Prefrontal Structural Correlates of Cognitive Control during Adolescent Development: A 4-Year Longitudinal Study

Nandita Vijayakumar1, Sarah Whittle1,2, Murat Yücel1,2,3, Meg Dennison1, Julian Simmons1, and Nicholas B. Allen1

Abstract

Maturation of cognitive control abilities has been attributed to the protracted structural maturation of underlying neural correlates during adolescence. This study examined the relationship between development of two forms of cognitive control (proactive and reactive control) and structural maturation of the ACC, dorsolateral pFC, and ventrolateral pFC (vlPFC) between early and mid adolescence using a longitudinal design. Adolescents (n = 92) underwent baseline assessments when they were 12 years old and follow-up assessments approximately 4 years later. At each assessment, structural MRI scans were acquired, and a modified Stroop task was performed. Results showed longitudinal improvements in reactive control between early and mid adolescence. Furthermore, magnitude of the improvement in proactive control was associated with reduced thinning of the right vlPFC across the sample, whereas the magnitude of the improvements in reactive control was associated with reduced thinning of the left ACC in men alone. These findings suggest that individual differences in the maturation of ACC and vlPFC underlie the development of two distinct forms of cognitive control between early and mid adolescence as well as highlight sex differences in this relationship.

INTRODUCTION

Adolescence is a period of significant maturation of cognitive control, which refers to the ability to flexibly adapt and direct cognitive processing. It enables individuals to engage in goal-directed behavior, such as control of impulses, inhibition of unwanted thoughts, and regulation of emotions (Hofmann, Schmeichel, & Baddeley, 2012; Heatherton & Wagner, 2011). Deficits in cognitive control have been related to deficits in social behavior, poorer school competence (Chica & Rueda, 2011; Rueda, Chica, & Rothbart, 2010; Blair & Razza, 2007), and various forms of psychopathology, including ADHD (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Carr, Henderson, & Nigg, 2010; King, Colla, Brass, Heuser, & Von Cramon, 2007), substance use (Hester, Lubman, Cohen, Stenger, & Carter, 2004; Botvinick, Nystrom, Fissel, Carter, & Cohen, 1999).

Recent research suggests that cognitive control can be differentiated into a number of component processes. One such model argues for two distinct operating modes of cognitive control: “proactive” and “reactive” (Braver, Gray, & Burgess, 2007). Proactive control refers to preparatory/anticipatory processes that are sustained over the duration of a given task, whereas reactive control refers to transient processes that are implemented once a stimulus has been perceived. This model differentiates between the role of the lateral and medial pFC in cognitive control. Lateral regions of pFC, such as the dorsolateral pFC (dlPFC) and ventrolateral pFC (vlPFC), are hypothesized to be crucial for proactive control, as these regions are thought to bias attention and information processing toward task-relevant goals, whereas the medial pFC, particularly the ACC, is thought to be crucial for reactive control, given its role in evaluation and monitoring of conflict (Kerns et al., 2004; van Veen, Holroyd, Cohen, Stenger, & Carter, 2004; Botvinick, Nystrom, Fissel, Carter, & Cohen, 1999).

Development of Cognitive Control during Adolescence

Although little research has assessed maturation of proactive and reactive control across adolescence, a number of studies have found age-related improvements in more generalized measures of cognitive control (Huizinga, Dolan, & van der Molen, 2006; Leon-Carrion, Garcia-Orza, & Perez-Santamaria, 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004). It is postulated that these developmental improvements are supported by the concurrent maturation of underlying neural regions (Steinberg,
2010; Giedd, 2008; Paus, 2005). Indeed, the structural properties of underlying neural regions have also been found to mature during adolescence, with research consistently identifying a reduction of gray matter thickness across most areas of the cortex (Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014; Mutlu et al., 2013; Brown et al., 2012; van Soelen et al., 2012; Shaw, Lerch, et al., 2006; Gogtay et al., 2004). However, limited research has specifically investigated the relationship between the development of brain structure and cognitive control during adolescence (Pfeifer & Allen, 2012). The only longitudinal study to date found that improvements in working memory, as indexed by a keep track task, were related to reductions in cortical volume of the prefrontal and posterior parietal regions in 8- to 20-year-olds (Tamnes et al., 2013). However, research on cortical volume limits the conclusions that may be drawn about underlying neurobiological mechanisms, given that volume is a global measure of cortical thickness and surface area, which are two genetically and phenotypically independent characteristics of the cortex (Winkler et al., 2009, 2010; Panizzon et al., 2009). Studies on cortical thickness have been limited to cross-sectional samples, with inconsistent results. Although two studies failed to identify a relationship between maturation of cortical thickness and working memory abilities in adolescents (Fjell et al., 2012; Østby, Tamnes, Fjell, & Walhovd, 2011), one study found that greater cortical thinning of parieto-occipital regions was associated with superior performance on an anti-saccade task whereas less cortical thinning of lingual and fusiform cortices was associated with superior performance on the Stroop task. Therefore, although cortical thinning is postulated to underlie cognitive development during adolescence, further research is needed to gain a better understanding of this relationship given the inconsistent findings to date.

An important limitation of existing research is that most studies have modeled “development” using cross-sectional samples consisting of a wide age band, which can produce great intersubject variability and results that differ to those arising from longitudinal studies investigating within-subject change over time (e.g., Durston & Casey, 2006). Furthermore, research parsing proactive and reactive control in children and adolescents has been limited (Yücel et al., 2012; Andrews-Hanna et al., 2011), with no studies investigating structural maturation in relation to these dual mechanisms of control.

The Current Study

The current study investigated the concurrent relationship between development of proactive and reactive control, and thickness of underlying cortical regions between early and mid adolescence using a longitudinal design, with a strictly constrained age range during each period of assessment. It was hypothesized that proactive and reactive control, as assessed by performance on a modified Stroop task, would improve with age. It was also hypothesized that thinning of ACC would be associated with superior development of reactive control whereas thinning of the dLPCF and vLPCF would be associated with superior development of proactive control.

METHODS

Participants

The sample described in the current study was derived from a larger longitudinal cohort enrolled in the Orygen Adolescent Development Study, conducted in Melbourne, Australia. Two thousand four hundred fifty-three students in the final year of primary school were recruited from schools across metropolitan Melbourne to participate in an initial school-screening phase, which involved completion of the Early Adolescent Temperament Questionnaire-Revised (EATQ-R; Capaldi & Rothbart, 1992). On the basis of their scores on this measure, a smaller sample of 425 students was selected to be part of the study, which has previously been described in detail by Yap et al. (2011). Adolescents at the extreme ends of the temperamental distribution were oversampled to maximize interindividual differences in psychological well-being.

Of the selected adolescents, 245 agreed to participate in further research. These participants were screened for Axis I disorders using the Schedule for Affective Disorder and Schizophrenia for School-Aged Children: Present and Lifetime Version (Kaufman & Schweder, 2004), and those who met the criteria for current or past MDD, substance use disorder, or eating disorder were excluded because of the broader aims of the study. Remaining participants were invited to take part in brain MRI and cognitive assessments (see below for details) at two time points, when they were aged approximately 12 and 16 years, respectively. IQ was also assessed at baseline using a short form of the Weschler Intelligence Scale for Children, Fourth Version (Wechsler, 2003), and socioeconomic classification was assessed based on the Australian National University Four (ANU4) Scale (Jones & McMillan, 2001). A number of adolescents declined participation in the MRI assessments, resulting in 120 participants completing all assessments at both baseline and follow-up. On the basis of visual inspection of processed MRI data (i.e., FreeSurfer cortical parcellation, see below for details) by a researcher trained in neuroanatomy, 17 of these participants were excluded because of poor MRI image quality and parcellation. Only 11 participants were predominantly left-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Given that this number was too small to examine handedness effects, left-handers were excluded to avoid potential laterality effects (Good et al., 2001).

Following MRI and handedness exclusions, 92 participants (n = 47 girls) were available for analysis. Boys and girls did not differ on the demographic and cognitive variables listed in Table 1 (all ps > .05). The
Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>45</td>
<td>47</td>
<td>92</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>12.67; 0.42; 11.37–13.61</td>
<td>12.65; 0.46; 11.95–14.08</td>
<td>12.67; 0.44; 11.37–14.08</td>
</tr>
<tr>
<td>Age at follow-up (years)</td>
<td>16.42; 0.46; 14.96–17.27</td>
<td>16.44; 0.54; 15.28–17.49</td>
<td>16.43; 0.50; 14.96–17.69</td>
</tr>
<tr>
<td>Delay (years)</td>
<td>3.76; 0.17; 3.48–4.12</td>
<td>3.78; 0.30; 2.69–4.56</td>
<td>3.77; 0.24; 2.69–4.56</td>
</tr>
<tr>
<td>Estimate full-scale IQ</td>
<td>107.06; 11.02; 79–128</td>
<td>104.07; 10.92; 87–123</td>
<td>105.53; 11.02; 79–128</td>
</tr>
<tr>
<td>Socioeconomic classification$^b$</td>
<td>58.98</td>
<td>58.53</td>
<td>58.76</td>
</tr>
</tbody>
</table>

Values represent mean; standard deviation; range.

$^a$Delay between baseline and follow-up MRI scan.

$^b$Data missing for one female participant.

The final sample did not differ from the initial school screening sample ($n = 2453$) on socioeconomic disadvantage ($t(2439) = 0.60; p = .55$) or sex (Pearson’s $\chi^2 = 0.80; p = .94$). Fifteen participants of the final sample met the criteria for past or current psychiatric disorder at baseline and 26 participants met the criteria for a psychiatric diagnosis between baseline and follow-up (of which 17 had not met any criteria at baseline). Refer to Table 2 for further detail on psychiatric diagnoses. Informed consent was obtained from the child and at least one parent/guardian at each time point, consistent with the guidelines of the Human Research Ethics Committee at the University of Melbourne, Australia.

MRI Acquisition and Analysis

Image Acquisition

At baseline, MRI scans were performed on a 3-T GE scanner at the Brain Research Institute, Austin, and Repatriation Medical Centre, Melbourne, Australia, with the following parameters: repetition time = 36 msec, echo time = 9 msec, flip angle = 35°, field of view = 20 cm$^2$, 124 T1-weighted contiguous slices (voxel dimensions = 0.4883 × 0.4883 × 1.5 mm). MRI scans at follow-up were performed on a 3-T Siemens scanner at the Royal Children’s Hospital, Melbourne, Australia, with the following parameters: repetition time = 1900 msec, echo time = 2.24 msec, flip angle = 9°, field of view = 25 cm, 176 T1-weighted contiguous 0.9-mm thick slices (voxel dimensions = 0.9 mm$^3$).

Image Processing

Images were transferred to an SGI/Linux workstation for morphometric analysis. Cortical reconstruction was performed using the FreeSurfer image analysis suite (surfer.nmr.mgh.harvard.edu/). To address issues arising from longitudinal and/or multisite studies (such as geometric distortion and voxel dimension drift), images were processed through the longitudinal stream of FreeSurfer version 5.1 (Reuter, Schmansky, Rosas, & Fischl, 2012), which creates a within-unbiased subject template space and average image from both time points using robust, inverse consistent registration (Reuter & Fischl, 2011). The template is used as an estimate to initialize subsequent segmentation processes in the longitudinal stream for each time point, providing common information regarding anatomical structures. This process can deal with different intensity scales, guarantees inverse consistency (i.e., symmetry), and automatically estimates a sensitivity parameter to detect outlier regions in the image. It significantly improves the repeatability and power of cortical thickness measurements, having superior robustness with respect to noise, intensity scaling, and outliers when compared with alternate registration tools (Reuter, Rosas, & Fischl, 2010). All images were also corrected for tissue signal inhomogeneity using FreeSurfer’s N3 correction (optimized for 3-T images), a nonparametric nonuniformity intensity normalization method, which reduces sensitivity to changes in scanner platform and improves accuracy and robustness during cortical segmentation (Zheng, Chee, & Zagorodnov, 2009).

Table 2. Psychopathology Characteristics of the Sample

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorder not otherwise specified, $n = 2$; simple phobia, $n = 6$; social phobia, $n = 3$; posttraumatic stress disorder, $n = 1$; obsessive compulsive disorder, $n = 1$; oppositional defiant disorder, $n = 2$; attention deficit disorder not otherwise specified, $n = 1$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between Baseline and Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder, $n = 13$; simple phobia, $n = 1$; social phobia, $n = 4$; posttraumatic stress disorder, $n = 1$; separation anxiety disorder, $n = 1$; adjustment disorders with depressed mood, $n = 3$; adjustment disorder with anxious mood, $n = 1$; eating disorder not otherwise specified, $n = 1$; substance dependence, $n = 1$; conduct disorder, $n = 6$; oppositional defiant disorder, $n = 2$</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Boyes et al., 2008). All FreeSurfer image processing was conducted on a high-performance computing facility at the Melbourne Neuropsychiatry Centre, Melbourne, Australia.

**ROI Delineation**

A customized ACC ROI was created by combining the rostral and caudal ACC labels defined by FreeSurfer’s automated cortical parcellation procedure (Desikan et al., 2006). The dLPFC ROI was created by combining the superior frontal, rostral middle frontal, and caudal middle frontal gyri, whereas the vLPFC ROI was created by combining the pars opercularis, pars triangularis, and pars orbitalis, as labeled by FreeSurfer. A coronal cut was applied at Talairach coordinate \( y = 26 \) to the dLPFC and vLPFC ROIs so that only prefrontal regions were included (to conform to the conservative Talairach criteria described by Rajkowska and Goldman-Rakic, 1995). In addition, another cut was made along the superior edge of medial wall of the brain for the dLPFC ROI to exclude the medial surface of the brain.

**Cortical Development**

Annualized percentage change (APC) was calculated for each ROI as an index of cortical development using the following formula:

\[
\text{APC} = \left( \frac{\text{Thickness 2} - \text{Thickness 1}}{\text{Thickness 1}} \right) \times \left( \frac{1}{\text{Time interval}} \right) \times 100.
\]

Time interval was the time in years between baseline (Thickness 1) and follow-up (Thickness 2) for each individual. Positive APC scores reflect an increase in cortical thickness over time, whereas negative scores reflect a reduction in thickness.

**Interscanner Reliability**

Given that different scanners were used at Times 1 and 2, a reliability analysis was undertaken to address concerns that changes in cortical thickness over time may be because of measurement bias from the different scanner platforms and acquisition parameters. Four individuals, aged 23, 28, 35, and 36 years, were each scanned at RCH and BRI within a 2-week period. The same acquisition parameters were used at each location to those described above, as well as the same semiautomated methods of processing to extract ROI thickness.

On the basis of mean absolute thickness difference, interscanner variability was found to vary from 0.04 to 0.09 mm across ROIs, as shown in Table 3. These variations are consistent with within scanner estimates previously reported by Han et al. (2006). Table 3 also contains test–retest reproducibility errors and 95% confidence intervals for ROIs. The reproducibility errors for each participant were calculated as the absolute test–retest percent change relative to the mean test–retest value. These values were then averaged across participants. These results did not reveal a systematic bias because of changing scanners, as the confidence intervals for reproducibility errors contained zero for all ROIs apart from the right dLPFC.

Given the importance of this issue, the data from the interscanner reliability analysis was applied to the current sample using the descriptive procedure proposed by Lebel and Beaulieu (2011). They produced established thresholds for determining whether the amount of change observed in the study sample was likely to have occurred over and above that expected from scanner effects. Specifically, standard deviations for each ROI were calculated for each person within the reliability study based on their scores from each scanner. The group average standard deviation was then calculated for each ROI (mean SD across all participants), which are listed in Table 3. These values provide estimates of the measurement variability in each ROI that can be expected from scanner differences alone. The average SD data were applied to the study sample to determine the proportion (i.e., percentage) of participants that experienced greater change, either increases or decreases, than the average SD. For each participant, change for each

Table 3. Reliability Statistics Based on a Separate Sample of Individuals Scanned at Both Neuroimaging Sites

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mean Absolute Difference (mm)</th>
<th>Reproducibility Error (%)</th>
<th>95% CI for Reproducibility Error (%)</th>
<th>Average SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ACC</td>
<td>0.043</td>
<td>1.40</td>
<td>−1.15, 3.95</td>
<td>0.030</td>
</tr>
<tr>
<td>Right ACC</td>
<td>0.074</td>
<td>2.53</td>
<td>−1.67, 6.73</td>
<td>0.053</td>
</tr>
<tr>
<td>Left dLPFC</td>
<td>0.090</td>
<td>2.37</td>
<td>−0.32, 7.22</td>
<td>0.064</td>
</tr>
<tr>
<td>Right dLPFC</td>
<td>0.081</td>
<td>1.40</td>
<td>0.91, 3.76</td>
<td>0.057</td>
</tr>
<tr>
<td>Left vLPFC</td>
<td>0.087</td>
<td>2.27</td>
<td>−0.38, 6.83</td>
<td>0.061</td>
</tr>
<tr>
<td>Right vLPFC</td>
<td>0.083</td>
<td>1.99</td>
<td>−0.70, 6.25</td>
<td>0.059</td>
</tr>
</tbody>
</table>

The group reproducibility error for each structure is derived averaging the reproducibility errors across participants, where for each participant the error is estimated as the absolute test–retest thickness percent change relative to the mean test–retest thickness.
ROI was calculated using a difference score (i.e., cortical thickness for Time 2 − Time 1). Those with difference scores within 1 SD (determined from the reliability study) were considered to not change, whereas those with difference scores greater than 1 SD were considered to experience true change (over and above scanner effects). When the majority of participants (i.e., >50%) experienced longitudinal change over and above that expected from scanner effects, this is taken as evidence that changes in cortical thickness identified by the mixed models in the study sample was reliable. The results from our sample, presented in Figure 1, indicate that for each ROI the majority of individuals (>50%) experienced greater reduction in thickness over time than would be attributed to interscanner variance alone based on the reliability estimates.

**Modified Stroop Paradigm**

Participants completed a modified version of the Stroop task at baseline and follow-up, which has been validated by Carter et al. (2000). Similar to the original Stroop task, participants were required to respond to the color of written stimuli, which were themselves names of colors. Stimuli were either congruous (i.e., the word “blue” written in blue: BLUE) or incongruous (i.e., the word “red” written in blue: RED). Incongruent trials required participants to select a weaker, task-relevant response (naming the color) in the face of a competing stronger, but task-irrelevant response (reading the word). The response competition usually increases RT for incongruent trials, resulting in an “interference effect,” which is the difference between RT for congruent and incongruent trials.

In addition, our paradigm modified the proportion of incongruent trials within task blocks to examine proactive versus reactive aspects of cognitive control as per Yücel et al.’s (2012) study. Participants completed 48 practice trials, followed by two blocks of 96 experimental trials. One block was manipulated to have a higher proportion of congruent trials (Mostly Congruent [MC]: 75% probability; 72 congruent and 24 incongruent trials), whereas the other block had a higher proportion of incongruent trials (Mostly Incongruent [MI]: 75% probability; 72 incongruent and 24 congruent trials). It is purported that proactive control is supported by the dlPFC and vlPFC and is employed during conditions of high probability of incongruent trials in the MI block, as participants can predict these trials and employ conscious top-down control to adjust the relative influence of word reading on color naming and reduce the amount of response competition for incongruent trials. Comparatively, during conditions of high expectancy of congruent trials in the MC block, participants cannot develop such cognitive strategy and use reactive/evaluative control for each trial, which is supported by ACC. This is thought to result in less control over the prepotent word reading tendency, thus causing greater response conflict for incongruent trials. The order of administration of MI and MC blocks was counterbalanced across participants. The task was presented using Presentation 0.70 software (Neurobehavioural Systems, Albany, CA) on a PC laptop.

**Statistical Analysis**

All analyses were conducted using SPSS version 20, and results were considered significant at $p < .05$. Analyses were conducted using Stroop interference scores, which were calculated by subtracting mean RT for congruent trials from mean RT for incongruent trials, with larger scores indicating poorer response inhibition. General linear models were used to analyze the data, with separate models employed for the two expectancy conditions (MI and MC). A backward elimination method was employed to remove interaction effects that were not significant.
The first analytic model investigated the development of cognitive control between baseline and follow-up, including the main effect of Time (within-subject factor) and Sex (between-subject factor), and the interaction between Time and Sex. Subsequently, six models (3 ROIs × 2 Hemispheres) were fitted to identify the longitudinal relationship between cortical development of each ROI and cognitive development. These models included Time (within-subject factor), Sex (between-subject factor), Cortical Development (i.e., APC scores; between-subject factor), and all two- and three-way interactions. In addition, these models were rerun controlling for average cortical development of the relevant hemisphere to investigate the specificity of our findings to the ROIs. Age at baseline was also incorporated into all models.

### Treatment of Missing Data

Twelve participants in the final sample had missing Stroop data at either baseline or follow-up. In addition, one participant’s Stroop scores were excluded on the basis of errors being greater than 50%. Little’s MCAR test was found to be nonsignificant ($p > .05$), indicating that

### Table 4. Mean (SD) of RT and Interference Score at Baseline and Follow-up Assessments for the Stroop Task

<table>
<thead>
<tr>
<th></th>
<th>Mostly Congruent</th>
<th>Mostly Incongruent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incongruent RT</td>
<td>Congruent RT</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1061 (189)</td>
<td>851 (152)</td>
</tr>
<tr>
<td>Boys</td>
<td>1080 (162)</td>
<td>857 (125)</td>
</tr>
<tr>
<td>Girls</td>
<td>1044 (214)</td>
<td>847 (175)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>901 (171)</td>
<td>733 (130)</td>
</tr>
<tr>
<td>Boys</td>
<td>898 (173)</td>
<td>750 (128)</td>
</tr>
<tr>
<td>Girls</td>
<td>904 (171)</td>
<td>716 (130)</td>
</tr>
</tbody>
</table>

INT = interference score.

**Figure 2.** Mean interference scores in boys and girls at baseline and follow-up for the MC expectancy condition.
the data were missing completely at random, and thus, missing data were imputed using the Expectation Maximization procedure in SPSS version 20.

RESULTS

Behavioral Data

Table 4 shows the mean RT and interference scores for the Stroop task during baseline and follow-up. Analyses conducted on interference scores revealed a significant interaction between Time and Sex for the MC condition ($b = 65.81$, $t(179) = 2.09$, $p = .038$). As illustrated in Figure 2, boys did not differ in interference scores from girls at baseline, $F(1, 179) = 1.38$, $p = .24$, but they exhibited significant reductions in the interference score between baseline and follow-up, $F(1, 179) = 11.19$, $p = .001$, whereas girls did not exhibit change over time, $F(1, 179) = 0.19$, $p = .666$. This resulted in a trend toward a significant difference between the two sexes at follow-up, $F(1, 179) = 3.17$, $p = .077$. No significant time or sex effects were identified for the MI condition.

Cortical Development (Change over Time)

Table 5 shows mean cortical development (APC) over time for boys and girls. Independent samples $t$ tests did not reveal sex differences in cortical development for any of the ROIs. Models investigating the effects of cortical development on the MC condition revealed a significant three-way interaction between left ACC development, between baseline and follow-up, $F(1, 179) = 11.19$, $p = .001$, whereas girls did not exhibit change over time, $F(1, 179) = 0.19$, $p = .666$. This resulted in a trend toward a significant difference between the two sexes at follow-up, $F(1, 179) = 3.17$, $p = .077$. No significant time or sex effects were identified for the MI condition.

Figure 3. Change in interference score in relation to left ACC development for the MC expectancy condition in men. Cortical development is calculated as APC, with negative scores indicating greater thinning over time. Change in interference is the difference between baseline and follow-up scores, with negative scores indicating a reduction in interference (i.e., improved cognitive control).
sex, and time ($b = 45.20; t(175) = 2.03, p = .044$). Post hoc analyses conducted separately for the two sexes revealed a significant two-way interaction between left ACC development and time in boys ($b = 29.42; t(85) = 2.32, p = .023$), but not in girls ($b = -15.79; t(89) = -0.84, p = .401$). As illustrated in Figure 3, boys with less cortical thinning experienced greater reduction in the interferences score over time, compared with those with greater thinning. No other ROIs were found to have a significant effect on the MC condition. The pattern of significant and nonsignificant effects remained the same when controlling for change in average thickness of the relevant hemisphere.

Figure 4. Change in interference score in relation to right vIPFC development for the MI expectancy condition. Cortical development is calculated as APC, with negative scores indicating greater thinning over time. Change in interference is the difference between baseline and follow-up scores, with negative scores indicating a reduction in interference (i.e., improved cognitive control).

Figure 5. Overall interference score (i.e., averaged across time) in relation to right ACC development for the MI expectancy condition. Cortical development is calculated as APC, with negative scores indicating greater thinning over time.
Models investigating the effects of cortical development on the MI condition revealed a significant two-way interaction between right vlPFC development and time \((b = 18.87; t(178) = 2.26, p = .025)\). As illustrated in Figure 4, less cortical thinning was associated with greater reductions in the interferences score over time, compared with greater thinning. Analyses also revealed a significant main effect of right ACC development \((b = 8.49; t(179) = 2.10, p = .057)\). As illustrated in Figure 5, greater cortical thinning was associated with lower Stroop interferences scores across time periods (i.e., average interferences score). There were no significant main effects or interaction involving any of the remaining ROIs. The pattern of significant and nonsignificant effects remained the same when controlling for change in average thickness of the relevant hemisphere.

**DISCUSSION**

To our knowledge, this study is the first to describe the relationship between maturation of cognitive control and cortical thickness of underlying neural substrates during adolescence using a longitudinal design. Our findings demonstrate improvements in response inhibition in boys during conditions of reactive control between early and mid adolescence, as measured by performance on the MI condition in our modified Stroop task. Development of cognitive control was also found to be associated with structural maturation of underlying neural regions. Specifically, less thinning of the left ACC was related to greater improvements in reactive cognitive control (i.e., response inhibition within the MI condition) in boys, and less thinning of the right vlPFC was related to greater improvements in proactive cognitive control (i.e., response inhibition within the MI condition) across both boys and girls. In comparison, greater thinning of the right ACC was related to superior response inhibition across assessments (i.e., lower interference scores averaged across time).

Improvements in response inhibition during conditions of reactive control, as found on the MI condition of the Stroop task, were identified in boys, but not in girls. This finding is consistent with previous studies that have identified continued improvements in response inhibition using the classic Stroop task (i.e., no manipulation of expectancy) throughout adolescence (Huizinga et al., 2006; Leon-Carrion et al., 2004). The specificity of this finding to boys suggests that they alone experienced significant development of reactive control during the assessment period, whereas girls did not exhibit such behavioral improvements. It is possible that girls may have experienced earlier development compared with boys (i.e., before our assessment period), as past research indicates earlier development of executive abilities (Vuontela et al., 2003; Klenberg, Korkman, & Lahti-Nuuttila, 2001) and underlying neural regions (Lenroot et al., 2007; Giedd et al., 1999) in girls. The current study failed to identify any improvements in response inhibition during conditions of proactive control, as found on the MI condition of the Stroop task. This finding is not surprising given the age range studied and past findings of protracted maturation into adulthood of regions underlying strategy generation and maintenance (Gogtay et al., 2004). Furthermore, Andrews-Hanna et al.’s (2011) functional neuroimaging study of 14- to 25-year-olds identified earlier development of neural regions implicated in reactive control and later development of those supporting proactive control, using a modified Stroop task.

As hypothesized, right vlPFC development was specifically related to proactive control, which is consistent with past research that has found involvement of this region during top–down attentional control (Braver, Paxton, Locke, & Barch, 2009). By comparison, left ACC development was related to improvements in reactive control in boys. This finding is also consistent with past research that has identified involvement of this region during conditions of high conflict, when strategic processes are not engaged, highlighting its role in the evaluation and monitoring of information (Grandjean et al., 2012; Carter et al., 2000). No significant effects were identified involving dlPFC development, which may be related to this region begin among the last to reach adult levels of maturity (Shaw et al., 2008).

Surprisingly, the results indicate that less cortical thinning of the right vlPFC and left ACC was related to improvements in cognitive control (i.e., decrease in interferences scores over time). Interpretation of our results is made difficult by the use of only two waves of imaging data, which precludes identification of nonlinear trajectories. However, we speculate that less cortical thinning may reflect later maturation and/or less steep developmental curve. Therefore, our finding may suggest that participants with superior development of cognitive control reach peak cortical thickness later in age based on past studies that have identified inverted U-shaped developmental curves characterized by prepubertal thickening and postpubertal thinning (Shaw et al., 2008; Shaw, Lerch, et al., 2006). This is somewhat consistent with Shaw, Greenstein, et al.’s (2006) finding of individuals with higher IQ reaching peak cortical thickness later than those with average or low levels of IQ, although they did not examine cognitive development per se. Furthermore, recent studies have failed to identify prepubertal increases in cortical thickness (Mills et al., 2014; Brown et al., 2012; van Soelen et al., 2012; Tamnes et al., 2010). Our finding may also suggest that participants with superior development of cognitive control have slower and more protracted thinning. This is consistent to Tamnes et al.’s (2010b) cross-sectional study that found less cortical thinning of posterior brain regions to be associated with improvements in Stroop performance, although other measures/studies have provided conflicting results to date (Fjell...
Therefore, both these potential explanations of our results are partially supported by past findings, and further research is needed to untangle these effects and gain a better understanding of developmental brain–cognition relationships (Pfeifer & Allen, 2012).

Our findings also indicate that superior proactive control across assessments (i.e., averaged across time points) was related to greater cortical thinning of the right ACC. This is comparable to past findings that adolescents with superior attention and intelligence experience accelerated cortical thinning over this developmental period (Ducharme et al., 2012; Shaw, Greenstein, et al., 2006). The effect of right ACC development on proactive control is not surprising; although past research suggests greater involvement of ACC during reactive control, it has still been found to be active during conditions of proactive control (Grandjean et al., 2012). Furthermore, functional activation patterns during cognitive control tasks continue to change during adolescence, becoming more focal over time (Casey, Tottenham, Liston, & Durston, 2005; Durston et al., 2002).

Changes in cortical thickness during adolescence are thought to reflect neurobiological processes that act to increase the efficiency, stability, and temporal precision of neuronal firing patterns, including synaptic pruning, myelination, and changes in axonal caliber (Rutherford, Nelson, & Turrigiano, 1998; Huttenlocher & Dabholkar, 1997; Lewis, 1997). Indeed, higher levels of functional anisotropy in white matter, which is thought to reflect greater myelin-related restriction of water diffusion across axons, and in turn greater brain connectivity have been shown to increase during adolescence (Jernigan, Baaré, Stiles, & Madsen, 2011; Lebel & Beaulieu, 2011). It has also been related to better cognitive abilities in children and adolescents, including better response inhibition (Madsen et al., 2010), spatial working memory (Vestergaard et al., 2011), and global measures of verbal and performance intelligence (Tamnes et al., 2010a). As such, if cortical thinning is closely associated with white matter development, it could be assumed that greater thinning may indicate increased efficiency of neuronal networks. However, our findings challenge this notion given that less thinning was related to greater development of cognitive control.

Another potential explanation for our findings is that they may reflect activity-dependent plasticity in neural systems, as past research in adults has shown that practice and learning can impact on brain structure. For example, increased cortical volume in regions involving visuomotor function was identified in individuals who underwent juggling training (Draganski & May, 2008). Similar increases in gray matter have also been identified when learning a second language (Mechelli et al., 2004) and playing a musical instrument (Gaser & Schlaug, 2003). Although these studies involved volumetric measures, it is reasonable to assume that greater engagement in cognitive control may lead to thicker cortices in prefrontal regions.

It is important to note that our data does not provide insight into developmental trajectories before early adolescence that may be impacting on cognitive control abilities. Therefore, as highlighted by Jernigan and colleagues (2011), it is unclear whether our findings represent activity-dependent plasticity, advantageous preexisting neural structure, normative neurobiological maturation, or some form of interplay between these processes. This highlights the complexity of brain–behavior relationship from a developmental perspective and challenges the notion that greater thinning may be more adaptive. Rather, it can currently only be inferred that certain patterns of development (i.e., less or more thinning) may be related to greater cognitive development during particular periods of time. Further research on the underlying neurobiological mechanisms is needed to fully understand potential adaptive or maladaptive processes during adolescence.

Our findings also shed light on the importance of examining sex differences in adolescence, as reactive control was only related to left ACC development in boys. In combination with the behavioral improvements in reactive control that was identified in boys alone, this finding suggests that the period of early to mid adolescence is particularly crucial for the development of reactive control abilities in boys. As mentioned earlier, girls may have experienced earlier development compared with boys given previous findings that they exhibit earlier development of executive abilities (Vuontela et al., 2003; Klenberg et al., 2001). Sex differences have also been identified in cognitive control during adolescence, and more specific to our paradigm, strategy use has been found to differ between boys and girls using our modified Stroop task (Yücel et al., 2012) and has also been hypothesized to account for sex differences in other Stroop tasks (Li, Zheng, Wang, Gui, & Li, 2009; Shen, 2005; Mekarski, Cutmore, & Suboski, 1996). Furthermore, past research has shown differences between boys and girls in developmental trajectories of the brain as well as regional specificity of these differences (Lenroot et al., 2007). Therefore, future research may benefit from examining sex differences in the relationship between cognitive and cortical development.

Limitations

These findings must be considered within the context of the study’s limitations. As mentioned above, the availability of neuroimaging data from only two time points limits modeling of development to linear patterns. Furthermore, as the time period studied for cortical development was restricted to early to mid adolescence, we were not able to model the entire period of protracted adolescent development. Age was also the only measure of development used in the current analyses, and future...
research should investigate other measures of maturation, especially pubertal effects.

Our analyses were driven by a priori hypotheses given the extensive literature on ACC and lateral pFC involvement in Stroop performance. However, future studies could examine less implicated regions, such as the parietal lobe, that are also active during cognitive control.

Another potential limitation of this study was that scans were acquired on different scanners at each time point. The interscanner reliability study, however, suggests that between-scanner variance in our study was no greater than previous estimates of within-scanner variance and that the significant change in cortical thickness observed in our sample of adolescents is unlikely to be because of interscanner bias. Furthermore, it is highly unlikely that between-scanner variance would be significantly and meaningfully related to psychological constructs, such as cognitive control.

Conclusions
The findings from this study highlight the relationship between maturation of the pFC and two distinct forms of cognitive control in adolescents as well as sex differences in this complicated relationship. Although previous research has focused on the neural correlates of cognitive control using cross-sectional samples, our findings highlight the importance of studying neural correlates of cognition using a longitudinal framework during this developmental period.

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Note
1. In support of this hypothesis, further exploratory analyses revealed that girls had quicker RTs than boys at baseline and similar RTs to boys at follow-up, despite experiencing less change over time. Furthermore, girls did exhibit reductions in RT for both incongruent and congruent trials despite the lack of improvements in interference score.

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