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Limbic Dysfunction in Schizophrenia and Mania

A Study Using ^{18}F-Labelled Fluorodeoxyglucose and Positron Emission Tomography

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Background. Diagnostic classes (derived from CATEGO) can be correlated with regional brain metabolism in patients with major psychiatric disorders.

Method. Seventeen patients with schizophrenia, 15 with mania, 10 with depression and 10 healthy volunteers were examined with positron emission tomography (PET) and ^{18}F-labelled fluorodeoxyglucose, as a marker for glucose metabolism. The number of possible comparisons of regions of interest was reduced by principal-components analysis, and differences in factor scores were determined between diagnostic groups.

Results. Four independent factors, representing distributed brain systems, emerged: an anterior–posterior (1), a left–right temporal (2), a temporofrontal (3), and a mediofrontal (4) system, of which (1), (2) and (3) were abnormal in schizophrenia, (1) and (2) in mania, and (1) in depression.

Conclusions. Abnormal patterns of metabolism could be detected, in decreasing order, in schizophrenia, mania and depression. Some of these abnormalities are likely to be due to medication, but others will be associated with structural or functional abnormalities of the frontolimbic system in the diagnostic groups.

The claim for a link between psychosis and abnormal function of the limbic system (Davison & Bagley, 1969; Trimble, 1990) is supported by postmortem findings of temporolimbic tissue loss in schizophrenia (Bogerts *et al*, 1985; Brown *et al*, 1986; Altshuler *et al*, 1987; Conrad *et al*, 1991), as well as by structural abnormalities in the temporal lobes (Bogerts *et al*, 1990; Suddath *et al*, 1989, 1990). Positron emission tomography (PET) has demonstrated decreased glucose uptake in the hippocampus and anterior cingulate cortex in schizophrenia (Tamminga *et al*, 1992), and altered regional cerebral blood flow (rCBF) in the left parahippocampal gyrus and right posterior cingulate associated with chronic stable delusions and hallucinations (Liddle *et al*, 1992). Furthermore, secondary mania appears to be associated with right-sided lesions of limbic or limbic-connected areas, such as the caudate and thalamus (Cummings & Mendez, 1984; Starkstein & Robinson, 1989).

We examined actively psychotic patients with schizophrenia and mania, with the prediction that glucose uptake in limbic areas of the brain, that is, the amygdala, hippocampus, parahippocampal gyrus and mediofrontal cortex, including the anterior cingulate, would be abnormal. We used PET with ^{18}F-labelled fluorodeoxyglucose (FDG), and recruited healthy volunteers and depressed patients as controls. Schneiderian diagnostic criteria (Schneider, 1959) have been regarded as pointers to limbic pathology (Trimble, 1990), so we decided to use the derived CATEGO system (Wing *et al*, 1974) to classify our patients. In CATEGO, schizophrenic psychosis is characterised by the presence of Schneider's first-rank symptoms, while mania is defined, along with manic mood disturbance, by other psychotic features. Our aim was, therefore, to determine to what extent schizophrenia and mania in particular, as compared with psychosis in general, are associated with a specific metabolic dysfunction of the limbic system.

Method

Subject recruitment and clinical assessment

Patients were recruited from acute wards in Aberdeen psychiatric hospitals. They were considered for the study if:

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(a) according to the responsible clinician, they were suffering from a psychotic illness
(b) they were older than 17 years
(c) they were judged by their own consultant psychiatrist and one of the research psychiatrists (AHA) to be capable of giving informed consent
(d) they were actively psychotic at the time of examination, that is, had at least one psychotic symptom (items 55–92 of the ninth version of the Present State Examination, PSE–9; Wing *et al*, 1974)
(e) they were free from major disorder of the central nervous system (CNS) or systemic disorder
(f) there was no evidence of drug or alcohol use which could account for their psychiatric disturbance.

A group of actively depressed patients were also included. All subjects were approached personally by the first author and given adequate explanation of the study procedure. They were asked to give written informed consent after having the opportunity to discuss their participation in the study with a relative or friend.

The procedure followed a study protocol approved by the Administration of Radioactive Substances Advisory Committee (ARSAC) at the Department of Health and by the Joint Ethical Committee of the Grampian Health Board and the University of Aberdeen.

Fifty-eight patients entered the study. Five were excluded because the imaging procedure had to be terminated prematurely owing to mental state deterioration; in four the required head position could not be maintained, because the patients were too restless; three were excluded after the discovery of organic lesions; the data on four patients were excluded because raters could not agree about the matching of PET to appropriate sections on magnetic resonance imaging (MRI). This left 42 patients, who were all right-handed according to Annett's hand preference questionnaire (Annett, 1970). All the patients were in good general health with normal physical examination and routine laboratory investigations. Ten right-handed healthy volunteers were included for comparison. These were recruited from hospital staff and their friends, and were of comparable mean age, years of education and male:female ratio (see Table 1).

Clinical history, current and recent medication (over the previous four weeks) and sociodemographic characteristics, including years of education and employment status, were recorded for each patient. Additionally, each patient was assessed using the full version of the PSE. The PSE syndromes (according to the PSE syndrome check-list; Wing *et al*, 1974) and diagnostic classes were generated with the CATEGO-4 computer program.

Image acquisition and processing

Four brain sections were chosen to show the limbic structures (amygdala, hippocampus, parahippocampal gyrus, mediofrontal cortex including the anterior cingulate), neocortex (frontal and temporal) as well as subcortical structures such as the basal ganglia (caudate putamen, globus pallidus) and thalamus. These were selected to match the four postmortem levels in the atlas of Aquilonius & Eckernäs (1980) at 63, 76, 83, and 89 mm from the brain vertex (Fig. 1).

Before PET scanning, these sections were defined for each subject using the University of Aberdeen Mark II MRI scanner, with a 0.08 T magnet, 2.5 mm resolution and 12 mm slice thickness. Each subject was positioned with the help of two laser beams, with the orbitomeatal line marked on the skin. A complete set of proton density images was acquired; four sections were identified and rechecked with the help of immediate video display. These slices were reproduced with the PET scanner by repositioning the subject according to the measurements made in the MRI scanner and using the same individually moulded polystyrene headrest.

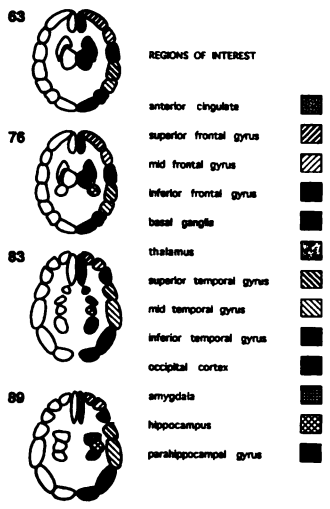


Fig. 1 Templates used for the ROI analysis.

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Subjects were instructed to relax and close their eyes during the examination but no further instructions were given and they were not spoken to during the procedure. For attenuation correction, transmission scans were acquired with a germanium-68 ring source, using an Ortec ECAT II scanner (in-plane resolution 17.2 mm full width half-maximum, 19.8 mm slice thickness). The patients were given 185 MBQ of [^{18}F]2-deoxy-*D*-glucose intravenously, and 35–40 minutes were allowed for uptake before the emission scan. During this period the subject was lying on the imaging bench in subdued light and a relatively noise-free environment.

The acquisition time was 10 minutes per slice. Image processing was carried out on a Sun SPARC station 1+ using software developed by NE. Scans were first checked for adequacy of counts and the existence of head movement and other artefacts. Images were then centred and rotated to enable subsequent matching with the corresponding MRI sections. The PET images were rechecked for correspondence with MRI and standard atlas slices by AHA and GWA, who matched them independently and without reference to name or diagnostic group. If the two raters did not agree, the subject was excluded from the analysis. For each image, the brain border was defined as 50% of the maximum image intensity. The mean pixel count density within this contour was found. Templates for regions of interest (ROIs) were drawn for the four levels on the basis of the brain atlas (Aquilonius & Eckernäs, 1980; Fig. 1), and these were laid over the corresponding PET images; the mean count density for each ROI was then determined. Fitting the templates to each slice by rescaling each image to the template preserved the relative relationship of ROIs to each other. The ROIs constituting an anatomical area across the four slices were combined to form 26 larger ROIs (Fig. 1, Table 2). To control for the confounding effect of inter-individual differences in global uptake (Buchsbaum *et al*, 1984, 1992*a*), ROI values were expressed as relative metabolic ratios normalised to the area-weighted mean of all ROIs. This normalisation method has been used by other investigators (Gur *et al*, 1987*a*; Buchsbaum *et al*, 1992*a*; Tamminga *et al*, 1992; Ebmeier *et al*, 1993), and has the advantage of being less affected by variability in ventricular size than whole-slice normalisation.

Statistical procedures

To reduce the number of comparisons and the likelihood of a type I error, we did a principal-components analysis on regional metabolic values, extracting factors with eigenvalues greater than 1, followed by orthogonal (Varimax) rotation; factor scores were calculated using regression. Eleven regions with Kaiser–Myer–Olkin measures of sampling adequacy less than 0.75, indicating small data variability, were excluded from the analysis (Fig. 2). A repeated-measures multivariate analysis of variance (ANOVA) with four rotated factor scores as within-subjects repeated variables and group membership as a between-subjects factor was used as an omnibus test to reduce further the chance of type I error. A significant factor by diagnosis interaction justified further one-way ANOVAs for each factor separately, followed by post hoc Scheffé tests to determine individual group differences. The effect of age was assessed using analysis of covariance (ANCOVA). Years of education, height and weight were compared among the groups using the Mann–Whitney test, while the male:female ratio was assessed with the χ^2 statistic. All statistical tests were performed in the Statistical Package for the Social Sciences (SPSS for Windows release 6; SPSS Inc., 1993) on an IBM-compatible personal computer.

Results

Subjects and clinical results

Patients fell into the following PSE categories: schizophrenic psychosis ($n=14$, CATEGO class S+); paranoid psychosis ($n=3$, CATEGO class P+); manic psychosis ($n=15$, CATEGO class M+); depressive psychosis ($n=6$, CATEGO class D+); non-psychotic depression ($n=4$, CATEGO class R+).



FACTORS	LOADINGS +	LOADINGS −	NAME	S	M	D	C	p	SCHEFFE
Factor 1	■	■	ANTERIOR-POSTERIOR	0.03	-0.61	-0.24	1.10	0.0001	S,M,D<C
Factor 2	■	■	LEFT AMYGDALA-RIGHT TEMPORAL	-0.38	-0.40	0.44	0.80	0.002	S,M<C
Factor 3	■	■	LEFT FRONTAL-RIGHT LIMBIC	-0.43	-0.12	-0.02	0.93	0.004	S<C
Factor 4	■		ANTERIOR CINGULATE	0.49	-0.47	0.24	-0.37	0.02	n.s.

Fig. 2 Regions with positive and negative loadings on factors 1 to 4 (only highest regional loading). Empty ROIs did not show sufficient variability to be included in the principal-components analysis. Mean factor scores for schizophrenia (S), mania (M), depression (D) and healthy controls (C), with post hoc Scheffé tests.

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Table 1 gives the clinical profile of the controls and the patients. Nine out of 42 (21%) patients were presenting for the first time; six of these had schizophrenia, one mania and two depression. Nine of 10 depressed patients had unipolar depression and only one was in the depressed phase of a bipolar illness. Seven patients were medication free at the time of scanning: four with schizophrenia (three medication naive and one medication free for 23 days), two with mania and one with depression. The proportions of patients with schizophrenia and with mania who were off neuroleptics were not significantly different, nor were the mean daily doses of neuroleptics at the time of the PET scan and over the previous two and four weeks (Table 1). Three schizophrenic patients, eight manic, and none of the depressed patients were on anticholinergic medication at the time of scanning. Nine patients were receiving antidepressants: one schizophrenic and one manic patient (both amitriptyline); and seven depressed patients (three amitriptyline, three lofepramine and one dothiepin). Ten patients were on temazepam as night sedation: one schizophrenic patient, six manic and three depressed patients. One schizophrenic patient received sodium valproate.

The manic group was significantly older than the schizophrenic group ($P=0.02$, Mann–Whitney U test). Apart from this, there were no significant differences between the patient groups and normal controls in mean age and years of education, and the male:female ratio between the groups did not differ significantly.

Regional glucose uptake

Table 2 gives the raw regional uptake ratios for the four diagnostic groups, to allow for a comparison with other studies. Principal-components analysis extracted four factors which explained 77.5% of the variance (Fig. 2). After rotation, factor 1 (41.8% of the variance) represented an anterior–posterior dimension with positive loadings in bilateral superior and right mid-frontal gyri and negative loadings in left occipital cortex and left parahippocampal gyrus; the factor loadings were 0.7, 0.9, 0.6, 0.8, −0.9 and −0.7, respectively. Factor 2 (19.9%) had positive loadings in the left amygdala and negative loadings in the right superior and right mid-temporal gyri; factor loadings were 0.7, −0.8 and −0.9, respectively. Factor 3 (9.1%) had positive loadings for the left mid- and left inferior frontal gyri, negative in the right amygdala and right hippocampus, with factor loadings of 0.7, 0.8, −0.5 and −0.8, respectively. Factor 4 (6.7%) had positive loadings in the left and right mediofrontal cortex (including anterior cingulate); the factor loadings were 0.6 and 0.9, respectively.

There was a highly significant diagnosis by factor interaction (Hotelling's test: $F_{9,134}=4.1$, $P=0.0005$). One-way ANOVA showed significant group effects for factor 1 ($F_{3,48}=8.95$, $P=0.0001$), factor 2 ($F_{3,48}=5.6$, $P=0.002$), factor 3 ($F_{3,48}=4.97$, $P=0.004$) and factor 4 ($F_{3,48}=3.5$, $P=0.02$). A *post hoc* Scheffé test for repeated measures revealed that for factor 1 the means for the three patient groups were significantly lower than that for the normal controls. For factor 2 the schizophrenic and manic

Table 1
Clinical profile of patients and controls

	Schizophrenia (n=17)	Mania (n=15)	Depression (n=10)	Normal controls (n=10)
Mean (s.d.) age: years	34.4 (11.2)	44.4 (11.7)	50.5 (20.5)	40.1 (12.4)
Sex (m/f)	13/4	7/8	5/5	5/5
Mean (s.d.) years in education	13.7 (1.0)	13.6 (1.4)	13.3 (0.6)	13.8 (2.7)
Mean (s.d., range) illness duration: months	59.12 (81.27, 1–324)	119.47 (110.1, 3–360)	137 (109.2, 4–348)	n/a
Mean (s.d.) chlorpromazine equivalents per day				
at time of scan/(n; range)	291.9 (208.4) (n=12; 50–800)	299.2 (105.2) (n=13; 100–400)	114.3 (79.5) (n=3; 43–200)	0
over 2 weeks before scan	312.7 (345.6) (n=14)	261.4 (167.5) (n=13)	123.9 (95.1) (n=3)	0
over 4 weeks before scan	286.1 (377.6) (n=14)	149.3 (97.2) (n=13)	85.7 (37.9) (n=3)	0
Mean (s.d.) lithium dose per day: mg (n; range)	666.7 (472.6) (n=3; 300–1200)	900.0 (258.2) (n=4; 600–1200)	800 (n=1)	0

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Table 2
Mean (s.d.) raw regional uptake ratios (normalised to average of all ROIs)

Region of interest	Schizophrenia	Mania	Depression	Normal controls
L amygdala[1]	0.85 (0.04)	0.83 (0.02)	0.90 (0.03)	0.85 (0.03)
R amygdala[1]	0.88 (0.04)	0.91 (0.03)	0.89 (0.05)	0.84 (0.05)
L hippocampus[1]	0.88 (0.04)	0.90 (0.03)	0.90 (0.03)	0.86 (0.03)
R hippocampus[1]	0.86 (0.03)	0.87 (0.04)	0.84 (0.05)	0.84 (0.03)
L parahippocampal g[1]	0.88 (0.05)	0.93 (0.04)	0.91 (0.05)	0.86 (0.04)
R parahippocampal g	0.87 (0.06)	0.88 (0.06)	0.85 (0.06)	0.82 (0.03)
L mediofrontal cortex[1]	1.09 (0.05)	1.07 (0.05)	1.10 (0.06)	1.14 (0.04)
R mediofrontal cortex[1]	1.03 (0.05)	0.98 (0.05)	1.01 (0.04)	1.01 (0.05)
L basal ganglia	1.04 (0.05)	0.99 (0.04)	1.07 (0.02)	1.01 (0.04)
R basal ganglia	1.08 (0.04)	1.05 (0.06)	1.05 (0.04)	1.05 (0.03)
L thalamus	0.98 (0.05)	0.94 (0.04)	0.93 (0.05)	0.98 (0.05)
R thalamus	1.03 (0.06)	1.00 (0.04)	0.98 (0.09)	1.02 (0.05)
L superior frontal g[1]	1.03 (0.04)	1.03 (0.03)	1.05 (0.05)	1.16 (0.03)
R superior frontal g[1]	0.96 (0.06)	0.93 (0.04)	0.97 (0.06)	1.04 (0.02)
L mid-frontal g[1]	0.99 (0.04)	0.98 (0.03)	1.01 (0.06)	1.09 (0.04)
R mid-frontal g[1]	0.88 (0.08)	0.83 (0.08)	0.86 (0.07)	0.91 (0.06)
L inferior frontal g[1]	1.12 (0.03)	1.12 (0.03)	1.14 (0.06)	1.21 (0.04)
R inferior frontal g	0.95 (0.08)	0.93 (0.06)	0.90 (0.06)	0.91 (0.07)
L superior temporal g	1.06 (0.03)	1.09 (0.03)	1.06 (0.03)	1.07 (0.03)
R superior temporal g[1]	0.97 (0.04)	0.98 (0.04)	0.95 (0.05)	0.92 (0.04)
L mid-temporal g	1.05 (0.03)	1.05 (0.03)	1.06 (0.03)	1.03 (0.03)
R mid-temporal g[1]	1.00 (0.03)	1.01 (0.05)	0.97 (0.04)	0.95 (0.03)
L inferior temporal g	1.00 (0.04)	0.99 (0.03)	0.99 (0.03)	0.98 (0.02)
R inferior temporal g	0.95 (0.04)	0.97 (0.02)	0.92 (0.06)	0.94 (0.04)
L occipital cortex[1]	1.12 (0.04)	1.15 (0.04)	1.13 (0.04)	1.07 (0.05)
R occipital cortex	1.08 (0.05)	1.08 (0.03)	1.10 (0.09)	1.05 (0.03)

L, left; R, right; g, gyrus.
1. Regions included in the principal-components analysis.

groups were significantly lower than the controls, whereas for factor 3 only the schizophrenic group showed decreased uptake in comparison with the normal controls. No significant group differences were detected for factor 4 (anterior cingulate/mediofrontal metabolism).

Only factor 3 was significantly negatively correlated with age ($t=-2.8$, $P=0.01$). However, after allowing for the effect of age, significant multivariate group effects remained (Hotelling's test: $F_{12,128}=11.7$, $P=0.0005$), as did group effects for each of the four factors after one-way ANCOVA (factor 1, $F_{3,47}=8.4$, $P=0.0005$; factor 2, $F_{3,47}=5.2$, $P=0.004$; factor 3, $F_{3,47}=6.7$, $P=0.001$; factor 4, $F_{3,47}=3.1$, $P=0.03$).

Discussion

In spite of a high drop-out rate (16 of 58), the number of schizophrenic patients ($n=17$) was comparable to that in many PET studies, while the number of manic patients ($n=15$) is to our knowledge the largest number of acutely ill manic patients in the functional imaging literature. The 10 depressed patients provided an additional comparison for the manic and schizophrenic groups.

The factor analysis allows for an exploration of functional and structural brain changes in our subjects. An empirical approach to data reduction is preferable to an *a priori* approach, since covariation of glucose uptake must be the most valid pointer towards functional localisation. We found that regional FDG uptake in our study sample could be reduced to four independent factors representing an anterior–posterior gradient (factor 1), a left amygdala–right temporal uptake factor (factor 2), a left frontal–right limbic factor (factor 3), and a mediofrontal/anterior cingulate factor (factor 4). Because of the relatively small number of subjects, this factor structure is exploratory and unlikely to be stable, but it represents spatial domains generally thought to be affected in psychotic illness.

Group differences for the first factor mostly reflect relatively decreased FDG uptake in the dorsolateral prefrontal cortex (DLPFC) bilaterally and increased uptake in the left occipital cortex in the three patient groups in comparison with the

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normal controls (Fig. 2). This is consistent with other studies that have found hypofrontality in patients with schizophrenia (DeLisi *et al*, 1985; Berman *et al*, 1986; Siegel *et al*, 1993) and depression (Buchsbaum *et al*, 1986; Baxter *et al*, 1989; Cohen *et al*, 1989; Austin *et al*, 1992; Bench *et al*, 1992). We found that decreased frontal uptake also occurs in mania during the acute illness. To our knowledge this is the first demonstration of an abnormal anterior–posterior gradient in acutely ill manic patients. Other imaging studies which demonstrated reduced frontal metabolism in bipolar patients (Buchsbaum *et al*, 1986; Cohen *et al*, 1989) had done so during the depressed phase, or included a very small number of subjects ($n=2$) in the manic phase (Cohen *et al*, 1989).

The reasons for the observed reduction of the anterior–posterior gradient in the three patient groups are not entirely clear. It may be linked to similarities in mental state or the underlying pathophysiology, but it may also be an effect of neuroleptic medication. A number of studies have attempted to determine the effect of neuroleptics on regional cerebral metabolism. Acute or short-term neuroleptic administration appears either not to alter cerebral metabolism or to produce increases in cortical and basal ganglia metabolism (Gur *et al*, 1987*b*; Szechtman *et al*, 1988; Bartlett *et al*, 1991; Jibiki *et al*, 1992), while prolonged neuroleptic administration may contribute to hypofrontality (Szechtman *et al*, 1988).

Significant changes in factor 2 (left amygdala–right temporal uptake) were in the direction of reduced uptake in the left amygdala and increased uptake in the right temporal cortex in the schizophrenic and manic patients in comparison with the normal controls. This finding is consistent with the study of Tamminga *et al* (1992), who reported (non-significantly) decreased metabolic rates in the amygdala, more so on the left side, in drug-free schizophrenic patients. Our result may represent an abnormality related to the psychotic mental state of patients with schizophrenia and mania (Ebmeier *et al*, 1993), although it may plausibly also be related to neuroleptic medication (Reynolds, 1983).

We found reduced left frontal uptake and increased right amygdala and right hippocampal uptake in schizophrenic patients only, compared with the healthy controls (Fig. 2). This is unlikely to be a medication effect, since it was missing in our manic patients, and is in line with the findings of Musalek *et al* (1989), who reported increased rCBF to the hippocampus and amygdala in patients with auditory hallucinations, and Liddle *et al* (1992), who reported a (mostly left-sided) increase of rCBF to the medial temporal lobe associated with delusions and hallucinations, and a left dorsolateral prefrontal decrease in perfusion associated with the psychomotor poverty syndrome.

We were able to examine four brain slices with a limited number of ROIs and a resolution in the 2 cm range. An exploration of metabolic changes in a larger number of brain regions, or using a pixel-by-pixel method of analysis with a multislice high-resolution PET scanner, might produce further and more localised changes.

The study included mostly medicated patients: only seven were drug free. The medication comprised neuroleptics, lithium, antidepressants, and anti-Parkinsonian (anticholinergic) agents. The difficulty in recruiting medication-free, actively psychotic patients remains a major weakness of the study. A restriction of recruitment to unmedicated patients, however, might have led to an unrepresentative, self-selected study group. Ideally, our findings should be replicated in comparable drug-free patient groups. Our patients were symptomatic at the time of scanning, that is, their clinical symptoms were not controlled by the medication, suggesting that illness variables might have been the major determinants of the metabolism in the brain. The proportion of patients on neuroleptics in the two main psychotic groups, schizophrenia and mania, and the mean daily dose of neuroleptics (in chlorpromazine equivalents) was similar at the time of scanning and in the four weeks before this.

Clinical implications

- There appear to be four distributed brain systems involving frontolimbic structures in patients with major psychiatric illness and healthy volunteers.
- These are an anterior–posterior (1), a left–right temporal (2), a temporofrontal (3), and a medial frontal (4) system, which co-vary across subjects.
- Most of these are abnormal in schizophrenia (1–3), fewer in mania (1+2), and least in depression (1).

Limitations

- As in all PET studies, subject numbers were limited and the study needs replication.
- The majority of patients were medicated, making the interpretation of abnormalities more difficult.
- Examination with a multislice, higher-resolution PET scanner might identify further and more localised changes.

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In conclusion, this study has found evidence of metabolic dysfunctions in limbic brain regions in patients with schizophrenia and mania. These dysfunctions appear to involve brain circuits connecting limbic regions with the frontal, and mostly right temporal, neocortex. These changes are more apparent in the schizophrenic and manic patients than the depressives, which may relate to shared aspects of pathophysiology, or the common effect of neuroleptic medication. A decrease in the anterior–posterior gradient is common to patients with schizophrenia, mania and depression. This replicates earlier studies in patients with schizophrenia and depression and extends the finding to actively ill patients with mania.

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References

ALTSHULER, L. L., CONRAD, A., KOVELMAN, J. A., *et al* (1987) Hippocampal pyramidal cell orientation in schizophrenia. *Archives of General Psychiatry*, **44**, 1094–1098.

ANNETT, M. (1970) A classification of hand preference by association analysis. *British Journal of Psychology*, **61**, 303–321.

AQUILONIUS, S.-M. & ECKERNÄS, S.-A. (1980) *A Colour Atlas of The Human Brain Adapted to Computed Tomography*. New York: Raven Press.

AUSTIN, M.-P., DOUGALL, N., ROSS, N., *et al* (1992) Single photon emission tomography with ^{99}Tc-exametazime in major depression and the pattern of brain activity underlying the psychotic/neurotic continuum. *Journal of Affective Disorders*, **26**, 31–44.

BARTLETT, E. J., WOLKIN, A., BRODIE, J. D., *et al* (1991) Importance of pharmacologic control in PET studies: effects of thiothixene and haloperidol on cerebral glucose utilization in chronic schizophrenia. *Psychiatry Research: Neuroimaging*, **40**, 115–124.

BAXTER, L. R., SCHWARTZ, J. M., PHELPS, M. E., *et al* (1989) Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, **46**, 243–250.

BENCH, C. J., FRISTON, K. J., BROWN, R. G., *et al* (1992) The anatomy of melancholia. Abnormalities of regional cerebral blood flow in major depression. *Psychological Medicine*, **22**, 607–615.

BERMAN, K. F., ZEC, R. F. & WEINBERGER, D. R. (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia II. Role of neuroleptic treatment, attention, and mental effort. *Archives of General Psychiatry*, **43**, 126–135.

BOGERTS, B., MEERTZ, E. & SCHONFELDT-BAUSCH, R. (1985) Basal ganglia and limbic system pathology in schizophrenia: a morphometric study of brain volume and shrinkage. *Archives of General Psychiatry*, **42**, 784–791.

———, ASHTARI, M., DEGREEF, G., *et al* (1990) Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Research: Neuroimaging*, **35**, 1–13.

BROWN, R., COLTER, N., CORSELLI, J. A. N., *et al* (1986) Postmortem evidence of structural brain changes in schizophrenia: differences in brain weight, temporal horn area and parahippocampal gyrus compared with affective disorder. *Archives of General Psychiatry*, **43**, 36–42.

BUCHSBAUM, M. S., CAPPELLETTI, J. & BALL, R. (1984) Positron emission tomographic image measurement in schizophrenia and affective disorders. *Annals of Neurology*, **15**, 157–165.

———, WU, J., DELISI, L. E., *et al* (1986) Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with F-2-deoxyglucose in affective illness. *Journal of Affective Disorders*, **10**, 137–152.

———, HAIER, R. J., POTKIN, S. G., *et al* (1992*a*) Frontal–striatal disorder of cerebral metabolism in never-medicated schizophrenics. *Archives of General Psychiatry*, **49**, 935–942.

———, POTKIN, S. G., SIEGEL, B. V. Jr, *et al* (1992*b*) Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. *Archives of General Psychiatry*, **49**, 966–974.

COHEN, R. M., SEMPLE, W. E., GROSS, M., *et al* (1989) Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Neuropsychopharmacology*, **2**, 241–254.

CONRAD, A. J., ABEBE, T., AUSTIN, R., *et al* (1991) Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. *Archives of General Psychiatry*, **48**, 413–417.

CUMMINGS, J. L. & MENDEZ, M. F. (1984) Secondary mania with focal cerebrovascular lesions. *American Journal of Psychiatry*, **141**, 1084–1087.

DAVISON, K. & BAGLEY, C. R. (1969) Schizophrenia-like psychoses associated with organic disorders of the central nervous system: a review of the literature. In *Current Problems in Neuropsychiatry, British Journal of Psychiatry Special Publication No. 4* (ed. R. N. Herrington), pp. 113–184. Ashford, Kent: Headley Brothers.

DELISI, L. E., BUCHSBAUM, M. S., HOLCOMB, H. H., *et al* (1985) Clinical correlates of decreased anteroposterior metabolic gradients in positron emission tomography of schizophrenia patients. *American Journal of Psychiatry*, **142**, 78–81.

EBMEIER, K. P., BLACKWOOD, D. H. R., MURRAY, C., *et al* (1993) Single photon emission computed tomography with ^{99m}Tc-exametazime in unmedicated schizophrenic patients. *Biological Psychiatry*, **33**, 487–495.

GUR, R. E., RESNICK, S. M., ALAVI, A., *et al* (1987*a*) Regional brain function in schizophrenia I. A positron emission tomography study. *Archives of General Psychiatry*, **44**, 119–125.

———, ———, GUR, R. C., *et al* (1987*b*) Regional brain function in schizophrenia. II. Repeated evaluation with positron emission tomography. *Archives of General Psychiatry*, **44**, 126–129.

JIBIKI, I., MATSUDA, H., YAMAGUCHI, N., *et al* (1992) Acutely administered haloperidol-induced pattern changes of regional cerebral blood flow in schizophrenics. *Neuropsychobiology*, **25**, 182–187.

LIDDLE, P. F., FRISTON, K. J., FRITH, C. D., *et al* (1992) Patterns of cerebral blood flow in schizophrenia. *British Journal of Psychiatry*, **160**, 179–186.

MUSALEK, M., PODREKA, I., WALTER, H., *et al* (1989) Regional brain function in hallucinations: a study of regional cerebral blood flow with ^{99m}Tc-HMPAO-SPECT in patients with auditory hallucinations, tactile hallucinations and normal controls. *Comprehensive Psychiatry*, **30**, 99–108.

REYNOLDS, G. P. (1983) Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. *Nature*, **305**, 527–529.

SCHNEIDER, K. (1959) *Clinical Psychopathology* (trans. M. W. Hamilton). New York: Grune & Stratton.

SIEGEL, B. V., BUCHSBAUM, M. S., BUNNEY, W. E., *et al* (1993) Cortical–striatal–thalamic circuits and brain glucose metabolic

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activity in 70 unmedicated male schizophrenic patients. *American Journal of Psychiatry*, **150**, 1325–1336.

SPSS INC. (1993) *SPSS for Windows: Advanced Statistics, Release 6*. Chicago: SPSS Inc.

STARKSTEIN, S. E. & ROBINSON, R. G. (1989) Affective disorders and cerebrovascular disease. *British Journal of Psychiatry*, **154**, 170–182.

SUDDATH, R. L., CASANOVA, M. F., GOLDBERG, T. E., *et al* (1989) Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. *American Journal of Psychiatry*, **146**, 464–472.

———, CHRISTISON, W., TORREY, E. F., *et al* (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, **322**, 789–794.

SZECHTMAN, H., NAHMIAS, C., GARNETT, S., *et al* (1988) Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Archives of General Psychiatry*, **45**, 523–532.

TAMMINGA, C. A., THAKER, G. K., BUCHANAN, R., *et al* (1992) Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Archives of General Psychiatry*, **49**, 522–529.

TRIMBLE, M. R. (1990) First rank symptoms of Schneider: a new perspective? *British Journal of Psychiatry*, **156**, 195–200.

WING, J. K., COOPER, J. E. & SARTORIUS, N. (1974) *Measurement and Classification of Psychiatric Symptoms*. Cambridge: Cambridge University Press.

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