The Relationship Between Volumetric Brain Changes and Cognitive Function: A Family Study on Schizophrenia

Timothea Toulopoulou, Anton Grech, Robin G. Morris, Katja Schulze, Colm McDonald, Ben Chapple, Sophia Rabe-Hesketh, and Robin M. Murray

Background: We examined the cerebral correlates of intelligence, memory, and executive processing in 56 patients with schizophrenia or schizoaffective disorder and 90 of their nonpsychotic relatives to establish whether the pattern of structure–function relationships in these two groups was different from that in 55 control subjects.

Methods: Magnetic resonance imaging data were acquired, and volumetric measurements were made for whole brain, prefrontal region, lateral ventricles, third ventricle, temporal lobes, hippocampus, and cerebellum.

Results: In the total sample, full intelligence quotient (IQ) and verbal IQ correlated with the volume of the whole brain and right hippocampus; the latter was also associated with performance IQ. Left hippocampal size was associated with verbal IQ and, in control subjects and nonpsychotic relatives only, with estimated full IQ. Delayed verbal memory was linked to cerebellar and inversely to left hippocampal volume. Discrepancies in the relationship pattern emerged in patients with schizophrenia between left hippocampus and measures of IQ and verbal memory.

Conclusions: The latter data indicate a loss of a normal structure–function relationship in schizophrenia and might reflect a functional compensation occurring secondary to early neurodevelopmental impairment.

Key Words: Cognition, executive processing, intelligence, intelligence quotient, magnetic resonance imaging, memory

The presence of structural brain abnormalities and neuropsychological impairments is well established in schizophrenia (Davidson and Heinrichs 2003; Heinrichs and Zakzanis 1998; Wright et al 2000), and these abnormalities have been found to a lesser extent in the first-degree relatives of patients with schizophrenia (Baare et al 2001; Cannon et al 2000; Lawrie et al 1999; Staal et al 2000a, 2000b; Touloupolou et al 2003a, 2003b). What is less firmly established is whether the pattern of correlations between brain structure and function in patients also deviates from normal. A number of studies have attempted to identify the structural abnormalities that mediate the functional deficits in patients (Allen et al 2001; Bilder et al 1995; Sanfilipo et al 2002). For example, Sanfilipo et al (2002) found a different set of structural–functional relationships in patients with schizophrenia compared with control subjects, especially for the prefrontal and hippocampal regions, whereas Bilder et al (1995) found that reductions in anterior hippocampal formation were associated with worse performances on tasks thought to be sensitive to the integrity of the frontal lobe systems.

Few studies, however, have examined such relationships in the relatives of patients with schizophrenia (Goldberg et al 1994; O’Driscoll et al 2001; Seidman et al 2002). Of these, the study by Seidman et al (2002) focused on total cerebrum and hippocampus, and that of O’Driscoll et al (2001) focused on amygdala and hippocampus; Goldberg et al (1994) examined hippocampal volumes and ventricular size. All three studies found associations between verbal memory and measures of hippocampus; Driscoll et al also reported that decreased volume of the amygdala was associated with poorer performance.

We recently found (McDonald et al 2002) that both patients with schizophrenia and their relatives display enlargements of the lateral and third ventricles and, in the case of relatives, these increases are proportional to the likelihood of carrying genes for schizophrenia. In other words, a subsample of the nonpsychotic relatives who seem to transmit genetic risk to their affected children (presumed obligate carriers) were more likely than the other unaffected relatives to show the same brain abnormalities as the probands. We also reported (Touloupolou et al 2003a) that schizophrenic patients and their relatives show a selective deficit in verbal memory, implying that such impairment constitutes a familial, probably genetic, risk factor for schizophrenia.

In this article, we relate cognitive deficits to the underlying neuropathology of schizophrenia, as measured by magnetic resonance imaging (MRI), in a large sample of patients and their relatives and examine whether the pattern of function–structure relationships in these two groups differs from that of control subjects. We examine performance on tasks assessing intelligence, memory, and executive processing in relation to the volumetric measures pertinent to these processes, including whole-brain volume, prefrontal cortex, temporal lobes, hippocampi, ventricles, and cerebellum.

Methods and Materials

Subjects

The study was approved by the local research ethics committee, and all participants gave written informed consent. Participants were drawn from a larger cohort of the Maudsley Family Study (Frangou et al 1997a, 1997b; Griffiths et al 1998). The subjects who took part in the neuropsychological (Touloupolou et al 2003a, 2003b) and MRI components of the study (McDonald et al 2002; Schulze et al 2005) are included in the present report. A total of 201 of the 251 subjects who participated in the
Neuropsychological component of the Maudsley Family Study agreed and were suitable to undergo an MRI brain scan. Subjects were suitable for an MRI scan if they had no contraindication (e.g., metal fragments from previous injury) and could tolerate the confined space for the duration of the procedure without significant head movement. Fifty-six were patients (17 female, 39 male) with schizophrenia (n = 51) or schizoaffective disorder (n = 5); 90 were nonpsychotic relatives (56 female, 34 male), of whom 52 were parents, 31 siblings, 4 adult offspring, and 3 second-degree relatives (2 aunts and 1 uncle); and 55 were normal control subjects (28 female, 27 male). The second-degree relatives were nonpsychotic relatives of second-degree to the proband, who had themselves first-degree relatives who suffered from schizophrenia but who did not participate in the neuropsychological component of the study. Fourteen of the patients included in this study had relatives who did not agree or who had a contraindication to undergoing a brain scan. The number of members that contributed in each family were as follows: 1 family had 9 members, 3 families had 6 members, 3 families had 5 members, 9 families has 4 members, 10 families had 3 members, 12 families had 2 members, and 14 families had 1 member contributing to this particular part of the study.

Every individual included in this report underwent an MRI scan and completed at least some neurocognitive tests, if not all. In particular, 19 of the 201 individuals did not contribute to every single cognitive test; this was mainly because the assessment had to be discontinued owing to the tiredness experienced by the participant. The missing data on cognitive tests are totally random and are not systematic in any way. Families were referred from clinics and voluntary organizations across the United Kingdom. Control subjects were ascertained from a pool of research participants obtained for previous studies conducted at the Institute of Psychiatry, from members of staff at the Bethlem and Maudsley Hospital Trust, and through advertisements in the local press. A more detailed description of the sample can be found elsewhere (Toulopoulou et al 2003a, 2003b).

All the patients met DSM-IV criteria for schizophrenia (American Psychiatric Association 1994) and were receiving antipsychotic medication at the time of the assessment. Among the nonpsychotic relatives, five individuals had had a single episode of major depression, five had had recurrent depressive disorder, and one bulimia nervosa. These were lifetime diagnoses, and none of the relatives was unwell at the time of testing. Two of the control subjects had also a lifetime diagnosis of major depression. All participants had English as their primary language.

Exclusion criteria for all participants were head trauma resulting in loss of consciousness, substance or alcohol dependence in the 12 months before assessment, organic brain disorder, English not the primary language, and intelligence quotient (IQ) of less than 80. An additional exclusion criterion for relatives only was the presence of psychosis that did not meet DSM-IV criteria for schizophrenia or schizoaffective disorder. To be eligible for the study, control subjects had to be free of personal or family history of psychotic illness.

Neuropsychological Assessments

The neuropsychological battery has been described in detail previously (Toulopoulou et al 2003a, 2003b). Briefly, modality-specific immediate and delayed recall was investigated with the Logical Memory and Visual Reproduction tests of the Wechsler Memory Scale (WMS; Wechsler and Stone 1945). The Associate Learning subtest of the WMS was used to assess verbal learning. Current general intellectual function was assessed with the block design, object assembly, vocabulary, comprehension, and similarities subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981). Executive functioning was measured by administering tests of 1) spatial working memory and strategy formation, assessed with Executive Golf (Morris et al 1988; Owen et al 1990), a computerized procedure that involves searching around a set of specific locations on a computer screen and subsequently remembering not to return to successful positions; and 2) planning ability, measured with the three-dimensional, computerized Tower of London (Morris et al 1995, 1998), which requires the subject to reproduce a target arrangement in a specified number of moves.

MRI Data Acquisition and Analysis

Magnetic resonance imaging data were acquired with a GE 1.5-Tesla scanner (General Electric Medical Systems, Milwaukee, Wisconsin) over a 4-year period. A set of 1.5-mm-thick, contiguous coronal MRI images extending through the entire brain were obtained with a three-dimensional spoiled gradient echo sequence, according to the following protocol: echo time (TE) = 5 msec, repetition time (TR) = 35 msec, number of excitations = 1, field of view = 20 cm, acquisition matrix 256 × 256, and flip angle 35°. or a shorter one but with the same resolution: TE = 3.7 msec, TR = 14.7 msec, number of excitations = 1, field of view = 20 cm, acquisition matrix 256 × 256, and flip angle 20°. All subjects, irrespective of whether they were patients, relatives, or control subjects, were scanned interchangeably over the same period.

Images were analyzed with MEASURE software (version 0.8, Johns Hopkins University, Baltimore, Maryland), an image-analysis program that uses stereologically unbiased estimation of volume (Barta et al 1997; Frangou et al 1997b). Briefly, a grid is applied over the whole brain, and grid points falling into the structure of interest are manually marked, taking into consideration all three orthogonal views. The MEASURE program calculates the volume of a structure by multiplying the number of marked grid points by the volume of an elementary cuboid. Before any measurements, head tilt was corrected by aligning each brain along the anterior–posterior commissure axis in the sagittal plane and along the interhemispheric fissure in the coronal and axial planes. All images were coded and rated blind to group affiliation.

Volumetric measurements were obtained for whole-brain volume, prefrontal region, lateral ventricles, third ventricle, left/right (L/R) temporal lobes (this measurement included the hippocampus), L/R hippocampi, and cerebellum. The boundaries, grid settings, and reliability estimates for each structure have been described in detail previously (McDonald et al 2002; Schulze et al 2003; Sharma et al 1998). Briefly, we followed the criteria used by Delisi et al (1991) for measurement of regional brain volumes. The third ventricle was bounded by the anterior commissure, the fornix, the stria medullaris, the pineal body, the superior and inferior colliculi, the midbrain and mamillary body, the thalamus, and the hypothalamus. The hippocampus, in the coronal plane, was measured from the first slice in which the mamillary bodies were present until the first slice in which the fornix was clearly visible. The inferior boundary was the white matter of the parahippocampal gyrus and the superior boundary. The prefrontal region was defined from the frontal pole to the section rostral to the rostrum of the corpus callosum. All inter- and intrarater reliability estimates were high, ranging from .86 to .99.

The MRI and neuropsychological evaluations were done for
the vast majority of the subjects on the same day. If that was not possible, the MRI and neuropsychological assessments were done within a few days or at most a few weeks of each other.

Data Analysis

The results of the volumetric analyses and the neuropsychological performance in a sample that substantially overlaps with the present one have already been published (McDonnell et al 2002; Touloukian et al 2003a, 2003b). However, here we re-ran the analyses to include this particular group of research participants. Standard linear regression analyses were used with the volume of each of the structures or a neuropsychological measure as the dependent variable. The regression models included the predictors age, gender, and group (dummy variables for patients and relatives) to obtain estimates of differences in group means after adjusting for age and gender. Because many of the observations both within and between groups were of individuals within families and thus not independent from each other, we performed regression analyses for clustered observations, using a robust estimator for the variances of the regression coefficient estimates, as implemented in the STATA software program (version 8.0; Stata Corporation, College Station, Texas). All tests were two-tailed and used a .01 level of significance.

Partial Correlations Assessing the Relationship Between Structure and Function

All distributions of residuals were tested for deviations from normality and, when appropriate, the dependent variable was transformed according to the transformation method that was suitable in each case for achieving normalization of the residuals. The residuals of the visual reproduction, Tower of London, and Executive Golf tasks were not normally distributed and were transformed with either log or square root transformations. After the transformations, a regression analysis was used in the combined sample, with each neuropsychological score as the dependent variable and brain region, group membership, height, gender, and age as the predictors. Height was used as the independent variable to control for head size because it is a good predictor of general head size (Andreasen et al 1994) and is independent of any disease-specific processes. Because age and gender can have an effect on neuropsychological performance and brain volume, age and gender were included in the model to control for the effects of these factors on the relationship between cognition and brain volumes. To examine whether there were any group differences in the relationship between brain structure and performance in neuropsychological tests, an interaction term was also included in the regression model. The regression analyses were mostly used 1) to examine whether there were any significant interaction effects; and 2) to obtain the partial correlations. Because it would have been inefficient to perform significantly worse on immediate recall of verbal memory (B = −1.3, 95% CI = −2.70, .05, p = .06) and strategy formation (B = .7, 95% CI = .04, 1.4, p = .04).

Additional analyses examining how the partial correlations change when whole-brain volume, handedness, verbal memory, and IQ are controlled for were also performed on some of the observed significant partial correlations. We know, for example, that performance in specific tasks, such as memory and executive function, is related to general intellectual level and that the size of hippocampus is related to whole-brain volume. Similarly, because visual stimuli can be encoded in a verbal format, performance in tests assessing visual memory can be influenced by the ability to recall verbal information. Furthermore, we know that handedness, an index of hemispheric dominance, can have an effect in the conventional left–verbal, right–visual relationships. We examined, therefore, how the partial correlations change when these factors are controlled for in those correlations between structure and function that turned out to be significant. Inferences were based on robust standard errors for clustered data (the sandwich estimator; see, e.g., Williams 2000), to take into account of the clustering of individuals in families. Because the data analysis involved multiple statistical comparisons that inevitably increased the probability of falsely declaring nonsignificant differences significant, significance is reported at the 1% level; however, as always, owing to the large number of tests, caution should be exercised when interpreting the results. All partial correlation analyses were conducted with the STATA program (version 7.0).

Results

Demographic and Clinical Characteristics

The demographic characteristics of the sample are shown in Table 1.

Brain Volumetric Measures and Neuropsychological Performance in Patients and Relatives Compared with Control Subjects

As anticipated, overall results were similar to those we reported previously, based on a sample that substantially overlapped with the present one. In terms of the MRI, patients displayed enlargement of the third ventricle (B = .20, 95% confidence interval [CI] = .04, .37, p = .01) and showed nonsignificant trends for reductions in the left temporal lobes (B = −2.7, 95% CI = −7.65, .25, p = .06) and left hippocampi (B = −.09, 95% CI = −2.0, .01, p = .08). Regarding neuropsychological performance, patients performed worse than control subjects on all measures considered, including estimated full IQ (B = −16.0, 95% CI = −22.48, −9.62, p < .0001), verbal IQ (B = −15.8, 95% CI = −21.8, −9.75, p < .0001), performance IQ (B = −13.4, 95% CI = −20.7, −6.172, p < .0001), immediate and delayed recall of verbal memory (immediate recall: B = −4.5, 95% CI = −5.99, −3.10, p < .0001; delayed recall: B = −4.5, 95% CI = −5.98, −2.98, p < .0001), immediate and delayed recall of visual memory (immediate recall: B = −3.03, 95% CI = −4.35, −1.7, p < .0001; delayed recall: B = −3.3, 95% CI = −4.7, −1.94, p < .0001), associate learning (B = −3.90, 95% CI = −5.38, −2.43, p < .0001), planning (B = −0.65, 95% CI = −0.25, 1.05, p = .002), spatial working memory (B = 2.5, 95% CI = 1.4, 3.6, p < .0001), and strategy (B = 1.7, 95% CI = .97, 2.3, p < .0001). Relatives performed significantly worse on immediate recall of verbal memory (B = −1.7, 95% CI = −3.01, −.4, p = .01) and showed a nonsignificant trend for delayed recall of verbal memory (B = −1.3, 95% CI = −2.70, .05, p = .06) and strategy formation (B = 0.7, 95% CI = .04, 1.4, p = .04).

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Correlations with IQ

In the total sample, estimated full-scale IQ and verbal IQ correlated with whole-brain volume (full-scale IQ r = .28, p = .005; verbal IQ r = .28, p = .004) and right hippocampal volume (full-scale IQ r = .31, p = .001; verbal IQ r = .26, p = .008). The latter was also associated with performance IQ (r = .28, p = .005). Further analyses of the specific measures of IQ contributing to the correlation with the right hippocampus showed that three of the five measures used to estimate current IQ were correlated with the right hippocampus (block design: r = .25, p = .01; object assembly: r = .26, p = .007; comprehension: r = .29, p = .003; similarities: r = .23, p = .02; vocabulary: r = .22, p = .02).

Correlations with Verbal and Visual Memory

Delayed recall of verbal memory was linked to the cerebellum (r = .25, p = .01) and inversely to the left hippocampus (r = −.22, p = .006). Further analyses suggested that the latter correlation might be due to the effect of patients only (patients: r = −.22, p = .02; relatives: r = −.14, p = .17; control subjects: r = −.15, p = .14). Immediate and delayed recall of visual memory was associated in relatives only with left hippocampal volume (immediate recall: r = .25, p = .009; delayed recall: r = .35, p < .001) and the cerebellum (immediate recall: r = .25, p = .01).

Left hippocampal size was associated with verbal IQ (r = .26, p = .005) and, in control subjects and relatives only, with the estimated full-scale IQ (control subjects: r = .35, p < .001; relatives: r = .36, p < .001). All measures used to calculate verbal IQ contributed to the association between verbal IQ and left hippocampal volume (similarities: r = .29, p = .003; comprehension: r = .28, p = .004; vocabulary: r = .26, p = .009). The nonpsychotic relatives also showed an association between left hippocampal volume and performance IQ (r = .37, p < .001), with both WAIS-R subtests, which contributed to the performance IQ, showing a correlation with the left hippocampus (block design: r = .45, p < .0001; object assembly: r = .29, p = .004).

Table 2. Age, Gender-, Group Membership-, and Height-Adjusted Partial Correlations with Robust Standard Errors and p Values Between MRI and Neuropsychological Measures in the Combined Sample

<table>
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<tr>
<th>FIQ</th>
<th>VIQ</th>
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| Values are partial correlations (r), p values. MRI, magnetic resonance imaging; FIQ, VIQ, PIQ, estimated full-scale intelligence quotient (IQ), verbal IQ, and performance IQ, respectively; LMi, logical memory, immediate recall; LMd, logical memory, delayed recall; VRI, visual reproduction, immediate recall; VRd, visual reproduction, delayed recall; AL, associate learning; TLacc, Tower of London, accuracy (number of moves); EGe, Executive Golf, between-search errors; EGs, Executive Golf, strategy. 

Table 3 for partial correlations and p values per group.

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that we selected to derive the IQ scores correlated with hippocampal volume, hence confirming its involvement in several cognitive processes. Consistent with this, Bedwell et al (1999) found an association between decreases in hippocampal volumes and a smaller increment in the information raw score of the WAIS among adolescents with childhood-onset schizophrenia; this could reflect an inability to acquire new knowledge.

In addition, we found an association between delayed recall of verbal memory and the volume of the cerebellum, adding to reports that the cerebellum acts as a modulator of cognitive function (Allin et al 2001; Cabeza et al 2002; Desmond 2001; Justus and Ivry 2001). It has been implicated in the pathophysiology of several psychiatric disorders, including schizophrenia (Andreasen et al 1998; Rapoport 2001), though MRI data are inconsistent. We did not find cerebellar volume changes in our patients (McDonald et al 2002), nor did we find a differential relationship between cerebellum and memory in the schizophrenia sample relative to the other two groups.

Consistent with reports on neurosurgical patients with either frontal lobe or temporal lobe excisions or patients who had undergone amygdalo-hippocampectomy (Owen et al 1996), we found an association between the number of errors made in the spatial working memory task and the size of the right temporal lobes, with smaller temporal volumes predicting more errors. The Executive Golf task involves searching through a set of specific locations and remembering not to return to successful positions. Thus, it provides a measure of on-line processing of spatial information and explores the extent to which implementation of strategic algorithms facilitates task performance. To explore the extent to which strategy impairment might have contributed to the correlation between spatial working memory and temporal lobes, we repeated the analyses with the strategy scores as the covariate in the analyses. The results suggested a loss of strength and of statistical significance in the correlation, consistent with previous reports that other regions might be more important in mediating strategy generation.

Discussion
Structure–Function Relationships Observed in the Combined Sample
Our results support previous studies in showing a relationship between brain volume and intelligence in healthy individuals (Andreasen et al 1993; Posthuma et al 2002; Tan et al 1999; Wickett et al 2000) and extend the finding to schizophrenic patients and their healthy relatives. We found a small but significant relationship between estimated full-scale and verbal IQ with whole-brain volume, suggesting, as noted previously (Andreasen et al 1993), that although brain size is not everything, it does nonetheless explain some of the variance in IQ. Our study shows that this is true not only for healthy individuals but also for people who suffer from schizophrenia.

We also found, as did Andreasen et al (1993), a relationship between IQ and the hippocampus. All measures of IQ, including estimated full-scale, performance, and verbal IQ, correlated with the right hippocampal volume. In addition, verbal IQ was also associated with left hippocampal volume. Most of the subtests that we selected to derive the IQ scores correlated with hippocampal volume, hence confirming its involvement in several cognitive processes. Consistent with this, Bedwell et al (1999) found an association between decreases in hippocampal volumes and a smaller increment in the information raw score of the WAIS among adolescents with childhood-onset schizophrenia; this could reflect an inability to acquire new knowledge.

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Differential Structure–Function Relationships in Patients with Schizophrenia
Although the relationship between structure and function is similar in many measures for patients and control subjects, there are instances in which patients with schizophrenia seem to differ from the norm. Consistently, we found correlations between left hippocampal volume and estimated full-scale IQ and performance IQ in relatives and control subjects (control subjects showed a trend with the performance IQ) but not in the patient group. This suggests a dissociation in schizophrenia between left hippocampus and the subtests that were used to estimate IQ.

Delayed recall of verbal memory was also correlated, but

Table 3. Age-, Gender-, and Height-Adjusted Partial Correlations with Robust Standard Errors and p Values Between MRI and Neuropsychological Measures per Group when the Relationship Between Brain Volume and Neuropsychological Measure Differs Significantly Between the Three Groups

<table>
<thead>
<tr>
<th>Structure</th>
<th>FIQ</th>
<th>PIQ</th>
<th>VRI</th>
<th>VRd</th>
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<tr>
<td>Left Hippocampus</td>
<td>(.36, &lt;.001 \text{ REL})</td>
<td>(.37, &lt;.001 \text{ REL})</td>
<td>(.25, .009 \text{ REL})</td>
<td>(.35, &lt;.001 \text{ REL})</td>
<td>(-.22, .02 \text{ REL})</td>
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<td>Right Hippocampus</td>
<td>(.35, &lt;.001 \text{ CON})</td>
<td>(.35, &lt;.001 \text{ CON})</td>
<td>(.25, .009 \text{ REL})</td>
<td>(.35, &lt;.001 \text{ REL})</td>
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<td>Lateral Ventricles</td>
<td>(.25, .01 \text{ REL})</td>
<td>(.26, .008 \text{ SCH})</td>
<td>(.25, .009 \text{ REL})</td>
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Values are partial correlations (r), p values. MRI, magnetic resonance imaging; FIQ, PIQ, estimated full-scale intelligence quotient (IQ) and performance IQ, respectively; VRI, visual reproduction, immediate recall; VRd, visual reproduction, delayed recall; EGe, Executive Golf, between-search errors; REL, relatives; SCH, schizophrenic patients; CON, control subjects.
Difference in measures of IQ and verbal memory. These latter discrepancies between patients with schizophrenia between left hippocampus and cerebellum. These correlations are nullified between visual memory (immediate and delayed recall) and left hippocampal volume, and memory function. For example, we have previously reported (Schulze et al 2003) hippocampal volume reductions in a sample overlapping with this patient group that was linked to obstetric complications. It is possible that, owing to the plasticity of the developing brain, these reductions have had a knock-on effect on the organization and allocation of brain function. In general, findings of a relationship between hippocampal volume and memory in schizophrenia are inconsistent, with most studies failing to show a positive relationship (Weiss and Heckers 2001), some of those that do find such a relationship use more refined measures that discriminate between anterior and posterior hippocampus (Goldberg et al 1994; O'Driscoll et al 2001). It is possible, therefore, that if we had separated anterior and posterior hippocampus, we might have found a different pattern of relationships.

Between-search errors also correlated in the patient group only with lateral ventricular size. Loss of a normal structure-function relationship, as seems to be the case in at least this sample of schizophrenic patients, might indicate compensatory mechanisms whereby certain areas are recruited to subserve functions normally associated with a specific brain region. This could have occurred, as indicated above, as a result of an early brain insult and would be compatible with a wide range of evidence suggesting a neurodevelopmental component in the etiology of schizophrenia (Murray and Lewis 1987; Weinberger 1987). Nonetheless, age-related reallocation or shift of certain aspects of cognitive function to different brain networks, suggesting a dynamic nature of a functional change that can occur at any point throughout life, is also possible (Hazlett et al 1998). Therefore, we cannot determine with certainty, on the basis of the results of this study, when the loss of the relationship has occurred. Because the dissociation does not extend to relatives, we must presume that the changed pattern is related to the pathophysiology of schizophrenia per se.

Differential Structure–Function Relationships in the Relatives of Patients with Schizophrenia

Our results also suggest an association for the relatives only between visual memory (immediate and delayed recall) and left hippocampus and cerebellum. These correlations are nullified when intelligence and, in the case of cerebellum, intelligence and verbal memory are considered as covariates in the analyses. These results are consistent with the hypothesis that the relatives use different pathways to process visual information, perhaps reflecting a variation in encoding strategy. Such encoding strategy might involve the processing of visual information more verbally relative to the other two groups. This hypothesis could explain why the association between visual memory and cerebellum is canceled when verbal memory is used as a covariate in the analyses.

In summary, we examined the pattern of correlations between structure and function in a group of schizophrenic patients, in nonpsychotic relatives, and in control subjects and found a number of similar patterns across the three groups; however, discrepancies in the relationship pattern emerged in patients with schizophrenia between left hippocampus and measures of IQ and verbal memory. These latter discrepancies are consistent with the hypothesis of dissociation in pathologic processes underlying structural and cognitive abnormalities for at least these measures.

Financial support was given by the Stanley Medical Research Institute.


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Biol Psychiatry 2004;56:447–453

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