An MRI Study of Midbrain Morphology in Patients with Schizophrenia: Relationship to Psychosis, Neuroleptics, and Cerebellar Neural Circuitry

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Background: The midbrain contains the perikarya of all the dopamine neurons in the human brain. Although other neurochemicals may well be involved, dopamine dysregulation is central in the pathophysiology of psychosis. Despite this, few imaging studies have evaluated the morphology of the midbrain.

Methods: Using high-resolution magnetic resonance imaging, morphology of three posterior fossa and brain stem structures were measured: midbrain, pons, and medulla. The patient sample consisted of 50 men with schizophrenia, matched by gender and age to 50 healthy control subjects.

Results: Patients had significantly smaller midbrain measures compared with control subjects. There were no differences between groups in measures of pons or medulla. Furthermore, midbrain size was significantly and inversely correlated with positive symptoms and cumulative neuroleptic exposure, but not with negative or disorganized symptoms. After controlling for the effect of cumulative neuroleptic exposure, the relationship between midbrain morphology and positive symptoms remained significant.

Conclusions: Midbrain morphology of patients with schizophrenia is abnormal, being smaller in patients compared with control subjects. Although this appears to be specifically related to psychotic symptoms, there is also a robust medication effect, with greater exposure to neuroleptics being associated with greater morphologic abnormality. We discuss the role of dopaminergic dysregulation and possible neural circuit involvement.

Key Words: Schizophrenia, midbrain, mesencephalon, brain stem, magnetic resonance imaging, neuroleptics

Introduction

The mesencephalon or midbrain represents the smallest and least differentiated segment of the infratentorial brain stem. The midbrain contains the source nuclei for the three dopaminergic systems in the human brain: the nigrostriatal pathway, the mesolimbic pathway, and the mesocortical pathway. Although the “dopamine hypothesis” of pathophysiology in schizophrenia continues to be modulated and expanded, there appears to be no doubt that dopamine dysregulation plays a key role in the pathology of psychosis. Despite this fact, there is a paucity of studies that have evaluated the morphology of the midbrain, either histologically or grossly in neuroimaging studies.

In regard to histopathology, the only study to date evaluating the mesencephalon was done by Bogerts et al. (1983). On a sample of nine controls and six age-matched brains of patients with schizophrenia who lived and died before the advent of neuroleptics, the dopaminergic neurons of the nigrostriatal and mesolimbic system were evaluated. These researchers reported a significant decrease in the volume of the nigrostriatal area due to mean volume reduction of glial nuclei. In the mesolimbic system, the mean volume of the nerve cells was diminished.

Neuroimaging studies evaluating the midbrain are equally sparse. A study by Aylward et al. (1994) measured midsagittal areas of posterior fossa structures (including midbrain) in patients with schizophrenia and healthy control subjects. Although the midbrain was smaller in patients, this did not reach statistical significance; however, in a case report, a 40-year-old woman was documented to have developed a syndrome consistent with the diagnosis of schizophrenia, which was associated with a midbrain tegmental lesion (Minabe et al 1990).

The development of the midbrain is intimately involved with the development of the cerebellum, especially the vermis (Hallonet and Le Douarin 1993; Hallonet et al 1990; Urbanek et al 1997; Yachnis and Rorke 1999). The vermis of the cerebellum has been documented to be morphologically abnormal in patients with schizophrenia.
the time of their assessment were in the midst of a psychotic
episode. To obtain a maximally valid assessment of cognitive
ability, testing was done when patients were stable enough to
cooperate with testing.

At the time of assessment, 11 of the 50 individuals were
first-episode patients (defined on the basis of first psychiatric
hospitalization). Average age of onset (defined in the CASH as
age at which significant symptoms emerged) was 21 years, and
average duration of illness was 89.9 months or 7.49 years. The
“Dose Year” formula (Miller et al 1995) was used to measure
neuroleptic exposure, which was calculated as cumulative dose at
the time of scan. This requires conversion of neuroleptic medica-
tion (typical and atypical) to chlorpromazine equivalents
(Davis 1974). The older equivalents recently have been extrap-
olated to atypical neuroleptics (Herz 1997). Exposure is calcu-
lated over time, weighted for dose.

With regard to type of neuroleptics, the MRI scans used in this
analysis were obtained from 1991 to 1994. Thus, few patients
had exposure to atypical neuroleptics. We categorized patients
into four groups regarding medication exposure: 1) neuroleptic
naive, 2) almost neuroleptic naive, 3) typical antipsychotic
exposure only, and 4) typical and atypical antipsychotic expo-
sure. None of the patients had exposure to only atypical medi-
cations. Of the 50 patients, five had never received neuroleptics
or were “neuroleptic naive.” In addition, nine patients had
minimal exposure to neuroleptics (dose-year of 0.10 or less,
equivalent of less than 2 weeks on 5 mg of haloperidol per day).
All of the patients in this category (“almost neuroleptic naive”) had
typical neuroleptic exposure only. The largest group was
comprised of those with more than minimal exposure to neuro-
leptics, but exclusively typical (n = 32). Only four patients had
exposure to atypical medication. Two of these were on clozapine,
and two were taking risperidone at the time of the scan; however,
in all four of these cases, patients had been taking typical
neuroleptics before being placed on clozapine or risperidone.
In only one of the four cases was the amount of time spent on an
atypical greater than had been spent on typical antipsychotics.

The control group consisted of 50 healthy men, matched by
age and gender to the patient group. These subjects were
volunteers recruited from the community through newspaper
advertising. Each control subject was evaluated using an abbre-
viated version of the CASH. Volunteers were excluded if there
was any history of psychiatric illness, including substance abuse,
or a family history of schizophrenia. Patients and controls were
excluded if they had a lifetime history of serious head trauma,
neurologic illness, or serious medical or surgical illness.

After complete description of the study to the subjects, written
informed consent was obtained. Demographics of the two study
groups are shown in Table 1.

Our study group comprises a subset of the sample used in our
recently published report on cerebellar vermis morphology (Nop-
oulos et al 1999). Therefore, there are both brain stem and
cerebellar vermis measures available for the entire study group.

Methods and Materials
Subjects
The patient group consisted of 50 men, consecutive participants
in the University of Iowa Mental Health Clinical Research
Center (MH-CRC) protocols. Typically, these patients were
either neuroleptic naive or undergo a 3-week medication wash to
participate in neuroimaging studies. Each patient was diagnosed
as having schizophrenia using DSM-III-R criteria and based on
data obtained using the Comprehensive Assessment of Sympt-
oms and History (CASH) (Andreasen et al 1992b). Symptoms were
rated as the worst in the past month using the Scale for the
Assessment of Negative Symptoms (SANS; Andreasen 1983)
and Scale for the Assessment of Positive Symptoms (SAPS;
Andreasen 1984) within the CASH. Summary scores for three
dimensions of symptoms (positive, negative, and disorganized)
were calculated using sums of global scores from the SANS/
SAPS. The positive symptom dimension was the sum of global
scores for hallucinations and delusions. The negative symptom
dimension score was the sum of global scores for alogia,
affective flattening, avolition–apathy, and anhedonia–asociality.
The disorganized symptom dimension was comprised of the
morphology of the global scores of positive formal thought dis-
order, disorganized or bizarre behavior, and inappropriate affect.

Cognitive functioning of patients was determined by admin-
istration of a battery of neuropsychologic tests, which include
assessment of general intellectual functioning as determined by
the WAIS-R: Full Scale IQ and the subscales of the Performance
IQ and Verbal IQ. Many of the patients that were hospitalized at
the time of their assessment were in the midst of a psychotic
episode. To obtain a maximally valid assessment of cognitive
ability, testing was done when patients were stable enough to
cooperate with testing.

At the time of assessment, 11 of the 50 individuals were
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oulos et al 1999). Therefore, there are both brain stem and
cerebellar vermis measures available for the entire study group.

Acquisition and Analysis of MR
The MR scans were obtained with a T1-weighted three-dimen-
sional SPGR sequence on a 1.5 tesla GE Signa Scanner (TE = 5,
TR = 24, flip angle = 40, NEX = 2, FOV = 26, matrix =
Table 1. Patient and Control Subject Demographics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 50)</th>
<th>Controls (n = 50)</th>
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<tbody>
<tr>
<td>Age</td>
<td>28.2 (6.88)</td>
<td>28.5 (6.10)</td>
</tr>
<tr>
<td>Parental SES*</td>
<td>2.90 (0.46)</td>
<td>2.76 (0.51)</td>
</tr>
<tr>
<td>Age of onset</td>
<td>21.0 (5.58)</td>
<td></td>
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<tr>
<td>Duration of illness</td>
<td>89.9 (87.4)</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>6.59 (2.78)</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>11.6 (4.01)</td>
<td></td>
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<tr>
<td>Disorganized symptoms</td>
<td>5.81 (3.60)</td>
<td></td>
</tr>
<tr>
<td>Dose years</td>
<td>40.59 (94.69)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–524</td>
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Values are means (SDs). SES, socioeconomic status.
*Based on a modified Hollingshead scale 1–5 with the higher the number, the higher the social class.

256 × 192) using the coronal plane, yielding 124 contiguous slices, 1.5 mm thick.

Processing of the images after acquisition was done using a locally developed family of software programs called BRAINS (acronym for Brain Research: Analysis of Images, Networks, and Systems). Details of the image analysis are published elsewhere (Andreasen et al 1992a, 1993, 1994).

**BRAIN VOLUME MEASURES.** A three-dimensional data set was created, and the images were realigned and resampled at a slice thickness of 1.0 mm. At this point, a general measure of intracranial volume was obtained by totaling brain tissue and cerebrospinal fluid volumes. Regional measurements were then ascertained by transformation into Talairach Atlas space (Talairach and Tournoux 1988) in which all of the boxes were assigned to specific brain regions: frontal, temporal, parietal, and occipital lobes. In addition, we adapted the method to include boxes that defined the cerebellum as well. We have developed automated measures of subregions (lobes), which were validated by comparison to manual tracings (the gold standard) and found to be an accurate measure compared with this gold standard (Andreasen et al 1994).

**MEASUREMENT OF BRAIN STEM STRUCTURES.** As part of the initial analysis of all brains, scans were aligned along the axis of a line connecting the anterior commissure (AC) with the posterior commissure (PC). In addition, scans were aligned with respect to the interhemispheric fissure. Area measurements were obtained using a midsagittal cut. This cut was determined as the one in which the cerebral aqueduct was most clearly visualized. Tracing of the brain stem structures was, in part, adapted from guidelines used by Aylward et al (Aylward et al 1994). The superior border of the midbrain was the floor of the cerebral aqueduct. The inferior border of the midbrain was determined by placing the cursor in the anterior landmark (pontine notch) and extending a line to the posterior wall of the brain stem that was parallel to the AC–PC line. This differed slightly from the Aylward method, in which the line was drawn to approximate a line perpendicular to the axis of the brain stem. We found the method of using the AC–PC line to be more reliable. The superior and inferior colliculi were not included in the midbrain tracing. The lower boundary of the midbrain demarcated the upper limit of the pons. The lower limit of the pons was determined by a line drawn parallel to the AC–PC line extending from the inferior pontine notch to the posterior wall of the brain stem. This also demarcated the superior limit of the medulla. The lower border of the medulla was determined as a line drawn parallel to the AC–PC line along the lower limit of the foramen magnum. Reliability was established on a separate sample of 28 brains by two independent raters (J.C. and E.G.). Intraclass correlations were as follows: midbrain 0.957, pons 0.963, and medulla 0.786.

**MEASUREMENT OF CEREBELLAR VERMIS.** This method is reported in detail elsewhere (Nopoulos et al 1999). Like the brain stem measures, the cerebellar vermis was measured as an area. A midsagittal cut was defined by the slice in which the aqueduct of Sylvius was visualized most clearly. Manual traces were then made of the cerebellar vermis and its three regions. The measure of total vermis area was the sum of all three regional areas.

**Statistical Analysis**

Initial analysis consisted of a t test comparing the mean area measures of each brain stem region. Next, analysis of covariance (ANCOVA) was used to control for variations in brain size. No covariate is ideal. Because the cerebellum and brain stem are intimately related in development, total cerebellum volume was used as a covariate; however, we also ran the analysis several different times using other covariates including intracranial volume, total brain volume, and cerebral volume.

To evaluate relationships between brain stem region of interest size and clinical correlates, correlations were calculated. When the measures were normally distributed, Pearson’s correlations were done; when any of the measures in the analysis were not normally distributed, nonparametric Spearman’s correlations were used.

**Results**

Table 2 shows the results of the t tests and ANCOVA (using total cerebellar volume as a covariate) on brain stem measures. The t test analysis showed that the mean area of the midbrain in patients was significantly smaller

<table>
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<tr>
<th></th>
<th>Patients</th>
<th>Control subjects</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>t</td>
<td>p</td>
<td>F*</td>
</tr>
<tr>
<td>t</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Midbrain</td>
<td>2.38 (0.31)</td>
<td>2.52 (0.27)</td>
</tr>
<tr>
<td>Pons</td>
<td>5.58 (0.56)</td>
<td>5.69 (0.67)</td>
</tr>
<tr>
<td>Medulla</td>
<td>4.17 (0.41)</td>
<td>4.23 (0.37)</td>
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*aUsing total cerebellar volume as covariate.*
than that of control subjects ($r = 2.94, p = .003$). There was no significant difference between groups in measures of the medulla orpons. In the ANCOVA analysis, there was a main effect of diagnosis on the area of the midbrain ($F = 6.93, p = .009$). There was no effect of diagnosis on size ofpons or medulla. When the analysis was run using the other covariates (intraparenchymal volume, total brain volume, and cerebralc volume), the results remained the same with patients having significantly smaller midbrain measures, though no difference from controls in size ofpons or medulla.

Spearman’s correlations were calculated to assess the relationship between midbrain morphology and the following clinical measures: positive symptoms, negative symptoms, disorganized symptoms, Full Scale IQ, dose-years of neuroleptics and duration of illness. The results are shown in Table 3. There was a significant inverse relationship between size of midbrain and positive or psychotic symptoms ($r = -.313, p = .028$), indicating that the greater the severity of psychotic symptoms, the smaller the size of the midbrain. There were no significant correlations between the other two symptom domains (negative and disorganized) and midbrain morphology. Furthermore, there was no correlation between midbrain size and Full Scale IQ.

<table>
<thead>
<tr>
<th>Clinical Measures</th>
<th>Correlation (p)</th>
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<tr>
<td>Positive symptoms</td>
<td>$- .313 (.028)$</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>$- .161 (.267)$</td>
</tr>
<tr>
<td>Disorganized symptoms</td>
<td>$- .045 (.754)$</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>$0.211 (.149)$</td>
</tr>
<tr>
<td>Dose year</td>
<td>$- .471 (.0005)$</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>$- .200 (.163)$</td>
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</table>

To evaluate the morphologic relationship between the cerebellar vermis area and midbrain area, Pearson’s correlations were calculated. The size of the midbrain was significantly correlated to the size of the cerebellar vermis in patients ($r = .34, p = .01$); however, there was no relationship between the size of the cerebellar vermis and that of the midbrain in the control subjects ($r = .14, p = .30$).

**Discussion**

We found that the morphology of the midbrain is abnormal in the brains of patients with schizophrenia. Specifically, the size or area of the midbrain was found to be smaller than that of control subjects. These findings would corroborate those of Bogerts and colleagues (Bogerts et al 1983), who found morphometric abnormalities in the midbrain of patients with schizophrenia at a microscopic level. On the other hand, the only other study to evaluate midbrain morphology with neuromaging methods found no significant difference in the size of the midbrain compared to controls. Although the study by Aylward (Aylward et al 1994) did find the patients to have smaller midbrain areas, the finding was not statistically significant. Our study used somewhat similar methods, yet our sample of patients was larger (50 compared with 36) and more homogenous (all men compared with 69% men). Abnormal brain morphology in patients with schizophrenia has been found to be more robust in male patients in general (Nopoulos et al 1997). Therefore, a larger sample that was limited to men only may have provided the power necessary to detect significant differences between groups.

**Relationship to Neuroleptic Exposure**

Analysis of the clinical correlates of midbrain morphology indicated a robust relationship with cumulative neuroleptic exposure with larger doses of medication over time being associated with smaller midbrain area. This was not an expected finding. Nonetheless, this is not the first study to document changes in brain morphology related to medications. Our group and others have documented that subcortical structures such as the caudate and lenticular nucleus increase in size after exposure to typical neuroleptics and decrease over time after exposure to atypical neuroleptics (Chakos et al 1994; Corson et al 1999; Elkashef et al 1994; Frazier et al 1996; Keshavan et al 1994). The current findings suggest an opposite effect from what is seen for the basal ganglia. That is, of the 45 patients who had been exposed to medication, 91% (n = 41) had exposure to typical neuroleptic only, and the correlation was inverse—the greater the drug exposure, the smaller the midbrain. Because only four patients had
exposure to atypical neuroleptics, this sample is too small to address the issue of differential effects of typical versus atypical neuroleptics.

Because the majority of this sample had been exposed to medication, the question remains as to whether or the abnormal morphology reported here reflects a primary structural defect in the midbrain or purely a medication effect. Do patients with schizophrenia who are neuroleptic naive have abnormal midbrain morphology? The majority of the current patient sample had been exposed to medications; however, in an attempt to address this question, we collapsed the neuroleptic naive group with the “almost” neuroleptic naive group (very minimal neuroleptic exposure) to comprise a sample of 14 subjects. A three (group) \( \times 1 \) (midbrain) ANCOVA was performed using total cerebellar volume as covariate. Adjusted means of midbrain area were as follows: neuroleptic naive group \( (n = 14) = 2.58 \); medicated group \( (n = 36) = 2.29 \); control subjects \( (n = 50) = 2.52 \). Post hoc \( t \) tests on these adjusted means showed that the neuroleptic naive group had significantly larger midbrain areas compared with the medicated group \( (t = 3.46, p = .000) \) but did not differ from control subjects. Though only a small sample, this suggests that in neuroleptic-naive patients, morphology of the midbrain may not be significantly smaller compared with control subjects.

What is the possible mechanism for the relationship between typical neuroleptics and smaller midbrain size? One possibility is that chronic neuroleptic treatment causes a tonic state of inactivation in midbrain dopamine cell activity. This is referred to as “depolarization blockade” (Bunney et al 1991). This phenomenon is a time-dependent process with slow transition of dopamine neurons into this state and appears to correlate with the therapeutic actions of typical neuroleptics such as haloperidol (Grace et al 1997). Chronic inactivation of these cells may possibly cause reduction in neuronal or neuropil volume. Moreover, several studies have suggested that the induction of depolarization blockage is mediated through the antipsychotic’s ability to block dopamine receptors in the striatum (Chiodo and Berger 1986; Chiodo and Bunney 1983; White and Wang 1983). This would suggest that typical neuroleptics might be more likely to induce this state than typical antipsychotics, which have less robust dopamine blockade in the striatum. In turn, this would predict that atypical neuroleptics might not have the same effects on the morphology of the midbrain as typical neuroleptics have.

**Relationship to Psychotic Symptomatology**

Even after controlling for the effects of neuroleptic treatment, there remains a significant relationship between the morphology of the midbrain and psychotic symptoms: the more abnormal the morphology, the greater the severity of psychotic symptoms. The relationship between psychotic symptoms and dopamine is well established; however, the details of how dopamine dysregulation occurs, what brain regions are primarily involved, and with what other neurochemical system(s) it interacts with is the subject of much research and discussion. Most recently, Carlsson and colleagues (Carlsson et al 1999) have put forth a glutamatergic deficiency model of schizophrenia in which they describe the balance of the glutamate–dopamine systems to be altered such that weakened glutamatergic tone results in relative excess of dopamine. The substrate is postulated to be feedback loops between the basal ganglia, thalamus, and cortex that are modulated by the midbrain dopaminergic pathways.

**Similar Concept, Different Substrate: The Cerebellar Connection**

Although the above model has strong support, an abnormal neural circuit involving the cerebellum may also be key to the pathophysiology of psychosis. In a recently published report, our group has found that the cerebellar vermis is morphologically abnormal in men with schizophrenia (Nopoulos et al 1999). Developmentally, the midbrain is intimately involved with the vermis of the cerebellum (Hallonet and Le Douarin 1993; Hallonet et al 1990; Urbanek et al 1997; Yachnis and Rorke 1999). The cortical connections of the cerebellar vermis have not been studied recently; however, older lesion and neurophysiology studies have identified circuits connecting the vermis of the cerebellum to mesolimbic regions via the ventral tegmental area of the midbrain (Snider 1975; Snider and Maiti 1976; Snider et al 1976). Moreover, several studies have linked cerebellar malfunction to forebrain hyperdopaminergia (Anand et al 1959; Dempsey et al 1983, 1984; Heath et al 1978; Heath and Harper 1974; Snider and Maiti 1975; Snider and Snider 1977). The proposed neural circuit is as follows: Purkinje cells of the cerebellar cortex exert an inhibitory action (through \( \gamma \)-aminobutyric acid) on the deep nucleus of the vermis, the fastigial nucleus. The output of the fastigial nucleus is excitatory and projects to the nuclei in the midbrain, which have dopaminergic projections to the mesolimbic regions. Therefore, a “lesion” or malfunction of the cerebellar cortex would lead to disinhibition of excitatory projections of the fastigial nucleus to dopaminergic neurons in the midbrain resulting in a “hyperdopaminergic state.” Each “node” of this circuit (cerebellar vermis, Nopoulos et al 1999; Tran et al 1998; midbrain) (Bogerts et al 1983; this study; limbic regions such as hippocampus, Bogerts et al 1985, 1990) has been shown to be morphologically abnormal in patients with schizophrenia.
Morphologic Evidence of a Neural Circuit Involving the Midbrain and Cerebellum

Our study found the size of the midbrain to be significantly correlated to the size of the cerebellar vermis in patients ($r = .34$, $p = .01$); however, there was no relationship between the size of the cerebellar vermis and that of the midbrain in the control subjects ($r = .14$, $p = .30$). In the previous study of cerebellar vermis, patients were found to have a positive correlation between the size of the vermis and the size of the temporal lobe, with both of these regions being abnormally small compared with control subjects. Yet there was no correlation between vermis area and any cortical region in healthy control subjects. The suggestion that a significant correlation between two brain regions would indicate the existence of a circuit is an indirect and very crude measure; however, it is possible that if a particular brain circuit was abnormal, the “nodes” on the circuit would be similarly affected and therefore their size correlated.

Limitations

The MRI methods used for our study are actually quite crude, using an area measurement from one midsagittal slice as a proxy for volume measurement. In addition, the entire midbrain region was assessed, but more specific subregions would be of interest, such as substantia nigra or the red nucleus with its extensive connections to deep cerebellar nuclei and cerebral cortex. The fact that our study had significant results and fairly robust correlations suggests that the “signal” of abnormal morphology here is strong enough to withstand crude measurement techniques and calls for the need for further imaging studies with more sophisticated methodologies, which we are currently pursuing in our laboratory.

Summary

Male patients with schizophrenia have abnormally small midbrain regions compared with control subjects. This abnormality in the size of the midbrain appears to be independently related to both severity of psychotic symptoms and to exposure to neuroleptics. The greater the severity of psychosis, the smaller the midbrain, and the greater the exposure to neuroleptics, the smaller the midbrain. Whether the size difference between patients and control subjects is due to drug plasticity alone needs to be further addressed in studies that evaluate neuroleptic-naive patients. The midbrain may play an important role in a putative neural circuit involving the cerebellum and limbic cortical regions. Abnormal functioning of this circuit may be important in the pathophysiology of psychosis.

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