hence their origin from solution, is compelling. Uraninite occurring in fractures means that oxidizing solutions must have been present at a late stage in the Witwatersrand rocks. The scale of the regionally extensive alteration zones and their cross-cutting nature with respect to stratigraphy (Fig. 4) indicate that local remobilization[3,4] of gold and uranium is not responsible for the mineralization described here. There is no evidence for the rapid, small-scale variations in fluid and mineral chemistry that are a thermodynamic necessity to permit such a redistribution. □

Received 4 September 1996; accepted 11 February 1997.

1. Minter, W. E. L. *Can. Soc. Petrol. Geol. Mem.* **5,** 801–829 (1978).
2. Hallbauer, D. K. in *Mineral Deposits of Southern Africa* (eds Anhaeusser, C. R. & Maske, S.) 731–752 (Geol. Soc. S. Africa, Johannesburg, 1986).
3. Frimmel, H. E., Le Roux, A. P., Knight, J. & Minter, W. E. L. *Econ. Geol.* **88,** 249–265 (1993).
4. Robb, L. J. & Meyer, F. M. *Ore Geol. Rev.* **10,** 67–94 (1995).
5. Phillips, G. N., Myers, R. E. & Palmer, J. A. *Geology* **15,** 1027–1030 (1987).
6. Phillips, G. N. & Myers, R. E. *Econ. Geol. Monogr.* **6,** 597–607 (1989).
7. Coward, M. P., Spencer, R. M. & Spencer, C. E. *Early Precambrian Processes*, 243–269 (Spec. Publ. 95, Geol. Soc. Lond., 1995).
8. Phillips, G. N. & Law, J. D. M. *Ore Geol. Rev.* **9,** 1–31 (1994).
9. Schidolowski, M. *US Geol. Surv. Prof. Pap.* **1161N,** 1–29 (1981).
10. Phillips, G. N. *J. Metam. Geol.* **6,** 311–332 (1988).
11. Minter, W. E. L., Geodhart, M., Knight, J. & Frimmel, H. E. *Econ. Geol.* **88,** 237–248 (1993).
12. Gray, G. J., Lawrence, S. R., Kenyon, A. K. & Cornford, C. *J. Geol. Soc. Lond.* (in the press).
13. Ebert, L. B. *et al. Ore Geol. Rev.* **5,** 423–444 (1990).
14. Holland, H. D. & Feakes, C. R. *J. Geol.* **97,** 761–762 (1989).
15. Smith, N. D. *Geology* **17,** 91–92 (1989).

Acknowledgements. We thank A. G. Knowles, Consulting Geologist of AAC Gold and Uranium Division, for permission to publish this paper and for support for this project; and M. P. Coward for discussions on Witwaterstrand structural evolution. We also acknowledge help during work undertaken over the past six years from Anglo-American geologists.

Correspondence should be addressed to A.C.B. (e-mail: a.barnicoat@earth.leeds.ac.uk).

Subgenual prefrontal cortex abnormalities in mood disorders

Wayne C. Drevets*†‡§, Joseph L. Price‡, Joseph R. Simpson Jr†, Richard D. Todd*‖, Theodore Reich*‖, Michael Vannier†§ & Marcus E. Raichle†‡¶‖**

** Department of Psychiatry, † Division of Radiological Sciences, Mallinckrodt Institute of Radiology, ‡ Department of Anatomy and Neurobiology, ‖ Department of Genetics, ¶ Department of Neurology and Neurological Surgery (Neurology), ** McDonnell Center for Studies of Higher Brain Function, Washington University School of Medicine, St Louis, Missouri 63110, USA*

Pathological disturbances of mood may follow a 'bipolar' course, in which normal moods alternate with both depression and mania, or a 'unipolar' course, in which only depression occurs[1–3]. Both bipolar and unipolar disorders can be heritable illnesses associated with neurochemical, neuroendocrine and autonomic abnormalities. The neurobiological basis for these abnormalities has not been established[2,3]. Using positron emission tomographic (PET) images of cerebral blood flow and rate of glucose metabolism to measure brain activity, we have now localized an area of abnormally decreased activity in the prefrontal cortex ventral to the genu of the corpus callosum in both familial bipolar depressives and familial unipolar depressives. This decrement in activity was at least partly explained by a corresponding reduction in cortical volume[4], as magnetic resonance imaging (MRI) demonstrated reductions in the mean grey matter volume in the same area of 39 and 48% in the bipolar and unipolar samples, respectively. This region has previously been implicated in the mediation of emotional and autonomic responses to socially significant or provocative stimuli, and in the modulation of the neurotransmitter systems targeted by antidepressant drugs[3,5–10].

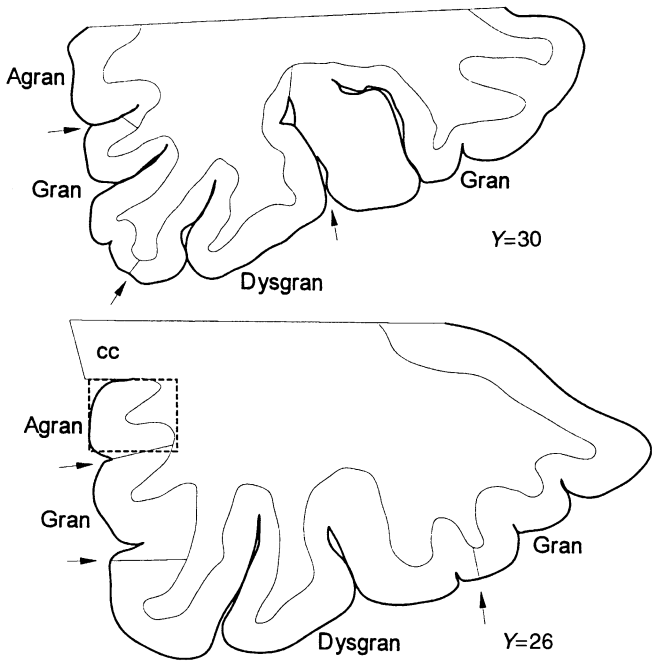

Figure 1 Drawings of coronal sections through the genu of the corpus callosum (CC) and subgenual and posterior orbital PFC of a human brain at levels 26 and 30 mm rostral to the anterior commissure. Agranular ('agran'), dysgranular ('dysgran') and granular ('gran') cortical regions are marked. The subgenual PFC consists of agranular cortex on the anterior cingulate gyrus immediately ventral to the genu of the corpus callosum[30]. Dashed line indicates the centre of the smaller ROI used for regional measures in the 953B images. This cylindrical ROI, 1 cm in diameter and spanning 1–9 mm ventral to the bicommissural plane, was placed[29] *a priori* in each subject's image over the coordinates of the peak $|t|$ value identified in the subgenual PFC in the t image from group A: $x = 5, y = 25, z = -6$ (in mm from the anterior commissure, with positive x as right, positive y as rostral, and negative z as ventral to the bicommissural plane[28]).

Low-resolution PET images of cerebral blood flow (BF) (full width at half-maximum (FWHM, 17 mm) from unmedicated, bipolar depressives and from controls were divided into two groups (A and B) for hypothesis generation and subsequent testing (Table 1). Using the images from group A, a statistical image composed of unpaired t values (the difference between the mean values for each subject sample divided by the standard error of this difference) was computed by subtracting the mean blood flow for the controls from that of the depressives at every voxel (volume element) and then dividing the resulting differences by the local variance[11]. Regions-of-interest (ROI) were defined in this t-image, which highlighted areas where blood flow inherently differed between the bipolar-depressives and controls from group A (ref. 11). The ROI containing the largest absolute difference in mean flow between groups was defined in the subgenual prefrontal cortex, where flow was decreased by 7.7% in the depressives relative to the controls from group A (the proximity of this abnormality to the midline precluded laterality determinations from the PET image data; Fig. 2 legend). The hypothesis that blood flow was abnormal in bipolar depression in this ROI was confirmed by comparing regional measures from the independent subject group B, in which mean flow was decreased by 6.6% in the depressives relative to the controls ($t = -4.3$, corrected d.f. = 16, corrected P(1-tailed) < 0.01).

§ Present addresses: Departments of Psychiatry and Radiology, University of Pittsburgh Medical Center, 3811 O'Hara Street, Pittsburgh, Pennsylvania 15213-2593, USA (W.C.D.); Department of Radiology, University of Iowa, Iowa City, Iowa 52242, USA (M.V.).

Table 1 PET image comparison of regional BF and metabolic rates for bipolar depressed, unipolar depressed, bipolar manic and control patients

Hypothesis:	Generating		Testing		Testing and extending		Extending	Extending
Subject group:	A		B		C		FPDD	Manic
PET camera	PETT VI		PETT VI		Siemens CTI 953B		953B	953B
Measure	Relative BF		Relative BF		Relative BF and MRglu		Relative MRglu	Relative MRglu
Subsample:	BP-D	Control	BP-D	Control	BP-D	Control		
n	6	24	5	15	7	12	10	4
Mean age, yr (± s.d.)	29 ± 5.5	29 ± 7.1	27 ± 6.5	27 ± 8.5	37 ± 8.7	33 ± 11	39 ± 7.3	30 ± 11
Right-handed (%)	100	100	100	100	86	92	100	100
Conclusion, subgenal PFC activity:			BF is reduced in BP-D versus control		BF and MRglu are both reduced in BP-D versus control		MRglu is reduced in FPDD versus control	MRglu appears raised in manic versus control, BP-D and FPDD

For abbreviations, see Methods.

To localize this abnormality more precisely, glucose metabolism images were acquired in a third, independent set of unmedicated, bipolar depressives and controls (group C in Table 1) using a higher-resolution camera (Siemens/CTI 953B; reconstructed resolution, 5 mm FWHM). A smaller ROI was stereotaxically positioned in each group C image at the coordinates of the $|t|$ value identified in the subgenual prefrontal cortex in the *t*-image from group A (Fig. 1). Mean normalized metabolism was decreased 16.3% and mean blood flow was decreased 18.5% in this ROI in the bipolar depressives relative to the controls (mean ± one standard deviation for metabolism $= 0.87 \pm 0.15$ and 1.04 ± 0.15, respectively; $t = -2.3$, corrected d.f. $= 12$, P(1-tail) < 0.025; and for blood flow $= 1.01 \pm 0.15$ and 1.24 ± 0.17, respectively, $t = -3.0$, corrected d.f. $= 13$, P(1-tail) < 0.01). The greater magnitude and variance of the differences measured in this sample was probably accounted for by the higher spatial resolution of the images.

The same high-resolution PET methods were applied to unipolar depressives with familial pure depressive disease (FPDD; criteria that exclude depressives with a family history of mania[12]) and to bipolar subjects scanned in the manic phase[1]. The unipolar group ($n = 10$; 7 female) met criteria for recurrent, major depressive disorder[1] and FPDD[12], and their mean age, depression severity (mean Hamilton Depression Rating Scale (HDRS) score, 25.5 ± 5.4) and medication free period (>4 weeks) were similar to those of bipolar group C (Table 1). The mean subgenual prefrontal cortex metabolism in the unipolar depressives (0.91 ± 0.11) was decreased 12.2% relative to the controls ($t = -2.3$, d.f. $= 20$, P(1-tail) < 0.025) and did not significantly differ from that of the bipolar depressives. Previously, the only functional neuroimaging finding consistently identified in both bipolar and unipolar depressives was located in the dorsolateral prefrontal cortex where reduced activity is thought to correlate with the neuropsychological manifestations of depression (for example, slowing of thought speed)[13–20].

The manic subjects ($n = 4$) met criteria for bipolar disorder–manic phase[1] (mean Mania Rating Scale[21] score was 20 ± 4.4, one female, one medicated within 4 weeks). In contrast to the findings in the depressed groups, the mean metabolism in the manic group (1.15 ± 0.054) was increased relative to that of the control ($t = 2.2$, d.f. $= 12$, P(2-tail) < 0.05), bipolar-depressed ($t = 4.6$, $P < 0.01$) and unipolar-depressed groups ($t = 5.5$, $P < 0.01$). Consistent with these differences, in one subject scanned in both phases, normalized metabolism in the subgenual prefrontal cortex was 0.84 while depressed and 1.11 eight weeks later while manic. Although these preliminary observations in mania require replication in a larger sample, they suggest that subgenual prefrontal cortex metabolism is mood-state dependent.

Decreased blood flow and metabolism in the subgenual prefrontal cortex in depression could reflect a regional reduction in either synaptic activity[22] or tissue volume (because of the low spatial resolution of PET, reductions in tissue associated with atrophy or hypoplasia reduce the magnitude of local blood flow and metabolic measures from PET images, a phenomenon known as the partial volume averaging effect)[4]. The grey matter volume of the corresponding cortex was therefore measured in MRI images acquired in mood-disordered and control subjects (Figs 2, 3). MRI scans were not available for the subjects in groups A and B, so to improve the sensitivity for detecting intergroup differences (regional brain volume measures have greater variability than PET measures), the sample sizes were increased by adding MRI data from subjects not involved in the PET comparisons. The expanded bipolar group included the unmedicated, bipolar depressives from group C together with two medicated-depressed, four manic and eight remitted (six medicated) subjects with bipolar disorder[1] (total $n = 21$; age $= 35 \pm 8.2$; 13 female; 20 right-handed; all had a parent or sibling with bipolar disorder). The expanded unipolar group combined the FPDD group with seven additional unipolar depressives who met criteria for recurrent, major depressive disorder[1], but not for FPDD[12] (total $n = 17$; mean age $= 35 \pm 9.4$; 10 female, 16 right-handed). Additional controls were combined with those from group C (total $n = 21$; age $= 34 \pm 8.2$; 11 female; 19 right-handed).

The left subgenual prefrontal cortex grey matter volume was reduced by 39% in the bipolar subjects and 48% in the unipolar depressives relative to the controls ($F = 9.8$; $P < 0.0002$, after covarying for age, gender and whole brain volume; Fig. 3), and did not significantly differ between the unipolar and bipolar groups. (Notably, post hoc tests showed that the volumetric differences identified in the expanded group of bipolar subjects were also significant when the controls were compared either to the seven bipolar subjects from group C ($P < 0.05$) or to the 14 bipolar subjects not included in group C ($P < 0.005$).) No significant differences in mean volume were found between the bipolar and control groups in other portions of the anterior cingulate gyrus, including the right subgenual prefrontal cortex (219 ± 95 and 209 ± 66 mm^3, respectively) or the dorsal anterior cingulate cortex (left: 418 ± 184 and 389 ± 211 mm^3, respectively, $t = 0.47$; right: 456 ± 134 and 406 ± 134 mm^3, respectively, $t = 1.2$). Post hoc analysis indicated that the volumetric difference in the subgenual prefrontal cortex is present irrespective of mood state in bipolar disorder (mean values for the symptomatic (manic or depressed) and remitted subsamples were 131 ± 72 and 146 ± 99 mm^3, respectively). The anatomical abnormality also persisted during antidepressant drug treatment in 15 of the unipolar depressives who were reimaged following a mean treatment period of 3.2 ± 3.5 months (the mean volume was 126 ± 66 mm^3 pre-treatment and 123 ± 61 mm^3 post-treatmnent). Thus, the reduction in the left subgenual prefrontal cortex grey matter volume in mood disorders, localized by synergistic use of PET and MRI image data, could reflect either an abnormality of brain development related to the tendency to develop mood episodes or a degenerative change resulting from recurrent illness.

In monkeys and other experimental animals, the subgenual prefrontal cortex has extensive connections with structures implicated in emotional behaviour and autonomic/neuroendocrine responses to stressors, including the amygdala, the lateral hypotha-

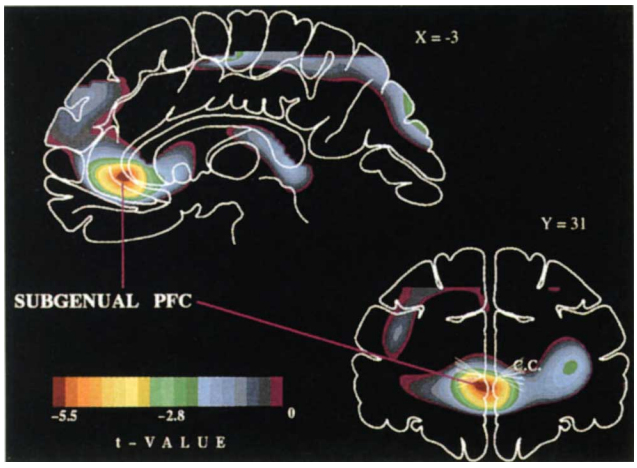

Figure 2 Coronal ($y = 31$ mm) and sagittal ($x = -3$ mm) sections showing negative voxel t values where metabolism is decreased in depressives relative to controls. This image, generated *post hoc* to provide optimal localization of the subgenual PFC abnormality, compares all unmedicated depressives scanned with the 953B (bipolar depressives from group C plus unipolar depressives with FPDD) with the group C controls. The stereotaxic centre-of-mass of this difference ($x = -2, y = 32, z = -2$) lay within one FWHM (17 mm for PET VI) from the peak BF difference in group A (Fig. 1) and from the centre-of-mass of the BF difference computed post hoc for the entire PET VI image set (groups A plus B): $x = 1, y = 25, z = -6$. All three coordinate sets localize to the agranular region of the anterior cingulate gyrus ventral to the CC (Fig. 1). The spatial resolution of PET procludes clear laterality distinctions. Anterior, or left, is to the left.

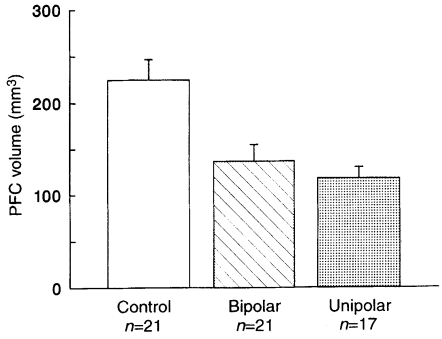

Figure 3 MRI-based volumes of the left subgenual prefrontal cortex (PFC) grey matter differed between the dipolar disordered, unipolar depressed and control groups (ANOVA, $F = 9.8$; $P < 0.0002$, co-varying for gender, age and whole brain volume). Post hoc tests (Tukey-Kramer) showed significant volumetric decreases in the bipolar and unipolar groups relative to the control group. Whole-brain MRI volume and skull X-ray measures (product of anterior-posterior distance between the inner tables of the skull at the estimated bicommissural segment[29] and perpendicular distance from the midpoint of the bicommissural segment to the vertex[29]) were slightly smaller in the unipolar group compared with the bipolar and control groups, and did not differ between the bipolar and control groups. The left subgenual PFC/whole brain volume ratio was also reduced in the bipolar and unipolar groups, being $1.8 \times 10^{-4} \pm 0.74 \times 10^{-4}$, $1.1 \times 10^{-4} \pm 0.64 \times 10^{-4}$, and $1.1 \times 10^{-4} \pm 0.51 \times 10^{-4}$ in the control, bipolar, and unipolar groups, respectively ($F = 8.4$; $P < 0.001$).

lamus, the nucleus accumbens, and the brainstem serotonergic, noradrenergic and dopaminergic nuclei (the function of these neurotransmitter systems appears to be blunted during depressive episodes and to be augmented by antidepressant drug treatments)[2,3,5–7]. Humans with lesions that include the subgenual prefrontal cortex demonstrate abnormal autonomic responses to emotional experiences, inability to experience emotion related to concepts that ordinarily evoke emotion, and impaired comprehension of the adverse consequences of pernicious social behaviours[8,9]. Based partly upon these observations, Damasio *et al.*[8,10] proposed that the ability to discern the outcome of social behaviour in terms of punishment and reward depends upon visceral feedback mediated through interactions between the ventromedial prefrontal cortex and autonomic centres. If so, disordered interactions between the subgenual prefrontal cortex and interconnected structures may be related to the pathological guilt or anxiety characterizing depression, or the rapid shifts between inappropriate euphoria and anger seen in mania[2,3]. The neural network formed by these structures may contain a disease process that is not confined to the subgenual prefrontal cortex, as reduced left amygdala volume[23] and third ventricle enlargement[18] (the subgenual prefrontal cortex shares substantial, predominantly ipsilateral connections with the amygdala and the medial thalamic nuclei surrounding the third ventricle[5]) have also been reported in bipolar disorder. Post-mortem histopathological assessments within this circuitry may elucidate the neurobiology of familial mood disorders. □

Methods

Subjects. Characteristics of subgroups appear in Table 1. The bipolar-depressed (BP-D) subjects met criteria for bipolar disorder, depressed phase[1], and had a parent or sibling with probable or definite bipolar disorder. Hamilton Depression Rating Scale (HDRS) scores (21 items)[24] were in the moderately-to-severely-depressed range (mean = 24.2 ± 3.5 (20–29) for groups A and B, and 23.4 ± 6.5 (16–35) for group C). Subjects had not received psychotropic or other drugs likely to alter blood flow (BF) or glucose metabolism for >4 weeks. Exclusion criteria included substance abuse within one year and major medical disorders.

Controls met the same exclusions and denied having had major psychiatric disorders. Group A controls consisted of 24 subjects involved in our previous study of unipolar depression[11], who also denied a family history of psychiatric disorders. This large, carefully screened control group was used to generate the composite normative image for the t-image computation. Group B controls were matched with bipolar subjects in group B (40% female in each) and group C controls with the bipolar subjects in group C (50 and 57% female, respectively) for age, handedness and gender.

Image acquisition. PET scans were acquired as subjects rested with eyes closed. For groups A and B, images were obtained using PETT VI and 60–80 mCi of $H_2{}^{15}O$ (ref. 25). Tissue radioactivity was measured, which over the range tested accurately reflects differences in regional BF[26].

For group C, images were acquired with a Siemens 953B tomograph (resolution was 5 mm FWHM, septa inserted). Glucose metabolism was measured using 5–10 mCi of [^{18}F]2-fluorodeoxyglucose, adaptions of the Sokoloff method,[27] and arterial blood sampling. A linear normalization was applied by dividing regional-by-global metabolic rate for glucose (MRglu; mean global values did not significantly differ across the control, bipolar-depressed, and unipolar-depressed (FPDD) groups, being 6.0 ± 0.95, 6.2 ± 1.2 and 5.7 ± 1.1 mg per 100 mg per min, respectively). The metabolic images were not filtered (that is, FWHM was 5 mm). Regional BF was also measured[25] and the reconstructed BF images were filtered to a 3-dimensional resolution of 14 mm FWHM. Technical problems precluded acquisition of the metabolic image for one bipolar depressive and the BF image for another.

Image analysis. To guide regional analyses, PET scans from group A were used to compute a composite statistical image highlighting differences between bipolar depressives and controls. After remapping primary images into a common, stereotaxic array[28,29], an image of unpaired t-values was computed, with each voxel representing the difference in mean BF between depressives and controls divided by the local variance[11]. The t image was searched for t values above a threshold $|t|$ that would correspond to $P < 0.05$ in a single test. ROI

were defined to encompass the voxel containing the peak $|t|$ value and adjacent voxels with similar t values. The size of each ROI was optimized by computing regional t for progressively larger ROI, and the ROI for which the regional t was maximized was selected. Eleven ROI were defined, located in the following regions (per cent difference in mean normalized flow in depressives relative to controls appears in parentheses): subgenual prefrontal cortex (PFC) (− 7.7%), right (R) insula (− 7.5%), R and left (L) temporoparietal cortex (− 7.4 and − 6.7%, respectively), R and L lentiform nucleus (− 6.3 and − 5.7%, respectively), rostral thalamus (− 6.1%), posterior cingulate (− 5.6%), L hippocampus (− 5.2%), L frontal pole (4.4%) and R precuneate (4.5%).

The hypothesis that BF differed between depressives and controls in each ROI was tested by comparing the mean BF of the depressed and control samples from group B in one-tailed t-tests, corrected for multiple comparisons (Bonferroni), with degrees of freedom corrected for unequal variance (Satterthwaite). Thus, the ROI used to obtain the BF measures for both groups A and B were identical in size and location, having been generated from the t-image from group A, and stereotaxically placed in each subject's PET image[11,28,29] The only mean BF difference between the depressives and controls from group B achieving significance after corrections from 11 tests was found in the subgenual PFC.

Because of the higher spatial resolution of the 953B images, regional measures in group C were obtained using the smaller ROI shown in Fig. 1. Thus, they were not guided by information regarding inherent differences between the depressives and controls from groups B or C.

Neuromorphometric measures. MR images acquired using a Siemens VISION 1.5T scanner and a 3D MPRAGE sequence (T1, 300 ms; TR, 9.7; TE, 4; flip angle, 12°; matrix, 256 × 256 × 128, 1 × 1 × 25 mm voxels) were resliced to 1 mm^3 voxels with coronal sections oriented perpendicular to the bicommissural line using ANALYZE. The grey matter was manually traced for the first full gyrus beneath the corpus callosum in all coronal slices between the anteriormost point of the callosum and the anteriormost plane where the internal capsule no longer divided the striatum. Segmentation was performed by one investigator (W.C.D.) blinded to diagnosis. Virtually identical mean intergroup differences were obtained by a second rater (J.R.S.) blinded to the measures of the first. Variance components estimates (intraclass correlation coefficients) showed that 1.0% of the total variability was due to interrater differences and 99% to inter-subject differences.

Received 12 September 1996; accepted 18 February 1997.

1. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)* (American Psychiatric Association, Washington, DC, 1987).
2. Goodwin, F. K. & Jamison, K. R. *Manic-depressive Illness* (Oxford University Press, New York, 1990).
3. Drevets, W. C. & Todd, R. D. in *Adult Psychiatry* (ed. Guze, S. B.) 99–142 (Mosby, St Louis, 1997).
4. Mazziotta, J. C., Phelps, M. E., Plummer, D. & Kuhl, D. E. Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. *J. Comput. Assist. Tomogr.* **5,** 734–743 (1981).
5. Carmichael, S. T. & Price, J. L. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J. Comp. Neurol.* **363,** 615–641 (1995).
6. Neafsey, E. J., Terreberry, R. R., Hurley, K. M., Ruit, K. G. & Frysztak, R. J. in *Neurobiology of Cingulate Cortex and Limbic Thalamus* (eds Vogt, B. A. & Gabriel, M.) 206–223 (Birkhauser, Boston, 1993).
7. Sesack, S. R., Deutch, A. Y., Roth, R. H. & Bunney, B. S. Topographic organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study using *Phaseolus vulgaris* leucoagglutinin. *J. Comp. Neurol.* **290,** 213–242 (1989).
8. Damasio, A. R., Tranel, D. & Damasio, H. Individuals with sociopathic behavior caused by frontal damage fail to respond automatically to social stimuli. *Behav. Brain Res.* **41,** 81–94 (1990).
9. Bechara, A., Tranel, D., Damasio, H. & Damasio, A. R. Failure to respond autonomically to anticipated future outcomes following damage to the prefrontal cortex. *Cerebr. Cort.* **6,** 215–225 (1996).
10. Damasio, A. R. *Descarte's Error: Emotion, Reason, and the Human Brain.* (Grosset/Putnam, New York, 1994; Picador MacMillan, London, 1995).
11. Drevets, W. C. *et al.* A functional anatomical study of unipolar depression. *J. Neurosci.* **12,** 3628–3641 (1992).
12. Winokur, G. The development and validity of familial subtypes in primary unipolar depression. *Pharmacopsychiatry* **15,** 142–146 (1982).
13. Baxter, L. R. *et al.* Cerebral metabolic rates for glucose in mood disorders. *Arch. Gen. Psychiat.* **42,** 441–447 (1985).
14. Baxter, L. R. *et al.* Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch. Gen. Psychiat.* **46,** 243–250 (1989).
15. Buchsbaum, M. S. *et al.* Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with [^{18}F]2-deoxyglucose in affective illness. *J. Affect. Dis.* **10,** 137–152 (1986).
16. Cohen, R. M. *et al.* Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Nauropsychopharmacology* **2,** 241–254 (1989).
17. Dolan, R. J. *et al.* Dorsolateral prefrontal cortex dysfunction in the major psychoses: symptom or disease specificity? *J. Neurol. Neurosurg. Psychiat.* **56,** 1290–1294 (1993).
18. Drevets, W. C. & Botteron, K. in *Adult Psychiatry* (ed. Guze, S. B.) 53–82 (Mosby, St Louis, 1996).
19. Drevets, W. C. & Raichle, M. E. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. *Cognit. Emot.* (in the press).
20. Drevets, W. C., Spitznagel, E. L., MacLeod, A. K. & Raichle, M. E. Discriminatory capability of PET measurements of regional blood flow in familial pure depressive disease. *Abstr. Soc. Neurosci.* **18,** 1596 (1992).
21. Young, R. C., Biggs, J. T., Ziegler, V. E. & Meyer, D. A. A rating scale for mania: reliability, validity and sensitivity. *Brit. J. Psychiat.* **133,** 429–435 (1978).
22. DiRocco, R. J., Kageyama, G. H. & Wong-Riley, M. T. The relationship between CNS metabolism and cytoarchitecture: a review of ^{14}C-deoxyglucose studies with correlation to cytochrome oxidase histochemistry. *Comp. Med. Imag. Graph.* **13,** 81–92 (1989).
23. Pearlson, G. D. *et al.* Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. *Biol. Psychiat.* **41,** 1–14 (1997).
24. Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiat.* **23,** 56–62 (1960).
25. Raichle, M. E., Martin, W. R. W., Herscovitch, P., Mintun, M. A. & Markham, J. Brain blood flow measured with intravenous $_2$^{18}O. II. Implementation and validation. *J. Nucl. Med.* **24,** 790–798 (1983).
26. Fox, P. T. & Mintun, M. A. Noninvasive functional brain mapping by change distribution analysis of averaged PET images of H_2^{15}O tissue activity. *J. Nucl. Med.* **30,** 141–149 (1989).
27. Phelps, M. E. *et al.* Tomographic measurements of local cerebral glucose metabolic rate in humans with [F-18]2-fluoro-2-deoxy-D-glucose: validation of method. *Ann. Neurol.* **6,** 371–388 (1979).
28. Talairach, J. & Tournoux, P. in *Co-Planar Stereotaxic Atlas of the Human Brain* 1–122 (Theime, Stuttgart, 1988).
29. Fox, P. T., Perlmutter, J. S. & Raichle, M. E. A stereotactic method of anatomical localization for positron emission tomography. *J. Comput. Assist. Tomogr.* **9,** 141–153 (1985).
30. Carmichael, S. T. & Price, J. L. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J. Comp. Neurol.* **346,** 366–402 (1994).

Acknowledgements. This work was supported by the US NIH and the Charles A Dana Foundation. We thank T. Videen and J. Haller, for advice on image analysis. W. Powers for guidance on metabolic imaging, E. Spitznagel and T. Pilgram for assistance with statistical analysis, and L. Gardner for technical assistance.

Correspondence and requests for materials should be addressed to W.C.D.

Relationship between subjective effects of cocaine and dopamine transporter occupancy

N. D. Volkow*†, G.-J. Wang*, M. W. Fischman‡, R. W. Foltin‡, J. S. Fowler§, N. N. Abumrad‖, S. Vitkun¶, J. Logan§, S. J. Gatley*, N. Pappas*, R. Hitzemann† & C. E. Shea§

* *Medical and § Chemistry Departments, Brookhaven National Laboratory, Upton, New York 11973, USA*

† *Department of Psychiatry and ¶ Department of Anesthesiology, State University of New York at Stony Brook, Stony Brook, New York 11794, USA*

‡ *Department of Psychiatry, Columbia University, New York, New York 10032, USA*

‖ *Department of Surgery, Northshore University Hospital, Manhasset, New York 11030, USA*

Cocaine is believed to work by blocking the dopamine transporter (DAT) and thereby increasing the availability of free dopamine within the brain[1–4]. Although this concept is central to current cocaine research and to treatment development, a direct relationship between DAT blockade and the subjective effects of cocaine has not been demonstrated in humans. We have used positron emission tomography to determine what level of DAT occupancy is required to produce a subjective 'high' in human volunteers who regularly abuse cocaine. We report here that intravenous cocaine at doses commonly abused by humans (0.3–0.6 mg kg^{-1}) blocked between 60 and 77% of DAT sites in these subjects. The magnitude of the self-reported high was correlated with the degree of DAT occupancy, and at least 47% of the transporters had to be blocked for subjects to perceive cocaine's effects. Furthermore, the time course for the high paralleled that of cocaine concentration within the striatum, a brain region implicated in the control of motivation and reward. This is the first demonstration in humans that the doses used by cocaine abusers lead to significant blockade of DAT, and that this blockade is associated with the subjective effects of cocaine. Although these findings provide justification to target the DAT for medication development they suggest that for drugs to be effective in blocking cocaine's effects they would have to be given at doses that achieve almost complete DAT occupancy.