A comprehensive method of assessing routine CT scans in schizophrenia

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Abstract

Morphological brain abnormalities are common in schizophrenia, although the aetiological and clinical significance of these findings is largely unknown. Substantial between-subject variability suggests that large samples are needed to study the full implications of brain pathomorphology. Computerized tomography (CT) is frequently used routinely in schizophrenia, and large numbers of scans are available for study. This article describes the development and statistical properties of a rapid and simple method of assessing CT scans. The CT Rating Scale for Schizophrenia (CTRSS) is minimally affected by variability in scanning procedures, is reliable, and accurately estimates area and volumetric measures of brain spaces. By promoting the comprehensive assessment of large numbers of routinely obtained scans, the CTRSS would allow the investigation of variables that may systematically affect results (e.g. gender and age) and variables with low prevalence. The CTRSS provides a useful adjunct to technologically more sophisticated methods of assessment such as magnetic resonance imaging (MRI).

Keywords

computerized tomography; brain morphology; schizophrenia

Introduction

Morphological brain abnormalities identified using computerized tomography (CT) remain one of the most consistent findings in schizophrenia research. The higher resolution images produced by magnetic resonance imaging (MRI) have allowed the detection of more subtle abnormalities (for reviews, see 1, 2), but this technique is not widely available, requires considerable compliance from subjects, and methods of analysing scans that are complex and time-consuming. Consequently, samples tend to be small and drawn from large

population centres. Schizophrenia is an illness that displays a great deal of variability in clinical presentation and brain morphology. These sources of variability may account for the limited success in identifying the clinical significance of abnormal brain morphology in the face of robust differences found between groups of schizophrenics and control subjects. Large patient samples would provide the statistical power to overcome the substantial between-subject variability. Compared to MRI, CT has the advantages of reduced expense, rapid acquisition of images, and availability in many centres worldwide. Because of this, large numbers of scans are available. However, at the present time there is no simple, reliable and valid methodology for the analysis of routinely obtained CT images. The aim of the present study was to develop a quick, reliable method of assessing routine CT scans that obtains the maximum amount of qualitative and quantitative information about neuropathology and brain morphology in psychiatric patients. The proposed method would complement the technologically superior brain measurement from MRI.

Material and methods

Development and description of the scale

The guiding principle in developing the CT Rating Scale for Schizophrenia (CTRSS) was to provide a quick method of assessing a number of brain regions that may have potential relevance to schizophrenia. The CTRSS consists of a series of criterion images ranging from normal to grossly abnormal, and is based on the approach developed in studies of dementia (3, 4) and schizophrenia (5, 6). In order to avoid floor and ceiling effects, the criterion images against which CT scans are to be compared were developed using scans from both normal subjects and patients with schizophrenia up to 72 years of age. Using CT images at the appropriate levels (Fig. 1), scans were rank-ordered according to the size of each region to be rated. From these rank-ordered scans, four were chosen that reflected equal intervals over the range of sizes, and these were given ratings of 1, 3, 5 and 7. Five aspects of the ventricles (third ventricle, and the body, the frontal horns, trigones and temporal horns of the lateral ventricles), sulci in five cortical regions (anterior frontal, posterior frontal, Sylvian, temporal and parietal-occipital) (7–9) and two cisterns (suprasellar cistern and temporal midbrain cistern) were assessed.

Method of using the scale

- i. Each scan should be reviewed by a neuroradiologist using a standardized check-list (available from the authors on request) to aid the identification of focal findings that could influence ratings, and to note any anomalies.
- ii. The neuroradiologist should also note whether there is significant lateral head tilt.
- iii. Ratings are made with reference to template photographs, and age is *not* taken into account. Ratings of bilateral spaces are made from each hemisphere separately. All CT slices on which a region of interest is visualized are used to establish each rating, and not only the slices corresponding to those presented in the templates.

- iv. Two independent judges should make all initial ratings in order to establish inter-rater reliability, and several scans should be re-rated at regular intervals in order to check for rater drift.

Subjects

Sample 1—The first sample (see Table 1) was scanned between 1983 and 1986 as part of a study of first-episode schizophrenia (10, 11). CT scans were obtained using a Siemens Somatom DR scanner with a slice thickness of 8 mm and no contrast medium, and care was taken to prevent significant lateral head tilt. Lateral ventricles were planimetrically measured, third ventricle width was measured, and a global rating of cortical sulcal dilation was made using a three-point scale. The inter-rater reliability was high for all three measures (11). Third ventricle size was larger in patients with schizophrenia than in control subjects, but no group differences were found for the ventricle to brain ratio (VBR) or cortical rating. CTRSS ratings were made by W.G.H. and/or G.N.S., who were blind to the measurements and diagnosis.

Sample 2—The second sample (see Table 1) consisted of the first 40 scans from a large series of patients with schizophrenia who were recruited between 1986 and 1988 (12). The CT scans were obtained using a Phillips Tomoscan 300 with a slice thickness of 9 mm and no contrast medium. Head tilt was present on 12 scans. Five ventricular regions (third ventricle, and the frontal horns, body, trigones, and temporal horns of the lateral ventricles) and five cortical regions (anterior and posterior frontal lobe, parietal-occipital lobe, temporal lobe and Sylvian fissure) were measured. Each scan was enlarged four times by overhead projection, the regions of interest were outlined on paper, and these outlines were measured by planimetry. The volume of each space and also the total brain volume were computed. Blind CTRSS ratings were made by W.G.H.

Sample 3—The third sample (see Table 1) consisted of 119 patients recruited as part of an ongoing study of treatment refractory psychosis (schizophrenia, $n = 85$; schizoaffective disorder, $n=14$; bipolar disorder, $n=3$; major depression with psychotic features, $n=6$; other, $n=11$). Patients were scanned at one of six hospitals in the Greater Vancouver Area. The choice of hospital to scan patients was an administrative decision and was not based on the clinical status of the patients. Three types of scanners were used (Siemens Somatom DR, $n=66$; GE 9800, $n=50$; GE 8800, $n=3$). Scans were performed using one slice thickness throughout (8 mm, $n=18$; 10 mm, $n=4$) or one thickness from the base of the skull to the top of the posterior fossa and another thickness from this point to the vertex (8 mm and 4 mm, $n=32$; 4 mm and 8 mm, $n=14$; 5 mm and 10 mm, $n=51$). Ratings were made by G.N.S. and/or W.G.H., who were blind to the diagnosis.

Assessment of reliability and validity

Inter-rater reliability and scan-rescan reliability—Inter-rater reliability was assessed in two samples of 50 subjects using intra-class correlations (ICC) (13). In sample 1, a standardized research-scanning protocol was used, and in sample 3 scans were obtained for clinical purposes using unstandardized methods. The level of agreement for rating bilateral

spaces was assessed using both the sum of left-and right-sided ratings and the rating from the hemisphere which showed the larger space.

In order to determine the extent to which ratings differ as a result of non-specific aspects of the scanning procedures, scan-rescan reliability was assessed in 40 patients who received two CT scans separated by an interval of 1 h to 5.7 years (mean interval ($\pm$ SD)=24 $\pm$ 20 months). The first and second scans were simultaneously examined by a neuroradiologist (J.S.L.) for signs of brain changes and, in order to minimize systematic bias, only the 33 patients in whom no changes were detected were included in the analysis. The 66 scans were obtained from three different CT scanners, and the slice thickness was 8 mm for 39 scans, 10 mm for 8 scans, 5 mm and 7 mm for 8 scans, 5 mm and 10 mm for 7 scans, and 4 mm and 8 mm for 4 scans. Ten scans showed evidence of a significant head tilt. The scan-rescan reliability was assessed using Pearson correlations.

Effects of slice thickness and lateral head tilt—The effect of slice thickness on ratings was assessed using two age-matched groups of patients from sample 3 whose images were obtained from the same scanner. Slice thickness was 4 mm and 8 mm for 14 patients and 8 mm and 4 mm for 21 patients. Differences in the magnitude of ratings were assessed using *t*-tests. The effects of significant head tilt on rating size were assessed using the scans of 34 patients with no tilt and 16 patients with tilt, all from sample 3. All scans were completed on the same scanner with a slice thickness of 5 mm and 10 mm. The effect of head tilt on the size of ratings was examined using *t* tests.

Inter-method agreement—All subjects from sample 1 were used to compare ratings of the lateral ventricles with the measure of ventricular area and VBR, the rating of third ventricle size to third ventricle width, and ratings of cortical sulci to the original global three-point rating (11). The 40 subjects from sample 2 were used to compare CTRSS ratings with measures of volume from nine brain regions. The size of the bilateral spaces was assessed using the sum of left- and right-sided ratings, and the rating from the hemisphere that showed the larger space was also used to determine whether a single rating could accurately estimate the size of bilateral spaces. Pearson correlations were used to compare ratings and measurements, and linearity was assessed using scatter plots.

Sensitivity for detecting known group differences—In our earlier study (10, 11), a comparison between patients and normal control subjects failed to reveal a group difference with regard to lateral ventricle size. In order to produce a difference artificially, control subjects with the largest VBRs were sequentially removed until a significant effect was obtained. This procedure resulted in the removal of the six control subjects with the largest ventricles, and yielded a small but significant group difference ($P=0.046$). The sensitivity of CTRSS ratings for detecting group differences in lateral ventricle size, third ventricle size and cortical sulci enlargement was assessed using *t*-tests.

Results

In sample 3, the full range of values (range, 1–7) was used for all brain regions except the frontal horns (range, 1–6), and values were normally distributed for all ventricular and

cortical regions of ratings. The distribution of ratings for the suprasellar cistern (Kolmogorov-Smirnov $Z=1.4$, $P=0.04$) and temporal midbrain cistern (Kolmogorov-Smirnov $Z=1.7$, $P=0.01$) was positively skewed. Samples 1 and 2 did not include the maximum value of 7 for several regions, and this may reflect the fact that these subjects were less severely ill and, in the case of sample 1, relatively young.

Inter-rater and scan-rescan reliability

Inter-rater reliability (G.N.S., W.G.H.) was high for all ratings in the sample with a standardized scanning protocol (sample 1: mean ICC=0.91, range=0.84–0.99) and the group for whom an unstandardized clinical scan was obtained (sample 3: mean ICC=0.93, range=0.70–0.99). Three ICCs from sample 3 were below 0.85, namely the temporal midbrain cistern (ICC=0.70), and the temporal lobe sulci from the left (ICC=0.77) and right (ICC=0.82) hemisphere. The level of agreement was also high when the sum of left- and right-sided ratings was used to estimate the size of bilateral spaces (sample 1: mean ICC=0.91, range=0.86–0.93; sample 3: mean ICC=0.92, range=0.80–0.97).

Scan-rescan reliability was greater than $r=0.70$ for all brain regions except the suprasellar cistern ($r=0.59$). The correlations were strengthened when the data were reanalysed including only those patients for whom the initial and repeat scans were made using the same scanner and slice thickness.

Effect of slice thickness and lateral head tilt

Slice thickness had no significant effect on rating size for any brain region except the temporal midbrain cistern (4 mm vs. 8 mm: 3.5 vs. 2.2, $t=2.54$, $df=34$, $P=0.02$) and temporal horns (4 mm vs. 8 mm: 3.8 vs. 2.8, $t=1.95$, $df=34$, $P=0.06$). The reduced size of ratings for 8-mm vs. 4-mm slices suggests that thicker slices produce an attenuated image of spaces at the base of the brain. No significant differences were found between ratings from scans showing head tilt and those showing no tilt for any brain region.

Inter-method reliability

A strong correlation was found between the sum of the left- and right lateral ventricle ratings and both the area of the lateral ventricles (not controlling for head size, $r=0.84$) and the VBR ($r=0.88$). The sum of the combined ratings of the left- and right frontal horns, lateral ventricles and trigones correlated strongly with lateral ventricle area ($r=0.89$) and VBR ($r=0.87$). Ratings from the hemisphere with the largest space were also strongly correlated with planimetric measures (lateral ventricle rating with area, $r=0.86$ and VBR, $r=0.88$; combined ratings of frontal horns, lateral ventricles and trigones with area, $r=0.87$ and VBR, $r=0.85$). No significant association was found between brain area and any ventricle rating or combination of ratings (all $r<0.1$). The rating of third ventricle size correlated strongly with the measure of third ventricle width ($r=0.83$). The mean of the five cortical ratings correlated strongly with the global rating of cortical atrophy ($r=0.71$).

The sum of the five lateral ventricle ratings correlated strongly with total lateral ventricle volume ($r=0.88$) and with the lateral ventricle volume-to-brain ratio ($r=0.85$). Correlations between the ratings of individual ventricular regions and the volumes of those regions were

strong for the frontal horns and the lateral ventricles, but weaker for the trigones, third ventricle and temporal horns (see Table 2). This was the case whether size was estimated by summing left- and right ratings or by using the ratings from the hemisphere in which the space was larger. The sum of all cortical ratings was strongly correlated with sulcal fluid volume ($r=0.90$) and sulcal volume-to-brain ratio ($r=0.85$). Moderately strong correlations were found between ratings and sulcal volume for all cortical regions except the temporal lobe sulci (see Table 2). Correlations between sulcal volume and ratings of each region from the hemisphere in which sulci were larger were very similar to those obtained when the sum of left- and right ratings was used.

Sensitivity for detecting known group differences

In our earlier study using sample 1 (10, 11) no significant group differences were found for lateral ventricle VBR, and the same result was obtained when CTRSS ratings were used. Removal of the six control subjects with the largest ventricles produced a statistically significant group difference for the VBR (6.7 vs. 5.6, $t=2.0$, $df=67$, $P=0.046$). Significant group differences were also found between patients and this selected control sample when CTRSS ratings were used (sum of all lateral ventricle ratings: 17.4 vs. 14.4, $t=2.17$, $df=67$, $P=0.03$; sum of ratings from the hemisphere with the largest ventricle: 9.9 vs. 8.1, $t=2.22$, $df=67$, $P=0.03$). Group differences were also detected using ratings from the body of the lateral ventricles (sum of left- and right: 5.5 vs. 4.3, $t=2.34$, $df=67$, $P=0.02$; largest ventricle: 3.1 vs. 2.4, $t=2.36$, $df=67$, $P=0.02$) and the frontal horns (sum of left- and right: 5.6 vs. 4.6, $t=2.12$, $df=67$, $P=0.04$; largest: 3.2 vs. 2.7, $t=2.02$, $df=67$, $P=0.05$), but not for the trigones or temporal horns. As was the case in our earlier study using a measure of width, significant enlargement of the third ventricle was found when a rating of third ventricle size was used (4.1 vs. 3.0, $t=2.88$, $df=73$, $P=0.005$). Unlike the findings from our earlier study, significant enlargement of the cortical sulci was observed when the sum of five ratings of sulcal size was used instead of a single global rating (18.0 vs. 13.0, $t=4.50$, $df=73$, $P<0.001$). All of the individual regional cortical ratings were significantly larger in the patient sample than in the control sample ($t=2.9$ – 4.1 , $df=73$, all $P<0.01$).

Discussion

The CT Rating Scale for Schizophrenia (CTRSS) provides a method of assessing several aspects of brain morphology that is relatively simple and rapid to complete, and requires only a light-table and template scans. The CTRSS promotes the careful assessment of brain morphology and the detection of subtle anomalies (14,15). The level of inter-rater reliability was high for ratings of all 12 brain regions that were assessed. The scan-rescan reliability was high for all ventricular regions and most cortical regions, but was lower for the temporal lobe sulci and the suprasellar cistern. The reliability for both of these regions was increased when rescan reliability was computed for only those patients who had the same scanner and slice thickness for both initial and repeat scans. This suggests that ratings of basal brain regions are significantly affected by scanning procedures. Investigation of two aspects of scanning indicates that slice thickness but not head tilt affects rating size in the lower part of the brain, but not in the more dorsal regions.

The spaces in the lower part of the brain are small, and in many cases were obscured by bone artefact (beam hardening). The use of relatively thick CT slices (e.g. 8 mm or 10 mm) increases the likelihood that the suprasellar cistern, temporal midbrain cistern, temporal horns and lower aspects of the temporal lobe sulci will be missed, or that the only slice that shows them will be distorted by artefact. The volumetric measurement of these spaces was difficult. Reliable measures of the suprasellar cistern and temporal midbrain cistern could not be obtained and, in some subjects, poor visualization of the temporal horns and lower aspects of the temporal lobe sulci prevented measurement. In other cases, the process of enlarging images in order to take measurements resulted in loss of definition, and for several subjects these spaces appeared to be too small to measure. However, inspection of these scans revealed that the size of the spaces was underestimated by the volumetric measure in several cases. It appears that ratings of spaces at the base of the brain, if taken from relatively thin CT slices (e.g. 4 mm or 5 mm), are at least as accurate, and in some cases more so, than the volumetric measures. Increased slice thickness in this region of the brain is likely to increase measurement error for both ratings and volume.

The sum of the ratings from the separate parts of the lateral ventricles provided very good estimates of both an area VBR and a volumetric VBR. This was the case whether all left- and right ratings were added or all ratings from the hemisphere with the largest ventricle were added. A strong correlation was also found between rating and volume measures for each of the four parts of the lateral ventricles. The rating of third ventricle size showed a very strong association with third ventricle width and a moderately strong association with third ventricular volume. Volume and area measures, whether taken from CT or MRI images, are sensitive indices of enlarged ventricles in schizophrenia (1), and measures from CT scans are strongly correlated with those from MRI images (16). We are unaware of any study of brain morphology in schizophrenia that has used ratings to estimate ventricle size. However, CT studies of dementia suggest that ratings of ventricle size can be sensitive indices of enlargement (3) and underlying neuropathology (17). The results of the present study support these findings, and suggest that ratings made using the CTRSS are useful for detecting subtle enlargement of the lateral and third ventricles in schizophrenia.

The sum of the five cortical ratings provided a good estimate of sulcal volume. This was the case for the sum of all left- and right cortical ratings and for the sum of the ratings from the hemisphere showing the largest sulci. In addition, each region-specific rating of sulcal size showed a strong correlation with the volume measure of the same region, except for the temporal lobe rating, which showed a moderately strong correlation. As noted above, it was very difficult to measure the volume of the temporal lobe sulci, and a rating may have advantages over volume measures for some scans. Several CT studies have used ratings to estimate sulcal dilation, and most of those studies indicate significant sulcal enlargement in schizophrenia (e.g. 5, 6, 18). However, in our earlier study no group differences were found using a global three-point scale (10), whereas significant sulcal enlargement was found when region-specific seven-point ratings were used. This suggests that the CTRSS is a more sensitive index of sulcal enlargement than a global three-point rating.

Computerized tomography is widely available throughout the world, and psychosis is a clinical indication for scanning (19, 20). The analysis of this rich source of data provides a

means of studying and comparing large and culturally diverse samples of patients. With large samples, patient characteristics that may systematically affect results (e.g. gender, age and handedness) can be experimentally controlled, and variables with low prevalence can be studied. In addition, the assessment of several brain regions, either individually or in combination, promotes the investigation of patterns of morphology rather than mere changes to individual regions (21, 22). Careful assessment of routine head scans also increases the likelihood of detecting abnormalities (15) and aspects of brain morphology that may have clinical implications (14). This research strategy would be useful in the generation of hypotheses that can be tested using more precise imaging technology, such as MRI.

The assessment of CT scans by means of a rating scale also has some inherent problems, and the CTRSS is not intended as an alternative to more precise methods of measurement. Sulcal and ventricular dilation are indirect estimates of underlying reductions in tissue volume, and it is unclear from the ratings precisely which regions have undergone changes. In addition, some regions of the brain that are abnormal in schizophrenia (e.g. amygdala-hippocampus; (23)) are subject to maximum measurement error when CT scans are used. The clarity of CT images for regions at the base of the brain may be obscured by scanning artefact and by the use of relatively thick slices. With thin slices, ratings of spaces in this region can be made reliably and appear to provide acceptable estimates of the size of spaces. In addition, we have not studied the effects of some aspects of scanning that may influence the apparent size of brain spaces (e.g. angle, contrast, window). The use of relatively simple methods of measurement, such as rating scales, may increase the likelihood of false-positive and false-negative results. However, the current evaluation of the CTRSS suggests that subtle group differences can be detected.

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Fig. 1.

Brain regions that can be assessed using the CTRSS. A, temporal horns; B, suprasellar cistern; C, temporal midbrain cistern; D, sylvian fissure; E, temporal lobe sulci; F, third ventricle; G, frontal horns; H, body of the lateral ventricles; I, posterior frontal sulci; J, anterior frontal sulci; K, parietal-occipital sulci; L, posterior horns-trigones. For cortical measures, the relationship to Brodmann areas is approximately as follows: anterior frontal (lateral aspect areas 8, 9 and 44; medial aspect areas 6, 24 and 32), posterior frontal (areas 3, 4, 6 and 8), sylvian fissure (temporal aspect areas 22, 38, 41 and 44; frontal aspect areas 40, 43–45, medial aspect insula), temporal lobe (areas 22, 41 and 42), parietal-occipital (areas 7, 17–19 and 39).

Table 1

Subjects used to assess reliability and validity

		Number of subjects in each analysis										
		Age (years)		Reliability			Lateral tilt		Slice thickness ^b			
		<i>n</i>	Mean ± SD	Range	Inter-rater	Scan-rescan ^a	Inter-method	Tilt	No tilt	4/8	8/4	Group difference
Sample 1												
Schizophrenia	31	22.8 ± 5.7	15–37	31	12	—	31	—	—	—	—	31
Control	44	23.2 ± 5.6	15–42	19	—	—	44	—	—	—	—	44
Sample 2												
Schizophrenia	25	38.6 ± 9.3	21–56	—	—	—	25	—	—	—	—	—
Control	15	41.6 ± 6.4	31–49	—	—	—	15	—	—	—	—	—
Sample 3												
Total	119	33.6 ± 11.6	16–68	50	21	—	—	16	34	14	21	—

^aThe subjects from samples 1 and 3 were combined in the assessment of scan-rescan reliability.

^bThe first number reflects slice thickness (expressed in mm) in basal brain regions, and the second number indicates slice thickness (in mm) in higher regions.

Table 2

Correlations between ratings and volume measures for sample 2

Brain region	Volume		Volume to brain ratio	
	Left + right	Largest	Left + right	Largest
Frontal horns	0.81	0.82	0.82	0.81
Lateral ventricle	0.88	0.85	0.84	0.81
Trigones	0.63	0.59	0.67	0.60
Third ventricle	—	0.68	—	0.72
Sylvian fissures	0.79	0.80	0.72	0.72
Temporal lobe sulci	0.58	0.56	0.52	0.50
Posterior-frontal sulci	0.75	0.84	0.69	0.79
Anterior-frontal sulci	0.74	0.75	0.72	0.70
Parietal-occipital sulci	0.81	0.79	0.76	0.73