A}$ receptors typically show an inverse relation to extracellular 5-HT levels; that is, they increase in density when extracellular 5-HT is low.\textsuperscript{9,10} If 5-HT$_{2A}$ receptors regulate normally in people with violent behaviour, then low cortex 5-HT$_{2A}$ BPND is unlikely to support a human model of low extracellular 5-HT in the cortex. To have low cortex 5-HT$_{2A}$ BP$_{nd}$ at the same time as low extracellular 5-HT in the cortex, there should be either fewer cells present that express 5-HT$_{2A}$ receptors or an abnormal regulation of these receptors relative to extracellular 5-HT levels. Future investigations are needed to ascertain which model best applies, but there is reason to reconsider the concept that low CSF 5-HIAA is the equivalent of low extracellular 5-HT in the prefrontal cortex in people with violent behaviour.

The results of this study differ from those of previous studies that sampled people who died by violent suicide. One possible reason is that the participants in the present study reported violent behaviour toward others, whereas in earlier studies, violent behaviour was the method of suicide.\textsuperscript{13,15-18,26} A violent method of suicide need not always imply violent behaviour toward others at different times of life.

![Figure 2](image-url): In people with violent behaviour, lower regional cortex serotonin$_{2A}$ (5-HT$_{2A}$) binding potential (BP$_{nd}$) is associated with more severe impulsivity. Cortex 5-HT$_{2A}$ BP$_{nd}$ scores were strongly associated with Barratt Impulsiveness Scale (BIS) scores such that lower 5-HT$_{2A}$ BP$_{nd}$ was associated with more severe impulsivity (analysis of covariance, age and BIS as covariates, regional 5-HT$_{2A}$ BP$_{nd}$ as dependent variable, effect of BIS, dorsolateral prefrontal cortex: $F_{1,13} = 7.95$, $p = 0.014$; orbitofrontal cortex: $F_{1,13} = 7.48$, $p = 0.017$; rostral anterior cingulate cortex: $F_{1,13} = 8.34$, $p = 0.013$; posteromedial temporal cortex: $F_{1,13} = 5.43$, $p = 0.037$). For the above figure, age-normalized 5-HT$_{2A}$ BP$_{nd}$ values to age 20 are shown. Age-normalized values were calculated by taking the difference between the individual subject age and the age normalized to slope (m) of the age-related decline in 5-HT$_{2A}$ BP$_{nd}$ (normalized 5-HT$_{2A}$ BP$_{nd}$ = raw 5-HT$_{2A}$ BP$_{nd}$ + diff*m).
A second possible reason for the difference between our study results and those of previous studies of violent suicide victims is that our sample was younger than most of the previous samples. Most samples in earlier, postmortem investigations of suicide had mean ages in the range of 35–51 years.\textsuperscript{13,15–18} Had we restricted our sample to participants aged 35 and older, the data set would have shown an elevation in participants with violent behaviour and would have resembled most postmortem data sets of participants who died by violent means. The second explanation seems less likely because Pandey and colleagues\textsuperscript{22} reported an elevation in prefrontal cortex 5-HT\textsubscript{2A} receptor expression in teenaged suicide victims.

The results of this study further support the argument that elevated 5-HT\textsubscript{2A} receptor density is a diagnostic and treatment-specific phenomenon rather than a suicide-specific phenomenon. The specific cortex 5-HT\textsubscript{2A} abnormality found in medication-free people with violent behaviour differs from that found in other diagnostic-specific studies of cortex 5-HT\textsubscript{2A} receptors. Relatively recent studies demonstrate other diagnostic-specific changes in indices of prefrontal cortex 5-HT\textsubscript{2A} density, including elevations in suicide completers who suffered from depression,\textsuperscript{19,27} elevations in individuals with depression and severe pessimism,\textsuperscript{3,46} reductions of mild-to-large magnitude in treated and recently treated individuals with depression\textsuperscript{20,26,27} and no change in 5-HT\textsubscript{2A} receptor density in elderly individuals with depression\textsuperscript{46} or in individuals with borderline personality disorder, suicidal ideation and a history of severe suicide attempts.\textsuperscript{25} In particular, because it is often assumed that the underlying neurobiology of borderline personality disorder and externally focused aggression are similar, it is notable that the age-related decline in prefrontal cortex 5-HT\textsubscript{2A} receptor BP\textsubscript{ND} did not differ between individuals with borderline personality disorder and healthy control participants in a study using the identical radiotracer and PET scanner.\textsuperscript{20}

Further research is needed to understand why cortex 5-HT\textsubscript{2A} BP\textsubscript{ND} is lower around age 20 years and why lower cortex 5-HT\textsubscript{2A} BP\textsubscript{ND} declines more slowly in people with violent behaviour. A possible explanation is that there is a different rate of survival and loss of neurons containing 5-HT\textsubscript{2A} in people with violent behaviour. Cortex 5-HT\textsubscript{2A} receptors decline considerably from age 20 to age 40 years, and then this decline levels off.\textsuperscript{13,15–18,27,28} Most 5-HT\textsubscript{2A} receptors are found in dendrites of pyramidal cell neurons,\textsuperscript{29} which also decline considerably in density from age 20 to 40 years, with the decline again tending to level off thereafter.\textsuperscript{29} It may be that, in people with violent behaviour, a neuronal cell type that contains 5-HT\textsubscript{2A} receptors such as pyramidal cell neurons has lower density early in life and a different survival duration, with the yearly rate of loss of these neurons being slower and reflected in the observed different age-related changes in cortex 5-HT\textsubscript{2A} BP\textsubscript{ND}. Other explanations could include differential expression of 5-HT\textsubscript{2A} receptors in other cell types over the lifespan\textsuperscript{29,30,34} or more extracellular 5-HT at a young age.

Reconsidering the traditional interpretation that prefrontal 5-HT is low in humans with aggressive behaviour (and antisocial personality disorder and/or conduct disorder) is clinically important because the low 5-HT theory of aggression is used to argue for treatment with selective serotonin reuptake inhibitors (SSRI) for aggression in people with antisocial personality disorder and/or conduct disorder. If it is unlikely that extracellular 5-HT is low in people with violent behaviour and these diagnoses, the use of SSRIs to voluntarily reduce violent behaviour in people with these diagnoses should be based on the empirical evidence of clinical trials. Only one double-blind, placebo-controlled trial is cited to argue for treatment of aggression with SSRIs in antisocial personality disorder and/or conduct disorder.\textsuperscript{49} That clinical trial shows relevance for aggression in borderline personality disorder. However, it is important to note that only 10% of the participants in that clinical trial met criteria for antisocial personality disorder (conduct disorder was not discussed). Therefore, the use of SSRIs to reduce violent aggressive behaviour in humans with antisocial personality disorder and/or conduct disorder should be viewed cautiously until placebo-controlled studies focusing on these specific syndromes are completed. We are not aware of a double-blind, placebo-controlled study of the use of SSRIs for the treatment of aggression in individuals with antisocial personality disorder.

This was the first study of brain 5-HT\textsubscript{2A} receptors in people with violent behaviour toward others. We found that cortex 5-HT\textsubscript{2A} BP\textsubscript{ND} was lower near age 20 years and higher near age 40 compared with healthy control participants. We also found that greater severity of impulsive behaviour correlated strongly with lower cortex 5-HT\textsubscript{2A} BP\textsubscript{ND}. Low cortex 5-HT\textsubscript{2A} BP\textsubscript{ND} is relevant to violent behaviour because it is most evident in those with more severely impulsive behaviour and because it occurs around age 20 years, when violent behaviour is more frequent in people with antisocial personality disorder and conduct disorder. These findings indicate that the hypothesis of low extracellular 5-HT and elevated 5-HT\textsubscript{2A} density in the cortex of people with violent behaviour must be reconsidered. They support alternative neurochemical models of violent aggression, such as decreased 5-HT turnover or general neuronal loss at an early age. These findings also suggest that abnormalities of cortex 5-HT\textsubscript{2A} receptors should be viewed as specific to particular mental disorders\textsuperscript{13,27} rather than to suicide itself. The findings of the present study make the hypothesis of low extracellular 5-HT in people displaying violent aggression unlikely, and therefore, the clinical practice of SSRI treatment to reduce violent behaviour in people with antisocial personality disorder or conduct disorder should be viewed with considerable caution because clinical trial data are not available.\textsuperscript{49}

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