Lateralisation of cortical function during cognitive tasks: regional cerebral blood flow studies of normal individuals and patients with schizophrenia

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Abstract

To assess cognitively-related regional asymmetries of brain function, regional cerebral blood flow (rCBF) was determined by the xenon[133] inhalation method while normal subjects performed 10 different tasks and also while they were at rest. In addition to healthy subjects, patients with schizophrenia were also studied. A total of 447 rCBF studies were carried out during the following conditions: the Wisconsin Card Sort Test, a numbers matching test, a symbols matching test, Raven's Progressive Matrices, an auditory discrimination test, an auditory control task, two versions of a visual continuous performance task, line orientation, semantic classification, and resting. On the whole, those tasks that seem to require or allow for internal verbalisation resulted in the greatest activation of the left hemisphere compared with the right; right hemisphere activation predominated only in the two tasks primarily involving attention and vigilance. Furthermore, a consistent regional topography of normal cerebral functional laterality was seen: under most conditions left prefrontal cortical activity exceeded that of right prefrontal cortex; during all non-auditory tasks, parieto-occipital cortical activity had an opposite pattern—greater right than left. During most conditions the schizophrenic patients displayed the same pattern. While several cognitively specific between-group differences were found, no single cortical region was consistently implicated and no specific direction of abnormal asymmetry predominated. These data suggest that there is a predominant task-independent functional pattern of cortical activity emphasising relatively greater left anterior and right posterior activation. This pattern may reflect the verbal and attentional primacy of these areas, respectively.

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The concept that the left and right cerebral hemispheres differ anatomically and functionally has been an important focal point in the understanding of the human brain for over a century.[1] Early investigations of hemispheric asymmetry were pioneered in 1861 and 1865 by Broca[2] who proposed a locus for language in the left hemisphere. Recent studies have demonstrated differential behavioural effects of lateralised brain lesions as well as differences in performance of the right and left hemispheres of commissurotomised patients on cognitive tasks.[3 4]

In the normal brain hemispheric specialisation has been inferred from a diverse body of experimental evidence. Indirect indicators of hemispheric function have been studied, including lateralisation of perceptual advantages and asymmetries of motor, autonomic and cognitive responses. New techniques for studying brain morphology and physiology in living patients provide more direct approaches to defining the normal topography of structural and functional lateralisation, potential disturbances of lateralisation and the neural networks underlying them. Anatomical differences between the two hemispheres have been demonstrated with radiographic computerised tomography (CT)[5 6] and with magnetic resonance imaging (MRI).[7] Furthermore, measurements of normal brain function *in vivo* using electrophysiological and regional cerebral blood flow (rCBF) techniques have confirmed that the two hemispheres are differentially active in response to the demands of different behavioural tasks.[8–10] Few studies, however, have systematically examined the regional topography and variability of these hemispheric differences across a variety of simple and complex tasks.

Alterations in lateralised brain organisation have also been hypothesised to play a role in a number of neurological and psychiatric disorders involving disturbances of higher cognitive function,[11 12] including dyslexia, Pick's disease and Alzheimer's disease,[11] as well as autism[13] and depression.[14] Schizophrenia, in particular, is a disorder in which a primary disturbance of laterality has been postulated and extensively studied.[14–16] For this reason, patients with this illness represent a potentially interesting comparison group for the study of normal cerebral lateralisation.

Observations of disturbed verbal behaviour in schizophrenia[17] and the occurrence of schizophrenia-like psychoses in patients with left hemisphere lesions,[18] notably temporal lobe epileptic foci,[19] have been taken by some to suggest greater left than right hemisphere dysfunction in schizophrenia. Opinions have differed as to whether this putative left hemisphere dysfunction represents left overactivation,[20] left hemisphere compensation for right hemisphere deficit,[21] left hypofunction, or disordered interhemispheric communication.[22 23] Others have concentrated on the

right hemisphere as the primary site[24][25] or on theories of bilateral dysfunction.[26] Regardless of the hemisphere implicated, a wide variety of experimental approaches, including tachistoscopic presentation of visual stimuli to a specific hemisphere[22] and dichotic listening tasks,[27] as well as examination of conjugate lateral eye movements,[20] skin conductance[28][29] and neuropsychological deficits,[14][30][31] have been used to search for altered lateralisation in schizophrenia. Although a sizeable body of literature has ensued (reviewed in refs 15 and 32), no cohesive pattern of findings has emerged.

Brain imaging techniques have also been applied to the study of schizophrenia. While most *in vivo* morphometric investigations of this illness have focused on bilaterally represented structural elements such as the lateral ventricles or cortical sulci, some studies of brain structure that are consistent with the notion of altered hemispheric differentiation have been reported.[33] However, no consistent anatomical asymmetries have been found.[34]

Similarly, direct measurements of brain function in schizophrenia have not yielded conclusive answers. For example, many electroencephalography (EEG) and evoked potential studies have reported abnormal asymmetries of brain electrical activity,[35] but the results have been inconsistent. Some show right hemisphere dysfunction to be more common in patients,[25] while others indicate more abnormalities on the left.[36-38] Similar disparities are reflected in rCBF[39-41] and positron emission tomography (PET) studies[42][43] of brain activity. In many such investigations the effects of experiential epiphenomena, which can significantly contaminate studies of brain function, have not been controlled for or considered in the interpretation of results.

Thus, despite compelling theoretical arguments about disordered laterality as applied to schizophrenia and despite the publication of well over 70 studies exploring the possibility of abnormal cerebral lateralisation in schizophrenia,[32] no clear consensus has been reached. This paper used one functional brain imaging technique, xenon[133] inhalation rCBF, to explore lateralisation of cortical function during a variety of cognitive tasks and states in normal individuals and in patients with schizophrenia.

Methods

Subjects The patient and normal control groups who participated in these 11 cognitive activation rCBF studies are described in table 1. Nine of the 11 studies included both a schizophrenic patient group and a healthy control group. For the Line Orientation and Semantic Classification studies the patient group consisted of dyslexics; the data for the dyslexics have been presented elsewhere,[44] and in the present paper only the results for normal subjects for these two tasks will be considered. Patients and their respective control groups did not differ in age, sex or hand preference as determined by the laterality index of the Halstead-Reitan Battery (table 1).

Each subject signed consent in accordance with the Institutional Review Board and Radiation Safety Committee requirements. All patients were housed on National Institute of Mental Health (NIMH) research wards at the NIMH Neurosciences Center of St Elizabeths, Washington, DC, or the National Institutes at the Health Clinical Center, Bethesda, Maryland. NIHM research patients tend to be moderately to severely ill, to have incomplete response to treatment and to require frequent admission to hospital. All patients in the current study fulfilled DSMIII-R criteria for chronic schizophrenia and all patients and normal subjects who had major medical problems were excluded. Control subjects were recruited from hospital staff and respondents to advertisements in the National Institutes of Health volunteer registry. They were screened for history of major psychiatric disorders, neurological disorders and drug abuse. Subjects were taking no medications that might affect rCBF at the time of the study. Furthermore, patients had been free of neuroleptic and all other medications for at least four weeks at the time of the study. Subjects were asked to refrain from nicotine and caffeine before the studies.

rCBF Measurements The xenon[133] inhalation technique described by Obrist and colleagues[45-47] and modified by Deshmuhk and Meyer[48] and Risberg and colleagues[9][49] was used to measure rCBF during eleven different cognitive conditions described below. We have instituted several further changes in the technique as described elsewhere.[50-52] In brief, tracer concentrations of the inert gas xenon[133]

Table 1   Subject demographics

Testing condition	Sample size		Age (SEM)				Sex (F/M)		Hand preference (R/L)	
	nml	sch	nml		sch		nml	sch	nml	sch
Resting	50	31	26·9	(0·9)	27·9	(1·3)	15/35	9/22	43/7	26/3
Wisconsin Card Sort	25	30	30·6	(1·6)	29·0	(1·3)	9/16	6/24	21/4	26/4
Numbers Matching	25	30	30·6	(1·6)	29·0	(1·3)	9/16	6/24	21/4	26/4
CPT-X	17	18	28·4	(2·1)	29·5	(1·9)	7/10	6/12	15/2	16/2
CPT-AX	17	18	28·4	(2·1)	29·5	(1·9)	7/10	6/12	15/2	16/2
Raven's Matrices	25	24	28·2	(0·9)	28·5	(1·0)	7/18	6/18	22/3	23/1
Symbols Matching	25	24	28·2	(0·9)	28·5	(1·0)	7/18	6/18	22/3	23/1
Auditory Discrimination	18	12	29·8	(1·9)	30·1	(1·6)	3/ 9	8/10	16/2	12/0
Auditory Control Task	18	12	29·8	(1·9)	30·1	(1·6)	3/ 9	8/10	16/2	12/0
Line Orientation	14	—	22·8	(0·8)	—		0/14	—	14/0	—
Semantic Classification	14	—	22·8	(0·8)	—		0/14	—	14/0	—

were inhaled by each subject for one minute and the rate of elimination of xenon[133] gamma rays from 32 cortical regions was monitored extracranially with 32 scintillation detectors over the next 11–14 minutes. Grey-matter rCBF was calculated as the initial slope (IS) of each clearance curve. This parameter has been defined and validated as a measure of grey-matter rCBF by Obrist and Wilkinson.[53]

rCBF Testing Conditions   Each subject had three consecutive rCBF measurements separated by a period of at least 30 minutes and carried out under three different testing conditions. The three measurements were performed in either a single morning or afternoon. Each subject's first rCBF determination was made during a "resting" condition. Following the initial resting state rCBF determination, the second and third procedures were carried out during two different cognitive activation conditions. On a single day each subject performed one of the following pairs of tasks: pair 1: the Wisconsin Card Sort (WCS) and the Numbers Match (NM); pair 2: two versions of a visual Continuous Performance Task (CPT); pair 3: Raven's Progressive Matrices and the Symbols Matching Task; pair 4: Auditory Discrimination and the Auditory Control task; or pair 5: Line Orientation and Semantic Classification. The sequence in which activation tasks were presented within each pair was counterbalanced across subjects to control for the possibility of an order effect.[54 55] The resting state condition and 10 cognitive activation tasks are described below. The results of non-lateralised analyses for some of the subjects have been previously reported.[44 51 56–58]

A two to four minute period preceded each rCBF measurement during which a reading of background radiation was made and this allowed subjects to adapt to the rCBF laboratory environment. Resting conditions or activation paradigms began approximately one minute before the xenon[133] inhalation and were continued throughout the entire 12 to 15 minute rCBF measurement period. Sensory and motor events extraneous to the testing condition being studied were kept to a minimum.

Resting condition   Subjects were asked to remain awake and motionless with eyes closed. Otherwise, this procedure involved no prescribed sensory, cognitive, or motor events. Resting studies reported here always constituted a subject's first exposure to rCBF measurements.

Wisconsin Card Sort   The Wisconsin Card Sort (WCS) is a problem-solving, abstract reasoning test validated by Milner[59 60] as a sensitive indicator of frontal lobe integrity in man. The WCS is particularly sensitive to dysfunction of dorsolateral prefrontal cortex,[61] and patients with schizophrenia, as well as those with dorsolateral prefrontal lesions, do poorly on this test.[51 59 60 62] A semi-automated version of this task was developed for use during rCBF procedures.[51]

Numbers Match (NM)   For the NM, subjects were shown slides of the numbers one to four which appeared in random order and which they were asked simply to match with one of four similarly numbered switches.

Continuous Performance Task-X (CPT-X)   The CPT is a test of sustained attention and vigilance.[63] For our visual versions of this task,[56] letters were flashed rapidly on a screen one at a time during the rCBF measurement. The subject was instructed to press a button, which was held in the right hand, as quickly as possible upon the appearance of the letter "X." If the subject responded quickly enough, a green reinforcement light showed and the response was scored as correct.

Continuous Performance Task-AX (CPT-AX)   During this version of the CPT subjects were asked to respond only to those "X's" which followed an "A." The CPT-AX was "dynamically paced" (that is, correct responses resulted in shorter stimulus durations, interstimulus intervals and available response times, allowing performance to be optimised over a wide range of ability levels). To ensure that subjects comprehended the instructions, short trial runs of each CPT were given before the rCBF procedure itself.

Raven's Progressive Matrices (RPM)   This abstract reasoning task, first described in 1938,[64] has been shown to correlate with formal measures of IQ.[65] During our automated version of this task subjects were shown slides, each consisting of a pattern, or "matrix," with a missing piece. The task was to choose one of eight possible pieces to correctly complete the pattern.

Symbols Matching Task   This test was designed as a control task for the RPM paradigm. Subjects were shown slides containing a test design (one of the stimuli from the RPM) and eight answer designs (also chosen from RPM stimuli), one of which was identical to the test design. The task was simply to match the test design to the identical answer design by pressing one of eight switches corresponding to the eight possible answers.

Auditory Discrimination   With eyes closed and patched, subjects listened to a tape on which were recorded a series of pairs of sounds which were either identical or slightly different. Subjects were asked to press one of two buttons after each sound pair—button 1 if the two sounds were the same, or button 2 if the two sounds were different. Before the rCBF procedure subjects were trained to criterion in associating the correct meaning to each button. Some sound pairs were moderately complex monotonal rhythm patterns taken from the Seashore Rhythm Test, and some were nonsense syllables taken from the Speech Sound Perception Test.[66]

Auditory Control Task   For this task subjects listened to the same tape as for the

Auditory Discrimination task. However, they were not asked to determine whether the sound pairs were the same or different, but only to press button 1 after each pair of sounds to indicate that they had heard the sounds.

Semantic classification For each trial of this task subjects were shown two slides. First, the stimulus slide consisted of a single word. This was followed by an answer slide on which was listed four numbered choices—1 Food, 2 Body Part, 3 Animal, 4 Tool—from which subjects were asked to choose the category to which the stimulus word belonged.

Line orientation Benton's Judgement of Line Orientation test, which is particularly sensitive to right hemisphere lesions,[51] was adapted for this task. Each item consisted of two slides: a stimulus slide showing two angled lines and a response slide with a protractor-like arrangement of lines from which the subject was asked to choose the line corresponding to the angle of the stimulus slide.

Statistical analysis
Statistical analyses were performed on rCBF laterality indices derived in the following manner. For each task the 32 grey-matter rCBF values for each subject were collapsed into 10 cortical regions (five per hemisphere): left and right prefrontal, precentral, temporal, parietal and parieto-occipital.[51] This approach reduced the possibility of falsely positive findings in the face of many statistical comparisons. Each regional rCBF value was calculated as the mean of the individual values comprising it. These regional values were then used to generate the laterality indices (as a percentage) by subtracting each right region from the homologous left region and dividing the difference by the mean of the left and right regions: $[L - R/((R + L)/2)]*100$. One advantage of the laterality index is that it is independent of blood carbon dioxide tension which has been shown to directly affect absolute rCBF[68-70] and is not affected by other potential rCBF artifacts (for example individual differences in partition coefficients, respiratory efficiency, etc).

Within-group comparisons of regional and hemispheric laterality indices To test for significant left-right differences within each subject group for a given task, we used Hotelling's T^2 test, a multivariate T statistic that can be applied to repeated measures and/or paired data.[71] This statistic evaluates the null hypothesis that the means of the multiple variables (that is, the five regional laterality indices) do not differ, and in this case that they do not differ from zero. Thus, if the left and right rCBF values for each region were similar, then each laterality index would approach zero, and Hotelling's T^2 would not be significant. Post hoc individual univariate analyses testing whether each regional index differed from zero were also carried out. Similarly, the difference between relative mean left and right *hemisphere* rCBF (as a percentage of whole brain-blood flow) for each task was also tested. Within the limits of sensitivity and resolution of the

xenon[133] rCBF technique, these analyses examine whether significant physiological lateralisation occurred during any of the tasks.

Between-groups comparisons of hemispheric and regional laterality indices To test for mean hemispheric laterality differences between the groups, mean hemispheric laterality indices were computed analogously to the regional laterality indices: [(left hemisphere—right hemisphere)/whole brain]*100. ANOVA was used to compare hemispheric laterality indices across groups for each task.

To test for overall regional laterality differences between the groups for each task, the five regional laterality indices were analysed with multivariate analysis of variance (MANOVA), a statistical approach that simultaneously accounts for the effects of all five regions and minimises Type 1 statistical error (that is, false positive results). This was followed by univariate analysis of variance (ANOVA) for each regional laterality index alone, a statistical approach that minimises Type 2 error (that is, falsely negative results).

Results
Laterality within each group
Hemispheric findings As seen in fig 1, both groups tended to have relatively higher left than right hemisphere blood flow in most conditions. The left-right hemispheric difference reached statistical significance for the Raven's and Symbols tasks in both groups and for the auditory discrimination task in the normal controls. In contrast, the only tendency for mean right hemisphere blood flow to exceed that of the left hemisphere was noted in normal subjects during both versions of the CPT ($p = 0.065$ for CPT-X; $p < 0.2$ for CPT-AX).
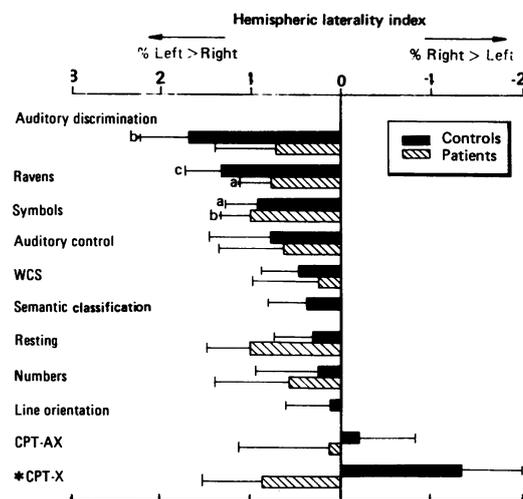
Figure 1 Hemispheric laterality indices for normal subjects and patients with schizophrenia. Sample sizes are given in table 1. Values were calculated as follows:

$$\frac{(left\ hemisphere - right\ hemisphere)}{entire\ brain} \times 100$$

$a = P \leqslant 0.05$ for within-group comparison
$b = P \leqslant 0.01$ for within-group comparison
$c = P \leqslant 0.005$ for within-group comparison
$d = P \leqslant 0.001$ for within-group comparison
$* = P \leqslant 0.05$ for between-group comparison
Bars represent standard error.

Table 2   Results of within-group regional laterality statistical analysis

Normal subjects

Testing condition	Prefrontal F	(p)	Precentral F	(p)	Temporal F	(p)	Parietal F	(p)	Parieto-occipital F	(p)	Hotelling's T^2 test F	(p)
Resting	7·1	(0·01)	0·6	ns	0·6	ns	1·6	ns	5·1	(0·03)	3·1	(0·016)
Numbers matching	11·5	(0·002)	0·9	ns	0·1	ns	0·0	ns	3·1	(0·09)	2·8	(0·042)
WCS	1·3	ns	0·4	ns	0·2	ns	2·9	(0·10)	0·1	ns	1·3	(0·308)
CPT-X	0·3	ns	1·7	ns	2·4	(0·14)	0·9	ns	3·3	(0·09)	1·1	(0·413)
CPT-AX	2·4	(0·14)	0·7	ns	0·2	ns	1·0	ns	1·9	(0·18)	1·9	(0·166)
Raven's	25·7	(0·0001)	1·1	ns	1·7	ns	0·0	ns	3·1	(0·09)	5·2	(0·003)
Symbols matching	25·0	(0·0001)	0·8	ns	2·4	(0·14)	0·2	ns	13·8	(0·001)	8·6	(0·0002)
Auditory discrimination	21·3	(0·0002)	2·6	(0·13)	4·7	(0·05)	13·2	(0·002)	0·3	ns	11·8	(0·0002)
Auditory control	10·9	(0·0042)	2·7	ns	0·0	ns	1·4	ns	0·6	ns	2·5	(0·086)
Line orientation	21·5	(0·0005)	1·2	ns	3·8	(0·07)	0·6	ns	10·4	(0·007)	14·2	(0·0005)
Semantic classification	9·92	(0·0077)	3·0	(0·11)	5·0	(0·04)	17·8	(0·001)	3·6	(0·08)	7·5	(0·0049)

Patients

Testing condition	Prefrontal F	(p)	Precentral F	(p)	Temporal F	(p)	Parietal F	(p)	Parieto-occipital F	(p)	Hotelling's T^2 test F	(p)
Resting	15·0	(0·0005)	0·7	ns	0·6	ns	0·5	ns	0·2	ns	4·2	(0·006)
Numbers matching	6·2	(0·02)	0·0	ns	0·4	ns	0·3	ns	16·7	(0·0003)	5·6	(0·001)
WCS	4·6	(0·04)	0·0	ns	0·7	ns	0·2	ns	1·2	ns	2·1	(0·104)
CPT-X	4·4	(0·05)	0·0	ns	0·0	ns	2·3	(0·15)	0·0	ns	1·3	(0·314)
CPT-AX	0·3	ns	0·0	ns	0·1	ns	2·1	(0·17)	4·2	(0·06)	3·3	(0·038)
Raven's	21·4	(0·0001)	0·1	ns	2·2	(0·15)	3·2	(0·09)	0·2	ns	11·7	(0·0001)
Symbols matching	22·4	(0·0001)	0·6	ns	0·4	ns	10·7	(0·003)	2·5	(0·13)	8·3	(0·0003)
Auditory discrimination	19·7	(0·001)	6·3	(0·03)	0·0	ns	3·2	(0·10)	0·3	ns	5·0	(0·029)
Auditory control	19·3	(0·001)	3·3	(0·10)	0·0	ns	1·3	ns	0·1	ns	13·2	(0·002)

ns = p ≥ 0·2; F indicates univariate ANOVA F for right-left comparison of a particular region.

Figure 2   A–K Regional laterality indices for normal subjects and patients with schizophrenia during 11 different cognitive conditions. Values were calculated as follows:

$$\frac{left - right}{(left + right)/2} \times 100$$

$A = P \leqslant 0.05$ for within-group multivariate comparison
$B = P \leqslant 0.01$ for within-group multivariate comparison
$C = P \leqslant 0.005$ for within-group multivariate comparison
$D = P \leqslant 0.001$ for within-group multivariate comparison
$a = P \leqslant 0.05$ for within-group univariate regional comparison
$b = P \leqslant 0.01$ for within-group univariate regional comparison
$c = P \leqslant 0.005$ for within-group univariate regional comparison
$d = P \leqslant 0.001$ for within-group univariate regional comparison
$\star = P \leqslant 0.05$ for within-group univariate regional comparison.

(e) Symbols — Regional laterality index

(f) CPT - X — Regional laterality index

(g) CPT - AX — Regional laterality index

(h) Auditory discrimination — Regional laterality index

(i) Auditory control task — Regional laterality index

(j) Semantic classification — Regional laterality index

(k) Line orientation — Regional laterality index
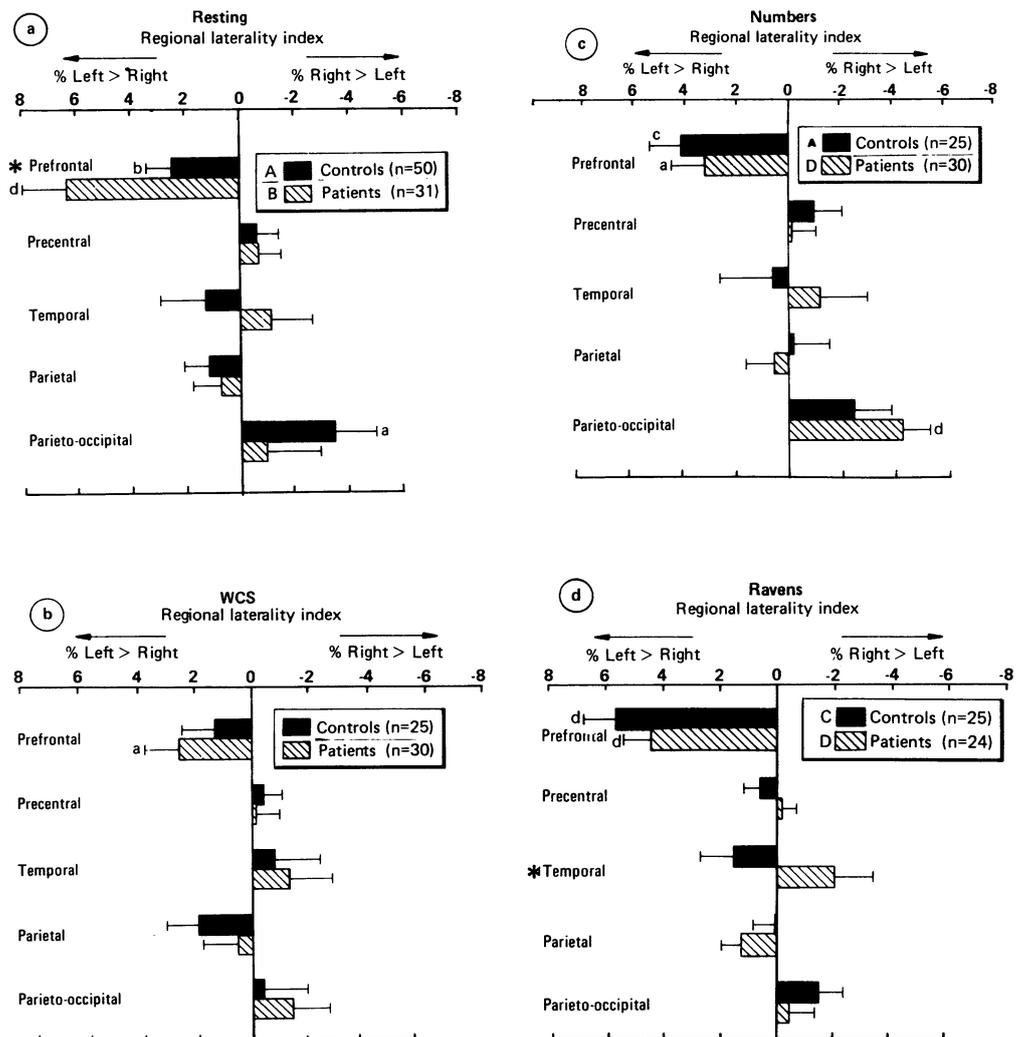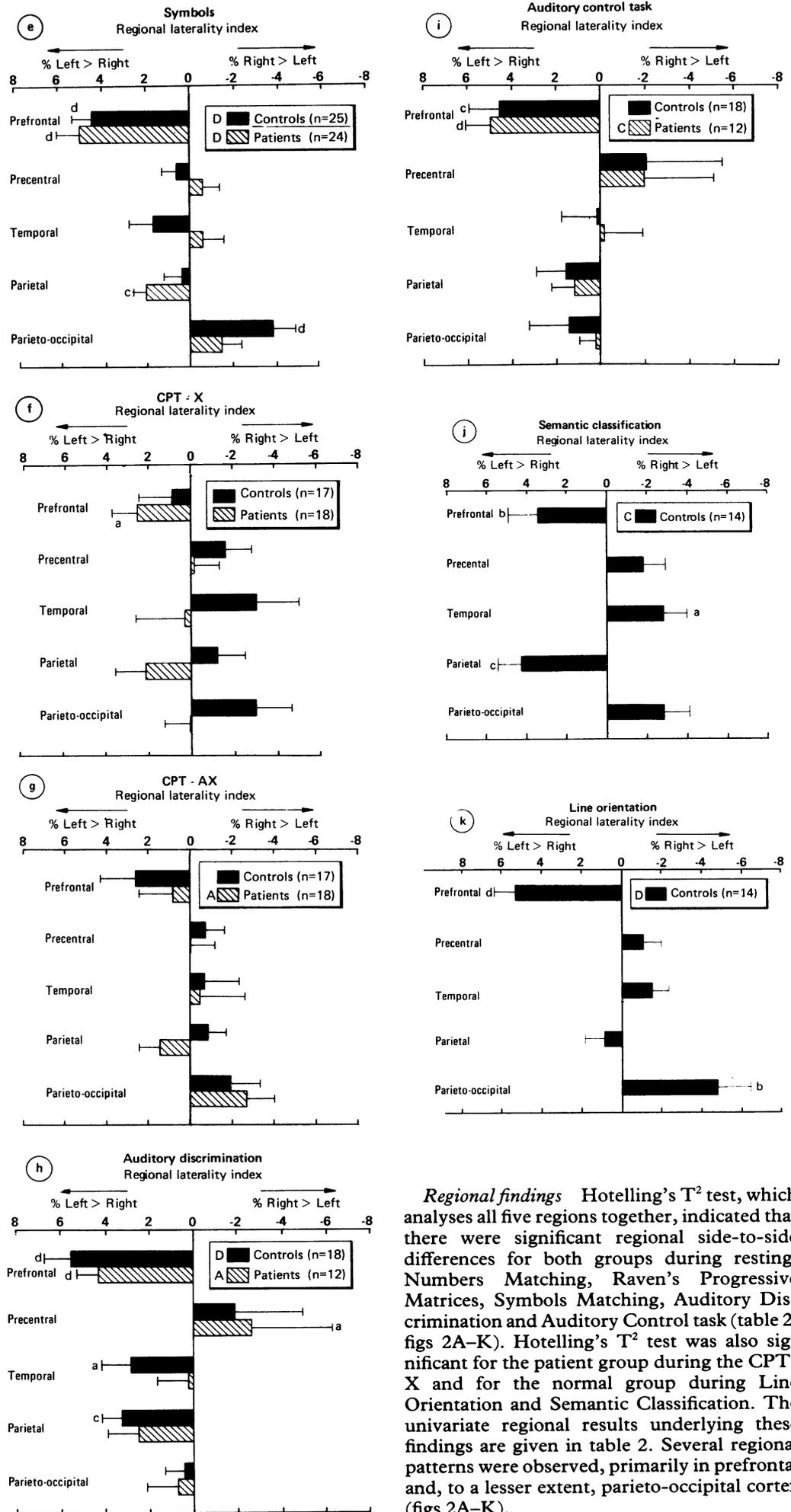
Regional findings Hotelling's T^2 test, which analyses all five regions together, indicated that there were significant regional side-to-side differences for both groups during resting, Numbers Matching, Raven's Progressive Matrices, Symbols Matching, Auditory Discrimination and Auditory Control task (table 2, figs 2A–K). Hotelling's T^2 test was also significant for the patient group during the CPT-X and for the normal group during Line Orientation and Semantic Classification. The univariate regional results underlying these findings are given in table 2. Several regional patterns were observed, primarily in prefrontal and, to a lesser extent, parieto-occipital cortex (figs 2A–K).

In all 11 conditions during which normal subjects were tested and all nine conditions during which patients with schizophrenia were tested, both groups showed relatively greater left than right prefrontal rCBF (sign test, p < 0·0001 for both groups). This relative left-right difference was highly significant for the normal control group in eight conditions (all but the WCS, CPT-X and CPT-AX), and in eight of the nine conditions (all but the CPT-AX) for the patient group.

In contrast, left-right differences for parieto-occipital rCBF were predominantly opposite in direction to those in the prefrontal region. That is, as seen in figs 2A–K, parieto-occipital rCBF tended to be greater on the right than the left in nine of 11 conditions for the control group (all but the two auditory tasks) and in six of nine conditions for the patients (all but the CPT-X and the Auditory Control task in which left and right parieto-occipital rCBF were approximately equal and the Auditory Discrimination Task in which left was slightly but not significantly greater than right).

For regions other than prefrontal and parieto-occipital, no consistent pattern was found and in only a few instances was rCBF lateralised to a significant degree. Lateralisation to the left was seen in parietal cortices of the patients during Symbols Matching, and those of normal subjects during Auditory Discrimination and Semantic Classification. Temporal cortex rCBF of normal subjects lateralised significantly to the left during Auditory Discrimination and to the right during Semantic Classification. Precentral rCBF of the patients lateralised to the right during Auditory Discrimination.

Laterality differences between patients and controls

Hemispheric findings ANOVAs performed on mean hemispheric laterality indices showed no significant between-group difference for eight of the nine conditions under which both patients and normal controls were studied (fig 1). During the CPT-X, mean hemispheric laterality differed significantly between the two groups. While patients tended to show relatively greater left hemisphere activity, controls had relatively greater mean activity in the right hemisphere.

Regional findings For each of the nine conditions, when patients were compared to normals using MANOVAs in which all five regional laterality indices were examined together, no overall difference between the groups was detected (figs 2A–K). Consistent with this observation, only one significant individual regional laterality difference between the groups was noted on univariate ANOVAs. During the resting condition, while both groups showed higher left than right prefrontal rCBF values, the degree of left prefrontal lateralisation was significantly greater in the patients (F = 4·85, p = 0·03; fig 2A). Also, during Raven's Matrices a trend toward different temporal lateralisation was

noted (F = 3·94, p = 0·053); normals showed temporal lateralisation to the left, while patients had relatively greater right temporal rCBF (fig 2D).

Discussion

Several methodological points will be addressed before discussion of the data. One technical limitation of xenon[133] inhalation rCBF measurements for studying laterality is "crosstalk." This refers to the possibility that each radiation detector detects gamma rays not only from the immediately underlying cortex, but also from brain tissue directly across the head. In other words, rCBF values measured for one side of the brain may also reflect a small part of the activity of the opposite hemisphere, thereby "washing out" some of the differences between the two hemispheres and rendering the technique less than optimally sensitive to measures of laterality. The effects of crosstalk can be minimised by arranging the detectors radially about the head,[73] as was done in this study. The degree to which crosstalk remains a limitation is unclear, but the results indicate that the sensitivity of the technique was sufficient to demonstrate a number of highly significant left-right differences within each group. Moreover, a consistent pattern of relatively greater left prefrontal and right posterior activity was found in each subject group. This suggests that, while crosstalk may have diminished the magnitude of the laterality indices, it alone cannot account for the relative paucity and inconsistency of the between-group laterality differences delineated above.

Some studies have suggested that men and women may have different cerebral lateralisation and different rCBF patterns.[10 74] Others have reported differences in left- versus right-handed persons.[10 75] In this study the relatively small numbers of women and left-handed subjects precluded their separate analysis. However, the patient and normal groups did not significantly differ in representation of women and left-handers (Fisher exact text, p > 0·1), and the normal subjects for the Line Orientation and Semantic Classification paradigms were all right-handed men. Moreover, additional analyses were performed with the women and non-right handed subjects excluded; while the results reflected the decreased statistical power imposed by the smaller sample size, the basic findings, both within and between groups did not change.

Normal lateralisation of cortical function

A large body of physiological data attests to the importance and complexity of normal lateralisation of cerebral function.[1] However, the regional topography of brain functional asymmetry in normal human subjects has been infrequently investigated by direct, noninvasive physiological observations. Early rCBF studies that delineated the normal functional landscape[76 77] were limited to measuring rCBF of one hemisphere at a time with an invasive intracarotid injection of xenon[133] dissolved in saline. For example, Ingvar and

Franzen[78] studied rCBF during RPM, as we did, but since they were only able to collect data from the dominant hemisphere, they could not examine laterality of function during this task. Roland and colleagues used the same technique to measure rCBF during stereognosis,[79] auditory and visual discrimination,[80][81] and attending to a tactile stimulus.[82] They measured both left and right hemisphere rCBF, but this was done with two separate subject groups. Thus, direct side to side statistical comparisons were not carried out.

Even when methods allowing simultaneous measurements in both hemispheres became available, relatively few investigators specifically reported on normal regional lateralisation. While a variety of activation paradigms have been studied with rCBF, many were not well controlled or standardised; the results of those that were are difficult to directly compare because of differences in the ways that various laboratories have applied the technique. Most studies in which regional data for both hemispheres are available differ in several important methodological aspects, such as different numbers and locations of detectors, a variety of derived blood flow parameters, varying testing and cognitive conditions and different approaches to data analyses.

An additional problem is that many investigators have reported rCBF activation data in comparison to a resting baseline, which is itself a poorly defined cognitive state with its own variable pattern of lateralisation. We derived hemispheric laterality indices from the published data for a number of resting state rCBF studies carried out by other investigators and found that the results obtained by different laboratories vary widely (from 5·1% to the left to 2·5% to the right), even for studies all carried out during a "resting state" (analyses available upon request). These discrepancies may reflect methodological variation and/or the poor reliability of *in vivo* rCBF and brain metabolic data derived during the resting state.[83] Attempts to systematically delineate a regional topography of functional lateralisation have been severely limited by these factors.

This paper reports the results of 11 different testing conditions carried out in the same laboratory by the same investigators and delineates what appears to be a predominant regional topography of cortical functional laterality. We found that under most conditions, left prefrontal cortical activity exceeds that of right prefrontal cortex. Parieto-occipital cortex, at least during non-auditory tasks, has an opposite pattern—that is, greater right than left activity. It is interesting that these physiological asymmetries contrast with anatomical asymmetries that have been demonstrated at postmortem examination and with CT. In those anatomical studies, frontal lobe has been shown to be longer and wider on the right, while the occipital lobe is longer and wider on the left.[1][5][84]

One explanation for the physiological asymmetries observed in the present studies may be the primacy of left anterior areas in speech and language functions, whether vocalised or internal, and the involvement of right posterior areas in attentional and visuo-spatial processes. Our demonstration of right parieto-occipital predominance during visual tasks agrees with the PET study of Kushner *et al*[85] which showed that, during visual stimulation, local cerebral metabolic rates were higher in the right lateral occipital cortex than in the left, regardless of whether the left or right visual hemifield was stimulated. Examination of fig 1 shows that relatively greater mean activity in the whole right hemisphere was seen in normal individuals only during the two tasks that predominantly test attention and vigilance, the CPTs. This observation supports the hypothesis that attentional processes may normally be preferentially mediated by the right hemisphere.[86–88]

In contrast, during the task that involves auditory discrimination of speech sounds and the two tasks that involve complex reasoning (RPM and WCS), the left hemisphere predominated. One clue to the meaning of this latter observation may be offered by the proposal of many investigators that inner speech and thought are related.[89] It is possible that while reasoning out the complex, abstract problems posed by RPM and the WCS, subjects may "talk to themselves" (subvocalise). Interestingly, Villardita[90] showed that aphasic patients had the poorest performance on RPM and emphasised "the importance of internal verbalisation processes for a correct choice . . . ." An alternative possibility is that solving these problems involves verbal/analytic cognitive processing that preferentially activates the left hemisphere.

The CPTs, on the other hand, are not complex tasks, and subjects may not subvocalise during them or use analytic cognitive processes. Indeed, many individuals experience the performance of these tasks as being almost automatic and unconscious. The CPT stimuli are presented at a much faster rate than are the stimuli for the other cognitive tasks employed, perhaps precluding inner speech and/or verbal/analytical cognition. The rapid pace and the need for close attention may favour the right hemisphere. It is interesting that the other five conditions that tended to be left lateralised, the Symbols Matching task, the Auditory Control task, Semantic Classification (itself a verbal task), the Numbers Matching task and the resting state, were not only nondemanding in terms of attention and reasoning, but may have afforded time and opportunity for contemplation, and perhaps analytical thinking if not inner speech. Of the 11 tasks, the Line Orientation task, which is classically associated with right hemisphere function, provoked the greatest degree of right parieto-occipital activation, though left and right mean hemispheric rCBF values were nearly equal.

These data also have implications for the interpretation of *in vivo* cerebral physiological imaging data. The details of what a subject is doing mentally during an rCBF procedure affect the results, at least in terms of laterality pattern. If he or she is primarily focusing attention or thinking in verbal terms, even if

the experimental condition itself requires neither, the rCBF pattern may vary to reflect this difference in mental behaviour. The degree to which such "state" variance in rCBF might obscure more important "trait" findings in pathological conditions requires further study.

Lateralisation of cortical function in schizophrenia

We did not find consistent rCBF laterality differences between patients free from medication with schizophrenia and normal control subjects. Moreover, when conservative multivariate statistical analysis was applied, there were no significant overall laterality differences between the groups; only with a liberal statistical approach (that is, multiple univariate between-group region-by-region comparisons) did any laterality difference emerge. Thus, these data do not lend strong support to the notion of a unitary disorder of cerebral lateralisation underlying schizophrenia. However, the results do not rule out that some subgroup of (or some patients with) schizophrenia may have dysfunction of one hemisphere or the other under some conditions. In fact, several isolated group differences were found in the present studies.

First, during the CPT-X attentional task mean hemispheric rCBF was higher on the right in normal subjects and higher on the left in patients. This may be viewed as consistent with the findings of Gur et al[40 41] which were interpreted as left hemisphere overactivation. However, since the *normal* response to the CPT-X was shown to involve right hemisphere preponderance, an equally plausible interpretation, that these data represent right hemisphere underactivation in the patients, may also be inferred. Interestingly, attentional deficits or neglect are noted to occur following right-sided lesions of both cortical and subcortical origin[91 92] and, as previously discussed, a role for the right hemisphere in mediating attention has been proposed.[86 87] Thus, one possible explanation for (or consequence of) the failure of the patients to activate right hemisphere preferentially during this attentional task may be that they were paying less attention than the control group. Our data suggest a pathophysiological correlate of the attentional deficits commonly seen in schizophrenia[93–95] and their poor performance on this vigilance test.[52]

A second lateralisation difference between the two groups was noted during the resting condition. During rest, patients showed significantly more left lateralisation of prefrontal rCBF than normal subjects. These data, like the CPT-X results mentioned above, may be viewed as "left overactivation" on the part of the patients, but are just as consistent with right underactivation. Also, since the resting condition has been shown to be particularly difficult to control and standardise between and even within subjects, these findings might reflect physiological concomitants of different subjective states experienced by the two groups. Perhaps the patients talked to them-

selves more during the procedure, thereby increasing activity in left hemisphere speech areas. Thus, whether this finding has primary bearing on the illness itself or whether it may be epiphenomenological, remains to be ascertained.

Finally, the third group difference noted was of borderline significance and was opposite in direction to those discussed above. During Raven's Progressive Matrices normal subjects showed lateralisation to the left in temporal cortex, while patients showed greater right temporal rCBF. This result differs from that of Gur et al[40 41] and emphasises the importance of cognitive state in laterality measurements.

In summary, the diversity of the current findings parallels the lack of consensus in the literature regarding disordered lateralisation in schizophrenia. It also highlights the state-dependency of functional laterality. Whether lateralisation is relatively to the right or left, and whether patients and normal subjects differ, depends on what they are doing during the examination and on what brain region one examines. We did not find a consistent disorder of cerebral lateralisation in schizophrenia, and the several individual group differences that did emerge were not restricted to one hemisphere or the other or to a single brain area. Furthermore, the direction of the difference varied depending upon the cognitive condition and the brain region examined. These data indicate that state variables and testing conditions must be carefully considered and controlled in studies of lateralisation of brain function.

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