The Maudsley Early Onset Schizophrenia Study: Cognitive Function Over a 4-Year Follow-Up Period

Sophia Frangou1,2, Michael Hadjulis2, and Apostolos Vourdas2

2Section of Neurobiology of Psychosis, Institute of Psychiatry (PO66), Kings College London, De Crespigny Park, London SE5 8AF, UK

Generalized cognitive deficits have been consistently reported in adolescents with early onset schizophrenia (EOS; defined as onset before the age of 17 years). The impact on cognition of potential interactions between disease pathology and brain maturation remains unclear. We therefore compared cognitive function between 20 EOS patients and 20 healthy controls matched on age, gender, and parental socioeconomic status at 2 time points, when aged 15.58 (2.27) and after a mean interval of 4.61.08 years when aged 19.46 (2.21) years. Repeated measures analyses revealed no differences between patients and controls in the degree of change over this time period in general intellectual function and planning ability as measured by the Tower of London. There was deterioration in the verbal memory and attentional control index scores from the Wechsler Memory Scale-Revised but relative improvement in Part A of the Trail Making Test. Patients’ level of symptomatology as well as the type and dose of medication were comparable at both time points. We conclude that most aspects of cognitive function remain relatively stable in EOS patients during adolescence; there is evidence for deterioration in immediate verbal memory and attention while speed of information processing may show improvement.

Key words: memory/intellectual function/longitudinal/adolescent

Introduction

Early onset schizophrenia (EOS), defined here as schizophrenia with onset before the 17th birthday, shows high diagnostic stability over time1,2 and is associated with significant clinical morbidity and psychosocial disability.3 Younger age at first admission shows a linear relationship with longer duration of hospitalizations and higher rate of readmissions.4 Premorbidly, EOS patients fail to attain developmental and social milestones.5,6 Following disease onset, interruptions in education, employment, and peer relationships add to their psychosocial disadvantage.5,7 A large body of evidence has confirmed that cognitive deficits are part of the extended phenotype of schizophrenia. Adult onset patients show widespread abnormalities in cognition with the largest effect size seen in general intellectual ability, verbal memory, and executive function.8 Cognitive deficits are also present in adolescents with schizophrenia. In one of the earlier studies, Johnstone et al9 found that EOS patients had poor language abilities and deficits in long-term memory. Subsequent studies have reported additional impairments in intelligence quotient (IQ), verbal memory and learning, and in executive function.10–13 The profile of cognitive changes in EOS seems broadly similar to that observed in adult first-episode patients14 with the possible exception of attention, which may be less impaired in adolescents12,13,15 although the findings are not consistent.11,16

Schizophrenia may have neurodevelopmental origins, but its pathophysiology seems to impact brain structure and function throughout the lifespan. Longitudinal neuroimaging studies of first-episode patients (aged 26–30 years when first scanned) reported increases in ventricular volume17,18 and reduction in gray matter volume, particularly within the frontal lobes, over periods of 2–5 years.19,20 This prefrontal cortical gray matter loss may be more pronounced in adolescents with schizophrenia.21,22

It is less clear whether there is a similar progression in cognitive dysfunction. Most studies in adults with first-episode schizophrenia report either stability or minor improvements over a 2- to 20-year period.23–28 Kurtz29 who reviewed the relevant literature concluded that, in patients with schizophrenia tested between the ages of 20–65 years, general intellectual function as well as other measures of cognition remain stable after illness onset, over most of the life span. In contrast, population-based studies point to a premorbid decline in intellectual function from childhood to adolescence as a significant risk factor for schizophrenia.30,31 Cognitive dysfunction in apparently healthy adolescents can identify those who later
develop schizophrenia with a high degree of specificity and sensitivity.\(^{30}\) This is perhaps not surprising given that adolescence is a period of significant brain remodeling\(^{32}\) and suggests the possibility that cognition may decline during this developmentally critical period and stabilize thereafter. Existing findings are very limited but suggest that developmental and disease-related mechanisms might not have a uniform impact on cognition. Gochman et al.\(^{33}\) in a 13-year follow-up study of childhood-onset schizophrenia cases, reported that decline in general intellectual function was not associated with a particular developmental period but occurred, on average, in the 2 years preceding and following the onset of psychosis and remained stable thereafter. Thaden et al.\(^{34}\) however, found that the magnitude of deviance in attentional control in EOS cases increased with age during adolescence.

Based on the above, the aim of this study was to explore further the effect of brain developmental mechanisms and schizophrenia-related pathophysiology on cognition during adolescence. We therefore examined general intellectual ability, memory, and executive function in 20 adolescents with schizophrenia over a 4-year period using a case–control design. We hypothesized that general intellectual function would probably remain stable; because previous studies of EOS cases had reported exacerbated gray matter loss during adolescence in the prefrontal cortex,\(^{21,22}\) we expected cognitive deterioration in cognitive processes thought to engage prefrontal regions such as attentional control, planning, and mental flexibility.

**Methods**

**Subjects**

Twenty-three patients (13 boys and 10 girls) were recruited from the adolescent services of the South London and Maudsley National Health Service Trust based on the following criteria (a) diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition, DSM-IV),\(^{35}\) (b) age of onset of schizophrenia before the 17th birthday, and (c) absence of any comorbid lifetime DSM-IV Axis I disorder. At baseline, they were individually matched on age (within 6 months), gender, and parental socioeconomic status to an equal number of healthy controls without a personal history of psychiatric disorder or family history of psychosis. Healthy controls were recruited by advertisement and resided in the same geographic area as patients. Exclusion criteria for all participants included: (a) personal history of neurological disorder or a family history of any inherited neurological disorder, (b) history of any head injury resulting in loss of consciousness, (c) alcohol or substance abuse in the preceding 6 months, and (d) IQ below 70. Written informed consent was obtained from participants over 16 years and from the parents of younger subjects. At the time of their initial assessment, participants were informed that they would be contacted for follow-up evaluation and had agreed to this.

After a mean interval of 4.00 ± 1.08 years (range 30–68 months), all patients in the initial sample were contacted for follow-up assessment, and 20 (10 male and 10 female) agreed to participate. At baseline, the mean age of the patients who participated at follow-up was 15.58 years (range 13.3–16.9). None had an age of onset of psychosis below the age of 12 years; 4 patients had manifested psychosis before their 15th birthday, and the remaining were aged between 15 and 17 years at illness onset. Sixteen were right, and 4 were left handed. Sixteen were British White, 2 were Afro-Caribbean, and 2 of Asian parentage. Parental occupation was classified as skilled in 18 patients, professional in 1, and unskilled labor in 1. Additional details of the patient sample at baseline and follow-up are given in table 1. Their 20 matched controls were also invited and agreed to participate. The controls’ mean age at baseline was 15.98 ± 0.75 years and 19.76 ± 1.09 years at follow-up.

**Assessment**

**Clinical Assessments.** Confirmation of the diagnosis of schizophrenia in patients and the absence of mental...
health problems in controls was based on personal interview by qualified psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders. At baseline, the interview was supplemented by the Structured Clinical Interview for DSM-IV Childhood Diagnoses for patients aged less than 16 years. Additional information was obtained from parents, patients’ medical records, and treating physicians. Handedness was assessed by the Annett Handedness Questionnaire and parental socioeconomic status by the Standard Occupational Classification (categories condensed to 1 skilled or partly skilled, 2 professional or managerial, 3 unskilled or unemployed). Age of onset of schizophrenia was defined as the age when positive symptoms, either delusions or hallucinations, first manifested. Calculation of the number of hospitalizations during the follow-up period and information about medication was obtained from the patients, their parents, and medical notes. Psychopathology at baseline and follow-up was rated with the Positive and Negative Syndrome Scale (PANSS). Antipsychotic medication dosage was converted into chlorpromazine equivalents.

**Cognitive Evaluation.** Both at baseline and at follow-up, patients were assessed when in clinical remission (defined as total PANSS positive symptom score less than 28) for at least 2 weeks having been on the same type and amount of medication for the same period of time.

Intellectual ability was assessed by age-appropriate forms of the Wechsler Intelligence Scales. The Wechsler Intelligence Scale for Children, Third Edition UK (WISC-III-UK) was administered to participants aged 13–16 years, and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) to those older than 16 years. WAIS-R scores were converted into WISC-III equivalents derived from 16-year-olds tested with both instruments.

Memory function was assessed using the Wechsler Memory Scale-Revised (WMS-R). For those aged 15 years (4 patients, 2 controls), index scores were estimated by reference to the youngest normative group (16- to 17-year-olds) because differences between the 2 age bands were presumed too small to distort interpretation of scores.

Planning and problem solving were assessed by the Three-Dimensional Computerised Tower of London Test (TOL). In this test, participants are shown 2 different displays of colored discs inserted into vertical rods. They are asked to rearrange the discs in the lower display to match the pattern of the top in as few movements as possible. Three outcome measures from the highest difficulty level (level 5) were used in the statistical analysis; the number of moves and initial and subsequent planning time (the time taken to plan the first and each subsequent moves to achieve the target pattern).

Sequencing and mental flexibility were assessed by a computerized version of the Trail Making Test (TMT), which requires participants to connect quickly and consecutively alphabetically lettered circles and then by alternating between sequentially numbered and alphabetically lettered circles. Incorrect responses were followed by a warning sign, and participants could only continue if they corrected the error. Total time to complete the alphabetical sequencing (20-letter task, Trail Making A) and alphanumeric sequencing (20-number/letter task, Trail Making B) were recorded and used in subsequent analyses. The TOL and TMT were administered on a laptop computer fitted with a touch-sensitive screen.

**Statistical Analyses**

Group differences in demographic and clinical variables were assessed using Student’s t-test or Pearson’s chi-square as appropriate. The normality of the distribution of the cognitive test scores for each outcome variable at baseline and at follow-up was examined using 1-sample Kolmogorov-Smirnov tests. WAIS-R, WMS-R, and TMT test scores were normally distributed, but this was not the case for any of the TOL outcome measures. Data were not transformed because this did not yield a more symmetric distribution and would add interpretational complexity.

In order to assess changes in cognitive test performance between baseline and follow-up, 4 multivariate repeated measures analyses of variance (MANOVA), one for each neuropsychological test, were conducted with diagnosis (patient vs healthy volunteer) as between and time (baseline vs follow-up) as within subject factors. Dependent variables for each repeated measures MANOVA were (a) WAIS-R: verbal, performance, and full scale IQ; (b) WMS-R: verbal, visual and general memory, attentional control, and delayed recall; (c) TOL: number of moves, initial and subsequent thinking time; and (d) TMT: total time to completion for Part A and Part B. Post hoc univariate comparisons were conducted only when the overall model showed a significant effect of diagnosis or a time by diagnosis interaction. Because of the small sample size, partial eta-squared ($\eta^2$) values were given for the nonstatistically significant results as a measure of effect size.

We also used Pearson correlation coefficient to examine the relationship between cognitive variables, symptom scores, and dose of antipsychotic medication both at baseline and follow-up. In total, we conducted 30 correlational analyses and used Bonferroni correction to adjust the level of significance to 0.001.

**Results**

At baseline, there were no differences between patients and controls in age ($t = -0.4$, $df = 38$, $P = .60$), gender (Pearson’s $\chi^2 = 0.2$, $df = 1$, $P = .50$), ethnic origin (Pearson’s $\chi^2 = 4.1$, $df = 3$, $P = .10$), handedness (Pearson’s $\chi^2 = 2.2$, $df = 2$, $P = .30$), or parental social class.
(Pearson's \(\chi^2 = 4.9, df = 4, P = .20\)). At follow-up, the diagnosis of schizophrenia (Paranoid Type, DSM-IV code 295.30) was confirmed in all patients, while the controls remained free of psychopathology. There were no differences in type or dose of medication or in symptom scores between baseline and follow-up (all \(P\) values > .31). Six patients were on clozapine at baseline, and this was increased to 9 at follow-up. Participants' scores on the cognitive tasks at baseline and follow-up are shown in Table 2.

### General Intellectual Ability

With respect to general intellectual function, there was a significant effect of time (\(F = 6.27, df = 3, 36, P = .002\)) with both groups showing marginal improvement; there was no effect of diagnostic group (\(F = 1.96, df = 3, 36, P = .13, \text{partial } \eta^2 = 0.11\)) or group by time interaction (\(F = 0.22, df = 3, 36, P = .88, \text{partial } \eta^2 = 0.03\)).

### Memory

In the WMS-R, we found a significant effect of diagnosis (\(F = 7.87, df = 5, 34, P = .0001\)); patients performed worse than controls on all memory indices both at baseline and follow-up (all \(P\) values < .01) except for attentional control and visual memory where there were no group differences at baseline (\(P > .80\)). There was no significant effect of time (\(F = 1.38, df = 5, 34, P = .25, \text{partial } \eta^2 = 0.37\)). The interaction of group by time was statistically significant (\(F = 6.17, df = 5, 34, P = .0001\)). Patients' and controls' test scores on delayed recall showed very little change. Controls improved in all other memory indices while patients' performance showed evidence of decline, which was statistically significant for verbal memory (\(P = .05\)) and attentional control (\(P = .007\)). The visual memory index was higher than the verbal memory index for both groups and at both time points. This difference was not significant for controls either at baseline or follow-up (\(P > .12\)) but was significant for patients at both time points (\(P < .007\)).

In order to describe better the pattern of deficits emerging in patients at follow-up, we examined the relationship between (a) WAIS-R and WMS-R composite scores and (b) different WMS-R composite scores.

The difference between WAIS-R IQ and WMS-R General Memory Index (GMI) is thought to reflect learning relative to general intellectual ability. At baseline, GMI was lower than IQ by an average of 6.70 (15.82) points in patients and 2.21 (17.17) in controls; at follow-up, mean GMI was lower than mean IQ by 15.5 (14.68) points in patients and 0.54 (10.57) points in controls. We also examined the difference between WAIS-R IQ and WMS-R Delayed Recall Index (DRI) which is considered a measure of information consolidation and retrieval relative to general intellectual competence. At baseline, mean DRI was 3.98 (18.05) points lower than IQ in patients and 1.16 (17.17) in controls; at follow-up, mean GMI was lower than mean IQ by 8.91 (16.30) points in patients and higher by 1.18 (11.17) points in controls. We calculated the difference between GMI and DRI which is considered to reflect the relative magnitude of impairment in short-term memory compared with delayed recall. DRI was higher for both patients and controls by 2.71 (9.15) and 1.05 (11.06), respectively, at baseline and by 6.58 (7.47) and 1.72 (11.23) follow-up.

### Table 2. Cognitive Test Scores of Patients (\(n = 20\)) and Controls (\(n = 20\)) at Baseline and Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Patients Baseline</th>
<th>Patients Follow-up</th>
<th>Controls Baseline</th>
<th>Controls Follow-up</th>
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<tbody>
<tr>
<td><strong>General intellectual ability</strong></td>
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<tr>
<td>Full-scale IQ</td>
<td>92.53 (17.97)</td>
<td>99.32 (17.32)</td>
<td>101.74 (15.63)</td>
<td>102.86 (12.12)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>96.52 (16.99)</td>
<td>97.84 (15.68)</td>
<td>101.96 (13.73)</td>
<td>100.73 (10.26)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>89.36 (17.74)</td>
<td>101.20 (19.29)</td>
<td>101.74 (18.80)</td>
<td>106.86 (17.30)</td>
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<tr>
<td><strong>Wechsler memory scale-revised</strong></td>
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<tr>
<td>Verbal memory</td>
<td>84.89 (20.20)</td>
<td>77.46 (17.0)</td>
<td>101.33 (19.32)</td>
<td>105.91 (13.15)</td>
</tr>
<tr>
<td>Visual memory</td>
<td>96.78 (18.16)</td>
<td>98.73 (23.25)</td>
<td>105.5 (17.28)</td>
<td>109.12 (14.00)</td>
</tr>
<tr>
<td>General memory</td>
<td>86.03 (21.02)</td>
<td>80.29 (19.27)</td>
<td>100.10 (22.43)</td>
<td>102.82 (15.23)</td>
</tr>
<tr>
<td>Attentional control</td>
<td>87.10 (15.52)</td>
<td>79.75 (20.43)</td>
<td>86.26 (15.08)</td>
<td>96.27 (11.40)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>88.75 (23.04)</td>
<td>86.88 (21.61)</td>
<td>101.15 (15.23)</td>
<td>104.50 (12.13)</td>
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<tr>
<td><strong>Trail making test</strong></td>
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<tr>
<td>Trails A</td>
<td>28.49 (10.32)</td>
<td>20.49 (5.65)</td>
<td>26.90 (11.78)</td>
<td>20.08 (2.06)</td>
</tr>
<tr>
<td>Trails B</td>
<td>38.89 (10.80)</td>
<td>31.63 (7.20)</td>
<td>35.06 (7.61)</td>
<td>29.47 (6.52)</td>
</tr>
<tr>
<td><strong>Tower of London task—level 5</strong></td>
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<tr>
<td>Number of moves</td>
<td>7.65 (1.55)</td>
<td>7.36 (2.33)</td>
<td>5.90 (1.28)</td>
<td>6.18 (1.35)</td>
</tr>
<tr>
<td>Initial planning time</td>
<td>7.08 (6.94)</td>
<td>10.34 (12.10)</td>
<td>12.41 (12.43)</td>
<td>12.75 (8.84)</td>
</tr>
<tr>
<td>Subsequent planning time (per move)</td>
<td>1.97 (1.06)</td>
<td>2.13 (1.69)</td>
<td>2.24 (2.00)</td>
<td>1.88 (1.20)</td>
</tr>
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**Note:** IQ, intelligence quotient.
Although patients were more impaired than controls on this measure \((P = .02)\), the GMI–DRI difference showed no significant effect of time \((F = 0.30, \, df = 1, 38, \, P = .58)\) or diagnosis by time interaction \((F = 1.14, \, df = 1, 38, \, P = .29)\). To assess the relationship of attentional deficits to memory performance, we correlated the attentional control index (A/CI) with the IQ-GMI and IQ-DRI difference scores using Pearson’s correlation coefficient but did not find any significant correlations \((A/CI \, r = -0.23, \, P = .11; \, A/CI \, r \, with \, IQ-DRI \, r = 0.25, \, P = .09)\).

**Planning and Mental Flexibility**

In the TOL task, we found an overall effect of diagnosis \((F = 3.41, \, df = 3, 36, \, P = .04)\), with patients making more moves than controls at both time points \((P < .04)\). There was no significant effect of time \((F = 1.74, \, df = 3, 36, \, P = .2, \, \text{partial } \eta^2 = 0.08)\) or group by time interaction for the number of moves, initial or subsequent planning time \((F = 1.43, \, df = 3, 36, \, P = .27, \, \text{partial } \eta^2 = 0.07)\).

In the TMT, there was no significant effect of diagnosis \((F = 0.02, \, df = 2, 38, \, P = .86; \, \text{partial } \eta^2 = 0.08)\) or time \((F = 2.14, \, df = 2, 38, \, P = .15, \, \text{partial } \eta^2 = 0.11)\), but the interaction of diagnosis with time was significant \((F = 6.19, \, df = 2, 38, \, P = .01)\) because patients completed the alphabetical sequencing faster at follow-up compared with baseline.

There were no significant correlations between cognitive measures and symptom levels \((P \, values > .04)\) or dose of antipsychotic medication \((P \, values > .26)\) at either time point. Although they did not survive Bonferroni correction, potentially meaningful correlations with a correlation coefficient of 0.40 and above were noted at both time points between PANSS positive and negative symptom scores and IQ measures and \((r \, values \, ranged \, between \, -0.57 \, and \, 0.49)\) with visual memory \((r \, values \, ranged \, between \, -0.60 \, and \, -0.52)\) and Trails Part A and B \((r \, values \, ranged \, between \, 0.57 \, and \, 0.62)\). At follow-up, PANSS negative symptom score correlated with all WMS measures \((r \, values \, ranged \, between \, -0.63 \, and \, -0.54)\).

**General Intellectual Ability**

General intellectual function, both in patients and in their matched healthy controls, showed evidence of minor but statistically significant improvement over time. As Gochman et al\(^{33}\) noted, measures of intellectual ability assessed on multiple occasions over a period of over 13 years show some degree of variability both in schizophrenia patients and in controls. In this study, full-scale IQ and performance IQ mean scores increased by 6.75 and 11.84 points, respectively, in patients and by 1.12 and 5.12 points in controls between baseline and follow-up. Verbal IQ scores for both groups were essentially unchanged.

Longitudinal studies of changes in IQ suggest fluctuations in IQ scores that are either minor or transient and inconsequential (eg, Moffitt et al\(^{48}\)), and perhaps this is the most likely explanation for our findings. Measurement error is another possibility particularly because baseline IQ measures for all participants were converted to WISC-III equivalents, while at follow-up current IQ scores were obtained with the WAIS-R.

Very few studies have examined the effect of transition from the childhood to adult versions of the Wechsler Intelligence Scales on IQ scores in healthy individuals. Sirois et al\(^{49}\) examined this in 30 healthy young people who participated as controls in a longitudinal study of cognition in children and adolescents with hemophilia who were administered the children and adult versions with a 2-year interval. As in our sample, they found a negligible decrease in verbal IQ and a statistically significant increase of 3.8 points in performance IQ which is comparable with the increase observed in our control sample.

**Attention**

Attentional dysfunction is a well-replicated finding in adult onset schizophrenia and is present even in first-episode patients\(^{50,51}\). Most EOS studies have failed to find attentional deficits\(^{12,52–55}\), although there have been exceptions.\(^{11}\) Our results together with those of Thaden et al\(^{34}\) suggest that the discrepancy between adult and EOS studies could be accounted for by an increase in the divergence in attentional function, during adolescence, between patients and controls. Thaden et al\(^{34}\) compared attentional function in 59 EOS cases to 53 healthy controls aged 10–20 years at the time of testing. They found that the magnitude of deviance in patients increased gradually across the tested age range primarily as a function of improved performance in older controls.

In our study, differences between EOS patients and controls emerged only at follow-up and were due both to improvement in controls but also decline in patients. This finding suggests an interaction between developmental and disease-related mechanisms impacting neural substrates involved in attentional control.
Memory
In our sample, controls showed marginal improvement in WMS-R memory indices, while patients’ test scores showed evidence of decline which was statistically significant for verbal memory \( P = .05 \) and attentional control \( P = .007 \). We then examined differences between IQ and the GMI (IQ-GMI) and between IQ and the DRI (IQ-DRI) which provide additional information about potential differential deficits, relative to general intellectual function, in immediate memory and in consolidation and retrieval. The IQ-GMI and IQ-DRI differences in controls were minimal and showed minimal change over time. Changes in these differences between baseline and follow-up are not directly comparable because IQ measures at baseline were standardized on WISC-III and can only be considered as very approximate. In patients, the IQ-GMI difference at follow-up averaged 15.5 points which points to a relative deficit in new learning compared with general intellectual function even allowing for the fact that the mean IQ of the WMS-R standardization sample favored IQ by 4 points. Similarly, the IQ-DRI difference increased in patients at follow-up and was approximately double that of the standardization sample IQ-DRI difference of 3.7 points. Although this finding implies deficits in consolidation and recall of information, both at baseline and follow-up, the difference between GMI and DRI in patients favored DRI by 2.17 and 6.58 points, respectively. This difference did not show a significant effect of time or diagnosis by time interaction. The most parsimonious explanation for these findings is that memory deficits in EOS remain relatively stable and are mostly seen in measures reflecting acquisition of new learning rather than consolidation and recall. There is some suggestion that impairment in new learning may have increased over the 4-year interval in EOS patients mostly in verbal rather than visual material and may be associated with a decrement in patients’ attention and concentration.

Planning and Mental Flexibility
The TOL is considered a measure of response planning, a multifaceted concept that incorporates core cognitive components of response inhibition, selection and initiation, and working memory. Studies that have examined the effect of age on TOL performance have found improvement in planning accuracy, longer initial and shorter subsequent planning time when comparing children (between 8 and 14 years) to adolescents and adults. TOL performance has been found to be similar between adolescents and adults. \(^{56-58}\) The lack of any effect of time in our control sample is in line with these findings because the majority of participants were adolescents at the time of study entry and therefore no major changes were expected over the follow-up period. Performance on the TOL is considered to reflect the functional integrity of the prefrontal cortex; task-associated activations within the lateral prefrontal cortex (Brodmann Areas [BA] 9, 10, 46), the parietal lobe (BA 7, 40), and the pre-motor cortex (BA 6, 8) have been repeatedly found in magnetic resonance (fMRI) studies of the TOL in healthy individuals. \(^{59-63}\)

Although EOS patients had poor planning accuracy compared with controls both at baseline and at follow-up, there was little change in their performance with time suggesting relative stability in the functional status of the network underpinning TOL performance. The TMT is presumed to test visual search and motor speed (particularly Part A) as well as mental flexibility (particularly Part B). \(^{64}\) In our study, patients’ performance in Part A improved at follow-up compared with baseline, and this effect was not seen in controls. No evidence of practice effects has been found for time intervals longer than a year, \(^{65}\) so practice is an unlikely explanation for the observed improvement. Similarly, although symptoms and medication are known to impact on performance on the TMT, we found no significant correlation with either; neither did symptom levels or type of medication differ between baseline and follow-up. As already discussed, with reference to general intellectual ability, scores on cognitive tests can fluctuate transiently and idiosyncratically over time, and therefore our finding should not be overinterpreted. Performance on the TMT is a very sensitive indicator of neuropsychological impairment, and it is primarily thought to reflect speed of information processing especially Part A. \(^{65}\) Speed of information processing is known to mature during adolescence across a number of cognitive tasks, \(^{56,67}\) and perhaps the improvement seen in patients reflects this process. The TMT is of limited value in pointing to deficits in discrete brain regions or networks. Zakzanis et al\(^{68}\) adapted the TMT for use during fMRI and found that in healthy individuals performance in Part B compared with Part A of the task involved large, mostly left-sided activations widely distributed in dorsal prefrontal and temporal cortical regions, the cingulate gyrus, the insula, and paracentral lobule. Because performance in Part B in our patient sample remained unchanged over time, it could be argued that the function of this network also did not change substantially over the follow-up period.

The overall pattern emerging from our results is that of relative stability in cognitive function in EOS patients because they go through adolescence. Contrary to our initial prediction tests that are purported to be intimately connected with the functional integrity of the prefrontal cortices such as the TOL or delayed recall showed little change over time. The same applied to composite measures of cognitive competence such as the IQ. We identified persistent deficits in EOS in new learning particularly in the verbal memory domain, while there was also evidence of worsening in attentional control. At the same time, we also found some improvement in information processing.
speed, as reflected in better performance in the TMT, suggesting that some aspects of brain maturation in adolescent may progress “normally” in these patients.

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