26. Tanksley, S. D., Zamir, D. & Rick, C. M. Evidence for extensive overlap of sporophytic and gametophytic gene expression in *Lycopersicon esculentum*. *Science* **213,** 453–455 (1981).

Acknowledgements. We thank B. Charlesworth for input, counsel and support, and J. Greenberg, T. Morton and J. Mach for assistance with the manuscript. This work was supported by a grant from the NIH (to D.C. and B. Charlesworth).

Correspondence and requests for materials should be addressed to D.S.G. (e-mail: dguttman@midway.uchicago.edu).

Evidence for striatal dopamine release during a video game

M. J. Koepp, R. N. Gunn, A. D. Lawrence, V. J. Cunningham, A. Dagher, T. Jones, D. J. Brooks, C. J. Bench & P. M. Grasby

MRC Cyclotron Unit, Hammersmith Hospital, DuCane Road, London W12 0NN, UK, and Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine, St Dunstan's Road, London W6 8RP, UK

Dopaminergic neurotransmission may be involved in learning, reinforcement of behaviour, attention, and sensorimotor integration[1,2]. Binding of the radioligand ^{11}C-labelled raclopride to dopamine D_2 receptors is sensitive to levels of endogenous dopamine, which can be released by pharmacological challenge[3–8]. Here we use ^{11}C-labelled raclopride and positron emission tomography scans to provide evidence that endogenous dopamine is released in the human striatum during a goal-directed motor task, namely a video game. Binding of raclopride to dopamine receptors in the striatum was significantly reduced during the video game compared with baseline levels of binding, consistent with increased release and binding of dopamine to its receptors. The reduction in binding of raclopride in the striatum positively correlated with the performance level during the task and was greatest in the ventral striatum. These results show, to our knowledge for the first time, behavioural conditions under which dopamine is released in humans, and illustrate the ability of positron emission tomography to detect neurotransmitter fluxes *in vivo* during manipulations of behaviour.

We used ^{11}C-labelled raclopride (RAC) to detect changes in levels of extracellular dopamine induced by a behavioural task. During the first 50 minutes of a [^{11}C]RAC–PET scan, eight male volunteers played a video game, which involved learning to navigate a tank for a monetary incentive. This task is comparable to tasks in animal studies in which dopamine is released during the anticipatory or appetitive phase of motivated behaviour, where dopamine is involved in learning which environmental stimuli or actions predict rewarding or aversive outcomes[2,9–11]. During a second [^{11}C]RAC–PET scan, subjects looked at an empty screen. The scanning order was randomized for each subject. Differences in [^{11}C]RAC-binding potential between scans were used to infer changes in levels of extracellular dopamine[12,13]. Binding of [^{11}C]RAC to dopamine D_2 receptors was measured in the ventral and dorsal striata, which are areas involved in goal-directed motor behaviour[2,14–16].

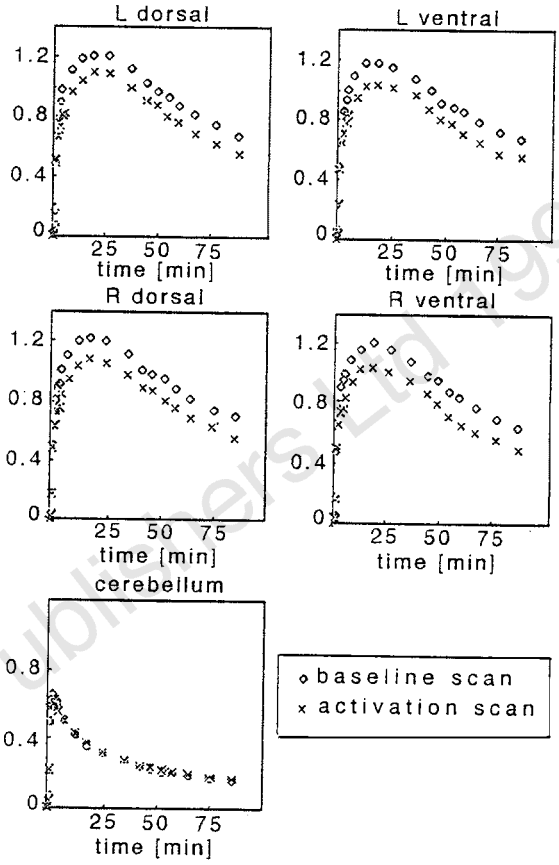

Figure 1 Mean time-activity curves for [^{11}C]RAC uptake, normalized for radioactivity injected, for the four striatal ROIs and the reference region (cerebellum). Data are given from time of radioligand injection to the end of scanning period (up to 90 min). R, right; L, left.

Striatal [^{11}C]RAC-binding potential was reduced (analysis of variance (ANOVA) $F = 7.72$, $P < 0.01$) during the video game, particularly in the ventral striatum (Table 1). Our results are compatible with a task-related increase in levels of extracellular dopamine reducing the number of D_2-receptor sites available for binding to [^{11}C]RAC. The magnitude of change of [^{11}C]RAC-binding potential (ventral striatum mean, −13%; range, +8 to −42%) was considerably greater than the reported 'within subject test/retest variation' in striatal [^{11}C]RAC-binding potential (mean, 4–6%)[17,18], and was similar to that observed following intravenous injection of amphetamine[8] (striatum mean, −16%; range, −3 to −24%) or methylphenidate[6] (striatum mean, −23%; range, +3 to −46%). Microdialysis studies of non-human primates

Table 1 [^{11}C]RAC-binding potential, relative tracer delivery and size of the region of interest in striatal regions

	LD B	LD T	ΔLD (%)	RD B	RD T	ΔRD (%)	LV B	LV T	ΔLV (%)	RV B	RV T	ΔRV (%)
BP	2.47	2.23	−8.9	2.38	2.22	−6.1	2.22	1.93	−11.8	2.27	1.92	−13.9
(s.d.)	(0.36)	(0.42)	(16.4)	(0.34)	(0.41)	(16.1)	(0.28)	(0.33)	(18.8)	(0.31)	(0.35)	(20.5)
R_1	0.98	0.88	−8.5	0.94	0.87	−6.5	0.98	0.89	−8.5	1.03	0.91	−10.5
(s.d.)	(0.13)	(0.08)	(13.8)	(0.12)	(0.07)	(12.1)	(0.12)	(0.13)	(14.4)	(0.11)	(0.12)	(14.7)
ROI size	8,151	8,300	1.9	7,600	8,188	7.9	4,747	4,280	−8.7	4,692	4,215	−9.3
(s.d.)	(711)	(846)	(8.2)	(567)	(574)	(7.2)	(628)	(612)	(16.2)	(680)	(691)	(15.7)

BP, [^{11}C]RAC-binding potential; R_1, relative tracer delivery; ROI, region of interest (mm^3); s.d., standard deviation; L, left; R, right; D, dorsal; V, ventral; B, baseline conditions; T, task conditions. Changes in BP, R_1 and ROI size between conditions (Δ) are given as a percentage change from the baseline, calculated as: $(T - B)/B \times 100$. R_1 was significantly decreased during the video game ($F = 11.3$, $P = 0.001$), but reductions in R_1 were not correlated with reductions in BP ($r^2 = 0.05$, $P = 0.24$). There was no difference in striatal ROI size across conditions ($P = 0.64$) and no correlation between changes of BP and ROI size ($r^2 = 0.02$, $P = 0.45$), indicating that head movement probably did not contribute significantly to our results.

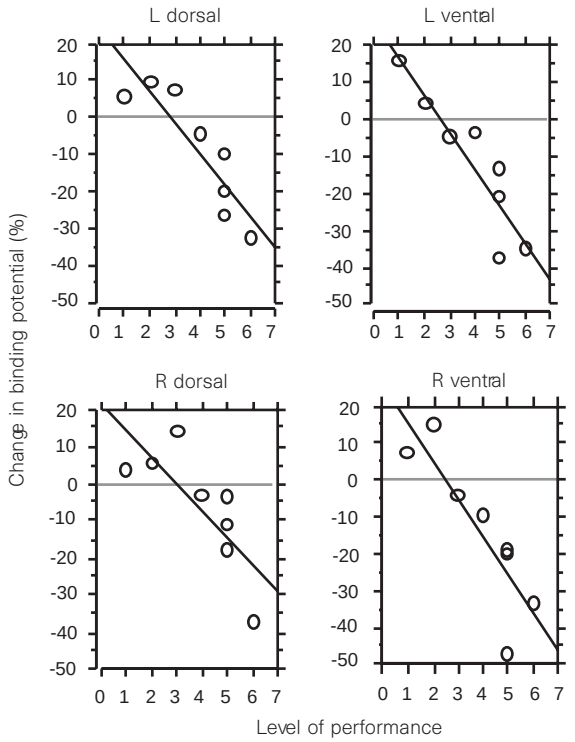

Figure 2 Percentage change in [^{11}C]RAC-binding potential between task and baseline conditions, plotted against performance level. A significant inverse correlation is seen in all striatal regions (Spearman rank correlation coefficients for left and right ventral and left dorsal striatum: $r = -0.86$, $P = 0.017$; right dorsal striatum: $r = -0.83$, $P = 0.020$).

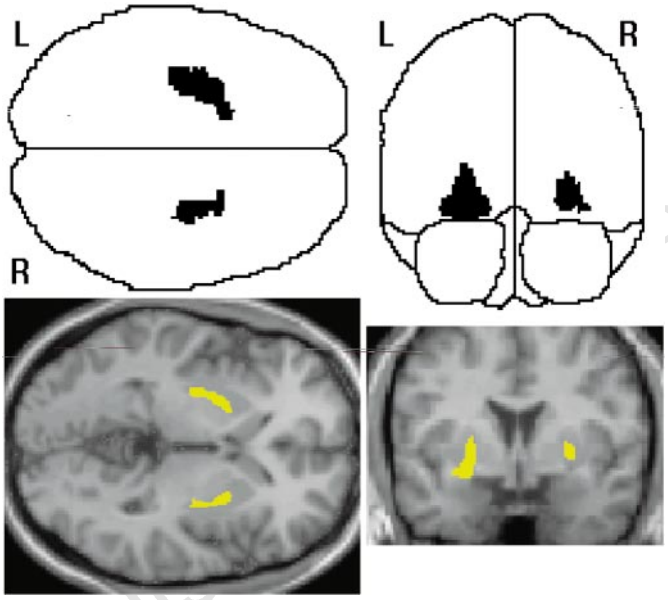

Figure 3 Regions of the brain in which there was a statistically significant correlation between reduced [^{11}C]RAC-BP and task performance; such a correlation was more pronounced in the ventral striatum. Upper row, the transverse and coronal glass brain views show those voxels with a significant inverse correlation of [^{11}C]RAC-BP with the highest performance level reached (threshold for display, $P < 0.05$). Lower row, three-dimensional SPM projections superimposed on representative transaxial and coronal magnetic resonance image brain slices (threshold for display, $P < 0.05$).

indicate that a 1% decrease in striatal [^{11}C]RAC binding reflects at least an 8% increase in extracellular endogenous dopamine levels[8]. Thus, the 13% reduction in [^{11}C]RAC-binding potential in the ventral striatum reported here suggests at least a twofold increase in levels of extracellular dopamine. Computer simulations have shown that this magnitude of change should be detectable with [^{11}C]RAC–PET[13].

After 50 min, the game ended, but the time–activity curves (TACs) for [^{11}C]RAC binding remained below the baseline curves without convergence (Fig. 1). A similar effect has been reported following pharmacological challenges[4,19], and may simply reflect the kinetic properties of [^{11}C]RAC and the diffusion and re-uptake kinetics of dopamine. Sustained alterations in dopamine concentrations after a period of behavioural manipulation have been described in the rat[20], providing a biological explanation for the continued separation of the TACs for [^{11}C]RAC binding after the video game ended.

There was a significant correlation between performance level achieved and reduced [^{11}C]RAC-binding potential in all striatal regions (Fig. 2); the significance of this correlation was confirmed by an independent analysis using statistical parametric mapping (SPM)[21]. SPM revealed that this significant correlation mainly encompassed the ventral striatum, predominantly the left side (Fig. 3). These results further validate the putative link between the behavioural manipulation and dopamine release, and complement electrophysiological studies of behaviour in awake animals, in which dopaminergic neurotransmission was associated with sensorimotor functions related to rewarding, aversive and stressful stimuli[1,22,23]. In monkeys, most dopaminergic neurons in the ventral tegmental area and pars compacta are activated by unexpected primary appetitive rewards and reward-predicting cues[1,9,15].

Here, regional differences in [^{11}C]RAC displacement within the striatum might correlate with the role of dopamine in the dorsal and ventral striata[2]. The dorsal striatum receives inputs from motor, sensory, premotor, and dorsal prefrontal cortices[14,16], whereas the ventral striatum receives afferent inputs from orbitofrontal cortex, amygdala, hippocampus, and anterior cingulate[14,16]. On the basis of these anatomical connections, we interpret changes in ventral striatal [^{11}C]RAC binding to be related to affective components of the task, whereas dorsal striatal dopamine release may be related to sensorimotor coordination and response selection[2]. This new method of detecting neurotransmitter release during behavioural manipulation extends the success of brain-perfusion mapping in humans to the study of a true 'cognitive neurochemistry of behaviour'. □

Methods

PET-scan acquisition. Eight healthy, male, right-handed volunteers (range 36–46 years of age) took part in the study (approved by the local Ethics Committee). Informed consent was obtained for all subjects. Each received two [^{11}]RAC–PET scans (total injected dose of 16–20 mCi), one during the behavioural task (video game) and one under baseline conditions (blank screen). Subjects played the video game from 10 min before to 50 min after [^{11}C]RAC injection. PET scans were acquired on separate days using a 953B-Siemens/CTI PET camera in three-dimensional mode. Head movement during scanning was minimized by the use of a moulded head rest and external head markings.

Behavioural task. The video game involved moving a 'tank' through a 'battlefield' on a screen using a mouse with the right hand. Subjects had to collect 'flags' with the tank while destroying 'enemy tanks'. Enemy tanks could destroy the three 'lives' of the subjects' tank. If subjects collected all flags, they progressed to the next game level, which required more flags to be collected. A reward of £7 was given per game level achieved.

Region-of-interest (ROI) analysis. TACs of [^{11}C]RAC binding were derived for ventral and dorsal striata and cerebellum. From these TACs, binding potential (BP), and the relative rate of ligand delivery (R_1) in the striatum

compared to the cerebellum were estimated using a simplified reference region model[24,25]. The model derives BP from the ratio of the volumes of distribution of the ligand in the striatum relative to the cerebellum. BP is a composite function of parameters, as follows:

$$\mathrm{BP} = \frac{f_2 B_{\max}}{K_{\mathrm{D_{Tracer}}}\left(1 + \sum_i \frac{F_i}{K_{\mathrm{D}_i}}\right)}$$

where $B_{\max}$ is the total concentration of specific binding sites, $K_{\mathrm{D_{Tracer}}}$ the equilibrium dissociation constant of the ligand, f_2 is the 'free fraction' of unbound ligand in the tissue, and F_i and K_{D_i} are the concentrations and equilibrium dissociation constants, respectively, of i competing endogenous ligands. Changes in BP are attributed to changes in F_i for endogenous dopamine. Striatal ROIs were outlined on an add-image of summated time frames, using an edge-fitting algorithm set at a fixed threshold (40%) of the image maximum. The ventral (comprising the ventral half of the putamen) and dorsal (comprising the dorsal half of the putamen and the body of the caudate nucleus) striata were operationally defined. The cerebellum was defined by cluster analysis[26]. BP and R_I values were calculated for the striatal ROIs using the TACs for [^{11}C]RAC binding up to 50 min after injection[25]. Differences in [^{11}C]RAC-BP at baseline and during the task were tested with repeated-measure ANOVA, with three 'within-subject' factors (task versus baseline, left versus right hemisphere and dorsal versus ventral striatum). Spearman rank correlation coefficients were calculated for the relationship between changes in [^{11}C]RAC-BP and the highest performance level during the game for each ROI.

SPM analysis. Parametric images of [^{11}C]RAC-BP[24] were analysed using SPM96 (ref. 21). The [^{11}C]RAC-R_I images were used to define the stereotactic transformation parameters for the [^{11}C]RAC-BP images. Contrasts of the condition effects at each voxel of the [^{11}C]RAC-BP images were assessed using the t-value, with the highest performance level entered as a covariate of interest, giving a statistical image for each contrast.

Received 23 September 1997; accepted 20 March 1998.

1. Schultz, W., Apicella, P. & Ljungberg, T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.* **13,** 900–913 (1993).
2. Robbins, T. W. & Everitt, B. J. Functions of dopamine in the dorsal and ventral striatum. *Semin. Neurosci.* **4,** 119–127 (1992).
3. Hume, S. P. *et al.* Quantitation of carbon-11 labelled raclopride in rat straitum using positron emission tomography. *Synapse* **12,** 47–54 (1992).
4. Laruelle, M. *et al.* Microdialysis and SPECT measurements of amphetamine-induced dopamine release in non human primates. *Synapse* **25,** 1–14 (1997).
5. Farde, L. *et al.* Positron emission tomography analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Arch. Gen. Psychiatry* **49,** 538–544 (1992).
6. Volkow, N. D. *et al.* Imaging endogenous dopamine competition with [^{11}C]raclopride in the human brain. *Synapse* **16,** 255–262 (1994).
7. Dewey, S. L. *et al.* Effects of central cholinergic blockade on striatal dopamine release measured with positron emission tomography in normal human subjects. *Proc. Natl Acad. Sci. USA* **90,** 11816–11820 (1993).
8. Breier, A. *et al.* Schizophrenia is associated with elevated amphetamine induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc. Natl Acad. Sci. USA* **94,** 2569–2574 (1997).
9. Ljunberg, T. J., Apicella, P. & Schultz, W. Responses of monkey dopamine neurons during learning of behavioural reactions. *J. Neurophysiol.* **67,** 145–163 (1992).
10. Salamone, J. D., Cousins, M. S., McCullough, L. D., Carrier, O. D. L. & Berkovitz, R. J. Nucleus accumbens dopamine release increases during instrumental level pressing for food but not free food consumption. *Pharmacol. Biochem. Behav.* **49,** 651–660 (1994).
11. Richardson, N. R. & Gratton, A. Behaviour-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. *J. Neurosci.* **16,** 8160–8169 (1996).
12. Fisher, R. E., Morris, E. D., Alpert, N. M. & Fischman, A. J. *In-vivo* imaging of neuromodulatory synaptic transmission using PET: a review of relevant neurophysiology. *Hum. Brain Mapp.* **3,** 24–34 (1995).
13. Morris, E. D., Fisher, R. E., Alpert, N. M., Rauch, S. L. & Fischman, A. J. *In vivo* imaging of neuromodulation using positron emission tomography: optimal ligand characteristics and task length for detection of activation. *Hum. Brain Mapp.* **3,** 35–55 (1995).
14. Graybiel, A. M., Aosaki, T., Flaherty, A. W. & Kimura, M. The basal ganglia and adaptive motor control. *Science* **265,** 1826–1831 (1994).
15. Schultz, W. Dopamine neurons and their role in reward mechanisms. *Curr. Opin. Neurobiol.* **7,** 191–197 (1997).
16. Brooks, D. J. The role of the basal ganglia in motor control: contributions from PET. *J. Neurol. Sci.* **128,** 1–13 (1995).
17. Volkow, N. D. *et al.* Reproducibility of repeated measures of [^{11}C]raclopride binding in the human brain. *J. Nucl. Med.* **34,** 609–613 (1993).
18. Logan, J. *et al.* Effects of blood flow on [^{11}C]raclopride binding in the brain: model simulations and kinetic analysis of PET data. *J. Cereb. Blood Flow Metab.* **14,** 995–1010 (1994).
19. Endres, C. J. *et al.* Kinetic modelling of [^{11}C]raclopride: combined PET-microdialysis studies. *J. Cereb. Blood Flow Metab.* **9,** 932–942 (1997).
20. Yamamuro, Y., Hori, K., Iwano, H. & Nomura, M. The relationship between learning-performance and dopamine in the prefrontal cortex of the rat. *Neurosci. Lett.* **177,** 83–86 (1993).
21. Friston, K. J. *et al.* Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* **2,** 189–210 (1995).
22. Thierry, A. M., Tassin, J. P., Blanc, G. & Glowinski, J. Selective activation of the mesocortical dopaminergic system by stress. *Nature* **263,** 242–244 (1976).
23. Wise, R. A. The dopamine synapse and the notion of "pleasure centres" in the brain. *Trends Neurosci.* **3,** 91–94 (1980).
24. Gunn, R. N., Lammertsma, A. A., Hume, S. P. & Cunningham, V. J. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* **6,** 279–287 (1997).
25. Lammertsma, A. A. & Hume, S. P. Simplified reference tissue model for PET receptor studies. *Neuroimage* **4,** 153–158 (1996).
26. Ashburner, J., Haslam, J., Taylor, C., Cunningham, V. J. & Jones, T. in *Quantification of Brain Function Using PET* (eds Myers, R., Cunningham, V., Bailey, D. & Jones, T.) 301–306 (Academic, London, 1996).

Acknowledgements. M.J.K. was supported by a grant from the Theodore and Vada Stanley Foundation Research Program; R.N.G., V.J.C., D.J.B. and P.M.G. were supported by the Medical Research Council; and A.D.L. was supported by a fellowship from the British Brain and Spine Foundation. We thank P. Dayan and L. Farde for discussions and comments on the manuscript; and K. Friston, A. Holmes and J. Ashburner for statistical advice and help with the SPM analysis.

Correspondence and requests for materials should be addressed to P.M.G. (e-mail: grasby@cu.rpms.ac.uk).

The role of dendrites in auditory coincidence detection

Hagai Agmon-Snir*, Catherine E. Carr† & John Rinzel*‡

** Mathematical Research Branch, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, USA*
† Department of Zoology, University of Maryland, College Park, Maryland 20742, USA

Coincidence-detector neurons in the auditory brainstem of mammals and birds use interaural time differences to localize sounds[1,2]. Each neuron receives many narrow-band inputs from both ears and compares the time of arrival of the inputs with an accuracy of 10–100 μs (refs 3–6). Neurons that receive low-frequency auditory inputs (up to about 2 kHz) have bipolar dendrites, and each dendrite receives inputs from only one ear[7,8]. Using a simple model that mimics the essence of the known electrophysiology and geometry of these cells, we show here that dendrites improve the coincidence-detection properties of the cells. The biophysical mechanism for this improvement is based on the nonlinear summation of excitatory inputs in each of the dendrites and the use of each dendrite as a current sink for inputs to the other dendrite. This is a rare case in which the contribution of dendrites to the known computation of a neuron may be understood. Our results show that, in these neurons, the cell morphology and the spatial distribution of the inputs enrich the computational power of these neurons beyond that expected from 'point neurons' (model neurons lacking dendrites).

Over the past 40 years it has become widely accepted that dendrites play a major role in neuronal computation[9]. Despite intensive efforts to decipher this role[10–16], however, the contribution of the dendrites to the function of the single neuron remains elusive. Nevertheless, the existence of different dendritic geometries and their plausible effect on computation have been used as evidence for dendritic computation[11,12,17]. As analysis of dendritic computation is most powerful when the role of the neuron is understood, we used brainstem auditory coincidence detectors to demonstrate the computational advantages of having synaptic inputs on the dendrites rather than on the cell body.

Coincidence detectors of the auditory brainstem are binaural neurons that respond maximally when they receive simultaneous inputs from the two ears. This condition is met when delay line inputs from each ear exactly compensate for a delay introduced by an interaural time difference (ITD, the time difference between the

‡ Present address: New York University, Center for Neural Science and Courant Institute of Mathematical Sciences, New York 10003, USA.