Single-photon emission tomography imaging of monoamine transporters in impulsive violent behaviour

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Abstract. Several studies have shown that impulsive violent and suicidal behaviour is associated with a central serotonin deficit, but until now it has not been possible to use laboratory tests with high sensitivity and specificity to study this kind of deficit or to localize the sites of serotonergic abnormalities in the living human brain. The aim of this study was to test the hypothesis that monoamine transporter density in brain is decreased in subjects with impulsive violent behaviour. We studied serotonin (5-HT) and dopamine (DA) transporter specific binding in 52 subjects (21 impulsive violent offenders, 21 age- and sex-matched healthy controls, and ten non-violent alcoholic controls) with single-photon emission tomography (SPET) using iodine-123-labelled 2β-carbomethoxy-3β(4-iodophenyl)tropane ([^{123}I]β-CIT) as the tracer. The blind quantitative analysis revealed that the 5-HT specific binding of [^{123}I]β-CIT in the midbrain of violent offenders was lower than that in the healthy control subjects (P<0.005; t test) or the non-violent alcoholics (P<0.05). The results imply that habitual impulsive aggressive behaviour in man is associated with a decrease in the 5-HT transporter density.

Key words: Alcoholics – Impulsiveness – Monoamine transporters – Receptors – Single-photon emission tomography

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Introduction

Violence is an important public health problem in many industrialized countries; for example, in the United States homicide is the second most common cause of death among young males [1]. However, the aetiology of violence has not been studied as extensively as that of AIDS or even traffic accidents by the medical sciences, and so far, medicine has not had any major impact on the prevention of violent behaviour.

A large number of studies have described a central serotonin deficit in alcoholic impulsive violent offenders and arsonists [2–7]. Although these offenders have low mean cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations when compared with healthy volunteers, a relatively large proportion of them have CSF 5-HIAA levels within the normal range [8, 9]. Monoamine transporters [noradrenaline, serotonin (5-HT), dopamine (DA)] are specialized carrier proteins in the presynaptic cell membrane [10], and radiolabelled tracers for DA transporter have been developed [11–13]. The anatomical distribution of DA and 5-HT post- and presynaptic receptors in humans has been studied in vitro with audioradiographic methods [14] and in vivo with positron emission tomography (PET) and single-photon emission tomography (SPET) [15–19]. Results obtained from a human post-mortem autoradiography study indicate that the density of serotonin re-uptake sites is highest in the diencephalon, the striatum and the cingulate cortex [20]. However, until recently it has not been possible to image properly monoamine transporters in the living human brain.

An iodine-123-labelled cocaine congener, 2β-carbomethoxy-3β(4-iodophenyl) tropane ([^{123}I]β-CIT), has been used for SPET imaging of a combination of DA and 5-HT re-uptake sites in the brain of monkeys [21–23], and a few human studies have also been performed with β-CIT [24–28]. Recently, it was shown that DA and 5-HT re-uptake sites can be separated in non-human primates by simultaneous treatment with citalopram, a 5-HT re-uptake inhibitor, in conjunction with β-CIT [29]. The aim of this study was to image 5-HT and DA re-uptake sites in the living human brain, and to compare the specific binding of [^{123}I]β-CIT in habitual impulsive violent offenders with that in of normal age- and gender-matched control subjects and non-violent alcoholic control subjects.

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Material and methods

Study subjects. The procedure was approved by the local ethical committee (Kuopio University Hospital), and all subjects provided their informed consent after complete description of the study. All 52 subjects were white Finnish citizens. [^{123}I]β-CIT SPET was performed in 21 healthy control subjects with no neurological or psychiatric disorders or any kind of medication (19 males, 2 females, aged 19–50 years; mean 32 years), in 21 index subjects (19 males and 2 females, aged 19–55 years; mean 30 years) and in ten non-violent alcoholic control subjects (all males, aged 35–50 years; mean 42 years). Sixteen of 21 controls were members of staff (students, nurses, physicians and secretaries). Paired *t* tests were done by comparing sex- and age-matched groups. The anamnestic, demographic and diagnostic data of the index subjects are shown in Table 1.

Twenty of the 21 index subjects had committed previous impulsive violent offences under the influence of alcohol. All 21 subjects had been committed for forensic psychiatric examination in a state mental hospital after being involved in a homicide (six subjects), an attempted homicide (seven subjects), an aggravated violent assault (four subjects), arson (two subjects), hostage-taking (one subject) or assault (one subject). All patients were subjected to an extensive forensic psychiatric examination including a psychiatric evaluation, standardized psychogical tests such as the Wechsler Adult Intelligence Scale (WAIS), the Rorschach test (Ro), and the Minnesota Multiphasic Personality Inventory (MMPI), a Structured Clinical Interview for DSM-III-R (SCID), evaluation of physical condition with laboratory tests and electroencephalography (EEG), and observation of the offender by the staff in the security ward of the hospital for 4–8 weeks. After examination, 17 subjects were diagnosed as typical type 2 alcoholics [30] with co-existing antisocial personality or mixed-type personality disorder with antisocial features, and four subjects suffered from severe alcoholism which had developed after the age of 25 years. The biological fathers of ten index subjects were alcoholics. None of the index subjects had had access to alcohol or any psychotropic medication during the 2 months preceding the SPET study (seven subjects were drug-naive).

Because 20 of the 21 index subjects were alcoholics, ten additional non-violent alcoholic controls were studied to investigate the effect of alcoholism per se on the monoamine transporters. All subjects were recruited with the help of a local rehabilitation centre for alcoholics, where all subjects had obtained non-pharmacological treatment to their alcoholism. The subjects were selected from the patient population by a psychiatric nurse who chose those subjects who had little or no psychiatric or somatic co-morbidity and no use of antidepressants or neuroleptics. All subjects had had difficulties in their job because of alcoholism, but none of them had committed any criminal offences. The problems caused by alcohol occurred between the ages of 25 and 47 years. Six subjects were drug-naive, and four had used benzodiazepines occasionally. The anamnestic, demographic and diagnostic data are presented in Table 2. All subjects were interviewed by a psychiatrist and completed structured interview questionnaires of the Hopkins Symptom Checklist (HSC-90) and the Michigan Alco-

Table 1. The demographic, diagnostic and anamnestic data of the index subjects

Age	Gender	Diagnosis (DSM-III-R)	Latest offence	Serious problems caused by alcohol since the age of (years)
19	M	301.70, 303.90*	Homicide etc.	14
19	M	301.70, 303.90*	Homicide	14
19	M	301.70, 303.90*, 304.90[1]	Hostage-taking	16
20	M	301.70, 303.90*	Attempted homicide, etc.	15
21	M	309.00	Aggravated assault	–
22	M	301.90, 303.90*	Attempted homicide	17
24	M	301.70, 303.90*	Homicide	17
24	M	301.83, 303.90*, 304.90	Assaults, etc.	18
25	M	301.90, 303.90*, 304.10	Homicide	15
25	M	301.70, 303.90*	Arson, damaging of property	15
25	F	301.70, 303.90*, 304.40, 304.10	Attempted homicide	17
28	M	301.70, 303.90*, 304.90[2]	Aggravated assaults, etc.	17
29	M	301.70, 303.90*, 304.90[3]	Attempted homicide, etc.	17
30	F	301.70, 303.90*	Attempted homicide	21
34	M	301.70, 303.90*	Attempted homicide	13
35	M	301.90, 303.90*	Aggravated assault	25
40	M	301.83, 303.90	Aggravated assault, arson	31
43	M	301.90, 303.90	Attempted homicide	33
45	M	301.90, 303.90*	Homicide	24
50	M	301.20, 303.90	Arson	38
55	M	9070A, 303.90	Homicide	49

301.20=Schizoid personality disorder; 301.70=antisocial personality disorder; 301.83=borderline personality disorder; 301.90=mixed-type personality disorder with antisocial features; 303.90=alcoholism, *=type 2 alcoholism; 304.10=anxiolytic dependence; 304.40=amphetamine dependence; 304.90=polysubstance dependence (304.90[1]=cannabis and benzodiazepine dependence; 304.90[2]=amphetamine and benzodiazepine dependence; 304.90[3]=amphetamine, benzodiazepine, opioid and cocaine dependence); 309.00=adjustment disorder with depressed mood; 9070A=temporal cortical atrophy. None of the index subjects had had access to alcohol or any psychotropic medication during the 2 months preceding the study (seven subjects were drug-naive)

Table 2. The demographic, diagnostic and anamnestic data of non-violent alcoholic control subjects

Age	Gender	Diagnosis (DSM-III-R)	Criminal offences	Serious problems caused by alcohol since the age of (years)	Duration of abstinence (weeks)
35	M	303.90	None	34	12
37	M	303.90	None	30	10
39	M	303.90	None	25	2
40	M	303.90, 300.02	None	30	200
41	M	303.90, 300.21	None	25	21
43	M	303.90	None	38	120
44	M	303.90, 296.22	None	33	2
45	M	303.90, 301.81	None	44	1
46	M	303.90	None	28	12
50	M	303.90	None	47	10

296.22=Major depressive disorder; 300.02=generalized anxiety disorder; 300.21=social phobia; 301.81=narcissistic personality disorder; 303.90=alcoholism. None of the subjects had abuse of other substances than alcohol

holism Screening Test (MAST). However, it was not possible to quantify accurately the total amount of cumulative lifetime ethanol exposure.

Single-photon emission tomography. The first SPET scan was taken between 1.0 and 1.5 h after injection of tracer (total scan time of 30 min) using the high-resolution Siemens MultiSPECT 3 gamma camera with an image resolution of 8–9 mm [31, 32]. The doses administered were same the in each group and varied from 160 to 210 MBq with a mean of 183 MBq. Subjects received 20 mg citalopram per os (a specific 5-HT re-uptake inhibitor) immediately after the first SPET scan and the second scan was performed 21–23 h after the injection of tracer.

Transaxial slices oriented in the orbitomeatal (OM) line (3.5 mm thick) were reconstructed after Chang's attenuation correction and visually surveyed. Two consecutive slices were summarized, and irregular regions of interest (ROIs) were semi-automatically drawn over an area corresponding to the midbrain (representing the 5-HT transporter), over the entire striatum (representing the DA transporter), and over the white matter (58–65 mm superior to the OM line; Fig. 1). One control subject was dynamically scanned up to 4.5 h in order to test when the midbrain radioactivity reached equilibrium (Fig. 2). The technologist (J.Y.) who performed the ROI analysis did not know the history of the study subjects. The average counts of each region were used for semi-quantification. We used white matter as a reference region (free + non-specific binding) because neocortical regions as well as cerebellum have 5HT re-uptake sites [19,20]. The specific binding of [^{123}I]β-CIT was calculated according to the equation:

specific binding=1–white matter/ROI_i, (1)

where ROI_i corresponds to the average counts of the region of interest *i*. The following ROIs were used in analysis: (1) midbrain at 1.0–1.5 h and (2) basal ganglia at 21–23 h.

Brain blood flow, effects of citalopram and reproducibility. In addition, 550 MBq of technetium-99m ethyl cysteinate dimer ([^{99m}Tc]ECD) (a brain perfusion marker) and 160 MBq of [^{123}I]β-CIT were simultaneously administered in six control subjects and six impulsive violent patients with type 2 alcoholism. Dual-isotope SPET scans were obtained 1.0–1.5 h after injection of these two tracers in order to establish whether the early [^{123}I]β-CIT uptake in the midbrain represents monoamine transporter density or mainly different distributional blood flow to this region of the brain. The energy overlap of ^{123}I photons into the ^{99m}Tc window was less than 15%. Midbrain activities were related to the cerebellum and the ^{123}I midbrain-to-cerebellum ratios were compared with those of ^{99m}Tc. We did not repeat the perfusion study in the patients with type 1 alcoholism because Nicolás et al. have previously shown that after 2 months of ethanol abstinence hypoperfusion normalized in type 1 alcoholics [33].

Six healthy control subjects were studied with [^{123}I]β-CIT SPET twice; the second time they received 20 mg citalopram 2–3 h prior to injection of tracer. This was done to test with a subtraction technique whether 5-HT re-uptake inhibitor prevents extrastriatal β-CIT binding (for the procedure, see ref. [24]).

Four healthy control subjects were scanned twice in order to test the reproducibility of the method. There was a 1-year interval between the scans but the camera performance parameters were same in both scans. Reproducibility of the specific binding ranged from –2% to +14% for the 1.0–1.5 h [^{123}I]β-CIT scan (reflecting mainly 5-HT transporter binding) and from –13% to 1% for the 21–23 h [^{123}I]β-CIT scan [DA transporter (DAT) binding].

Results

Figure 3 demonstrates regional uptake at 1.0–1.5 h after injection of 185 MBq of [^{123}I]β-CIT in one index subject, in his age-matched control and in one control subject pretreated with citalopram. The index subject had very little radioactivity in the midbrain, the anterior mesial frontal gyrus or the occipital cortex, whereas he had normal radioactivity in the basal ganglia. The control subject showed prominent [^{123}I]β-CIT uptake in these areas, whereas the control subject treated with citalopram showed reduced regional uptake except in the basal ganglia.

Differences between the groups with regard to the mean counts/voxel/dose injected in the midbrain failed to attain statistical significance (control subjects: 116±28; type 1 alcoholics: 116±27; and violent offenders: 109±22). Corresponding figures for the white matter

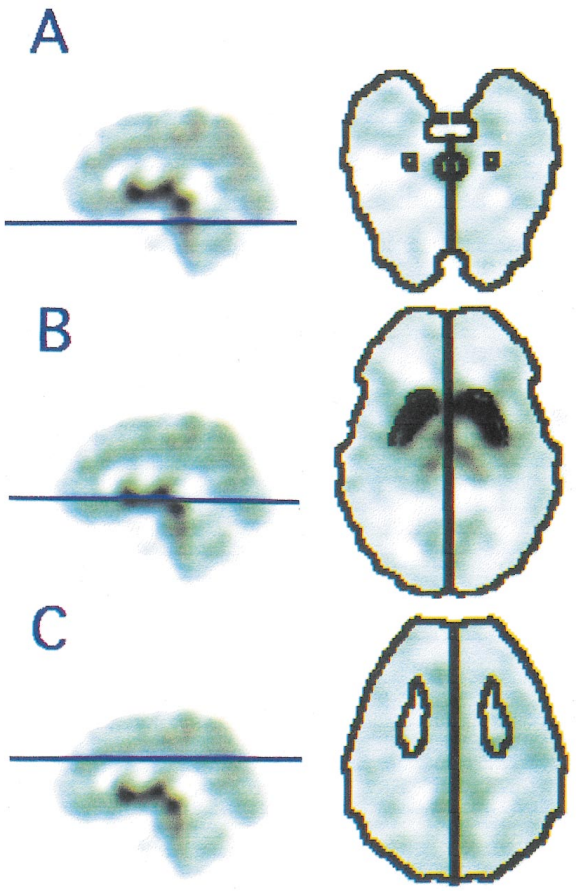

Fig. 1A–C. Regions of interest. **A** Midbrain; **B** basal ganglia; **C** white matter

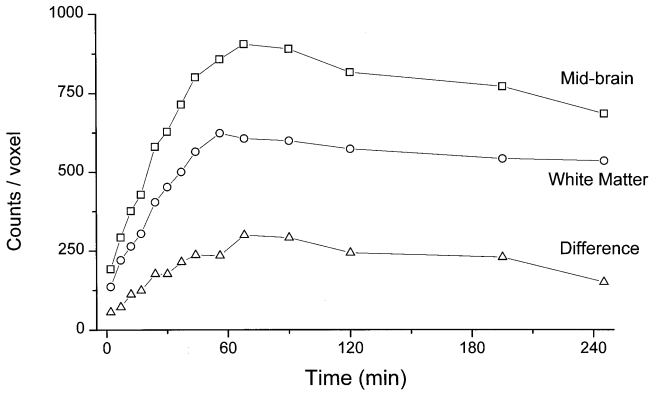

Fig. 2. Time-activity curves of [^{123}I]β-CIT binding in a 50-year-old healthy male in whom dynamic SPET was performed. □, mid-brain; ○, white matter; △, difference. The dose administered was 185 MBq and the data were acquired in a matrix size of 64×64

were 67±12, 68±13, and 69±11, respectively. Following calculation of the specific binding (Eq. 1), the statistical significance of differences was determined. Figure 4 shows scatter plots of the 5-HT specific binding of [^{123}I]β-CIT in the midbrain. The specific binding was on average 18% higher in control subjects (0.334±0.047; mean ±SD; P<0.005) and in type 1 alcoholics (0.332±0.061; P<0.05) than in violent offenders

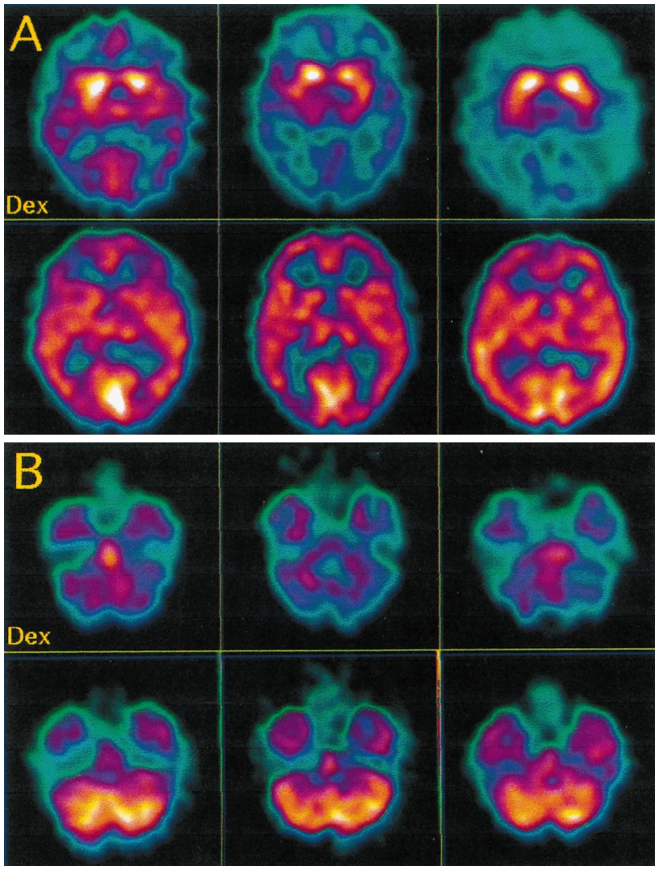

Fig. 3. A Transaxial slices oriented in the OM line at the level of the basal ganglia in a healthy male (*left*), a male with impulsive violent behaviour (*middle*) and a healthy male pretreated with 20 mg citalopram (*right*). The images were taken 1.0–1.5 h after injection of [^{123}I]β-CIT (*upper row*) and [^{99m}Tc]ECD (*bottom row*). The slice thickness used was 7.0 mm. **B** Corresponding slices at the level of the midbrain. Note decreased uptake of [^{123}I]β-CIT in the mesial frontal cortex (**A**) and the midbrain (**B**) of the violent offender and the healthy subject treated with citalopram

(0.283±0.056). The duration of abstinence did not correlate with β-CIT binding in the midbrain (r=0.13, NS) among type 1 alcoholics. Interestingly, the 5-HT specific binding among violent offenders increased with age (4%/10 years; r=0.21), whereas it decreased slightly with age (–1%/10 years) in healthy controls (r=–0.07) and type 1 alcoholics (r=–0.10), although the correlations were not statistically significant. Twelve of the 21 (57%) violent offenders had 5-HT specific binding in the midbrain more than 1 SD below the mean value of healthy controls, while three of the ten type 1 alcoholics (30%) had such low values. All ten non-violent alcoholics (100%) had DAT specific binding (21–23 h measurement) more than 1 SD below the mean of healthy controls, while only two out of the 21 violent offenders (10%) had such low values.

The DAT specific binding (based on the [^{123}I]β-CIT uptake in the basal ganglia at 21–23 h p.i.) in violent offenders was slightly higher (0.922±0.012, n=21) than that in healthy controls (0.917±0.011, n=21) and signifi-

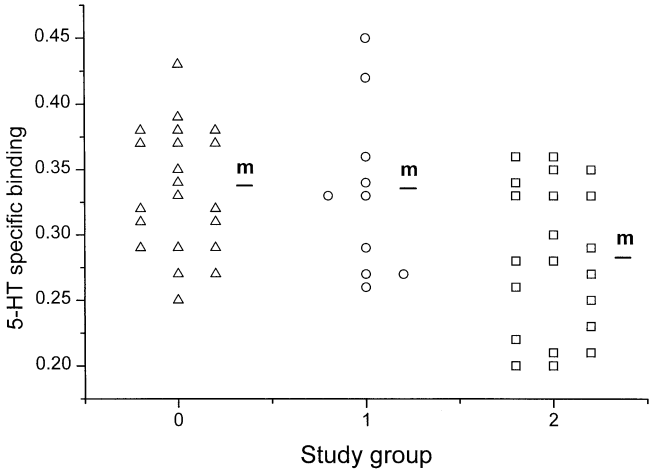

Fig. 4. Scatter plots of the 5-HT specific binding at 1.0–1.5 h p.i. (see Eq. 1) in healthy controls (△), type 1 alcoholics (○) and violent offenders (□). *m*, mean

cantly higher than that in non-violent alcoholic controls (0.887±0.013, n=10), as we have reported previously [34].

Comparison of early [^{123}I]β-CIT and [^{99m}Tc]ECD uptake at 1.0–1.5 h after injection of tracer showed that the midbrain-to-cerebellum ratio for [^{123}I]β-CIT was on average +18%± 8% greater than that for [^{99m}Tc]ECD in six control subjects; in six violent offenders with type 2 alcoholism the ratio for [^{123}I]β-CIT was clearly reduced by –13%±12% (the difference was significant; P<0.01, paired t test). There was no significant difference in regional [^{99m}Tc]ECD uptake between the control subjects and the violent offenders.

Comparison of 1.0–1.5-h [^{123}I]β-CIT scans in six subjects without and with 20 mg of citalopram given 2–3 h prior to SPET imaging showed that in the midbrain 5-HT specific binding was reduced by 37%±14% (t=5.91, P<0.001) with the citalopram pretreatment. The regional uptake of [^{123}I]β-CIT in the control subjects treated with citalopram resembled the findings in violent offenders (see Fig. 3).

Discussion

Recent epidemiological studies have shown that, at least in countries with relatively low crime rates, type 2 alcoholism is the most important mental disorder predisposing subjects to homicidal behaviour [35, 36]. There is evidence that this kind of early-onset alcoholism and impulsive aggressive behaviour is associated with dysfunction of the CNS serotonergic neuronal functions [2–8, 37], but the biochemical variables used to assess 5-HT turnover and tone have so far not been proven to be sufficiently sensitive or specific in differentiating index subjects from controls. The results of this study showed a decrease in the specific binding at 1.0–1.5 h, reflecting mainly 5-HT transporter binding, in the brains of the impulsive violent offenders. This indicates that lower β-CIT density in the midbrain is not associated with alcoholism per se but with coexisting habitual impulsive violent behaviour, as does the finding that among the violent offenders there was one subject who was not an alcoholic but had 5-HT specific binding as low as the other offenders. This is in line with the findings that imply that type 2 alcoholism represents a separate diagnosis, antisocial personality disorder, and not alcoholism itself [38]. Alcoholism is frequently associated with other psychiatric disorders, and in our study group of violent offenders there was one case of co-morbid schizoid personality and one case of cortical atrophy. It is difficult to estimate the role of co-morbidity in the results among these subjects, because there are no published data on the monoamine transporter densities in the aforementioned disorders. Future studies should contain a group of non-alcoholic habitually violent offenders to study the issue of habitually violent impulsive behaviour per se versus co-morbid alcoholism.

Chronic cocaine and amphetamine abuse has been reported to change DA transporter densities in the brains of abusers [39]. Data from an animal study indicate that monoamine oxidase inhibitors and specific 5-HT uptake inhibitors do not affect 5-HT transporter densities in the brain [40]. It has been suggested that ayahuasca, a psychoactive substance indigenous to Amazonia, would increase the platelet 5-HT transporter density [41], but this substance is not used outside South America. It is possible that chronic excessive alcohol abuse may affect serotonergic neurons [42], and our inability to quantify the lifetime alcohol consumption among the study subjects is a weakness. However, only seven of 21 violent offenders had abused substances other than alcohol, and the majority of them had been incarcerated in prison most of the time during recent years, having no access to alcohol. Therefore, it is unlikely that abuse of alcohol or other substances could explain the difference in the densities between violent offenders and non-violent alcoholic controls. Yet, we cannot totally rule out the possibility that more severe exposure to ethanol (or some factor associated with imprisonment) could have altered serotonergic neural networks leading to secondary impulsive violent behaviour among type 2 alcoholics. On the other hand, data obtained from a post-mortem autoradiography study indicate that the density of imipramine binding – which correlates with the density of serotonergic terminals – is the same or slightly higher in the cortex of alcohol users than in that of alcohol-free subjects [43]. This suggests that ethanol exposure is probably not a major explanatory factor for the differences between the study groups.

The rate of metabolism of [^{123}I]β-CIT in plasma may have varied widely between the study groups, which may have affected determination of the input function. The rate of metabolism of [^{123}I]β-CIT to lipophilic components has been shown to be slow [44], which indicates that when determining the outcome measure the metabo-

lism of [^{123}I]β-CIT is not such a problem after 1.0–1.5 h for the 5-HT transporter as it may be after 21–23 h for the DA transporter. In addition, a very important point concerning SPET imaging with [^{123}I]β-CIT must be mentioned here. This tracer is partly bound to adipose and lung tissues, and these tissues are an excellent sink for the first hours after injection, and then afterwards a source. Thus we cannot accurately measure the regional specific binding of [^{123}I]β-CIT without proper measurement of tracer input. Errors of Compton scatter and reconstruction artefacts also preclude accurate measurement of the true low count region (white matter).

The results of Fujita et al. showed clearly that while the specific binding of [^{123}I]β-CIT in rat brain was highest 4 h post injection in the DA-rich basal ganglia, the specific binding reached its peak as early as 1 h after injection in 5-HT-rich areas such as the midbrain and frontal cortex [45]. In the midbrain and frontal cortex, very little specific binding is left after 6 h. We think that the [^{123}I]β-CIT uptake at 1.0–1.5 h in the midbrain mainly represents the binding to 5-HT transporters. Recent studies both in vitro and in vivo showed that [^{123}I]β-CIT labels multiple 5-HT sites in the cerebral cortex, midbrain, hypothalamus and thalamus [14, 46]. In addition, these studies demonstrated that the 5-HT re-uptake blocker, citalopram, prevented [^{123}I]β-CIT labelling in the hypothalamus, the thalamus, the midbrain and the cerebral cortex, while dopamine re-uptake blocker did not affect the binding in the cerebral cortex. In the present study, comparison of regional cerebral [^{123}I]β-CIT and [^{99m}Tc]ECD uptake in six subjects also indicated that the radioactivity measured in the midbrain on [^{123}I]β-CIT scans was due to [^{123}I]β-CIT binding to the monoamine transporters rather than simply an effect on the volume of distribution of the label mediated by regional cerebral blood flow. This was supported by the data obtained from additional measurements in six healthy control subjects showing that citalopram prevented β-CIT binding in the midbrain at 1.0–1.5 h, but did not affect the binding in the striatum at 21–23 h. Our results are in line with recent post-mortem studies which demonstrated that 5-HT re-uptake site density in the human brain as well as in the living baboon is highest in the midbrain [19, 20].

In a recent study, Laruelle et al. obtained displacement of β-CIT binding with citalopram in the midbrain but not in the cortex in non-human primates [29]. On the other hand, Farde et al. [25] found that the neocortical binding of [^{11}C]β-CIT was at a low level but could be displaced by citalopram in the monkey brain. We also found a decreased uptake in the mesial frontal cortex of healthy controls after citalopram treatment (Fig. 3). Injury in the mesial frontal cortex leads to dysfunction in the regulation of human behaviour causing impulsive, hostile and antisocial behaviour [47, 48]. In a recent study of the classical case of Phineas Gage, the focal brain damage was localized to the mesial frontal cortex [49].

Early (5-HT phase) and late (DAT phase) [^{123}I]β-CIT SPET scans may prove to be a relatively sensitive and specific method to study habitually violent offenders and their high-risk offspring. However, we have to emphasize that β-CIT is not specific (only sensitive) for serotonin transporter imaging, which is a methodological weakness, and more selective tracers are needed. The DAT specific binding was lowest in the non-violent alcoholics. The violent offenders, 20 of whom were alcoholics, had slightly higher binding than normal controls, as we have reported previously [34]. On the basis of those results, it has been suggested that type 1 alcoholism is associated with a dopaminergic deficit and type 2 (violent) alcoholism with a serotonergic deficit [49].

It is well known that damage to the frontal lobe often leads to impulsive, irritable and violent behaviour [48], and several studies have suggested that drugs which enhance serotonergic activity – such as the 5-HT re-uptake inhibitor fluoxetine – are useful in the treatment of impulsive behaviour [50–53]. Therefore, it is hypothesized that the lower 5-HT re-uptake site density is a reflection of a decreased number of serotonergic neurons in the mesial frontal cortex. Data obtained from primate studies indicate that the low 5-HT tone is associated with impulsive and risk-taking behaviour and marked aggression, and that the CSF 5-HIAA levels stabilize by late infancy and do not undergo any major changes during adolescence and adulthood [54]. Inter-individual differences in CSF 5-HIAA concentrations in monkeys have been observed to be a consequence of genetic influences. However, the concentration can be modified by early experiences: infants raised by peers tend to have lower 5-HIAA levels later in life than infants raised by their biological parents [55]. It seems obvious that early behavioural therapy and social skills training should have a positive impact in the prevention of severe antisocial behaviour among boys whose fathers exhibit impulsive violent symptoms.

In conclusion, our results further support the hypothesis that type 1 (non-violent) alcoholism is associated with a dopaminergic deficit and type 2 (violent) alcoholism with a serotonergic deficit.

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