Decreased frontal serotonin 5-HT_{2a} receptor binding index in deliberate self-harm patients

Kurt Audenaert[1, 2], Koen Van Laere[2], Filip Dumont[3], Guido Slegers[3], John Mertens[4], Cees van Heeringen[1], Rudi A Dierckx[2]

[1] Unit for Suicide Research, Department of Psychiatry and Medical Psychology, 1K13, Ghent University Hospital, De Pintelaan 185, Ghent, Belgium
[2] Department of Nuclear Medicine, Ghent University Hospital, Belgium
[3] Department of Radiopharmacy, Ghent University, Belgium
[4] VUB-Cyclotron, Brussels, Belgium

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Abstract. Studies of serotonin metabolites in body fluids in attempted suicide patients and of post-mortem brain tissue of suicide victims have demonstrated the involvement of the serotonergic neurotransmission system in the pathogenesis of suicidal behaviour. Recently developed neuroimaging techniques offer the unique possibility of investigating in vivo the functional characteristics of this system. In this study the 5-HT_{2a} receptor population of patients who had recently attempted suicide was studied by means of the highly specific radio-iodinated 5-HT_{2a} receptor antagonist 4-amino-*N*-[1-[3-(4-fluorophenoxy) propyl]-4-methyl-4-piperidinyl]-5-iodo-2-methoxybenzamide or ^{123}I-5-I-R91150. Nine patients who had recently (1–7 days) attempted suicide and 12 age-matched healthy controls received an intravenous injection of 185 MBq ^{123}I-5-I-R91150 and were scanned with high-resolution brain single-photon emission tomography (SPET). Stereotactic realigned images were analysed semi-quantitatively using predefined volumes of interest. Serotonin binding capacity was expressed as the ratio of specific to non-specific activity. The cerebellum was used as a measure of non-specific activity. An age-dependent 5-HT_{2a} binding index was found, in agreement with previous literature. Deliberate self-harm patients had a significantly reduced mean frontal binding index after correction for age (P=0.002) when compared with controls. The reduction was more pronounced among deliberate self-injury patients (DSI) (P<0.001) than among deliberate self-poisoning patients (DSP). Frontal binding index was significantly lower in DSI patients than in DSP suicide attempters (P<0.001). It is concluded that brain SPET of the 5-HT_{2a} serotonin receptor system in attempted suicide patients who are free of drugs influencing the serotonergic system shows in vivo evidence of a decreased frontal binding index of the 5-HT_{2a} receptor, indicating a decrease in the number and/or in the binding affinity of 5-HT_{2a} receptors.

Keywords: Deliberate self-harm – Attempted suicide – Serotonin – Serotonin-2a receptor – Single-photon emission tomography

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Kurt Audenaert (✉)
Unit for Suicide Research,
Department of Psychiatry and Medical Psychology, 1K13,
Ghent University Hospital, De Pintelaan 185, Ghent, Belgium
e-mail: kurt.audenaert@rug.ac.be
Tel.: +32-9-2404395, Fax: +32-9-2404989

Introduction

The involvement of serotonin (5-HT), and specifically of the serotonin-2 receptor (5-HT_2), in the pathophysiology of suicide and suicidality has been the target of considerable research in the past decade. Both indirect measurements, comprising levels of 5-HT and its metabolite 5-HIAA in cerebrospinal fluid and in blood [1, 2], challenge tests for the serotonergic system [3], and quantification of 5-HT_2 receptors on blood platelets [4, 5], and direct measurements of brain serotonin function and receptor status in post-mortem research [6, 7, 8] have yielded varying results. The interpretation of these results is limited by the questionable validity of peripheral measures as markers of cerebral activity [9]. Post-mortem cerebral study results are also limited by lack of sampling from multiple regions [7] and rapid alterations in neurotransmitter concentration post-mortem [10]. Other reasons for the variability in the study results are the use of divergent classification systems for psychiatric diag-

noses, heterogeneity with regard to the nature of suicidal behaviour, and treatment with antidepressant drugs or neuroleptics at the time of the suicide attempt [11].

Functional imaging techniques, such as positron emission tomography (PET) and single-photon emission tomography (SPET), using specific 5-HT_2 receptor ligands, make it possible to evaluate in vivo the receptor binding index in patients with mood disorders and patients following a suicide attempt. Studies in unmedicated depressed patients found either no alteration or a decrease in the 5-HT_2 receptor binding index [12, 13, 14, 15]. This is the first report on functional imaging of the 5-HT_2 receptor in patients shortly after a suicide attempt.

Preliminary research in healthy subjects has indicated that radio-iodinated 4-amino-*N*-[1-[3-(4-fluorophenoxy) propyl]-4-methyl-4-piperidinyl]-5-iodo-2-methoxybenzamide, or ^{123}I-5-I-R91150, is a suitable ligand for imaging 5-HT_{2a} receptors in vivo. It binds reversibly and with high affinity in vitro to 5-HT_{2a} receptors [16]. On average, 2% of a bolus dose of ^{123}I-5-I-R91150 is taken up by the brain [17]. Effective blockade of 5-HT_{2a} receptors in vivo was demonstrated in a study of schizophrenic patients treated with risperidone or clozapine [18].

In the present study, the 5-HT_{2a} receptor in the brain of patients who recently attempted suicide was studied by means of this 5-HT_{2a} receptor antagonist using brain SPET. It was hypothesised that differences in the 5-HT_{2a} binding index in frontal cortex exist between suicide attempters and normal controls and furthermore between deliberate self-poisoning and deliberate self-injury patients.

Materials and methods

Patients. Patients were included in the study if they were aged between 18 and 60 years and if they were admitted following a suicide attempt. Suicide attempts included deliberate self-poisoning (DSP) and self-injury (DSI). The term DSP was used to describe the ingestion of more than the prescribed amount of medical substances, or the ingestion of substances never intended for human consumption, irrespective of whether harm was intended. The term DSI was used to describe any intentional self-inflicted injury, irrespective of the apparent purpose of the act [19]. Exclusion criteria were (1) electroconvulsive therapy in the preceding year, (2) antidepressant treatment in the preceding 6 months, (3) neuroleptic treatment in the preceding 6 months, (4) lithium or carbamazepine treatment in the preceding 6 months, (5) major medical or neurological disorder, (6) pregnancy or lactation period, (7) substance abuse, and (8) a Mini-Mental State [20] score less than 28.

The study group consisted of seven men and two women. Six patients attempted suicide by means of DSP and three by means of DSI. All patients were free of psychotropics for at least 6 months before scanning, except for benzodiazepines (n=4), barbiturates (n=1) or anti-epileptics (n=1), which were ingested while attempting suicide in the DSP group.

Patients were screened for alcohol intoxication and signs of chronic alcohol abuse by means of blood alcohol level on admission, mean erythrocyte corpuscular volume (MCV) and gamma-glutamyl transferase (γ-GT). Two patients were positive on alcohol screening (1.1 and 1.2 mg/100 ml) and had normal MCV and γ-GT. All other patients also had normal MCV and γ-GT.

Patients were clinically evaluated by two senior psychiatrists (K.A., C.V.H.) and were assigned DSM-IV diagnoses at the time of admission. Four patients were diagnosed as depressed and had a score on the Hamilton Depression Rating Scale [21] of 24 or more. Two patients reported one prior suicide attempt.

Healthy volunteers. Twelve age-matched healthy volunteers, six men and six women, were recruited from among the hospital staff. These subjects had no psychiatric or medical history, nor a family psychiatric history. None used psychotropics or other relevant medication or abused illegal drugs. All had a normal physical examination.

Ethical approval for the study was granted by the Local Ethics Committee. Both suicide attempters and healthy individuals provided written informed consent to participation in the study.

Tracer. ^{123}I-5-I-R91150 was synthesised by electrophilic substitution on the 5-position of the methoxybenzamide group of R91150, followed by purification with high-performance liquid chromatography. The product had a radiochemical purity of more than 99% and was negative for bacteria and pyrogen. A specific activity of 10 Ci/μmol was obtained.

The tracer is a 5-HT_{2a} antagonist with high affinity (K_d=0.11 n*M*) and selectivity for 5-HT_{2a} receptors. The selectivity of the ligand for 5-HT_{2a} receptors in relation to other neurotransmitter receptors such as other 5-HT receptors, including 5-HT_{2c}, dopamine receptors, adrenoreceptors and histamine receptors, is at least a factor of 50. The tracer was displaceable with ketanserin [16, 22].

SPET scanning. Thyroid blockade was achieved by administration of a single oral dose of 100 mg potassium chloride prior to injection. All subjects received an intravenous injection of 185 MBq ^{123}I-5-I-R91150 in normal sitting conditions. SPET scanning was performed at the Ghent University Hospital Division of Nuclear Medicine using a triple-headed high-sensitivity high-resolution Toshiba gamma camera GCA-9300 with fan-beam collimation. For ^{123}I, the resulting transaxial image resolution is 9.5 mm full-width at half-maximum.

Since sequential dynamic SPET brain scans have shown that the cortico-cerebellar ratio reaches a plateau between 90 and 110 min, reflecting pseudo-equilibrium, and remains stable thereafter for up to 8 h [17], acquisition was started between 110 and 140 min after tracer injection. Time-specific activity curves of a representative healthy volunteer (male, aged 25) are presented in Fig. 1A (with the corresponding frontal cortex-cerebellum ratio of activity in Fig. 1B).

A transmission scan (TCT scan) was acquired before the emission scan, using three gadolinium-153 rod sources. This scan was used for subsequent image co-registration.

Emission images were acquired during 40 min. The whole brain volume was acquired within the single scanning session.

Estimation of binding index. Analysis of the scans was performed blind to patient status. Images were corrected for scatter and attenuation. Mean images of the 5-HT_{2a} receptor binding index for normal volunteers and for DSP and DSI patients are depicted in Fig. 2.

After automatic image co-registration to stereotactic space (BRASS, Nuclear Diagnostics), a predefined volume of interest

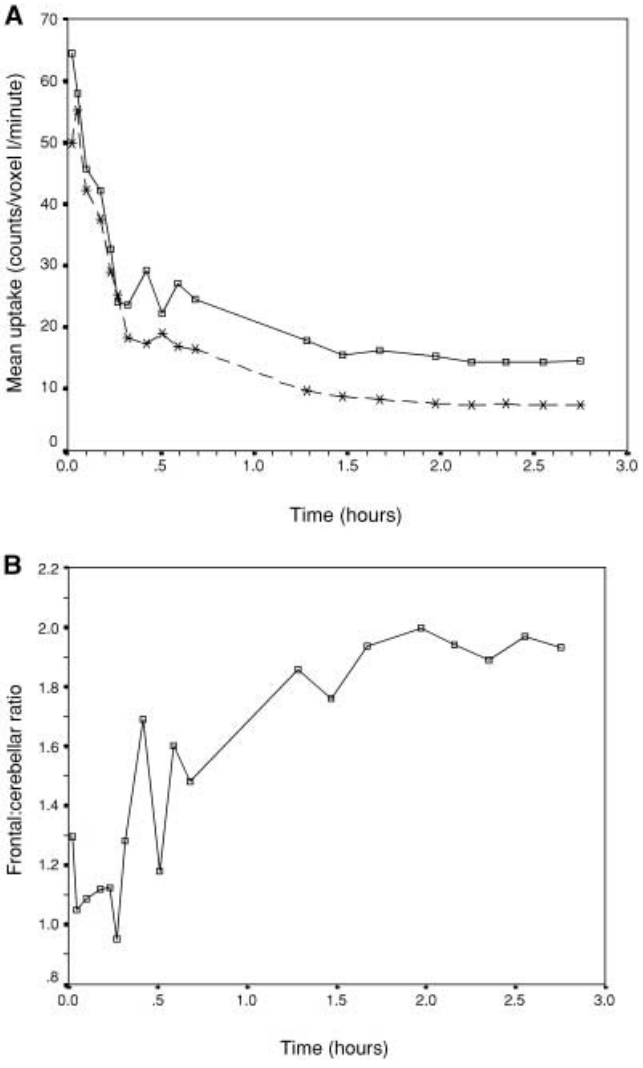

Fig. 1. A Time-activity curves of a representative healthy volunteer (male, age 25), expressed as mean activity per volume unit (counts/voxel/minute), normalized for decay, versus time (*open squares*, frontal cortex; *asterisks*, cerebellum). **B** Frontal cortex-cerebellum ratio of activity (a relative index of specific binding) for the same volunteer

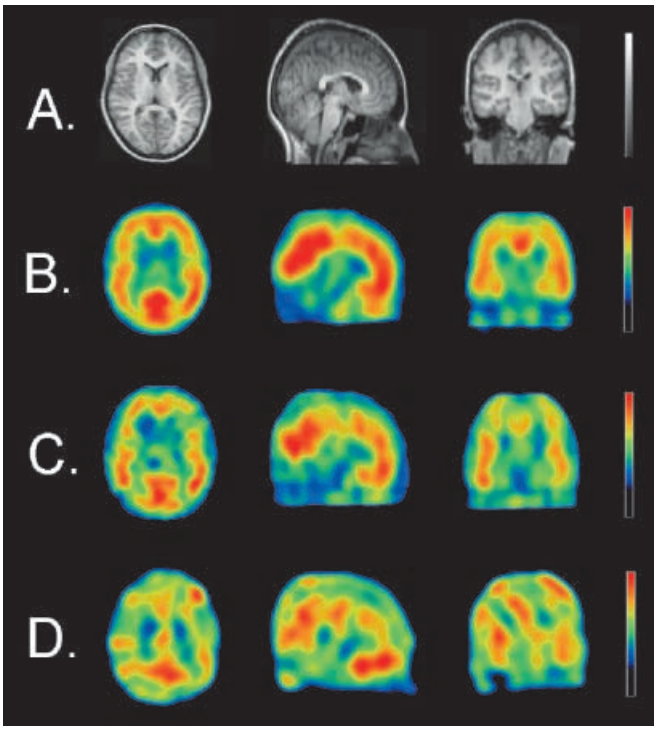

Fig. 2. A MRI template showing transverse, coronal and sagittal sections. **B–D** Cerebral uptake of 5-HT_{2a} ligand ^{123}I-5-I-R91150 (transverse, coronal and sagittal sections) in healthy volunteers (**B**, mean image), deliberate self-poisoning (DSP) suicide attempters (**C**, mean image) and deliberate self-injury (DSI) suicide attempters (**D**, mean image)

(VOI) analysis was performed with 12 cortical regions. Radioactivity estimates in the cortex were assumed to represent total ligand binding (specific + non-specific binding + free ligand) [18]. Since the cerebellum is devoid of serotonin receptors [23] and therefore represents non-specific activity, calculation of relative indices of specific binding index (BP) was done by VOI normalisation to the activity per volume element in the cerebellum. Under these pseudo-equilibrium circumstances, this binding index is directly related to the in vivo receptor density (B_{max}) and affinity (K_D). Binding index was defined as (target activity – background activity in brain)/(background activity), which was operationally estimated as (counts/pixel in frontal cortex)/(counts/pixel in cerebellum).

Statistical methods. The equality of age distributions between diagnostic categories was evaluated according to the Kruskal-Wallis test. As binding index levels were normally distributed, analysis of variance was used to compare mean levels between categories. Linear adjustment for age was done according to analysis of covariance. An a priori level of α=0.05 was chosen to indicate statistical significance. Model assumptions were checked by graphical inspection of Pearson residuals. None of the second-order interaction terms between diagnostic group, age and gender turned out to be significant at the 0.10 level.

Results

Effect of age

The sample of 21 subjects under study consisted of 13 men and 8 women. They were on average 30.4 years old (SD 9.2 years), with ages ranging from 19 to 48 years. Although statistically not significant, mean ages were slightly different between the three study groups, i.e. 29.0, 30.3 and 36.5 years for volunteers, patients with DSP and patients with DSI, respectively. Since previous research has suggested that BP levels decrease with age [24], age was taken into account as a potential confounding variable in our analyses. Therefore age correction was performed applying linear correction. All values were corrected to the mean age of the group, i.e. 29.4 years. In our study, a significant correla-

Table 1. Demographic characteristics, clinical diagnoses, description of suicide attempt and interval until scan acquisition in patients with deliberate self-harm and normal volunteers

Sex	Age (years)	Clinical disorder (DSM-IV)	Personality disorder (DSM-IV)	HAMD score	Type	Means	Interval[a] (days)
M	37	Major depressive disorder (296.22)	–	25	DSP	BDZ intoxication	7
F	19	Adjustment disorder (309.3)	Borderline (301.83)	10	DSP	Barbiturate intoxication	2
M	29	Major depressive disorder (296.22)	–	29	DSP	Phenytoin intoxication	6
M	34	Adjustment disorder (309.24)	Narcissistic (301.81)	11	DSP	Self-injection of insulin	1
F	48	Major depressive disorder (296.22)	–	27	DSI	Wrist-cutting	7
M	19	Adjustment disorder (309.9)	Narcissistic (301.81)	8	DSI	Wrist-cutting	3
M	19	Brief psychotic disorder (298.8)	–	7	DSP	BDZ intoxication	3
M	44	Major depressive disorder (296.32)	–	27	DSP	BDZ intoxication	1
M	43	Adjustment disorder (309.3)	Dependent (301.6)	8	DSI	Strangulation	1

DSM, Diagnostic and Statistical Manual – Fourth Edition; HAMD, Hamilton Depression Rating Scale; DSP, deliberate self-poisoning; DSI, deliberate self-injury; BDZ, benzodiazepines

[a] Interval between suicide attempt and image acquisition

tion between age and global frontal receptor binding index was demonstrated in the whole group. Since the study groups were quite comparable (Fisher's Exact Test P=0.37) and no effect of gender on 5-HT_{2a} binding index has been found [24], no adjustments for gender were made in further analyses. Additional details in respect of the patients are shown in Table 1.

Frontal binding index

The frontal binding index of the volunteers and patients is presented as a scatterplot in Fig. 3. Frontal BP levels were significantly lower in suicide attempters (mean 0.39, SE 0.04) than in volunteers (mean 0.68, SE 0.04) (P<0.001). A significant difference in binding index between normal volunteers and deliberate self-harm patients in the left (t=14.2; P=0.001) and right (t=8.9; P=0.008) frontal cortex was found.

In Table 2 the results of the co-variance model fit are given, comparing BP levels between the three study groups after linear adjustment for age. Both DSP (–0.14) as DSI (–0.46) suicide attempters had significantly lower BP levels compared with the volunteers. In this sample of 21 subjects, the model explained 73% of the variability in binding index levels. As shown in Fig. 3, mean BP levels in the three study groups (volunteers, DSP and DSI), adjusted for age, were 0.68, 0.53 and 0.21, respectively. A significant difference between the three groups (F=21.0; P<0.001) with respect to the total frontal

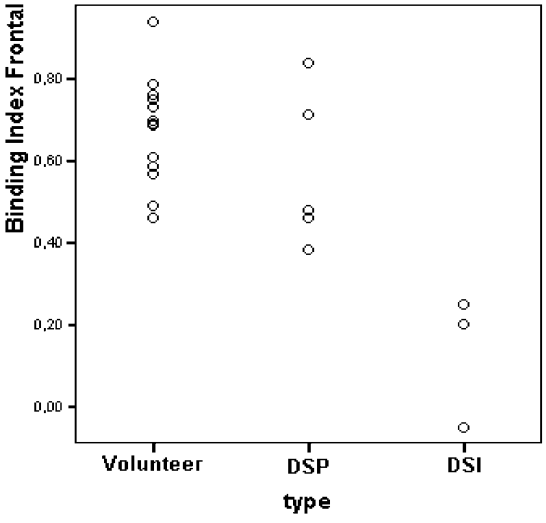

Fig. 3. Scatterplot of the binding index of the frontal cortex in healthy volunteers, deliberate self-poisoning patients (*DSP*) and deliberate self-injury patients (*DSI*)

(F=21.0; P<0.001), the left (F=17.4; P<0.001) and the right frontal cortex (F=18.4; P<0.001) was found (Table 3). Post hoc multiple comparison indicated a significant difference in binding index between normal volunteers and DSI patients in the total frontal cortex (P=0.041), which turned out to be significant only in the left (P=0.022), and not the right (P=0.137), frontal cortex. Post hoc multiple comparisons between the volun-

Table 2. Frontal binding index levels in suicide attempts and volunteers (analysis of co-variance)

	Estimated β (SE)	*t* value	Significance
Intercept	188.06 (9.36)	20.08	*P*<0.0001
Age (years)	–0.69 (0.30)	–2.30	*P*=0.03
DSP vs volunteers	–14.24 (6.06)	–2.35	*P*=0.03
DSI vs volunteers	–46.34 (8.17)	–5.67	*P*<0.0001

teers and the DSI group yielded significant differences for the total, left and right frontal cortex (all $P<0.001$). Post hoc multiple comparisons between the DSP and the DSI group yielded significant differences for the total ($P<0.001$), left ($P=0.003$) and right ($P<0.001$) frontal cortex binding index between volunteers and the DSI population.

Due to the limitations of the SPET technique in terms of spatial resolution, we did not report on the subregions of the frontal cortices that were significantly different with regard to binding index between the three populations. Since we analysed them initially, the binding index of the subregions is presented in Table 3.

Discussion

This is the first in vivo study of 5-HT_{2a} cerebral receptors in the prefrontal cortex of deliberate self-harm patients. When compared with normal controls, a significantly reduced 5-HT_{2a} binding index in frontal cortex was found. The reduction was significant in both the left and the right frontal cortex. A significantly larger reduction in the binding index was found in DSI patients than in DSP patients. Pairwise comparison between the three populations yielded significant differences for all comparisons, with the exception of the right frontal cortex binding index between the volunteers and the DSP population. We have no reasonable explanation for the latter finding, but expect that the difference between the normal volunteers and the DSP patients will become significant when the number of patients increases.

Although only four of the nine patients were diagnosed as depressed, our results are, at least partially, in keeping with the findings of other functional imaging studies in unmedicated depressed patients. Using the highly specific 5-HT_{2a} PET radioligands ^{18}F-altanserin and ^{18}F-setoperone, a significant decrease in the receptor binding index in frontal cortex [12, 14] and an unaltered receptor binding index were demonstrated, respectively [15]. Using a less specific 5-HT_2 SPET ligand in depressed patients, D'Haenen et al. found an increase in the left-to-right prefrontal cortex binding index, unlike the findings of our study [25]. However, it has to be noted that ^{123}I-ketanserin has a low signal-to-noise ratio in comparison with ^{123}I-I-R91150.

Results from in vitro and indirect 5-HT_2 measurement techniques are inconclusive. Post-mortem measurements of 5-HT_2 and 5-HT_{2a} receptor density, using various ligands with autoradiography, in depressed or non-depressed suicide victims have yielded discrepant results. Most studies have demonstrated an increase in 5-HT_2 or 5-HT_{2a} receptor binding, more specifically in the frontal cortex [6, 26, 27] of depressed patients who committed suicide but also in the prefrontal cortex of schizophrenic patients [28]. Other studies have found no significant differences in 5-HT_2 or 5-HT_{2a} receptor density in the prefrontal areas between normal controls and suicide victims, irrespective of psychiatric diagnosis [29, 30], or between controls and depressed patients [7, 31, 32, 33]. There have been reports of significant decreases

Table 3. Comparison of binding indices between volunteers and deliberate self-harm patients (DSH) and between volunteers, deliberate self-poisoning (DSP) and deliberate self-injury (DSI) patients. Post hoc multiple comparisons (Bonferroni corrected) are presented and indicate significant differences between the subgroups

Brain region	Population				Statistics				
	Volunteers	Attempted suicide patients			*t* test		ANOVA		
		DSH	DSP	DSI	*t*	Sign.	*F*	Sign.	Multiple comparison
L frontal cortex, total	0.69	0.41	0.52	0.19	14.2	0.001	17.4	0.000	VOL>DSP>DSI
L orbitofrontal cortex	0.71	0.55	0.62	0.43	1.7	0.216	1.3	0.298	
L dorsolateral prefrontal cortex	0.69	0.14	0.53	0.14	12.7	0.002	18.7	0.000	VOL>DSP>DSI
L frontal cortex, remaining	0.66	0.36	0.46	0.17	17.2	0.001	16.1	0.000	VOL>DSP>DSI
R frontal cortex, total	0.67	0.42	0.56	0.13	8.9	0.008	18.4	0.000	VOL=DSP>DSI
R orbitofrontal cortex	0.70	0.54	0.62	0.36	2.0	0.170	2.1	0.147	
R dorsolateral prefrontal cortex	0.68	0.41	0.57	0.08	8.5	0.009	19.9	0.000	VOL=DSP>DSI
R frontal cortex, remaining	0.64	0.39	0.54	0.10	8.0	0.011	17.5	0.000	VOL=DSP>DSI
L + R frontal cortex	0.68	0.39	0.53	0.13	12.3	0.002	21.0	0.000	VOL>DSP>DSI

L, Left; R, right; Sign., Significance

in B_{max} and K_D of the 5-HT_{2a} receptor, most markedly in the prefrontal cortex of depressed but antidepressant-free suicide victims who died violently [34], and of the 5-HT_2 receptor in the prefrontal cortex of suicide victims [8].

Indirect estimation of the BP of brain 5-HT_2 receptors can be done by platelet 5-HT_2 receptor measurement [5]. Elevated platelet 5-HT_2 receptor binding has commonly been found in depression, suicidal states and depression with recent suicide attempt, and has been attributed to a significant increase in receptor density, with no significant change in affinity (K_D) [4, 35]. Other studies, however, have not found changes in the concentration of 5-HT_2 receptors [36].

In the current study, a significant negative association between age and receptor binding index in frontal cortex was demonstrated in the whole group and in the group of suicide attempters. The magnitude of the decrease (6.9%±3.0% per age decade) is in agreement with previously published studies [23].

A possible confounder of the study results lies in the fact that a physical trauma, due to the recent suicide attempt, could have had an impact on the binding index of the tracer due to a decrease in cerebral blood flow. We cannot rule out this possibility; however, our results were fairly homogeneous irrespective of the method used in the suicide attempt. From a theoretical perspective, the results could be artifactual if the group of normal volunteers were to have had a slower metabolic rate for the tracer than the deliberate self-harm group. However, there are no indications in the literature to support this possible confounder.

In evaluating the data, one must also pay attention to the medication and alcohol that were ingested prior to or on the occasion of the suicide attempt. Indeed, a further possible confounder for the study could reside in an impact of consumption of large amounts of alcohol on the clearance of the ligand, possibly by induction of liver enzymes. Moreover, patients who are entrapped in a crisis often seek relief in alcohol. In our study sample, two patients were positive on alcohol screening (>0.8 mg/100 ml) when admitted to the hospital. Blood tests on mean erythrocyte corpuscular volume and γ-GT in all patients were normal. Patients did not use any alcohol during their stay in the hospital in the period between admission and scanning. None of the patients had a history of alcohol abuse. Hence, it is unlikely that results were confounded by an impact of abuse of large amounts of alcohol on clearance of the ligand.

Concerning psychotropic medication, it must be noted that some of the patients attempted suicide by means of DSP using psychotropics, and hence the possible effects of benzodiazepines, barbiturates and anti-epileptics on the results must be considered. Benzodiazepines have been reported to increase 5-HT_2 receptor numbers in animal studies [37], but an absence of any effect on 5-HT_2 receptor numbers has also been reported [38]. An effect of benzodiazepine withdrawal could not be ruled out, although patients showed no clinical withdrawal symptoms in the period following the intoxication. In this study and in a ^{18}F-setoperone study in depressed patients [14], the 5-HT_{2a} binding index fell within the same range in patients who received benzodiazepines and patients who were free of benzodiazepines. Hence, it is unlikely that a decrease in binding index, as observed in our study, might be induced by the ingestion of benzodiazepines. There are no reports of effects of barbiturates or phenytoin on 5-HT_{2a} receptor binding characteristics.

Patients were only enrolled in our study when there was evidence that they had not used neuroleptics or antidepressants for at least 6 months prior to their suicide attempt. This evidence was provided by interviews with the patients and contacts with their general practitioner. Systematic toxicological screening for butyrophenones, phenothiazines, tricyclic antidepressants, benzodiazepines and barbiturates was performed in the DSP patients. No screening was done for atypical neuroleptics or for the newer antidepressants. As the use of psychotropics could not be ruled out with certainty, and as some studies [7, 39], though not all [40, 41], have shown that chronic treatment with antidepressant drugs may cause down-regulation of the 5-HT_{2a} postsynaptic receptors, our results could be due to chronic use of tricyclic antidepressants. However, D'Haenen et al. reported no significant difference in uptake values with ^{123}I-ketanserin between patients who had not received any antidepressant drug for at least 3 weeks and those who had taken antidepressants up to 7 days before imaging [25]. The use of selective serotonin re-uptake inhibitors (SSRIs) has been reported to increase the number [37, 42, 43] and the binding index [13] of 5-HT_{2a} receptors. Thus, it is unlikely that the reduction in binding index could be attributed to the use of SSRIs. Moreover, the non-uniform reduction of the binding index in different cortical regions is another indication that the reduction is not likely to be attributable to medication.

Although a causal relation between a reduction in 5-HT_{2a} binding index and suicidality has never been demonstrated, the fact that SSRIs increase the number of 5-HT_{2a} receptors suggests that the results of this study could explain the pathophysiological basis of the findings of a controlled clinical trial of paroxetine that showed a reduction in the repetition rate of deliberate self-harm in non-depressed patients [44].

In conclusion, our study provides evidence of a decreased receptor binding index in drug-free deliberate self-harm patients. This decrease was most marked in patients who attempted suicide by DSI. Further cross-sectional studies should replicate these findings in larger populations. Longitudinal pharmacological intervention studies should evaluate the 5-HT_{2a} binding index in relation to clinical parameters of suicidality, and effects of treatment on repetition of suicidal behaviour.

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