a PET study of [^{11}C]β-CIT uptake in two cynomolgus monkeys (Farde *et al*, 1994). However, the shape and time-scale of the binding curves for the cynomolgus monkeys are strikingly different from those observed in other non-human primate species (Laruelle *et al*, 1993) and in humans (Farde *et al*, 1994; Laruelle *et al*, 1994; Pirker *et al*, 1995). This discrepancy is particularly pronounced for the cortical curve, and one wonders to what extent these data may be relevant to human studies. Be that as it may, the bulk of the evidence indicates that serotonin transporters are present in sufficient density to be measured reliably with [^{123}I]β-CIT only in the thalamus and brainstem, and not the cerebral cortex. The region of choice is the raphe area of the brainstem because the thalamus may have a substantial admixture of noradrenaline transporters (Farde *et al*, 1994) and because it is difficult to avoid scattered radiation from the much greater accumulation of activity in the striatum in a thalamic region of interest. We have found this to be true in our studies of serotonin transporters with [^{123}I]β-CIT, and we have observed that uptake in cortical regions does not differ significantly from the non-displaceable (non-specific) uptake seen in the cerebellum (Heinz *et al*, 1998). At extended times (>4 hours post-injection in humans), when specific binding to serotonin transporters in the brainstem approaches a near-equilibrium plateau and non-specific uptake continues to washout throughout the brain, it becomes clear that cortical uptake is 'tracking' that of the cerebellum.

This latter point raises a further methodological concern. Semple *et al* (1999) imaged [^{123}I]β-CIT uptake at 90 minutes post-injection hoping to assess radioligand binding to serotonin transporters. However, near-equilibrium conditions for β-CIT at serotonin transporters are not established in human brain earlier than about four hours post-injection (Laruelle *et al*, 1994; Pirker *et al*, 1995). Once near-equilibrium has been established, [^{123}I]β-CIT binding to serotonin transporters in the brainstem is quite stable and persists well into the following day (Laruelle *et al*, 1994; Pirker *et al*, 1995). Measurements at extended times of [^{123}I]β-CIT activity in human brainstem (following decay correction and subtraction of non-specific uptake) are simply proportional to the density of serotonin transporters (Laruelle *et al*, 1994). Unfortunately, this is not the case for the measurements of Semple *et al* (1999) at 90 minutes post-injection. At times this early, the system is not near equilibrium, and factors related to radioligand delivery and washout, rather than transporter binding *per se*, play a prevalent role in determining the appearance of [^{123}I]β-CIT images. Thus, it seems likely that factors such as blood flow, blood–brain barrier integrity, tissue permeability, etc. have confounded the cortical measurements that Semple *et al* (1999) have assumed to be due to serotonin transporters.

In summary, although Semple *et al* (1999) report an interesting reduction in β-CIT uptake in the cerebral cortex of MDMA users, there is no scientifically sound basis for ascribing this observation to a decrease in cortical serotonin transporters.

Farde, L., Halldin, C., Mueller, L., *et al* (1994) PET study of [C-11]β-CIT binding to monoamine transporters in the monkey and human brain. *Synapse*, **16**, 93–103.

Heinz, A., Ragan, P., Jones, D. W., *et al* (1998) Reduced serotonin transporters in alcoholism. *American Journal of Psychiatry*, **155**, 1544–1549.

Jagust, W. J., Eberling, J. L., Biegon, A., *et al* (1996) Iodine-123-5-iodo-6-nitroquipazine: SPECT radiotracer to image the serotonin transporter. *Journal of Nuclear Medicine*, **37**, 1207–1214.

Laruelle, M., Baldwin, R., Malison, R., *et al* (1993) SPECT imaging of dopamine and serotonin transporters with [123]β-CIT: Pharmacological characterization of brain uptake in non-human primates. *Synapse*, **13**, 295–309.

——, Wallace, A., Seibyl, J. P., *et al* (1994) Graphical, kinetic, and equilibrium analyses of in vivo [123-I]β-CIT binding to dopamine transporters in healthy human subjects. *Journal of Cerebral Blood Flow and Metabolism*, **14**, 982–994.

Parsey, R. V., Simpson, N., Hwang, D. R., *et al* (1999) Kinetic modelling of [C-11]McN5652, a serotonin transporter radioligand, in human volunteers. *Journal of Nuclear Medicine*, **40** (suppl.), 28P–29P.

Pirker, W., Asenbaum, S., Kasper, S., *et al* (1995) β-CIT SPECT demonstrates blockade of 5HT-uptake sites by citalopram in the human brain in vivo. *Journal of Neural Transmission*, **100**, 247–256.

Semple, D. H., Ebmeier, K. P., Glabus, M. F., *et al* (1999) Reduced *in vivo* binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *British Journal of Psychiatry*, **175**, 63–69.

Tauscher, J., Pirker, W., de Zwaan, M., *et al* (1999) In vivo visualization of serotonin transporters in the human brain during fluoxetine treatment. *European Neuropsychopharmacology*, **9**, 177–179.

A. Heinz, D. W. Jones NIMH SPECT Lab., CBDB/NIMH/NIH, 10 Center Dr. Rm 4C216, Bethesda, MD 20792-1364, USA

Authors' reply: By necessity, the discussion of methodological constraints had to be very concise in the published version of our paper (it was more detailed and included some of the arguments raised by Heinz & Jones in the originally submitted manuscript). We are therefore glad to have this opportunity to respond to the constructive comments of Heinz & Jones. They essentially make two claims: that β-CIT does not reliably label cortical serotonin transporters, so that our observed group difference must be due to an alternative mechanism; and at 90 minutes after tracer injection there is a significant admixture of other effects, such as blood flow, blood–brain barrier integrity and tissue permeability, with the same result.

The first claim is supported by some, but not all, displacement studies with SSRIs in monkeys, but inter-species comparisons of brain measures have to be judged with reserve, as Heinz & Jones point out. They also cite a very recently published abstract of a study in six humans, using an alternative (PET-) ligand. We look forward to the full paper; if the initially reported claim survives peer review, it may certainly call into question our interpretation. Moreover, it will specifically weaken the McCann *et al* (1998) paper, whose authors used the same PET tracer and found cortical reductions in serotonin transporter labelling. The design of our study was based on Kuikka *et al*'s (1995) original report. They examined relatively large numbers of healthy volunteers (28) and patients (9) at one and two hours after injection of β-CIT. They reported significant tracer washout with 20 mg citalopram from medial prefrontal cortex (Brodmann's area 12) in 25 subjects, 1–2 hours after injection. They also found significant specific binding of serotonin transporters in occipital cortex. Both are regions that showed activity reductions in our MDMA users. They further described reduced medial prefrontal cortex β-CIT activity at 1 hour in five (alcoholic) patients compared with controls, in the absence of perfusion differences measured with the single photon emission computed tomography (SPECT) ligand ^{99m}Tc–ethyl cysteinate dimer.

The second (weaker) claim made by Heinz & Jones is correct in the sense that group differences in β-CIT binding at 90 minutes do not necessarily reflect a difference in serotonin transporter binding. However, in the absence of *a priori* hypotheses about generalised cell loss, reductions in blood flow, increased blood–brain barrier integrity or reduced tissue permeability,

https://doi.org/10.1192/S0007125000264209 Published online by Cambridge University Press

our results are at least consistent with our interpretation. We think the writers overstate their point if they claim that at one hour non-specific factors are 'prevalent' in determining binding (Kuikka, 1995). Our β-CIT images clearly show activity patterns that parallel the known distribution of serotonin transporters, with relatively high activity in midbrain (Fig. 1 in Semple *et al*, 1999).

An important experiment that has not yet been performed is the displacement of β-CIT binding by 'cold' serotonin transporter ligands (e.g. citalopram) in areas that are found to be abnormal. It needs to be emphasised, however, that the more specific investigations also tend to be more invasive (e.g. PET with arterial blood sampling) or more of a burden to the subject (e.g. dynamic SPECT scan 4–24 hours after tracer injection with citalopram, resulting in corresponding increases in radiation dose or scan time). This can potentially increase measurement error and aggravate the selection bias of the study, thereby reducing its validity. What is gained in theoretical experimental power may well be lost in spurious or biased sampling, if subjects have to be paid to participate (ours were not) or if subjects are self-selected on the basis of some perceived problem. It behoves the reader to be sceptical about any claims based on small samples, as well as non-specific methodologies, and to scan the medical literature for replicable results, keeping in mind that there is publication bias in favour of positive findings. As far as MDMA-induced damage to human serotonin neurons is concerned, the jury is clearly still out.

Kuikka, J. T., Tijhonen, J., Bergström, K. A., *et al* (1995) Imaging of serotonin and dopamine transporters in the living human brain. *European Journal of Nuclear Medicine*, **22**, 346–350.

McCann, U. D., Szabo, Z., Scheffel, U., *et al* (1998) Positron emission tomographic evidence of the toxic effect of MDMA ('ecstasy') on brain serotonin neurons in human beings. *Lancet*, **352**, 1433–1437.

K. P. Ebmeier, D. M. Semple, M. F. Glabus, R. E. O'Carroll, E. C. Johnstone MRC Brain Metabolism Unit, Department of Psychiatry, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF

Substance misuse in first-episode psychosis

We read the article by Cantwell *et al* (1999) with interest. The study relates to an important aspect on the changing pattern of substance misuse in patients with first-episode psychosis. The authors have found that substance users were more likely to be males and to have a younger age at onset of psychosis. However, it would be more informative if the authors gave the prevalence figures in either gender and in different age groups to enable identification of high-risk groups for health promotion measures.

We would also like to highlight some discrepancies in the paper. The magnitudes of comorbid substance misuse among affective and delusional disorders have been miscalculated in Table 2. Considering the fact that affective disorders include manic psychosis and depressive psychosis in the study, the calculated prevalence of substance misuse among affective disorders is found to be 18.9% instead of 11.9%, and for delusional disorder it is 15.4% instead of 7.7% as reported by the authors. Similarly, the total number of stimulant misusers is four, instead of three given by the authors in Table 2. Based on this newly calculated substance misuse rate, there is no significant difference in the substance misuse between people with schizophrenia (23.5%) and those with affective disorders (18.9%) (χ^2=0.27, P=0.603). Therefore, the authors' observation that subjects with affective disorder were less likely to be substance misusers needs to be modified.

Cantwell, R., Brewin, J., Glazebrook, C., *et al* (1999) Prevalence of substance misuse in first-episode psychosis. *British Journal of Psychiatry*, **174**, 150–153.

N. Malik, M. M. Singh, S. C. Pradhan Institute of Human Behaviour and Allied Sciences, Dilshad Garden, Delhi 110 095, India

One hundred years ago

Glasgow District Asylum, Gartloch (Report for the year ending May 5th 1899)

The average number of patients resident in the asylum during the year was 465 and comprised 236 males and 229 females. The total admissions during the year were 203 – viz., 111 males and 92 females. Of these 140 were first admissions. Dr. L. R. Oswald, the medical superintendent, states in his report that seven of those admitted were over 70 years of age, two being over 85 years. "The nursing of these old people demands the greatest care and tact, for they are specially liable to accidents by reason of their frail condition and interfering ways. They must be kept apart from the acute and excited cases." Alcoholic intemperance is set down as having been the cause of the insanity in 50 of the persons admitted, but in many of these – as, indeed, in other cases – the illness was not due to one but to several causes, of which intemperance was the most prominent. "Intemperance, along with an enfeebled bodily condition, acting in conjunction with prolonged worry or mental strain, or following an influenzal attack, but with intemperance as the main factor," was the cause of insanity in the 50 cases referred to. General paralysis as a condition existed in 9 per cent. of the admissions, and in 16 per cent. a hereditary predisposition to insanity was established. The difficulty of obtaining reliable family histories was so great that it is considered probable that the proportion with hereditary taint was higher. During the year 98 patients were discharged as recovered, or 21 per cent. of the average population. Boarding-out, as a means of dealing with quiet and harmless cases, was largely practised during the year. 44 patients were thus sent out, but of that number seven were returned to the asylum for further

https://doi.org/10.1192/S0007125000264209 Published online by Cambridge University Press