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Structural brain abnormalities in male schizophrenics reflect fronto-temporal dissociation

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ABSTRACT

Background. Many studies have separately reported abnormalities of frontal and temporal lobe structures in schizophrenia, but little is known of structural fronto-temporal associations in this condition. We investigated whether male patients with chronic schizophrenia would show abnormal patterns of correlation between regional brain volumes.

Methods. Structural magnetic resonance images of the brain in 42 patients were compared with 43 matched unaffected controls. We explored the pattern of association between regional brain volumes by correlational analyses, and non-parametrically tested for significance of between-group differences by randomization.

Results. The schizophrenics demonstrated significant volume deficits in several brain regions (left temporal lobe and hippocampus, right dorsolateral prefrontal cortex), and significant volume increases in the ventricular system (third ventricle and left temporal horn of the lateral ventricle). Controls demonstrated large positive correlations ($r > 0{\cdot}4$) between prefrontal and temporal lobe regions. By contrast, inter-regional correlations significantly reduced in schizophrenics included those between prefrontal, anterior cingulate and temporal regions, and between posterior cingulate and hippocampus ($P < 0{\cdot}05$). The most salient abnormality in patients was a dissociation between prefrontal and superior temporal gyrus volumes ($P < 0{\cdot}01$).

Conclusions. These results support the existence of a relative 'fronto-temporal dissociation' in schizophrenia which we suggest may be due to lack of mutually trophic influences during frontal and temporal lobe development.

INTRODUCTION

Since the demonstration by Johnstone *et al.* (1976) that lateral ventricular size was increased in schizophrenics *in vivo*, studies have demonstrated consistent abnormalities of ventricular, frontal and temporal lobe volumes in schizophrenia (Woodruff, 1995). However, little is known about the overall pattern of regional structural abnormalities found in brains of schizophrenics. The aim of the present study was, therefore, to compare anatomical associations between brain regions in schizophrenics and controls.

Frontal and temporal lobe regions in schizophrenia

MRI studies have demonstrated frontal lobe abnormalities in schizophrenia (Andreasen *et al.* 1986, 1990; Breier *et al.* 1992; Zipursky *et al.* 1992; Seidman *et al.* 1994), consistent with post mortem studies (Benes *et al.* 1991; Akbarian *et al.* 1993*a*, *b*). Similar abnormalities of the temporal lobes and the hippocampi have been reported in schizophrenic patients compared with healthy controls (Woodruff, 1995).

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Associations between frontal and temporal structures

Primate and human post mortem studies demonstrate extensive connections between frontal and temporal lobe structures. These connections include those between the dorso-lateral prefrontal cortex (DLPFC) and the superior temporal gyrus (STG) (Seltzer & Pandya, 1989), and between hippocampus and parahippocampal gyrus both directly and via the anterior cingulate (Selemon & Goldman-Rakic, 1988; Vogt & Pandya, 1987). Structural connections imply a functional association. For instance, the DLPFC and STG activate concurrently during a verbal working memory task (Petrides *et al.* 1993). Loss of fronto-temporal functional association in schizophrenia (Frith *et al.* 1995) it has been argued, may reflect abnormal physical connections between frontal and temporal lobe structures (McGuire & Frith, 1996). Similarly, it has been argued that positive associations between volumetric measures of brain regions supports a functional relationship between them (Schlaepfer *et al.* 1994). An exploratory analysis of brain scans from a series of studies that included males and females revealed disruption of the association between different brain regions in schizophrenia (Tien *et al.* 1996). Although it is possible that some of these findings might have been confounded by gender differences in brain morphology, these results suggest that further exploration of the inter-relationship between brain structures in schizophrenia is warranted. We used brain measures on a group of male schizophrenics to test the hypothesis that there would be a dissociation between volumes of frontal and temporal lobe structures in a group of male schizophrenics.

METHOD

Subjects and assessment

Patients were recruited from the Camberwell Psychosis Follow-up Study (van Os *et al.* 1994). All right-handed males with $\leqslant 1$ left-handed item on the Annett scale (Annett, 1970) and who fulfilled DSM-III-R (APA, 1987) criteria for schizophrenia were contacted, of whom 42 consented to undergo MRI scanning and interview. Exclusion criteria (in addition to those in general for having MRI scans) included: age > 55 years, alcohol intake > 50 units/week in the past year, having taken illicit injectable drugs or steroids in the past year, a history of documented unconsciousness or neurosurgery. Duration of illness was taken from the time in months from the date of first in-patient admission to date of scanning. The National Adult Reading Test (NART) (Nelson, 1982) was used as an approximate measure of pre-morbid IQ. Controls, recruited from a local unemployment agency and local staff, were similarly screened and assessed.

Scanning

(*a*) *Image acquisition*

A 1.5 Tesla Philips Gyroscan scanner was used to obtain three T-1 weighted spin-echo sequences: (1) sagittal 5 mm-thick scans orientated exactly midline with aid of plan scans realigned in coronal and transverse planes (TR = 235 ms, TE = 20 ms, FOV = 240 mm, 4 signal averages); and (2) coronal scans, aligned perpendicular to the anterior–posterior commissure (ac–pc) line, they included (*i*) 3 mm-thick contiguous slices through the temporal lobe along the length of the corpus callosum (TR = 550 ms, TE = 20 ms, FOV = 220 mm, 4 signal averages) and (*ii*) 5 mm-thick contiguous slices through the entire brain (TR = 600 ms, TE = 20 ms, FOV = 220 mm, 2 signal averages).

The hardware and software of the scanner was upgraded before completion of the study after acquisition of images from 29 patients and 33 controls. This altered the grey scale intensity range of the scans. A two-way ANOVA used to examine interactions between 'group' and 'upgrade' revealed an effect on left hippocampal volume only ($F = 4{\cdot}3$; $P = 0{\cdot}04$). Mean pre-upgrade left hippocampal volumes were 1·76 cm^3 S.D. 0·26 for controls, and 1·66 cm^3 S.D. 0·29 for patients ($P = 0{\cdot}15$, t test). Mean post-upgrade left hippocampal volumes were 2·19 cm^3 S.D. 0·51 for controls and 1·75 cm^3 S.D. 0·36 for patients ($P = 0{\cdot}03$, t test). The composition of each group pre- and post-upgrade was equivalent in proportion of cases to controls (pre-: 29:33, post-: 13:10, $\chi^2 = 0{\cdot}63$, $P = 0{\cdot}43$, df = 1); and mean age (pre-31·0, S.D. 7·8, post-31·9, S.D. 5·7, $P = 0{\cdot}61$, t test).

(*b*) *Measurement of cerebral structures*

Images were transferred onto optical disc (by

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M.G.) to be analysed on a SPARC X workstation (SUN Microsystems Europe Inc.) using ANALYZE software (BRU, Mayo Foundation, MN, USA; Robb & Barrillot, 1989). Information that identified the subject and date of scanning was removed and replaced by a randomly generated code number. Scans with obvious motion artefact were excluded.

Establishing a CSF threshold

We used a method similar to that described by Howard *et al.* (1994). The cerebrospinal fluid (CSF) threshold was determined on each subject using the coronal slice at the level of the anterior commissure thus ensuring the maximal depth of CSF in the lateral ventricle. A rectangle was drawn to include ventricle and brain so a bimodal distribution of grey scale values was obtained. The point of rarity between the modes (usually midpoint between them) was taken as the grey scale CSF threshold.

Pixels of grey scale intensity less than this threshold were counted as CSF, and those of greater intensity were included as brain. Such thresholds were used in estimating CSF and structures containing CSF, e.g. whole brain, frontal and temporal lobe and ventricular volumes. Temporal lobe, hippocampus and parahippocampus measures were performed on 3 mm thick coronal slices; 5 mm thick coronal slices were used to obtain volumes of all other brain regions including that of the whole brain.

Definitions of brain regions

(1) Whole brain and CSF volumes were measured within a region defined by the inner skull border superiorly and laterally. In all slices except those most anteriorly and posteriorly (where the inner skull formed the inferior border), the inferior extent of brain was taken from the lower borders of the temporal lobes, across the quadrigeminal fossa and around the pons where it was contiguous with the cerebrum. Volumes of brainstem discontiguous with the cerebral hemispheres and the entire cerebellum were excluded.

(2) Frontal, cerebral and CSF volumes were calculated from measurement of these on all 5 mm thick coronal slices anterior to the genu of the corpus callosum.

(3) The boundaries of the DLPFC were defined on the second slice posterior to the genu of the corpus callosum by a wedge-shaped region delineated by the superior frontal and lateral sulci to include the middle and inferior frontal gyri. The superior and inferior borders of the DLPFC were defined by those of the wedge as it was moved anteriorly. Measurements were performed from one slice posterior to the anterior genu of the corpus callosum to the frontal pole.

(4) Ventrolateral prefrontal cortex included the frontal operculum and Broca's area on the left. The second and third slices posterior to the genu of the corpus callosum were used to measure the inferior frontal gyrus (within the borders of inferior frontal sulcus superiorly and inferior lateral sulcus inferiorly). The medial border was defined by a straight line drawn from the depth of the grey matter at the depth of the sulci.

(5) Anterior cingulate was measured around the gyral margins in three consecutive slices. The most anterior slice was at the level of the genu of the corpus callosum.

(6) Posterior cingulate was similarly defined anterior to the slice containing the splenium of the corpus callosum.

(7) Temporal lobes were measured from the anterior poles to the most posterior extent of the splenium of the corpus callosum. A border was traced from the depth of grey matter at the base of the lateral sulcus (Sylvian fissure) around the lobe to the supero-medial point medial to the hippocampus.

(8) The anterior extent of the hippocampi was immediately posterior to the amygdala where the hippocampal sulcus becomes visible and the cortico-spinal/bulbar tracts overlap the pons. The posterior limit was just anterior to the point where the inferior horn of the lateral ventricle joins the ventricular body where the aqueduct is clearly visible. Other boundaries included white matter laterally, CSF medially and the hippocampal sulcus superiorly.

(9) The parahippocampus was measured in the same slices as the hippocampus. The medial border was formed by the parahippocampal gyrus to the lip of the collateral sulcus. A line drawn between this point and the infero-lateral extent of the hippocampus formed the lateral margin.

(10) The STG was measured along the extent of the temporal lobe superior to the middle temporal gyrus bounded medially by the circular

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sulcus and laterally by the superior temporal sulcus, excluding the transverse temporal gyrus on the middle slices where this was visible.

(11) Lateral ventricles were measured on all slices where visible with a distinct border along the length of the brain. They were divided into right and left by the midline.

(12) Temporal horns were measured along those slices where the hippocampus was visible and where CSF was contained within the brain substance but separated from the bodies of the lateral ventricles.

(13) The posterior border of the third ventricle was defined as the slice on which the superior colliculi first fuse with the cerebrum, and the anterior border where the lower portion of the ventricle opens into CSF of the outer brain surface. The ventricle was bounded laterally by the thalamus, and superiorly by the crus of the fornix and the medial processes of the dorsomedial nucleus of the thalamus.

(14) The fourth ventricle was measured on the slice where it opened out below the cerebral aquaduct within the brainstem.

A maximum of five scans per brain region were excluded because of movement artefact, varying scanner resolution within the same scan, or insufficient coverage of the brain. Intra-rater reliabilities for CSF threshold were calculated on a sample of 15 patient and control brains (intra-class correlation coefficient $> 0{\cdot}9$). Inter-rater reliabilities for measurements of individual brain regions were calculated for right and left separately on at least nine representative slices from large structures (whole brain, temporal lobes and STG) or all slices within the regional volume of smaller structures on 5–10 different subjects. Intra-class correlation coefficients exceeded 0·89 for all regions except right and left parahippocampal gyri where intra-class correlation coefficients were 0·83 and 0·80 respectively.

Statistical analysis

A multiple regression model included cerebral volume as an independent variable to determine group differences whilst correcting for brain volume. Standardized effect sizes (adjusted for brain volume) of differences for each regional volume between patients and controls were calculated from the difference in adjusted means divided by the residual standard error (Rosenthal, 1984). Other group differences were measured using chi-squared and *t* tests as indicated in the results.

Correlation coefficients between each possible pair of ROIs were computed separately for controls and schizophrenics. The significance of between-group differences in each of these inter-regional correlations was assessed non-parametrically by randomization. To test the null hypothesis that observed group differences could have arisen by chance, we randomly reassigned each individual's set of regional measures to one or other of the two groups, recomputed the correlation matrix for each randomized group, and obtained the difference between randomized groups for each correlation coefficient. This procedure was repeated 200 times to sample the null distribution for the between-group difference in each correlation coefficient, and the 2·5 and 97·5 percentile elements of each distribution were used as critical values for two-tailed tests of the null hypothesis with probability of type I error $\leqslant 0{\cdot}05$.

RESULTS

Forty-two right-handed males were scanned from a total of 81 eligible schizophrenic patients, of whom 25 refused to be scanned and 14 were left- or mixed-handed.

Demographic data

The patient and control group were well matched for paternal social class (Table 1) and ethnicity ($\chi^2 = 2{\cdot}2$, df $= 1$, $P = 0{\cdot}14$). Schizophrenics were

Table 1. *Ethnic and paternal social class characteristics of the study population*

	Controls ($N = 43$)		Cases ($N = 42$)	
	N	%	*N*	%
Ethnic group				
Caucasian	33	76·7	26	61·9
Afro-Caribbean	10	23·3	16	38·1
Paternal social class*				
1, Professional	12	27·9	13	30·9
2, Intermediate	6	13·9	5	11·9
3, Skilled manual	8	18·6	6	14·3
4, Semi-skilled manual	12	27·9	8	19·0
5, Unskilled	4	9·3	8	19·0
Unknown†	1	2·3	2	4·8

* Registrar General's Classification.
† Subjects had never met and knew nothing about father.

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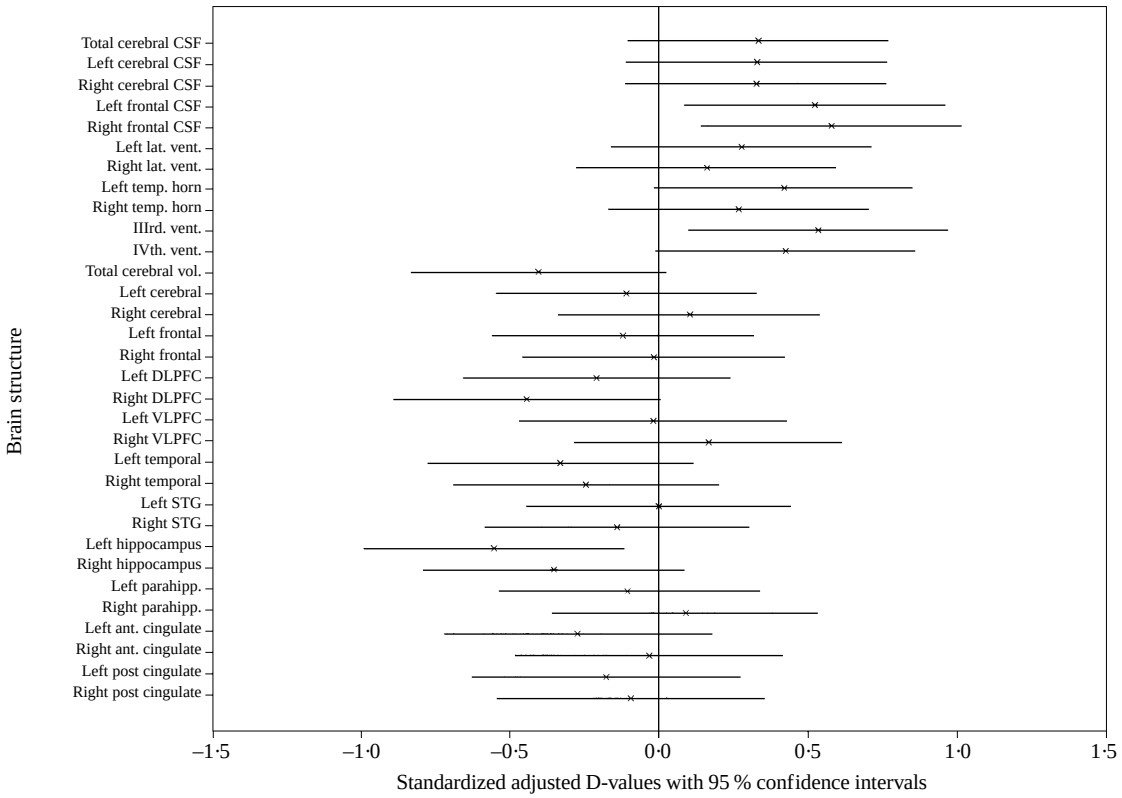


FIG. 1. Effect sizes adjusted for cerebral volume of differences in regional brain volumes between schizophrenics and controls. Standardized adjusted D-values with 95% confidence intervals are shown for each regional volume.

slightly older (32·4, S.D. 7·1 *v.* 30·2, S.D. 7·4; $P = 0{\cdot}17$, *t* test), had less years of education (12·7, S.D. 2·8 *v.* 14·9, S.D. 3·1; $P = 0{\cdot}001$, *t* test) and poorer NART scores (105·1, S.D. 10·2 *v.* 113·8, S.D. 7·9; $P < 0{\cdot}001$) than controls. Mean weekly alcohol intake was marginally less in patients than controls (8·3, S.D. 15·3 *v.* 8·8, S.D. 9·1; $P = 0{\cdot}85$, *t* test). Mean illness duration was 11·1, S.D. 7·5 (range 2–36) years.

Volumetric measures

In the schizophrenic group, there was a trend for total cerebral volume to be smaller (1110 cm^3 S.D. 98 *v.* 1154 cm^3 S.D. 62·4, $P = 0{\cdot}07$, *t* test) and total cerebral CSF volume was marginally greater (178·1 cm^3, S.D. 60·6 *v.* 161·5 cm^3 S.D. 47·6; $P = 0{\cdot}17$, *t* test) than in controls.

In a multiple regression model with cerebral volume as the dependent variable and case, age, alcohol consumption, paternal social class (1 or 2 *v.* 3, 4 or 5) and ethnicity as independent variables, the only statistically significant effect on cerebral volume was age ($B = -3{\cdot}6$, S.D. 1·7, $P = 0{\cdot}04$). The effect of age on cerebral volume was significant for controls ($B = -6{\cdot}8$, S.D. 2·5, $P = 0{\cdot}01$) but not for patients ($B = 0{\cdot}34$, S.D. 2·5, $P = 0{\cdot}89$). In contrast, the effect of age on cerebral CSF volume was significant for patients ($B = 4{\cdot}2$, S.D. 1·2, $P = 0{\cdot}002$), but not for controls ($B = -0{\cdot}49$, S.D. 0·99, $P = 0{\cdot}62$). When the effect of age was controlled for in the multiple regression model, the difference in total cerebral volume between patients and controls was not statistically significant ($B = 39{\cdot}0$, S.D. 24·0, $P = 0{\cdot}11$), neither was the difference in total cerebral CSF ($B = 13{\cdot}5$, S.D. 11·8, $P = 0{\cdot}26$).

Differences between schizophrenics and controls included: enlargement of third ventricular volume (0·80 cm^3 S.D. 0·48, *v.* 0·61 cm^3 S.D. 0·24; $P = 0{\cdot}02$, *t* test) and smaller left hippocampal volume (1·77 cm^3 S.D. 0·31, *v.* 1·86 cm^3 S.D. 0·37; $P = 0{\cdot}03$, *t* test), smaller right DLPFC (45·2 cm^3 S.D. 8·6, *v.* 51·2 cm^3 S.D. 10·4;

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	Frontal lobe	DLPFC	VLPFC	Temporal lobe	STG	Parahippo-campus	Hippo-campus	Posterior cingulate	Anterior cingulate
Frontal lobe		0·63	0·58[2]	0·29	0·01[1]	0·37	0·01	−0·04	0·04
DLPFC	0·70		0·70[2]	0·29[1]	0·11	0·26	0·19	0·14	−0·01
VLPFC	0·12[2]	0·30[2]		0·19	0·18	0·28	−0·04	0·24	0·11
Temporal lobe	0·48	0·61[1]	0·34		0·64	0·33[1]	0·29	−0·29[1]	0·1[1]
STG	0·54[1]	0·45	0·17	0·74		0·18	0·24	−0·14	−0·12
Parahippo-campus	0·31	0·50	0·45	0·64[1]	0·41		0·35	0·04	−0·39[1]
Hippocampus	0·38	0·41	−0·08	0·11	0·07	0·22		0·08[1]	−0·04
Posterior cingulate	0·19	0·19	0·10	0·02	0·07	0·12	0·47[1]		−0·06
Anterior cingulate	0·19	0·33[1]	0·19	0·47[1]	0·22	0·13[1]	−0·01	−0·22	

[1]Indicates ***less*** association between these regions in patients than controls $P < 0{\cdot}05$ (shaded grey).
[2]Indicates ***more*** association between these regions in patients than controls $P < 0{\cdot}05$.

FIG. 2. Correlation coefficients between brain regions (shown along left margin and top) for controls (lower left triangle) and schizophrenic patients (upper right triangle). Correlation coefficients with a superscript[1] within the grey shaded boxes indicate a less positive association between regions in patients than controls ($P < 0{\cdot}05$). Correlation coefficients with a superscript[2] indicate a more positive association between regions in patients than controls.

$P = 0{\cdot}006$, t test) and smaller temporal lobe volumes (statistically significantly smaller on the left, 73·8 cm^3 S.D. 9·5, *v.* 78·6 S.D. 10·3; $P = 0{\cdot}025$). Corrected effect-sizes of the differences in regional brain volumes between patients and controls are shown in Fig. 1.

Within the schizophrenic group, there was no significant correlation between the left hippocampus, left temporal horn, third or fourth ventricle or right DLPFC, or total frontal lobe CSF, with length of illness.

Correlations between brain structures

Volumetric measurements on nine regions of interest (ROIs) were available for 38 controls and 36 schizophrenics. Substantial positive correlations ($r > 0{\cdot}4$) were found in controls between bilaterally averaged regional measurements in frontal (e.g. DLPFC) and temporal lobes (STG, parahippocampal gyrus and hippocampus) (Fig. 2). There were also large positive correlations between: anterior cingulate, temporal lobes and DLPFC, as well as between posterior cingulate and hippocampus.

In schizophrenics, correlation coefficients between frontal and temporal lobe ROIs were all $< 0{\cdot}4$, while those between the DLPFC and VLPFC were substantially greater than in controls ($r > 0{\cdot}5$). The correlations between anterior cingulate and temporal lobe and between posterior cingulate and hippocampus were

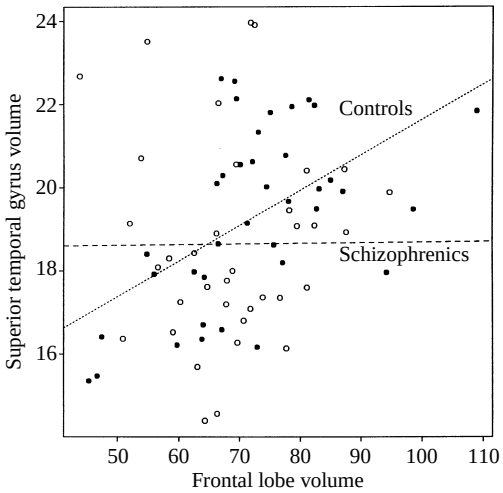


FIG. 3. Scatterplot of superior temporal gyrus (STG) volume against frontal lobe volume (in cm^3) with regression lines for controls (●) and schizophrenics (○) separately. Mean frontal lobe volume for controls was 72·02 ± 13·39 cm^3 and for patients, 68·73 ± 11·28 cm^3. Mean STG volume for controls was 19·29 ± 2·13 cm^3 and for patients, 18·65 ± 2·43 cm^3.

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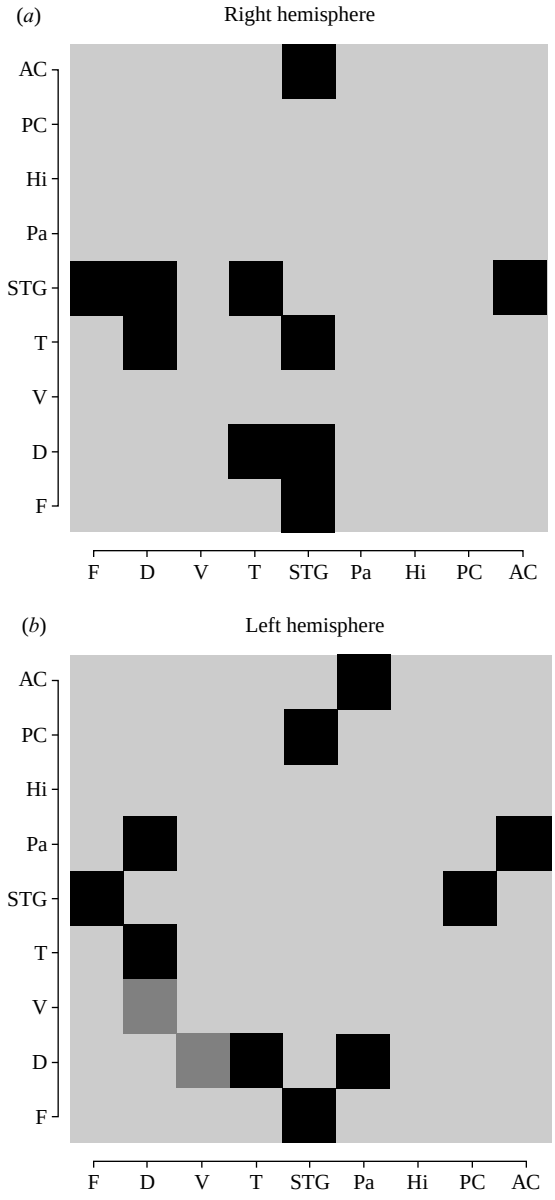


FIG. 4. Plot of brain regions: AC = anterior cingulate; PC = posterior cingulate; Hi = hippocampus; Pa = parahippocampus; STG = superior temporal gyrus; T = temporal lobe; V = ventrolateral prefrontal cortex; D = dorsolateral prefrontal cortex; F = frontal lobe. Black boxes represent brain regions which are significantly more correlated in controls than patients ($P < 0{\cdot}05$); grey boxes represent brain regions which are significantly less correlated in controls than patients.

$\leqslant 0{\cdot}1$. There was less association ($P < 0{\cdot}05$) in schizophrenics than controls between the following structures: frontal lobes and STG, DLPFC and temporal lobes, DLPFC and anterior cingulate, temporal lobes and parahippocampal gyri, temporal lobes and anterior cingulate, parahippocampal gyri and anterior cingulate, hippocampi and posterior cingulate. There was greater association ($P < 0{\cdot}05$) in schizophrenics than controls between VLPFC and DLPFC volumes. Scatter plots of STG volume against frontal volume demonstrated similar variance between these measures in patients and controls (Fig. 3).

Identical but separate analyses of the right and left hemispheric data revealed significantly reduced fronto-temporal correlations in schizophrenics compared with controls in both hemispheres. In the left hemisphere there was also significantly reduced fronto-hippocampal and temporo-parahippocampal correlations in the schizophrenic group (Fig. 4*a* and *b*).

Asymmetries

The normal asymmetries $(200 \times (\text{right} - \text{left})/(\text{right} + \text{left})$ of all brain regions were preserved in the schizophrenics. There was a marginally significant difference between controls and cases in asymmetry of the temporal horns (45·4 S.D. 64·9 *v.* 18·5 S.D. 57·3; $P = 0{\cdot}05$, *t* test). There was a relative increase in left temporal horn volume in patients although the right remained larger in absolute volume than the left in both groups.

DISCUSSION

Regional dissociation of brain regions in schizophrenia

The main difference between patients and controls was the loss of association, in schizophrenics, between frontal and temporal regions in accordance with the main hypothesis, i.e. DLPFC and STG, hippocampus and parahippocampus. In addition, associations between STG and anterior cingulate, and hippocampus and posterior cingulate were less in schizophrenics. These regions constitute parts of the cortico-limbic circuit proposed by Papez (1937), concerned with the integration of internal and external sensory systems (Maclean, 1992). Using different regional definitions from ours, Wible *et al.* (1995) showed left-sided correlations between hippocampal–amygdala complex, parahippocampal gyrus and pre-frontal grey and white

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matter volume in both schizophrenics and controls. They did not specifically look for differences between groups.

The most robust dissociation was between STG and frontal lobe, neither of which individually differed significantly in mean size between the schizophrenics and controls. It is possible that the significant difference in fronto-temporal correlation between groups reflects dissociation in their mutual development. This could be because the trophic effects of axonal connections are deficient, or because some other mutually trophic influence is lacking (Caviness & Takahashi, 1995; Ferrer *et al*. 1995; Herrup & Busser, 1995; Sable & Yeh, 1995). Alternatively, a dissociation between frontal and temporal brain regions could reflect disruption of programmed synaptic pruning (Keshavan *et al*. 1994). It could also be argued that the correlation between two brain regions will be reduced if one region alone is abnormal, without there being any specific impairment of the connections between regions. However, such a single abnormality would have to reduce substantially the covariance (or correlation) between them; and there is no evidence from our data of reduced variance of frontal or temporal lobar regions in the schizophrenics compared with the controls. The weakly positive correlations between the anterior cingulate and parahippocampus in controls makes it difficult to interpret the strongly negative correlation between these structures in patients as evidence for 'dissociation' between them. This may be a chance finding. Alternatively it is possible that the negative relationship only emerges in schizophrenia as other more distant connections fail to develop.

Methodological considerations

The size of brain structures and their relative asymmetry differs between males and females (Nasrallah *et al*. 1990; Gur *et al*. 1991, 1994; Harvey *et al*. 1993; Filipek *et al*. 1994); handedness also influences the volume of certain brain regions (Kertesz *et al*. 1986). Since the inclusion of females and left-handers in our study would have reduced the power for detecting group differences, we chose to study right-handed males only. The groups were well matched for paternal social class, ethnicity and alcohol history. Matching on age was acceptable, and age differences in adults aged less than 40 years are unlikely to affect brain volume significantly. In any case, age was controlled for in the relevant analyses. Lower NART scores and fewer years of education in the patient group may be a consequence of the pre-morbid cognitive deficits intrinsic to the condition (Jones *et al*. 1994) or subsequent cognitive deterioration (Crawford *et al*. 1992).

We intended to cover the whole brain and smaller structures like the hippocampus with sufficiently thin slices to minimize partial volume artefact. In so doing, we were unable to perform sequences for grey/white matter demarcation within the time that patients could tolerate being in the scanner. However, good contrast between brain and CSF was achieved. We attempted to minimize any bias in results due to scanner upgrade by ensuring that composition and age of subject groups was the same pre- and post-upgrade. Although the scanner upgrade *per se* did not affect the direction of group differences in brain measures, it may have increased the sensitivity for detecting group differences in volume of small structures like the hippocampus.

Using a Bonferroni correction to determine the significance of group differences in correlations between anatomic structures we considered too stringent because of non-independence of each ROI, confirmed by correlations between them.

Cerebral size

The trend for total intracerebral volume to be smaller in schizophrenics is consistent with a number of studies (see Woodruff & Murray, 1994). Age was a factor in determining this difference. The lack of significant association between cerebral reduction and advancing age in schizophrenics suggest the possibility that cerebral ageing (in addition to early maturation) may be abnormal.

Frontal and temporal lobe structures

The data demonstrate that DLPFC volume is particularly reduced in schizophrenics, there being a reduction in right DLPFC (but not VLPFC) volume in patients compared with that in controls. This effect bordered on statistical significance after correction for whole brain size. No significant difference was demonstrated between groups in cingulate gyrus volumes in

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the only other study to report this measurement using MRI in schizophrenics (Noga *et al.* 1995).

Both temporal lobe and hippocampal volumes were reduced in schizophrenics compared with controls (statistically significant only on the left) in line with the majority of previous structural studies. Left hippocampal volume reduction remained statistically significant after correction for cerebral volume, suggestive of localized pathology. However, the similar trend of hippocampal volume reduction on the right side may have become statistically significant with larger numbers of subjects. These left-sided findings may therefore be part of a more generalized brain abnormality.

CONCLUSION

It is possible that the lack, in schizophrenics, of the structural correlations found in controls between frontal and temporal regions reflects a dissociation in their normal parallel development. This dissociation could be due to loss of reciprocal trophic support of normally connected brain regions.

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