Relationship of neuropsychological and MRI measures to age of onset of schizophrenia


Age of onset of schizophrenia (AOS) may be largely determined by neurobiological factors. We examined in a diverse sample of schizophrenia out-patients the relationships of AOS with neuropsychological abilities and structural brain abnormalities as measured on cerebral magnetic resonance imaging (MRI). A total of 82 out-patients meeting DSM-III-R criteria for schizophrenia were evaluated with a comprehensive neuropsychological battery and semi-automated quantitatively analysed cerebral MRI. Earlier AOS correlated with poorer performance in learning and abstraction/cognitive flexibility, and with larger volumes of caudate and lenticular nuclei, and smaller volume of thalamus on MRI. A model for predicting AOS consisting of abstraction and thalamic and caudate volumes remained significant after controlling for duration of illness, current age and daily neuroleptic dose. In conclusion, AOS may be related to specific rather than general measures of cognitive performance and structural brain abnormalities.

Introduction

One potentially important method for elucidating the nature of the pathophysiology of schizophrenia is by studying factors that determine the age of onset of schizophrenia (AOS) (1). Although schizophrenia is often thought of as a disorder with onset during adolescence or early adulthood, a sizeable minority of schizophrenia patients do not manifest clinical symptoms until mid- or late life (2, 3).

Several lines of evidence suggest that AOS may be largely determined by pre-existing neurobiological, and possibly genetically controlled factors (4). Members with schizophrenia from the same family do not tend to develop the illness at the same time (as might be expected if the onset were primarily triggered by stress in the family or other similar environmental factors). However, they do tend to develop schizophrenia at similar ages (consistent with the notion that biological maturational events trigger onset in prone individuals) (1, 5, 6). A biological influence on onset is also suggested by the presence of consistent gender differences in AOS, with men having earlier onset than women (2, 7). Finally, there is remarkable similarity in the incidence and distribution of AOS across cultures and countries (1).

Besides its theoretical importance, AOS also affects the extent to which schizophrenia impacts upon a patient's adult life. Earlier onset leads to patients experiencing a larger portion of their lives with a disabling psychiatric illness. Important psychosocial activities of early adulthood (such as higher education, establishment of social relationships, dating, marriage, and holding a job) are more likely to be disrupted due to earlier AOS. Earlier onset also often entails exposure to a longer duration of treatment, and thus may be associated with an increase in iatrogenic conditions.

The relationship between neuropsychological (NP) functioning or structural brain abnormalities and AOS has not been fully established. Findings

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from one study suggest that earlier AOS is associated with poorer NP functioning (8). However, in another recent study no significant differences in NP functioning were observed among subjects with childhood onset compared to those with adult onset (9). Similarly, some neuroimaging (CT or MRI) studies suggest that earlier AOS is associated with larger ventricles (10, 11) or with greater asymmetry of the lateral ventricles (12), whereas others have found no differences in ventricular size (13), and yet others have reported larger ventricles among patients with later AOS (8).

The present study was conducted in order to explore the more specific aspects of brain structure and function that may be associated with AOS. We adopted a cross-sectional/retrospective design to examine factors that appear to be relatively stable, namely NP functioning and brain structure. The present study focused on abilities in several NP domains assessed with a comprehensive battery of tests, and on volumetric measures of several specific brain structures or areas as assessed via computer-assisted semi-automated quantitative analysis of MRI. This investigation was conducted as part of an ongoing research programme employing a large sample of schizophrenic outpatients with a wide range of current age and AOS. While parts of these data have been published previously (14–16), this manuscript represents our first attempt to evaluate comprehensively the NP and MRI associations of AOS in our largest available sample of patients. We hypothesized that earlier onset would be associated with poorer global cognitive functioning and greater non-specific structural brain abnormalities (e.g., ventricular enlargement). We also conducted exploratory analyses to examine the extent to which specific NP and MRI measures were associated with AOS, and to identify sets of these measures which jointly provided the best ‘prediction’ of AOS. We controlled for likely confounding factors (duration of illness and current age) and for measures of severity of illness (current level of psychopathology and daily neuroleptic dose), since AOS may relate to severity of schizophrenia.

Material and methods

Subjects

The sample included 82 clinically stable outpatients with schizophrenia who were participating in ongoing research at the University of California, San Diego Clinical Research Center for the Study of Late-Life Psychoses. Subjects were selected from a larger pool based on their meeting DSM-III-R (17) criteria for schizophrenia (one subject’s diagnosis was subsequently changed to schizoaffective disorder in the light of additional information obtained during a follow-up visit), as well as the availability of comprehensive neuropsychological and MRI data (described below). Most of the subjects have contributed data to previous published studies from our Center (15, 18–21). Patients in our Center were recruited from the University of California, San Diego (UCSD) Psychiatry Outpatient Clinic, County Mental Health Services, VA Medical Center, UCSD Medical Center, and local private physicians. The AOS of the current sample ranged from 6 to 64 years, and 25 patients had an AOS under 18 years.

Diagnostic procedures included administration of the Structured Clinical Interview for the DSM-III-R (SCID) (22) by trained post-doctoral fellows, in addition to appropriate medical evaluations. Patients with a history of head injury with loss of consciousness for 30 min or longer, or those who fulfilled DSM-III-R criteria for current substance abuse or dependence were excluded.

Information on AOS was based on patient and caregiver interviews, and available medical records. We took into account the various important methodological issues in the determination of AOS that have been discussed thoroughly by Maurer and Hafner (23). As reported elsewhere (24), the reliability of determination of AOS over a 2-year period was high (ICC[3,1] (25)=0.96, P<0.001).

While AOS was defined as age at onset of prodromal symptoms of schizophrenia, according to DSM-III-R (17) criteria, alternatives include age at onset of positive symptoms, and age at first psychiatric hospitalization. We examined all three potential definitions in a subsample of 13 subjects, and found that these three measures of AOS correlated significantly with each other. The Pearson correlation between age at onset of prodromal symptoms and age at onset of positive symptoms was r=0.97 (P<0.001). The Pearson correlation between age at onset of prodromal symptoms and age at first hospitalization was r=0.64 (P<0.05) (although 19% of the full sample had no history of psychiatric hospitalization, all 13 subjects in this subsample had at least one previous hospitalization). The correlation between age at onset of positive symptoms and age at first hospitalization was r=0.68 (P<0.05).

Psychiatric measures

Each patient’s psychiatric symptoms by definition appeared after the onset of schizophrenia, so psychiatric symptom ratings were not employed as ‘predictors’ of AOS. None the less, several standard scales were employed to permit general
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description of the psychiatric characteristics of this sample. Symptom rating scales included the Brief Psychiatric Rating Scale (BPRS) (26), Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, respectively) (27) and the Abnormal Involuntary Movement Scale (AIMS) (28) for dyskinesia. Daily neuroleptic dosages were converted to milligram chlorpromazine equivalents (CPZE) (29, 30). (The latter information was unavailable in the database for 13 subjects, for whom we frequently had information about the type of neuroleptic medication prescribed, but not about the precise daily doses.)

Neuropsychological (NP) assessment

We administered an expanded Halstead-Reitan Battery (31, 32) designed to assess the following eight major NP ability areas.

1) Verbal ability. Wechsler Adult Intelligence Scale Revised (WAIS-R; Vocabulary, Information, Comprehension and Similarities subtests) and the Aphasia Screening Test (verbal), Boston Naming Test, Thurstone Word Fluency and Complex Ideational Material subtest of the Boston Diagnostic Aphasia Examination.

2) Psychomotor speed. Aphasia Screening Test (spatial relationships), WAIS-R (Block Design and Object Assembly subtests), Trails A (total time) and Tactual Performance Test (TPT; total time).

3) Abstraction and cognitive flexibility. Category Test (errors), Trails B (total time) and the Wisconsin Card Sorting Test (perseverative responses).

4) Attention. WAIS-R (Digit Span and Arithmetic subtests), Rhythm Test, Speech Sounds Perception Test and Digit Vigilance (time and errors).

5) Learning. Figure and Story Memory Tests (learning), TPT (location and memory) and California Verbal Learning Test (CVLT; total recall trials 1 to 5).

6) Retention. Figure and Story Memory Tests (percentage retention) and CVLT (short-delay free recall vs. free recall trial 5; 20-min delayed recall vs. short-delay free recall).


8) Sensory Ability. Sensory Perceptual Examination and Tactile Form Recognition.

Raw test scores were converted to age-, education- and gender-corrected T-scores (based on a study of a large normative sample), which were coded such that higher T-scores represented better performance (32, 33). NP measures used for analyses included the mean T-scores for each of the eight ability areas, as well as the mean T-scores across the entire battery (global T-score).

The reliability of each of the NP ability domain T-scores and the global T-score was assessed in terms of 1-year test–retest reliability (ICC[3, 1] (25)) and was found to be as follows: verbal ability, 0.87; psychomotor speed, 0.87; abstraction and cognitive flexibility, 0.82; attention, 0.78; learning, 0.68; retention, 0.12; motor, 0.82; sensory, 0.63; global, 0.88. (The low reliability estimate for retention is partially due to the low variability of this measure, i.e. the patients with schizophrenia did not show any significant impairment in terms of delayed recall; 15.)

Cerebral magnetic resonance imaging (MRI)

Cerebral MRI was performed with a 1.5-Tesla superconducting magnet (Signa; General Electric, Milwaukee, WI) at the UCSD/AMI Magnetic Resonance Institute. Two spatially registered images were obtained simultaneously for each section with the use of an asymmetrical, multiple-echo sequence (repetition time=2000 ms; echo time=25 and 70 ms). The section thickness was 5 mm, with a 2.5-mm gap between successive sections in all instances. Image data-sets were assigned random numerical codes. Data-sets from this study were interspersed with data-sets from a variety of other patients and normal control subjects and all analyses were conducted blind to any subject characteristics. A segmentation procedure was employed to facilitate and standardize the determination of borders between adjacent structures. Details of this procedure have been described previously (34).

The brain regions used in the analyses described in this paper were as follows: supratentorial and infratentorial cranial (including cerebrospinal fluid (CSF), grey matter and white matter), cortical (sulcal) fluid, subcortical (ventricular) fluid, subcortical abnormal white matter, total cortical grey matter, anterior diencephalon, thalamus, caudate nucleus, lenticular nucleus, mesial temporal lobe volume, cerebral cortex volume excluding mesial temporal lobe and total white matter. Each of these brain regional volumes, except for the supratentorial and infratentorial cranial volumes, was converted to an age- and cranial size-corrected z-score using multiple regression analyses performed earlier with a group of 107 normal control subjects (14). This z-score is used to express volumes as their deviation from expected values given the patient's age and cranium size.
Inter-operator reliability was assessed by analysing 10 full image sets separately. Reliability coefficients (Pearson's $r$) ranged from 0.73 for lenticular nuclei to 0.99 for supratentorial and infratentorial volumes and for cortical and subcortical fluid.

Statistical methods

The distribution of each continuous variable was examined for normality. Variables that did not meet the criteria for parametric analyses in their raw form were transformed as appropriate. The degree of bivariate association between each of the NP and MRI variables and each of the clinical variables (AOS, duration of illness, current age and daily neuroleptic dose expressed as mg CPZE) was analysed with Pearson’s $r$. In addition, the relative, unique and joint contributions of sets of NP and MRI variables to the 'prediction' of AOS were explored via multivariable linear regression (partial $r$ for 'relative' contribution, semi-partial $r$ for unique contribution and multiple $R$ for joint contribution). We began by examining the significance of two-variable combinations of predictor variables using stepwise multiple regression. The number of models examined with two-variable predictors was restricted to those pairs containing at least one variable that was significantly associated with AOS in the univariable analysis. Building upon the significant two-variable pairs, we examined the effects of additions of a third predictor variable via stepwise multiple regression. (Similarly, we also attempted to build four-variable models of AOS.) Criteria for retention of models included significant multiple $R$ ($\alpha=0.05$, two-tailed) and significant partial correlations for each predictor variable in the model ($\alpha=0.05$). In addition, individual predictors had to have significant partial correlations regardless of the order of entry into the equation. Mallows’ $C_p$ (35, 36) was employed to determine whether the larger multivariable models were superior to smaller models based on two-variable subsets of the variables in those models.

We then explored the extent to which duration of illness, current age and daily neuroleptic dose (mg CPZE) affected the models produced. This was done by forcing each of these three variables into the stepwise regression model first, and then allowing the other variables in the model to enter the equation, i.e. to determine whether age, duration of illness or current daily CPZE were significant predictors of AOS with the other variables in the model and if the other variables remained significant with duration, age or CPZE in the model.

### Results

Demographic and psychiatric characteristics

These are described in Table 1.

Table 2 shows the correlations of all NP and MRI measures with AOS and its likely confounding factors, i.e. duration of illness, age and neuroleptic dose. (AOS did not correlate with total BPRS, which was used as a measure of current severity of illness.) Earlier AOS was significantly associated with lower T-scores in learning and abstraction/cognitive flexibility and with larger caudate and lenticular nuclei and, at a trend level, with smaller thalamic volume ($P=0.055$). The only significant relationship between duration of illness and NP performance (or MRI measures) was that longer duration of illness was associated with lower $T$-scores in the motor domain. Similarly, the only significant relationship between current age and NP (or MRI) measures was that older age was associated with poorer learning ability. (As mentioned in the Methods section, the NP test scores had been corrected for the effects of normal ageing based on a large normative study (32, 33).) Older current age was also associated with lower age-adjusted MRI volumes of cortical/sulcal fluid, less abnormal white matter and smaller lenticular vol-

### Table 1. Demographic and clinical characteristics of the sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Value</th>
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<tbody>
<tr>
<td>Male (%)</td>
<td>82</td>
<td>67.1</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>81</td>
<td>82.7</td>
</tr>
<tr>
<td>Never married (%)</td>
<td>82</td>
<td>87.8</td>
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<td>With paranoid subtype (%)</td>
<td>82</td>
<td>32.5</td>
</tr>
<tr>
<td>On neuroleptic medication (%)</td>
<td>80</td>
<td>76.8*</td>
</tr>
<tr>
<td>Mean age (years) (SD)</td>
<td>82</td>
<td>37.7 (15.3)</td>
</tr>
<tr>
<td>Mean education (years) (SD)</td>
<td>82</td>
<td>13.0 (2.2)</td>
</tr>
<tr>
<td>Mean age of onset of schizophrenia (years) (SD)</td>
<td>82</td>
<td>25.4 (14.1)</td>
</tr>
<tr>
<td>Mean duration of schizophrenia (years) (SD)</td>
<td>82</td>
<td>12.3 (10.7)</td>
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<tr>
<td>Mean daily neuroleptic dose (mg CPZE) (SD)</td>
<td>53</td>
<td>734.8 (1408.6)</td>
</tr>
<tr>
<td>Mean AIMS total (SD)</td>
<td>81</td>
<td>35.7 (10.8)</td>
</tr>
<tr>
<td>Mean SAPS total (SD)</td>
<td>81</td>
<td>61.1 (4.2)</td>
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<td>Mean SANS total (SD)</td>
<td>81</td>
<td>10.7 (5.4)</td>
</tr>
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<td>Mean MMSE total (SD)</td>
<td>71</td>
<td>0.3 (0.6)</td>
</tr>
<tr>
<td>Mean MMSE total (SD)</td>
<td>54</td>
<td>27.5 (2.0)</td>
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Aims, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; CPZE, chlorpromazine equivalents; MMSE, Mini-Mental State Examination; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

* In general, the patients not on neuroleptics at the initial study visit were those who had discontinued the medication of their own accord.

b Mean (SD) daily dose for patients on neuroleptics.
There were seven significant three-variable models in which earlier AOS was predicted by the following combinations: (i) lower scores on learning, larger lenticular nucleus and smaller thalamus ($R=0.524; F=9.82; df=3.78; P<0.001$); (ii) lower scores on abstraction, larger lenticular nucleus and smaller thalamus ($R=0.510; F=9.13; df=3.78; P<0.001$); (iii) lower scores on learning, larger caudate and smaller thalamus ($R=0.476; F=7.61; df=3.78, P<0.001$); (iv) lower scores on abstraction, larger caudate and smaller thalamus ($R=0.472; F=7.47; df=3.78, P<0.001$); (v) lower scores on learning, larger caudate and larger cortical fluid volume ($R=0.449; F=6.57; df=3.78, P<0.001$); (vi) lower scores on abstraction, larger caudate and larger cortical fluid volume ($R=0.433; F=5.99; df=3.78, P<0.001$); and (vii) lower scores on learning, larger lenticular nucleus and smaller volume of cerebral cortex (excluding the mesial temporal lobe) ($R=0.410; F=5.25; df=3.78, P<0.003$). Thus each three-predictor model contained one NP variable (either learning or abstraction) and two MRI volumetric measures, one of which was either the caudate or the lenticular nucleus and the second of which was either the thalamus, the cortical fluid or the cerebral cortex (excluding the mesial temporal lobe). None of the two-variable subsets of the three-variable models provided an adequate fit to the data compared to the respective full (three-variable) model.
variable) models according to Mallow's $C_p$ (35, 36). There were no significant four-variable models. The strongest three-variable predictor model of AOS was one in which earlier AOS was predicted by a combination of lower scores on learning, smaller thalamic volume and smaller lenticular volume. This model with $R=0.524$ explained 27.5% of the variance in AOS. However, after controlling separately for duration, age and CPZE, only the model with abstraction, thalamus and caudate remained significant. This model with $R=0.472$ explained 22.3% of the variance in AOS.

Discussion

We found that specific, rather than global or non-specific, NP and MRI measures were significant ‘predictors’ of AOS. The best multivariable prediction of AOS in terms of multiple $R$ was achieved with a model in which earlier AOS was predicted by a combination of lower scores on learning, larger lenticular volume and smaller thalamic volume. The best multivariable prediction of AOS in terms of stability of the model controlling for duration, age and neuroleptic dose was achieved with a model in which earlier AOS was predicted by a combination of lower scores on abstraction/cognitive flexibility, larger caudate and smaller thalamus.

Examining specific NP ability areas, we found that earlier AOS was associated with lower scores on learning and abstraction. Previous research in young adults with schizophrenia indicates that these NP ability areas are among the most likely to be impaired among schizophrenia patients in general (37). While learning and abstraction were the strongest predictors of AOS in the present study, the highest reliability coefficients were actually observed in the global $T$-score and verbal domain. Thus the relative power of certain NP variables to predict AOS did not appear to be attributable to greater reliability.

The negative association between AOS and lenticular and caudate volumes observed in the present study is also consistent with several published reports. Studies primarily involving younger early-onset samples have found that schizophrenia patients have larger caudate volumes than normal control subjects (38–41). The results of a previous study by Jernigan et al. (14), which included some of the younger patients in the present study, also suggest that schizophrenia patients have larger lenticular volumes relative to normal control subjects.

A number of investigators who have used functional neuroimaging with schizophrenia patients have reported abnormalities in metabolic rates or blood flow in the striatum (42–45). Some investigators have noted reduced blood flow or metabolism in the caudate (44, 46), although others have reported increased striatal blood flow or metabolism among schizophrenia patients (45, 47). The reasons for the discrepant findings with regard to the direction of metabolic and blood flow abnormalities across studies are not clear. However, the relationship of these specific regional abnormalities to AOS has not been evaluated adequately in the published literature.

There have been reports suggesting possible effects of neuroleptic treatment on striatal volumes. Frazier et al. (48) found a positive correlation between the volume of the globus pallidus on MRI and total neuroleptic exposure in 21 patients with childhood-onset schizophrenia. Chakos et al. (49) found that mean caudate volumes on MRI increased by 5.7% in a group of first-episode schizophrenia patients who were monitored over an 18-month period. Similarly, Keshevan et al. (50) observed substantial increases in MRI-caudate volumes in 9 of 11 neuroleptic-naive patients who were followed over a 1-year period of neuroleptic treatment. Two studies reported a reduction in the caudate volume when patients were treated with clozapine for 1 to 2 years (51, 52). (However, we should point out that none of our patients had been treated with clozapine.) At the same time, there are several lines of evidence which indicate that the relationship of AOS to lenticular and caudate pathology is not fully attributable to neuroleptic treatment. For example, Early et al. (53) observed abnormal blood flow in the globus pallidus of first-episode patients. Furthermore, we are not aware of any evidence of a progressive increase in the size of the caudate (or any other brain structure) with long-term neuroleptic use. Indeed, animal studies demonstrate no change or loss of neurones with chronic neuroleptic administration (54). In the present study, daily neuroleptic dose did not correlate with any NP or MRI predictors of AOS. (We did not have reliable information on the amount of total lifetime neuroleptic exposure.)

The finding of a positive association between AOS and thalamic volume is interesting in view of recent and growing interest in the involvement of the thalamus in schizophrenia. The thalamus is a major relay-station for most sensory information on its way to the cerebral cortex. Its functions include filtering stimuli, sensory gating, focusing attention and supporting learning/memory processes, all of which are impaired in schizophrenia. There have also been several neuropathological investigations reporting a decrease in neuronal number or density in the dorsomedial nucleus of thalamus in the brains of patients with schizophrenia (55–58). The
dorsomedial nucleus is one of the largest nuclei in the thalamus, with connections to the prefrontal cortex and other parts of the limbic system. Findings from an MRI study by Andreasen et al. (59) were consistent with a reduced volume of thalamus in schizophrenia. Buchsbaum et al. (60) noted a reduction in thalamic metabolic rate in PET scans of neuroleptic-free patients with schizophrenia. The present study suggests that a smaller thalamus is associated with earlier-onset schizophrenia. It should be pointed out that few, if any, of the patients included in the published reports of reduced thalamic volume or activity (57, 59–61) had late-onset schizophrenia (i.e. with AOS after the age of 45 years; 17). Pakkenberg (58) reported a comparable reduction in the volume of the mediodorsal nucleus of the thalamus in neuroleptic-treated and untreated patients with schizophrenia. Thus it is unlikely that the observed differences in thalamic volume can be entirely attributed to treatment history.

The present study did not include normal control subjects, nor did it compare early-onset schizophrenia patients with late-onset ones, since the goal of this analysis was to examine NP and MRI associations of AOS using the latter as a continuous variable. Recently we reported a larger thalamus in late-onset schizophrenia patients (defined as having AOS after the age of 45 years, as specified by the DSM-III-R criteria) (17) than in those with AOS before the age of 45 years (16). In the latter study, the values for the age-comparable normal controls were intermediate between those of the early-onset and late-onset schizophrenia groups; the differences compared to the controls did not reach the level of significance, probably because of the small sample sizes.

It is not known whether a larger thalamus in patients with later AOS is a protective factor or a pathological one. While the question remains open for further study, there is some evidence that both larger and smaller thalami may be pathological. Dupont et al. (62) found that patients with bipolar depression had significantly larger thalami than normal control subjects, while those with unipolar depression had significantly smaller thalami. The nature of the pathology associated with increased thalamic size, if any, is unclear.

The abnormalities in caudate and lenticular nucleus and thalamus could reflect neurodevelopmental processes, such as aberrations in the synaptic pruning which normally occurs during adolescence (63, 64). Disruption of such processes could yield abnormally large or small structures, or both. Keshevan (65) has suggested that the psychopathology of schizophrenia could reflect the combined effects of excessive synaptic pruning in some structures and/or insufficient pruning in others. Early brain injury could result in a dyspruned neural connectivity, i.e. loss of some neuronal connections that would normally have been retained and a compensatory retention and/or proliferation of some other connections that would normally have been pruned out (65). The possibility and nature of any association between excessive pruning in one area and defective pruning in another are unknown.

While there were significant correlations among thalamic, caudate and lenticular volumes, none of these correlated significantly with learning or abstraction scores, suggesting that the contributions of the NP and MRI measures to AOS appeared to be more independent than interrelated. The general lack of a relationship between NP and MRI measures is consistent with at least some previous schizophrenia research employing NP and MRI measures (66). The NP measures were not designed to map on to specific brain region volumes, but rather were designed to assess relatively broad cognitive constructs, such as ‘learning’ or ‘abstraction’. Moreover, most of the evidence concerning structure–function relationships comes from studies of subjects with acquired brain lesions. These relationships may be different in neurodevelopmental disorders as recent evidence suggests schizophrenia may be.

Our findings do not necessarily indicate whether the NP and MRI abnormalities associated with earlier AOS precede and/or follow the onset of schizophrenia. For example, it is conceivable that, in predisposed individuals, poorer learning or abstraction ability may predict an earlier AOS. This hypothesis is consistent with a recent report by Russell et al. (67) suggesting that the cognitive deficits in schizophrenia predate the clinical onset of the illness. Alternatively, earlier onset of schizophrenia may be followed by a greater reduction in those abilities during the first few years of illness compared to later-onset schizophrenia. Without prospective longitudinal studies, this issue cannot be resolved definitively.

The present study has several strengths in terms of the diversity of our sample with regard to AOS and current age, as well as the comprehensive assessments employed. Furthermore, because the patients were clinically stable out-patients, their NP test performance was likely to be relatively free of artefacts that might be observed with an acute inpatient sample. On the other hand, there are also several limitations, such as the retrospective/cross-sectional design. In the absence of a ‘gold standard’ for determining the validity of any measure of AOS, some degree of uncertainty about the precise accuracy of the AOS for any particular patient (in
this and virtually all other studies of AOS) must be acknowledged. AOS may reflect the general severity of the illness, although we did not find a significant correlation between AOS and total BPRS. Our MRI analysis was limited by factors such as slice thickness and the gap between slices. Since AOS is potentially confounded by treatment duration, some of the NP or MRI findings might be attributable to the effects of chronic illness and/or neuroleptic intake (49, 50, 68). None the less, duration of illness and current daily neuroleptic dose (in mg CPZE) did not significantly alter the best three-variable model of AOS.

Our study did not address the question of whether AOS is a continuous variable or a categorical one as implied in the DSM-III-R (17) definition of late-onset schizophrenia. However, the present findings should provide testable hypotheses for future studies using specific NP and brain imaging measures as predictors of AOS.

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