Growth of the Corpus Callosum in Adolescents Born Preterm

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Objective: To examine the growth of the corpus callosum between adolescence and early adulthood in individuals who were born before 33 weeks' gestation (very preterm [VPT]) and its relation to neuropsychological function.


Setting: A long-term follow-up study into perinatal predictors of outcome after preterm birth at University College Hospital, London.

Participants: A total of 72 VPT and 34 term-born individuals were assessed in adolescence (aged 15 years) and in early adulthood (aged 19 years). Adult assessments took place between June 6, 2002, and October 23, 2004.

Main Exposure: Birth before 33 weeks’ gestation.

Outcome Measure: The cross-sectional area of 4 segments of the corpus callosum, measured on the midsagittal slice of high-resolution structural magnetic resonance images in adolescence and young adulthood.

Results: Total corpus callosum size increased in term and VPT groups, but growth was much greater in the VPT group (13.4% in the VPT group vs 3.3% in the term group). There were significant associations between adult performance IQ and growth of anterior (P = .001), mid-posterior (P = .009), and posterior (P = .009) segments in the VPT group.

Conclusions: The corpus callosum grows dramatically in VPT adolescents, and this growth is associated with neuropsychological outcome. This may represent a delay of a normal maturational process in VPT individuals.

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Pujol et al. estimated that the corpus callosum continues to grow until around the age of 25 years. Giedd et al. found that anterior regions of the corpus callosum (the genu and rostrum) were the first areas to cease growing, with the posterior regions continuing to increase into young adulthood. It is not yet clear how such maturational processes interact with preexisting abnormalities of brain structure in VPT individuals.

In this study, we measured the midsagittal area of the corpus callosum using structural MRI at the age of 15 years and again at the age of 19 years in a group of individuals born before 33 weeks' gestation and in a group of term-born subjects. Both groups also underwent neuropsychological testing. We hypothesized that growth of the corpus callosum during adolescence would be reduced in the VPT group compared with the term-born group. We further hypothesized that corpus callosum growth would be associated with neuropsychological function.

**METHODS**

### VPT GROUP

The VPT individuals were recruited from a cohort born before 33 weeks' gestation between January 4, 1982, and December 29, 1984, who were admitted to the neonatal unit of University College London Hospital within 3 days of birth and later discharged. From this population, 302 survived and were recruited as part of a long-term follow-up study. The cohort was assessed at the ages of 1, 4, 8, and 15 years using a battery of neuropsychological tests. These results have been published elsewhere. At the age of 15 years, 111 of these individuals were assessed (the adolescent assessment). For the young adult assessment (June 6, 2002, and October 23, 2004), these individuals were recontacted. Seventy-four (66.7%) underwent successful imaging at both time points. Preterm individuals who were assessed did not differ significantly from those who were not assessed. Apgar scores at 1 minute (P = .86) and 5 minutes (P = .35), sex (P = .37), or social class (P = .87).

### TERM GROUP

A group of 71 individuals born between 38 and 42 weeks' gestation was recruited by advertisement in the local (south London) press for the adolescent assessments, to act as controls. These same individuals were invited for the young adult assessment at the ages of 15 years and again at the age of 19 years in a group of individuals born before 33 weeks' gestation and in a group of term-born subjects. Successful MRI was performed in 34 (47.9%) of the individuals at both time points.

### MRI DATA

Magnetic resonance images at both time points were performed on a 1.5-T machine (GE Signa Horizon; GE Medical Systems, Milwaukee, Wisconsin). The following sequences were acquired: sagittal, T2-weighted, fast spin-echo, 27 x 4-mm contiguous sections (repetition time, 2500 milliseconds; and effective echo time, 85 milliseconds); axial, T2-weighted, double-echo, fast spin-echo, 28 x 5-mm contiguous sections (repetition time, 2900 milliseconds; and effective echo time, 19 and 95 milliseconds); and a 3-dimensional, T1-weighted, gradient-echo sequence that allowed reconstruction in any plane of 124 1.5-mm sections (repetition time, 35 milliseconds; echo time, 5 milliseconds; and flip angle, 35°).

### CORPUS CALLOSUM MEASURES

The cross-sectional area of the corpus callosum was determined using a software package (Analyze; Biomedical Imaging Resource, Mayo Foundation, Rochester, Minnesota). Images were measured blind to group membership. The corpus callosum was divided into quarters (anterior, midanterior, midposterior, and posterior) following the method of Woodruff et al. In brief, a boundary box is drawn around the corpus callosum in the midsagittal section. This is used as the frame of reference for dividing the corpus callosum into quarters. The outline of the corpus callosum is traced manually. The interrater intraclass reliability coefficient, obtained from 5 randomly selected independent brains on the 4 subregions of the corpus callosum, was 0.98 (95% confidence interval [CI], 0.79-0.99; P < .001) for the anterior quarter, 0.99 (95% CI, 0.88-0.99; P < .001) for the midanterior quarter, 0.96 (95% CI, 0.66-0.99; P < .004) for the midposterior area, and 0.93 (95% CI, 0.60-0.99; P < .01) for the posterior quarter.

### NEUROPSYCHOMETRY

In young adulthood, the Wechsler Abbreviated Scale of Intelligence, a 4-subtest measure, was administered. Measures of verbal, performance, and full-scale IQ were derived. In addition, the Controlled Oral Word Association Test was administered. This measures the spontaneous production of words within 1 minute, either phonologically (words beginning with the letters F, A, and S) or within a particular semantic category (in this case, animals). The total number of words produced in each task was recorded.

### NEONATAL ULTRASONOGRAPHIC RATINGS

Ultrasonographic ratings were performed in the perinatal period using a linear ultrasonographic array. These ratings were used to divide the VPT subjects into 3 groups using the following classification: 0 indicates normal; 1, uncomplicated periventricular hemorrhage; and 2, periventricular hemorrhage and ventricular dilatation.

### ETHICS

This study was approved by the Medical Ethical Committee of the Institute of Psychiatry, King's College. At adolescence, written informed consent was obtained from a parent or guardian. All participants provided written informed consent in adulthood.

### STATISTICAL ANALYSIS

Analysis was performed using a commercially available software program (SPSS, version 11.0; SPSS Inc, Chicago, Illinois). Between-group differences were examined using the t test or χ² tests. Longitudinal between-group differences were assessed using repeated-measures analysis of variance, with corpus callosum segment (4-fold) by time point (2-fold). Significant effects were explored with post hoc paired-sample t tests. A measure of change in corpus callosum cross-sectional areas was derived (adult area–adolescent area). Relationships between change in corpus callosum cross-sectional areas and neuropsychological performance in young adulthood were determined using Kendall partial correlations, controlling for socioeconomic status, which is known to influence neuropsychological performance, and assessment age in adolescence and adulthood.
RESULTS

SAMPLE CHARACTERISTICS

A total of 72 VPT individuals and 34 term-born individuals underwent structural MRI at both time points. Distribution of sex (P = .54) and socioeconomic status (Registrar General’s classification) (P = .09) did not differ significantly between the 2 groups. The VPT individuals were slightly, but significantly, older than term individuals at both adolescent (mean difference, 0.40 years; 95% CI, 0.13-0.68 years) and young adult (mean difference, 0.52 years; 95% CI, 0.12-0.92 years) assessments. Neuropsychological performance in young adulthood differed between the groups. The VPT individuals had significantly lower full-scale IQ (mean difference, 6.9; 95% CI, 1.5-12.3) and verbal IQ (mean difference, 6.2; 95% CI, 0.2-12.4). Performance IQ, phonological verbal fluency, and semantic verbal fluency were lower in the VPT group than the term group, but these differences were not statistically significant (Table 1).

CORPUS CALLOSUM DEVELOPMENT

Repeated-measures analysis of variance (with corpus callosum regions [4-fold] by time point [2-fold]) and group as between-subject factor showed a main effect of time point (P = .003) and corpus callosum segment (P < .001) and a main effect of group (P = .04). There were no significant interactions between segment and time point (P = .52), between segment and group (P = .13), or between time point and group (P = .14).

In adolescence, the total corpus callosum cross-sectional area was 13.7% smaller in the VPT group than in the term group, statistically significant difference. In adulthood, callosum cross-sectional area was only 5.3% smaller in the VPT group than in the term group; this difference was not statistically significant. Total corpus callosum area increased by 13.4% between adolescence and adulthood in the VPT group, a difference that was statistically significant. During the same period, there was a nonsignificant increase of 3.3% in the corpus callosum area in the term group (Table 2).

Paired-sample t tests showed that the cross-sectional area of all 4 segments increased significantly in the VPT group between adolescence and young adulthood. In the term group, cross-sectional area increased significantly only in the midposterior segment over this time (Table 2).

CORPUS CALLOSUM SIZE AND NEUROPSYCHOLOGICAL FUNCTION

Relationships between the absolute cross-sectional area of corpus callosum segments and neuropsychological function in adolescence and young adulthood were assessed using Kendall partial correlations, controlling for age at assessment and socioeconomic status.

In Adolescence

In the VPT group, there were no statistically significant associations between callosal size and IQ. In the term group, there were significant negative correlations between full-scale IQ and midposterior and posterior segment size and between verbal IQ and size of the midposterior segment (Table 3). In Adulthood

In the VPT group, there were statistically significant positive correlations between full-scale IQ and anterior and midanterior segment size and between performance IQ and anterior, midanterior, and posterior segment size. In the term group, there were significant negative correlations between full-scale IQ and posterior segment size and between verbal IQ and anterior and posterior segment size (Table 3).

CORPUS CALLOSUM GROWTH AND ADULT NEUROPSYCHOLOGICAL FUNCTION

Relationships between change in size of the corpus callosum segments and IQ measures in adulthood in each group were assessed using Kendall partial correlations, controlling for socioeconomic status and assessment age in adolescence and adulthood. In the VPT group, adult performance IQ was correlated with growth of the anterior, midanterior, and posterior segments (but not with the midanterior segment). This was mainly accounted for by the block design subtest (Table 4). In addition, there was a correlation between full-scale IQ and growth of the anterior segment, but no correlations with verbal IQ, in the VPT group. There were no significant correlations between corpus callosum growth and adult IQ measures in the term group, with the exception of one weak negative correlation between the matrix reasoning subtest and growth of the midanterior segment. Growth of

<table>
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<th>Characteristic</th>
<th>VPT Group</th>
<th>Term Group</th>
<th>P Valueb</th>
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<tr>
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<tr>
<td></td>
<td>5</td>
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<td>(in adulthood)</td>
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<tr>
<td>Full-scale IQ</td>
<td>96.8 (13.3)</td>
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<td>94.4 (15.5)</td>
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<td>Performance IQ</td>
<td>99.8 (13.5)</td>
<td>104.1 (15.2)</td>
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<td>Phonological verbal fluency</td>
<td>36.1 (10.0)</td>
<td>39.9 (8.7)</td>
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<td>Semantic verbal fluency</td>
<td>19.9 (5.2)</td>
<td>21.7 (5.1)</td>
<td>.09</td>
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</tbody>
</table>

Abbreviation: VPT, very premature.

a Data are given as mean (SD) unless otherwise indicated.
b Using the χ² or t test.
c Data are given as number in each group.

Table 1. Demographic and Neuropsychological Characteristics of the Term and VPT Groups*
we demonstrate that the corpus callosum is growing in tal ultrasonographic severity (tween-subject factor. There was no main effect of neona-point (2-fold) and ultrasonographic classification as the be-

performed, with corpus callosum segment (4-fold) by time

change in semantic (tive correlations between anterior segment growth and

losum growth in either group. There were significant posi-

tional correlations between IQ change and corpus cal-

segment, 2.1%.

The corpus callosum is part of a late-maturing neural sys-

tem that is probably involved in the acquisition of adult-

level cognitive skills during adolescence.12 In this study,

in adulthood.24 We had, thus, expected that VPT corpus cal-

of life, but that its growth slowed down from week 2 to

ultrasonography in low-birth-weight infants. They found

ation. Direct evidence of growth impairment in the cor-

matter connectivity and impair subsequent myeliniza-

infants,23 possibly as a result of vulnerability of oligo-

secrete growth factors and inhibitors that guide axonal

The number of axons composing the corpus callosum

cross-sectional area during adolescence, in term-born and

VPT individuals. However, there are striking, and unex-

pected, differences in corpus callosum growth between

term and VPT groups, with 13% growth in the VPT group,

pared with 3% growth in the term group. This growth

was such that the corpus callosum size difference be-

between the 2 groups in adolescence was attenuated by the

time they reached young adulthood. To our knowledge,

a comparable growth pattern has not been reported pre-

viously in preterm individuals.

White matter pathological features are common in VPT

ants,22 possibly as a result of vulnerability of oligodendrocyte precursors to hypoxia13 and undernutrition.24 Because oligodendrocytes and their precursors also secrete growth factors and inhibitors that guide axonal growth,25 this kind of damage is likely to reduce white

matter connectivity and impair subsequent myeliniza-

Direct evidence of growth impairment in the corpus callosum early in postnatal life is provided by Anderson et al,21 who assessed corpus callosum growth using ultrasonography in low-birth-weight infants. They found that the corpus callosum grew normally in the first 2 weeks of life, but that its growth slowed down from week 2 to week 6. Reduced growth during this period was associated with later cerebral palsy and psychomotor delay. In rats, postnatal undernutrition is associated with reduced numbers of oligodendrocytes and with subsequent hypomyelination of the brain, which persists into adulthood.24 We had, thus, expected that VPT corpus callosum would remain abnormal during adolescence, but we had not predicted that it would show a growth spurt. What could be driving this increase in size?

The number of axons composing the corpus callosum is said to be at its maximum at birth, and it is unlikely that new long-range axonal connections are formed postnatally.10,26 The adolescent growth of the corpus callosum is, thus, unlikely to be because of the growth of more axonal

<table>
<thead>
<tr>
<th>Corpus Callosum Area, mm²</th>
<th>Term Group⁵</th>
<th>VPT Group⁵</th>
<th>Difference Between Term and VPT Groups⁵</th>
<th>Term Group⁶</th>
<th>VPT Group⁶</th>
<th>Difference Between Term and VPT Groups⁶</th>
<th>Term Group⁷</th>
<th>VPT Group⁷</th>
<th>Difference Between Term and VPT Groups⁷</th>
<th>Term Group⁸</th>
<th>VPT Group⁸</th>
<th>Difference Between Term and VPT Groups⁸</th>
<th>Term Group⁹</th>
<th>VPT Group⁹</th>
<th>Difference Between Term and VPT Groups⁹</th>
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<tr>
<td>Total</td>
<td>493.6 (94.2)</td>
<td>425.9 (107.2)</td>
<td>67.7 (25.1 to 110.3)</td>
<td>509.8 (101.3)</td>
<td>482.9 (106.5)</td>
<td>26.9 (−16.3 to 70.2)</td>
<td>172.1 (34.7)</td>
<td>166.3 (38.5)</td>
<td>5.8 (−9.6 to 21.3)</td>
<td>162.0 (−0.6 to 33.1)</td>
<td>160.4 (−0.4 to 33.1)</td>
<td>1.6 (−1.0 to 6.2)</td>
<td>10.4 (0.4 to 19.9)</td>
<td>10.4 (0.4 to 19.9)</td>
<td>0.0 (−1.8 to 2.8)</td>
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<tr>
<td>Anterior segment</td>
<td>168.0 (30.5)</td>
<td>155.8 (42.1)</td>
<td>12.2 (−3.9 to 28.2)</td>
<td>172.1 (34.7)</td>
<td>166.3 (38.5)</td>
<td>5.8 (−9.6 to 21.3)</td>
<td>162.0 (−0.6 to 33.1)</td>
<td>160.4 (−0.4 to 33.1)</td>
<td>1.6 (−1.0 to 6.2)</td>
<td>10.4 (0.4 to 19.9)</td>
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<td>0.0 (−1.8 to 2.8)</td>
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<td>Midanterior segment</td>
<td>77.8 (17.7)</td>
<td>67.1 (22.6)</td>
<td>10.7 (2.0 to 19.4)</td>
<td>80.6 (16.8)</td>
<td>77.4 (18.2)</td>
<td>3.2 (−4.1 to 10.6)</td>
<td>2.8 (−1.1 to 6.8)</td>
<td>10.3 (4.7 to 15.8)</td>
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<td>Midposterior segment</td>
<td>68.3 (17.9)</td>
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<td>12.7 (3.8 to 21.6)</td>
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<td>Posterior segment</td>
<td>164.6 (38.3)</td>
<td>143.5 (43.3)</td>
<td>21.1 (3.9 to 38.3)</td>
<td>168.0 (37.3)</td>
<td>157.2 (39.7)</td>
<td>10.8 (−5.3 to 26.9)</td>
<td>3.4 (−3.0 to 9.8)</td>
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</table>

Abbreviation: VPT, very preterm.

⁵Data are given as mean (SD) unless otherwise indicated.

⁶Data in parentheses are 95% confidence intervals.

⁷The difference in total area was 13.4%; in the anterior segment, 6.7%; in the midanterior segment, 15.4%; in the midposterior segment, 21.9%; and in the posterior segment, 9.5%.
connections. A more plausible mechanism is an increase in either myelinization or axon diameter (or both).

One possible explanation for the disproportionate growth of the corpus callosum in the VPT group is that it is a manifestation of a developmental delay. Perhaps the term group had already gone through a similar growth spurt before they were assessed at the age of 14 to 15 years. Giedd et al.10 found a linear relationship between age and corpus callosum size in a sample ranging in age from 4 to 18 years, which would argue against this explanation. However, the study by Giedd et al was not longitudinal and may have lacked the power to demonstrate nonlinearities of growth in adolescence. The study by Pujol et al11 did include a longitudinal component (imaging was repeated 2 years apart in subjects in various age ranges). They found corpus callosum growth to continue into the mid-20s, with the greatest rate of growth occurring between the ages of 15 and 20 years. However, to our knowledge, detailed data concerning growth trajectories of various brain structures are lacking in healthy and VPT populations.

An alternative possibility is that corpus callosum development in VPT individuals follows a different trajectory than in term individuals and that increased growth is a phenomenon particular to the VPT group. The late growth of the corpus callosum could represent a plastic response to environmental demands or stimuli.18 In animal studies, rats reared in “enriched environments” have a larger corpus callosum than rats reared in “deprived environments,” with larger-diameter and more extensively myelinated axons.19 In contrast, Teicher et al.20 reported an association between childhood neglect and reduced corpus callosum size in humans. As previously discussed, the VPT brain is likely to have reduced white matter connections. A more plausible mechanism is an increase in either myelinization or axon diameter (or both).27

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### Table 3. Kendall Partial Correlations Between Corpus Callosum Size and Cognitive Function in Adolescence and Young Adulthood

<table>
<thead>
<tr>
<th>Group</th>
<th>Anterior Segment</th>
<th>Midanterior Segment</th>
<th>Midposterior Segment</th>
<th>Posterior Segment</th>
<th>At Adolescence</th>
<th>P-value</th>
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<tr>
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<td>vIQ</td>
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<td>0.03</td>
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<td>.76</td>
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<td>.09</td>
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### Table 4. Kendall Partial Correlations Between Corpus Callosum Growth and Cognitive Function in Adolescence and Young Adulthood

<table>
<thead>
<tr>
<th>Group</th>
<th>Anterior Segment</th>
<th>Midanterior Segment</th>
<th>Midposterior Segment</th>
<th>Posterior Segment</th>
<th>At Adolescence</th>
<th>P-value</th>
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<td>.009b</td>
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</thead>
<tbody>
<tr>
<td>fsIQ</td>
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<td>-0.37</td>
<td>.06</td>
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<td>.37</td>
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<tr>
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<td>.02b</td>
<td>.10</td>
<td>.16</td>
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<tr>
<td>pIQ</td>
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<td>-0.07</td>
<td>-0.11</td>
<td>.60</td>
<td>.48</td>
<td>.71</td>
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Abbreviations: fsIQ, full-scale IQ; pIQ, performance IQ; vIQ, verbal IQ; VPT, very preterm.

a Data controlled for socioeconomic status and age at assessment.
b The correlation was significant.
tivity and delayed or reduced myelination. The late growth of the corpus callosum in the VPT group might, thus, represent a neuroplastic response of an “underconnected” brain attempting to preserve function by improving the efficiency (by myelination) of the connections that it does have. Whether such a process would be successful in allowing individuals to successfully transition to adulthood could be answered by follow-up of VPT individuals into their 20s and 30s. Our results suggest that the late growth of the corpus callosum is associated with better adult neuropsychological performance, but adults born VPT continue to underperform on neuropsychological tests compared with their term-born peers, suggesting that late neuroplasticity may not completely compensate for early white matter damage.

We did not find a relationship between birth weight or degree of prematurity and corpus callosum growth. This is consistent with the findings by Nosarti et al,3 who also found no relationship between corpus callosum size and birth weight or gestational age in a similar cohort at the age of 14 years. We also found no association between the severity of perinatal white matter damage (assessed by ultrasonography) and adolescent growth of the corpus callosum. This may reflect the limited spatial resolution of ultrasonography, which makes it much less sensitive to diffuse white matter abnormalities than MRI and may, thus, underestimate the prevalence and severity of perinatal brain lesions.31

White matter networks, including the corpus callosum, are necessary for distributed cognitive functions.32 We demonstrate different patterns of associations between neuropsychological performance and corpus callosum size in adolescence and adulthood. Particularly, there are no such relationships in adolescence in the VPT group, whereas strong associations are found between performance IQ and corpus callosum size in adulthood. The pattern in the term group is more complex, with weak negative and positive correlations, predominantly with verbal IQ, at both ages. The different patterns of relationships between neuropsychological performance and corpus callosum growth in the VPT and term groups would be consistent with the plastic reorganization of brain structure and connectivity in VPT brains.33 Nosarti et al3 did find an association between verbal fluency and the midposterior corpus callosum segment in VPT males at the age of 14 years, but this was not a longitudinal study, which may limit its comparability with the present report. In addition, in the term group, we find that growth of the anterior segment is correlated with improvement in verbal fluency performance (phonological and semantic). Because verbal fluency is a late-maturing “executive function” that requires integration of several distributed brain regions,34,35 it is plausible that myelination of the parts of the corpus callosum connecting frontal areas may be involved in its maturation. A similar pattern was not seen in the VPT group, again indicative of different patterns of associations between callosal growth and neuropsychological performance in the 2 groups. We demonstrate a correlation between adult performance IQ and corpus callosum growth in the VPT group. Performance IQ on the Wechsler Abbreviated Scale of Intelligence is estimated from 2 scaled subtests: block design and matrix reasoning.39 The associations that we demonstrate are predominantly with the block design subtest. The block design subtest is a timed test in which subjects are asked to reproduce patterns using bicolored cubes. It thus requires bimanual manipulation of objects near the visual midline and integration of sensory and motor information between hemispheres. The anatomical localization that we demonstrate in the VPT group is also plausible in this regard. In their healthy sample, Barnea-Goraly et al27 found white matter density to increase with age in the body of the corpus callosum, an area containing fibers linking hemispheric motor, sensory, and auditory processing areas. Growth of anterior callosal connections should allow rapid communication between frontal and premotor cortices,30-38 which would be essential to successful completion of the block design subtest. There were no correlations between midanterior corpus callosum growth and performance IQ in the VPT group. This region of the corpus callosum is likely to carry the relatively sparse connections between left and right motor and sensory cortices. It seems possible that such connections mature earlier than connections between association areas, where late maturation may underlie maturation of cognition.32 The fact that young adults (at the age of 18 years) born VPT have an excess of mirror movements (that are not attenuated by maturation) would be consistent with this.39

This was a relatively large follow-up study, but it only included 2 time points. Thus, we are unable to draw firm conclusions about growth trajectories in either the term or VPT group in adolescence. There was considerable dropout, particularly of the term group, between the ages of 15 and 19 years, and this may have introduced biases. The 2 subject groups were different in age, with the VPT group being slightly older at both assessment ages. The effect of this difference, however, would be to reduce the likelihood of finding a difference between the groups; in addition, we have attempted to correct for this in the statistical analyses. The correlations between corpus callosum growth and neuropsychological variables have not been corrected for the effect of multiple testing, so it remains possible that some of them are chance findings. The pattern of the correlations suggests a genuine effect, but these results should perhaps be regarded as preliminary.

In summary, we have demonstrated a striking pattern of enhanced growth of the corpus callosum in VPT adolescents. This late maturation of brain structure may be of clinical significance (eg, in deciding the timing of social and psychological interventions in VPT individuals).

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Author Contributions: Dr Allin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Allin, Nosarti, Wyatt, Rifkin,

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REFERENCES