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**

**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 mid sagittal 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 of 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 (registar general’s classification)22 (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, a 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 callosoal 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 1. Demographic and Neuropsychological Characteristics of the Term and VPT Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VPT Group</th>
<th>Term Group</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-male ratio</td>
<td>35:37</td>
<td>14:20</td>
<td>.47</td>
</tr>
<tr>
<td>Social classc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>.09</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>16</td>
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<td>3</td>
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<td>9</td>
<td>.26</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>4</td>
<td>.005</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2</td>
<td>.001</td>
</tr>
<tr>
<td>Age during assessment, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>15.4 (0.6)</td>
<td>15.1 (0.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Adult</td>
<td>19.2 (0.9)</td>
<td>18.6 (1.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Neuropsychological measure score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(in adulthood)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>96.8 (13.3)</td>
<td>103.7 (12.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>94.4 (15.5)</td>
<td>100.6 (12.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>99.8 (13.5)</td>
<td>104.1 (15.2)</td>
<td>.15</td>
</tr>
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<td>Phonological verbal fluency</td>
<td>36.1 (10.0)</td>
<td>39.9 (8.7)</td>
<td>.06</td>
</tr>
<tr>
<td>Semantic verbal fluency</td>
<td>19.9 (5.2)</td>
<td>21.7 (5.1)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviation: VPT, very preterm.
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.
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
level cognitive skills during adolescence.12 In this study,
The corpus callosum is part of a late-maturing neural sys-
change in semantic (tive correlations between anterior segment growth and
losum growth in either group. There were significant posi-
nificant correlations between IQ change and corpus cal-
lescence and adulthood were assessed using Kendall par-
bal fluency in either the term or the VPT group.
The 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
area, mm2
Corpus
Callosum
Adolescent
Young Adult
Corpus
Callosum
Area, mm2
Difference
Between
Term and
VPT Groups
b
Term
Groupa
VPT
Groupa
Difference
Between
Term Adult
and Term
Adolescentb,c
Difference
Between
VPT Adult
and VPT
Adolescentb,d
Total
493.6 (94.2)
425.9 (107.2)
67.7 (25.1 to 110.3)
509.8 (101.3)
482.9 (106.5)
26.9 (−16.3 to 70.2)
16.2 (−0.6 to 33.1)
57.0 (34.0 to 80.1)
Anterior
segment
168.0 (30.5)
155.8 (42.1)
12.2 (−3.9 to 28.2)
172.1 (34.7)
166.3 (38.5)
5.8 (−9.6 to 21.3)
4.1 (−2.7 to 10.9)
10.4 (0.9 to 19.9)
Midanterior
segment
77.8 (17.7)
67.1 (22.6)
10.7 (2.0 to 19.4)
80.6 (16.8)
77.4 (18.2)
3.2 (−4.1 to 10.6)
2.8 (−1.1 to 6.8)
10.3 (4.7 to 15.8)
Midposterior
segment
68.3 (17.9)
55.6 (23.1)
12.7 (3.8 to 21.6)
73.9 (20.7)
67.8 (21.7)
6.1 (−2.6 to 15.0)
5.6 (0.6 to 10.7)
12.2 (6.2 to 18.2)
Posterior
segment
164.6 (38.3)
143.5 (43.3)
21.1 (3.9 to 38.3)
168.0 (37.3)
157.2 (39.7)
10.8 (−5.3 to 26.9)
3.4 (−3.0 to 9.8)
13.7 (3.8 to 23.7)
Area, mm2
Abbreviation: VPT, very preterm.
bData in parentheses are 95% confidence intervals.
cThe difference in total area was 3.3%; in the anterior segment, 2.4%; in the midanterior segment, 3.6%; in the midposterior segment, 8.2%; and in the posterior segment, 2.1%.
dThe 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%.
the corpus callosum was not associated with adult ver-
bral fluency in either the term or the VPT group.
CORPUS CALLOSUM GROWTH AND CHANGE
IN NEUROPSYCHOLOGICAL FUNCTION
Changes in neuropsychological test scores between ado-
lescence and adulthood were assessed using Kendall par-
tial correlations, again controlling for age at assessment
and socioeconomic status. There were no statistically sig-
ificant correlations between IQ change and corpus cal-
sum growth in either group. There were significant posi-
tive correlations between anterior segment growth and
change in semantic (r = 0.39, P = .03) and phonological
(r = 0.45, P = .01) verbal fluency in the term group, but
not in the VPT group.
PERINATAL ADVERSITY AND
CORPUS CALLOSUM GROWTH
There were no significant correlations between change in
corpus callosum cross-sectional areas and either birth weight
(P = .12) or gestational age (P = .08) in the VPT group. The
VPT group was divided based on the severity of neonatal ultrasonographic appearances, following the method of Nos-
arti et al,26 and a repeated-measures analysis of variance was
performed, with corpus callosum segment (+fold) by time
point (2-fold) and ultrasonographic classification as the be-
tween-subject factor. There was no main effect of neon-
tal ultrasonographic severity (P = .66).

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, we demonstrate that the corpus callosum is growing in
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,
compared with 3% growth in the term group. This growth
was such that the corpus callosum size difference be-
tween 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
infants,23 possibly as a result of vulnerability of oligo-
dendrocyte precursors to hypoxia13-15 and undernutri-
tion.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-
tion. Direct evidence of growth impairment in the cor-
pus callosum early in postnatal life is provided by Anders-
on 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 associ-
ated with later cerebral palsy and psychomotor delay. In
rats, postnatal undernutrition is associated with re-
duced numbers of oligodendrocytes and with subse-
quent hypomyelinization of the brain, which persists into
adulthood.24 We had, thus, expected that VPT corpus cal-
losum 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 postna-
tally.12,26 The adolescent growth of the corpus callosum is,
thus, unlikely to be because of the growth of more axonal

Table 2. Midsagittal Cross-sectional Area of the Whole Corpus Callosum and of Its 4 Quarters

<table>
<thead>
<tr>
<th>Corpus Callosum Area, mm²</th>
<th>Term Groupa</th>
<th>VPT Groupa</th>
<th>Difference Between Term and VPT Groupsb</th>
<th>Term Groupa</th>
<th>VPT Groupa</th>
<th>Difference Between Term Adult and Term Adolescentb,c</th>
<th>Difference Between VPT Adult and VPT Adolescentb,d</th>
</tr>
</thead>
<tbody>
<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>16.2 (−0.6 to 33.1)</td>
</tr>
<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>4.1 (−2.7 to 10.9)</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Midposterior segment</td>
<td>68.3 (17.9)</td>
<td>55.6 (23.1)</td>
<td>12.7 (3.8 to 21.6)</td>
<td>73.9 (20.7)</td>
<td>67.8 (21.7)</td>
<td>6.1 (−2.6 to 15.0)</td>
<td>5.6 (0.6 to 10.7)</td>
</tr>
<tr>
<td>Posterior segment</td>
<td>164.6 (38.3)</td>
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<td>10.8 (−5.3 to 26.9)</td>
<td>3.4 (−3.0 to 9.8)</td>
</tr>
</tbody>
</table>

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connections. A more plausible mechanism is an increase in either myelinization or axon diameter (or both).27

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 al10 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 nonlineairties of growth in adolescence. The study by Pujol et al12 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.28 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.29 In contrast, Teicher et al30 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 connec-

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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>
</tr>
</thead>
<tbody>
<tr>
<td>VPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fsIQ</td>
<td>Correlation</td>
<td>0.09</td>
<td>0.04</td>
<td>−0.05</td>
</tr>
<tr>
<td>P value</td>
<td>.51</td>
<td>.78</td>
<td>.72</td>
<td>.65</td>
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<tr>
<td>vIQ</td>
<td>Correlation</td>
<td>0.02</td>
<td>0</td>
<td>−0.07</td>
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<tr>
<td>P value</td>
<td>.86</td>
<td>&gt;.99</td>
<td>.61</td>
<td>.64</td>
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<tr>
<td>pIQ</td>
<td>Correlation</td>
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<td>−0.04</td>
</tr>
<tr>
<td>P value</td>
<td>.43</td>
<td>.76</td>
<td>.79</td>
<td>.83</td>
</tr>
<tr>
<td>Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fsIQ</td>
<td>Correlation</td>
<td>−0.29</td>
<td>−0.07</td>
<td>−0.42</td>
</tr>
<tr>
<td>P value</td>
<td>.10</td>
<td>.69</td>
<td>.02b</td>
<td>.04b</td>
</tr>
<tr>
<td>vIQ</td>
<td>Correlation</td>
<td>−0.23</td>
<td>−0.24</td>
<td>−0.42</td>
</tr>
<tr>
<td>P value</td>
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<td>.19</td>
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<td>P value</td>
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<td>P value</td>
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<td>.009b</td>
<td>.009b</td>
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</tr>
<tr>
<td>fsIQ</td>
<td>Correlation</td>
<td>−0.34</td>
<td>−0.24</td>
<td>−0.17</td>
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<tr>
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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, 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.

White matter networks, including the corpus callosum, are necessary for distributed cognitive functions. 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. Nosarti et al 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, 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. 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 al 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, 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. 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.

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,
Role of the Sponsor: This study was supported by the Welcome Trust; the Peggy Pollak Fellowship in Developmental Psychiatry, Psychiatry Research Trust (Dr Allin); and grant 2005 BE 00226 from Generalitat de Catalunya (Dr Narberhaus).

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# REFERENCES


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