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Thinning of the lateral prefrontal cortex during adolescence predicts emotion regulation in females

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Adolescence is a crucial period for the development of adaptive emotion regulation strategies. Despite the fact that structural maturation of the prefrontal cortex during adolescence is often assumed to underlie the maturation of emotion regulation strategies, no longitudinal studies have directly assessed this relationship. This study examined whether use of cognitive reappraisal strategies during late adolescence was predicted by (i) absolute prefrontal cortical thickness during early adolescence and (ii) structural maturation of the prefrontal cortex between early and mid-adolescence. Ninety-two adolescents underwent baseline and follow-up magnetic resonance imaging scans when they were aged approximately 12 and 16 years, respectively. FreeSurfer software was used to obtain cortical thickness estimates for three prefrontal regions [anterior cingulate cortex; dorsolateral prefrontal cortex (dlPFC); ventrolateral prefrontal cortex (vlPFC)]. The Emotion Regulation Questionnaire was completed when adolescents were aged approximately 19 years. Results showed that greater cortical thinning of the left dlPFC and left vlPFC during adolescence was significantly associated with greater use of cognitive reappraisal in females, though no such relationship was evident in males. Furthermore, baseline left dlPFC thickness predicted cognitive reappraisal at trend level. These findings suggest that cortical maturation may play a role in the development of adaptive emotion regulation strategies during adolescence.

Keywords: emotion regulation; cognitive reappraisal; cortical development; adolescence; longitudinal study

INTRODUCTION

The transition to adolescence is characterized by significant psychological and social changes (Collins, 2003). Adolescents face the challenges of navigating novel social and emotional situations, along with a dramatic rise in emotional reactivity that occurs around the onset of puberty (Collins, 1999, 2003). Given these changes, the ability to engage in emotion regulation during this transition is fundamental to adaptive functioning (McRae *et al.*, 2012). Emotion regulation involves intrinsic and extrinsic processes that modulate the experience and expression of emotions (Thompson, 1994). Among the most effective and flexible methods of regulating emotions is cognitive reappraisal, which involves changing the way one interprets a situation to reduce its emotional impact (Lazarus and Alfert, 1964).

Individuals who successfully engage in cognitive reappraisal are able to negotiate emotionally stressful situations by being more optimistic, reinterpreting the stressful stimuli and actively mending their negative mood (Ochsner and Gross, 2005). Greater use of reappraisal has been associated with both greater positive and reduced negative emotions, fewer depressive symptoms and greater well-being/life satisfaction (Gross and John, 2003). Behavioral studies have found that active engagement in reappraisal modulates ratings of negative and positive affect (Gross, 1998; Giuliani *et al.*, 2008; Kober *et al.*, 2010), as well as neural indicators of emotional responding (Schaefer *et al.*, 2002; Ochsner *et al.*, 2004; Kim and Hamann, 2007).

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Cognitive reappraisal during adolescence

Given the increase in emotional reactivity and salience of social interactions during this developmental period (Collins, 2003), the ability to engage in cognitive reappraisal is thought to be crucial for adolescents. Less frequent and less successful engagement in cognitive coping strategies among adolescents has been related to increased symptoms of psychopathology (Garnefski *et al.*, 2002), as well as clinical level anxiety and depressive disorders (Silk *et al.*, 2007; Carthy *et al.*, 2010). Self-reported engagement in cognitive emotion regulation strategies has also been found to increase over time during adolescence (Garnefski *et al.*, 2002; McRae *et al.*, 2012).

Neurobiological bases of cognitive reappraisal

Cognitive reappraisal has been found to be largely reliant on the lateral prefrontal cortex (PFC). The dorsolateral prefrontal cortex (dlPFC) is involved in keeping goals active within working memory and directing attention, and the ventrolateral prefrontal cortex (vlPFC) is implicated in selection of goal-appropriate responses based on information from semantic memory, such as the causes, significance and potential outcomes of the situation (Ochsner and Gross, 2008; Kalisch, 2009). Additionally, the anterior cingulate cortex (ACC), which has been related to performance monitoring (Botvinick *et al.*, 1999) and reinforcement learning (Rushworth and Behrens, 2008), is implicated in tracking whether one has successfully changed their affective state (Ochsner *et al.*, 2002).

The continued development of cognitive reappraisal during adolescence appears to temporally map on the maturation of underlying neural regions, suggesting a link between these two phenomena. Functional neuroimaging studies have identified maturation of

prefrontal regions during adolescence, with cognitive regulatory networks becoming more focal and refined with age, as revealed in studies using tasks of executive function (Casey *et al.*, 1997; Bunge *et al.*, 2002; Durston *et al.*, 2002) and those using behavioral paradigms involving cognitive reappraisal of negative emotions (Lévesque *et al.*, 2004; Pitskel *et al.*, 2011), suggesting increased neural efficiency of regulatory systems with development.

Research on brain structural correlates of emotion regulation has identified larger cortical volumes in adults who engage in regulatory strategies more frequently. Greater engagement in cognitive reappraisal has been associated with larger dorsal ACC and amygdala volumes (Giuliani *et al.*, 2011a; Hermann *et al.*, 2013), whereas greater engagement in expressive suppression has been related to larger volumes of the anterior insula and the dorsomedial PFC, including the paracingulate gyrus (Giuliani *et al.*, 2011b; Kühn *et al.*, 2011; Hermann *et al.*, 2013). However, the focus of these studies 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 (Panizzon *et al.*, 2009; Winkler *et al.*, 2009, 2010). Therefore, this study will focus specifically on cortical thickness correlates of emotion regulation.

In addition, research on neural correlates of emotion regulation has not been conducted on adolescence, though it is likely to be complicated by the developmental trajectory of gray matter. Research has consistently found normative thinning of the gray matter during adolescence (Shaw *et al.*, 2008; Brown *et al.*, 2012; van Soelen *et al.*, 2012; Mutlu *et al.*, 2013; Mills *et al.*, 2014), which has been identified as an adaptive process in longitudinal studies on cognition. For example, Shaw *et al.* (2006), using a cohort-sequential design, found that adolescents with superior intellectual abilities exhibited greater peak thickness around puberty, followed by greater cortical thinning into adulthood. Further, greater cortical thinning has been related to improvements in cognitive control abilities during adolescence (Tamnes *et al.*, 2010b, 2013). These findings suggest that longitudinal thinning may be adaptive and associated with superior regulatory abilities during adolescence, though no studies have specifically investigated emotion regulatory outcomes.

This study

The aim of this study was to examine the relationship between PFC development and cognitive reappraisal abilities in a community sample using a longitudinal within-subject design. Structural properties of the PFC were assessed at two time points during early and middle adolescence and were related to cognitive reappraisal abilities assessed during late adolescence, with a strictly constrained age range during each period of assessment. The ACC, dlPFC and vlPFC were the focus of this study, given their well-established involvement in cognitive reappraisal. These three regions have been found to exhibit similar protracted development during adolescence, including similar amounts of reduction in thickness and patterns of change (Shaw *et al.*, 2008; Tamnes *et al.*, 2010a; van Soelen *et al.*, 2012; Mutlu *et al.*, 2013).

We investigated the relationship between cognitive reappraisal during late adolescence and (i) cortical thickness at early adolescence and (ii) change in cortical thickness between early- and mid-adolescence. Based on past research focusing on cortical development in relation to cognition (Shaw *et al.*, 2006; Tamnes *et al.*, 2013), it was hypothesized that superior reappraisal abilities would be associated with thicker cortices early in adolescence around the onset of puberty, as well as greater thinning of the PFC between early- and mid-adolescence. In addition, we examined the specificity of these developmental effects to adaptive emotion regulation (i.e. cognitive reappraisal) by investigating the relationship between maturation of these regions with an alternate form emotion regulation that has been found to be more maladaptive: expressive suppression. Expressive suppression is a response-focused strategy that aims to inhibit the outward display or expression of emotion after the emotional response has been generated (Gross and John, 2003). It has been shown to be associated with greater experience of negative emotions, less expression of positive emotions, poorer interpersonal functioning, self-esteem and general well-being (Gross and John, 2003). It was hypothesized that thicker cortices early in adolescence and greater thinning of the PFC between early- and mid-adolescence would be specifically related to measures of reappraisal but not suppression.

METHODOLOGY

Participants

The sample described in this study was derived from a larger longitudinal cohort study conducted in Melbourne, Australia. A total of 2453 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 and Rothbart, 1992), consisting of 65 items used to derive 10 subscales that load onto four higher order factors. Based on their scores on the EATQ-R, a smaller sample of 425 students was selected to be part of the study, as described by Yap *et al.* (2011). Adolescents at the extreme ends of the temperamental distribution were oversampled to maximize risk and resilience for development of psychopathology, while using a small enough sample to permit detailed assessment of biological, socioemotional and cognitive domains.

Of the selected adolescents, 245 agreed to participate in further research. These participants were screened for Axis 1 disorders using the Schedule for Affective Disorder and Schizophrenia for School-Aged Children: Present and Lifetime Version (Kaufman and Schweder, 2004), and those who met the criteria for current or past major depressive disorder were excluded due to the broader aims of the study. Remaining participants were invited to take part in brain magnetic resonance imaging (MRI) assessments at two time points, when they were aged approximately 12 and 16 years, respectively. A number of adolescents declined participation in the MRI assessments, resulting in 120 participants completing all assessments at both baseline and follow-up. Based on 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 due to 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 (47 = females) were available for analysis. Males and females did not differ on the demographic and cognitive variables listed in Table 1 (all P values > 0.05). IQ was assessed at baseline using a short form of the Weschler Intelligence Scale for Children, Fourth Version (Wechsler, 2003), composed of the vocabulary, matrix reasoning and symbol search subtests (Sattler and Dumont, 2004). Socioeconomic classification (SES) was based on the Australian National University Four (ANU_4) Scale (Jones and McMillan, 2001). The final sample did not differ from the initial school screening sample ($N = 2453$) on socioeconomic disadvantage ($t_{(2439)} = 0.598$; $P = 0.550$), temperamental Effortful Control ($t_{(96)} = -0.592$; $P = 0.555$) or gender (Pearson's $\chi^2 = 0.799$; $P = 0.939$). Fifteen participants met the criteria for past or current psychiatric disorder at time 1, 26 participants met the

Table 1 Sample characteristics

	Sex		Total
	Male	Female	
Sample size	45	47	92
Age at time 1 (years)	12.67; 0.422; 11.37–13.61	12.65; 0.457; 11.95–14.08	12.67; 0.438; 11.37–14.08
Age at time 2 (years)	16.42; 0.464; 14.96–17.27	16.44; 0.54; 15.28–17.49	16.43; 0.503; 14.96–17.69
Age at time 3 (years)	18.78; 0.502; 17.34–19.71	18.75; 0.420; 17.83–19.70	18.76; 0.460; 17.34–19.71
Delay time 1—2 (years)[a]	3.76; 0.166; 3.48–4.12	3.78; 0.295; 2.69–4.56	3.77; 0.240; 2.69–4.56
Delay time 2—3 (years)[b]	2.35; 0.326; 1.31–3.12	2.30; 0.333; 1.17–3.25	2.33; 0.329; 1.17–3.25
Delay time 1—3 (years)[c]	6.11; 0.350; 4.98–7.12	6.09; 0.286; 5.15–6.72	6.10; 0.317; 4.98–7.12
Estimate Full Scale IQ	107.06; 11.023; 79–128	104.07; 10.924; 87–123	105.53; 11.015; 79–128
Percentage Low SES[d]	58.98; 20.22; 14.4–96.0	58.53; 22.13; 14.0–100.0	58.76; 21.220; 14.0–100.0

Values represent mean; standard deviation; range. [a]Delay between baseline and follow-up MRI scan. [b]Delay between follow-up MRI scan and ERQ assessment. [c]Delay between baseline MRI scan and ERQ assessment. [d]Data missing for one female participant.

criteria for a psychiatric diagnosis between time 1 and time 2 (of which seventeen had not met any criteria previously) and 20 participants met the criteria for a psychiatric diagnosis between time 2 and time 3 (of which 10 had not met any criteria previously; refer to Supplementary Table S1 for further detail). 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 Tesla 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 ms; 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 Tesla Siemens scanner at the Royal Children's Hospital, Melbourne, Australia, with the following parameters: repetition time = 1900 ms; echo time = 2.24 ms; flip angle = 9°, field of view = 23 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 (http://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 *et al.*, 2012), which creates a within-unbiased subject template space and average image from both time points using robust, inverse consistent registration (Reuter *et al.*, 2010; Reuter and 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 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 *et al.*, 2010). All images were also corrected for tissue signal inhomogeneity using FreeSurfer's N3 correction (optimized for 3 Tesla images), a non-parametric non-uniformity intensity normalization method, which reduces sensitivity to changes in scanner platform and improves accuracy and robustness during cortical segmentation (Han and Fischl, 2007; Boyes *et al.*, 2008; Zheng *et al.*, 2009). All FreeSurfer image processing was conducted on a high performance computing facility at the Melbourne Neuropsychiatry Centre, Melbourne, Australia.

Table 2 Reproducibility errors (%) and confidence interval of the reproducibility errors (%) of ROI thickness for individuals scanned at both sites for reliability analysis

Structure	Mean absolute difference (mm)	Reproducibility error (%)	95% CI for reproducibility error (%)
Left ACC	0.043	1.400	−1.151, 3.952
Right ACC	0.074	2.531	−1.671, 6.734
Left dlPFC	0.090	3.450	−0.316, 7.216
Right dlPFC	0.081	3.141	0.907, 5.376
Left vlPFC	0.087	3.221	−0.383, 6.825
Right vlPFC	0.083	3.091	−0.700, 6.251

The group reproducibility error for each structure is derived averaging the reproducibility errors across subjects, where for each subject, the error is estimated as the absolute test–retest thickness percent change relative to the mean test–retest thickness.

Interscanner reliability

Given that different scanners were used at time 1 and time 2, a reliability analysis was undertaken to address concerns that changes in cortical thickness over time may be due to measurement bias from the different scanner platforms and acquisition parameters. Four individuals, aged 23, 28, 35 and 36 years were each scanned at the Royal Children's Hospital and Brain Research Institute, Austin and Repatriation Medical Centre within a 2-week period. The same acquisition parameters were used at each location to those used in the main study, as well as the same semi-automated methods of processing to extract region of interest (ROI) thickness.

Based on mean absolute thickness difference, inter-scanner variability was found to vary from 0.04 mm to 0.09 mm across ROIs, as shown in Table 2. These variations are consistent with within scanner estimates previously reported by Han *et al.* (2006). Table 2 also contains test–retest reproducibility errors and 95% confidence intervals for ROIs. The reproducibility errors for each subject were calculated as the absolute test–retest percent change relative to the mean test–retest value. These values were then averaged across subjects. These results did not reveal a systematic bias due to 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

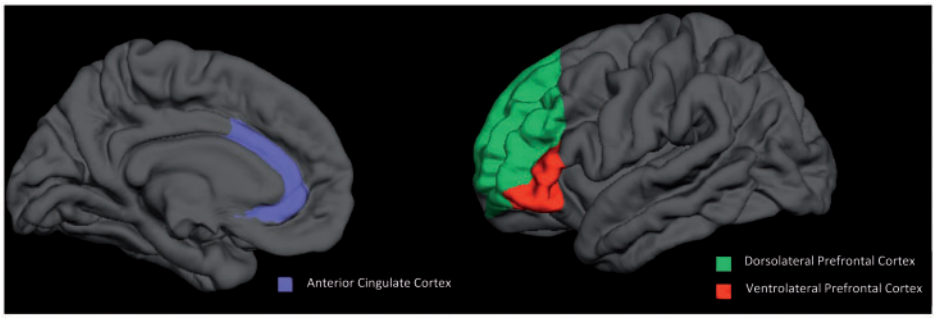

Fig. 1 Visualization of the ACC, dlPFC and vlPFC.

from the inter-scanner reliability analysis was applied to the current sample using the descriptive procedure proposed by Lebel and Beaulieu (2011). Details of the inter-scanner reliability study are presented in the Supplementary Material. In summary, the results indicated that, for all ROIs, the majority of individuals (>50%) experienced greater change over time, in the predicted direction, than would be attributed to inter-scanner variance alone based on the reliability estimates.

ROI delineation

A customized ACC ROI was created by combining the rostral and caudal ACC labels defined by FreeSurfer's automated cortical parcellation procedure (Fischl, 2004; 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. A visualization of the three ROIs is shown in figure 1.

Cortical development

Annualized percentage change (APC) was calculated for each ROI as an index of cortical development using the following equation (1):

$$\text{APC}: \left(\frac{\text{Thickness 2} - \text{Thickness 1}}{\text{Thickness 1}}\right) * \left(\frac{1}{\text{Time interval}}\right) * 100$$

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

Emotion regulation questionnaire

Participants completed the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) at time 3, which measures individual differences in the use of emotion regulation strategies, with 10 items tapping into emotional experience and expression. Individuals rate the extent to which they agree or disagree with each item using a seven-point Likert scale. Six and four items load onto the factors of cognitive reappraisal and expressive suppression, respectively. Higher scores on each factor indicate greater strategy use in everyday life.

Statistical analysis

General linear models were used to analyze the data, and backward elimination method was used to remove interactions effects that were not significant. Sex differences in ERQ scores at time 3 were initially investigated. Subsequently, separate models were employed to investigate the effect of baseline cortical thickness (time 1) and cortical development (APC) of each ROI on ERQ at time 3. In addition, models were re-run controlling for average baseline cortical thickness (time 1) or average cortical development (APC) of the relevant hemisphere to investigate the specificity of our findings to the ROIs. All models included SES and age at time 3 as covariates.

Treatment of missing data

Thirty participants in the final sample had missing ERQ data. Participants with and without ERQ data did not differ on age at each time point, time intervals between any of these points, gender, presence of psychopathology across the time points or SES ($P > 0.05$). IQ at T1 was found to be significantly greater in the group with missing data ($t_{(90)} = 2.14$, $P = 0.035$), though no differences were identified at T2 ($t_{(90)} = 0.10$, $P = 0.925$). They also did not differ on Effortful Control, a temperamental dimension that is closely related to emotion regulation ($t_{(90)} = -0.07$, $P = 0.924$). Little's MCAR test was found to be non-significant ($P > 0.05$), indicating that the data were missing completely at random, and thus, missing data were imputed using the Expectation Maximization procedure in SPSS version 20.

RESULTS

Table 3 shows the mean ERQ scores for cognitive reappraisal and expressive suppression in males and females at T3. Analyses did not reveal significant sex differences (reappraisal: $b = -1.158$; $t_{(88)} = -0.674$, $P = 0.502$; suppression: $b = 1.287$; $t_{(88)} = 0.949$, $P = 0.345$) or age effects (reappraisal: $b = 1.125$; $t_{(88)} = 0.597$, $P = 0.552$; suppression: $b = -0.509$; $t_{(88)} = -0.342$, $P = 0.733$) for either scale. There was a significant main effect of SES on Cognitive Reappraisal ($b = 0.104$, $t_{(88)} = 2.523$, $P = 0.013$), with participants from lower SES backgrounds tending to report less frequent use of cognitive reappraisal strategies. There was no effect of SES on Expressive Suppression ($b = -0.011$, $t_{(88)} = -0.336$, $P = 0.737$).

Baseline (time 1) cortical thickness

Table 4 shows the mean cortical thickness at baseline for males and females. Independent samples *t*-tests revealed that males had significantly thicker cortices for the right vlPFC and both right and left dlPFC at baseline ($P < 0.05$). Models investigating baseline thickness effects on Cognitive Reappraisal revealed a trend toward a significant interaction between left dlPFC and sex ($b = -21.813$, $t_{(86)} = -1.883$, $P = 0.063$). As evident from figure 2, thicker cortices were associated with higher

Table 3 Sex differences in Cognitive Reappraisal and Expressive Suppression scores at time 3

	Cognitive reappraisal		Expressive suppression	
	Mean	SD	Mean	SD
Females	27.62	9.149	15.96	5.837
Males	26.54	7.617	14.69	6.961
Total	27.10	8.406	15.31	6.421

Table 4 Cortical thickness (mm) of ROIs at baseline in males and females

	Mean (SD)			Sex differences (*t*-test)
	Total sample	Females	Males	
Right ACC	3.262 (0.227)	3.264 (0.248)	3.259 (0.207)	−0.118
Left ACC	3.265 (0.250)	3.229 (0.278)	3.302 (0.213)	1.418
Right dlPFC	3.155 (0.145)	3.118 (0.132)	3.194 (0.148)	2.625*
Left dlPFC	3.066 (0.154)	3.025 (0.147)	3.108 (0.152)	2.664**
Right vlPFC	3.129 (0.189)	3.083 (0.178)	3.178 (0.190)	2.467*
Left vlPFC	3.062 (0.178)	3.036 (0.172)	3.089 (0.183)	1.434

*$P < 0.05$; **$P < 0.01$.

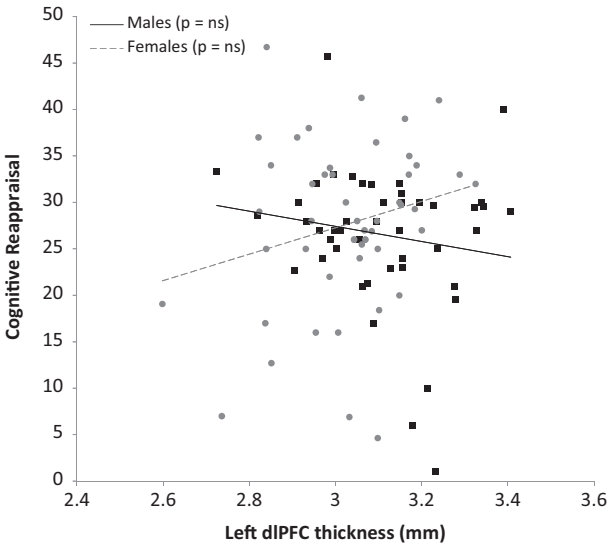

Fig. 2 Mean Cognitive Reappraisal scores at time 3 in relation to left dlPFC thickness (mm) at time 1, in males and females.

Cognitive Reappraisal scores in females, whereas the opposite relationship was present in males. There were no significant main effects or interactions involving any of the other ROIs. The pattern of significant and non-significant effects remained the same when controlling for change in average thickness of the relevant hemisphere.

Regarding Expressive Suppression, analyses revealed a significant interaction between left ACC and sex ($b = 13.149$, $t_{(86)} = 2.3389$, $P = 0.022$) and a similar trend toward an interaction between right dlPFC and sex ($b = 17.338$, $t_{(86)} = 1.774$, $P = 0.080$). As evident from figure 3, larger cortices at baseline were associated with lower Expressive Suppression scores in females, whereas the opposite relationship was present in males. *Post hoc* analyses did not find a significant main effect of left ACC thickness for either sex ($P > 0.05$). No significant main effects or interactions involving any of the other ROIs were identified. Most results remained the same when including average thickness at baseline of the relevant hemisphere into the models. The only exception was that left vlPFC thickness had a significant main effect ($b = 10.538$, $t_{(86)} = 2.165$, $P = 0.033$), with thinner cortices associated with lower Expressive Suppression scores.

Cortical development (APC)

Table 5 shows the mean cortical development (APC) for males and females. Independent sample *t*-tests did not reveal sex differences in cortical development for any of the ROIs. Analyses of Cognitive Reappraisal scores revealed a significant interaction between sex and both left dlPFC ($b = 3.418$, $t_{(86)} = 2.784$, $P = 0.007$) and left vlPFC development ($b = 2.575$, $t_{(86)} = 2.259$, $P = 0.026$). As evident from figure 4, greater thinning of the left lateral prefrontal regions was significantly associated with higher Cognitive Reappraisal scores at time 3 among females ($P < 0.01$) but was not significantly related to scores for males ($P > 0.05$). There were no significant main effects or interactions involving development of the right dlPFC, right vlPFC or the ACC in either hemisphere. The pattern of significant and non-significant effects remained the same when controlling for change in average thickness of the relevant hemisphere.

Regarding Expressive Suppression, analyses revealed significant interactions between sex and four ROIs [right ACC $b = -1.927$, $t_{(86)} = -2.066$, $P = 0.042$; left dlPFC ($b = -2.617$, $t_{(86)} = -2.682$, $P = 0.009$; right dlPFC $b = -3.498$, $t_{(86)} = -2.692$, $P = 0.009$; right vlPFC ($b = -2.509$, $t_{(86)} = -2.539$, $P = 0.013$]. A similar trend was also identified for an interaction between sex and the remaining two ROIs (left ACC: $b = -1.764$, $t_{(86)} = -1.816$, $P = 0.073$; left vlPFC: $b = -1.601$, $t_{(86)} = -1.736$, $P = 0.086$). As illustrated in figure 5, greater thinning of all ROIs was related to lower Expressive Suppression scores at time 3 in females but higher scores in males. *Post hoc* analyses revealed significant effects of the right ACC, vlPFC and dlPFC in males ($P < 0.05$) and significant effects of the right and left dlPFC, and right vlPFC in females ($P < 0.05$). When controlling for change in average thickness of the relevant hemisphere, results remained the same for models assessing gender and interactions effects. However, *post hoc* tests conducted separately for each sex failed to reach significance for all ROIs other than the right ACC in males.

DISCUSSION

This study is the first to describe the relationship between structural maturation of the prefrontal cortex and emotion regulation during adolescence. Maturational changes in the left dlPFC and left vlPFC significantly predicted cognitive reappraisal during late adolescence, with a moderating influence of sex. Specifically, greater thinning of these two regions was associated with superior cognitive reappraisal in females alone.

The association between the lateral PFC and cognitive reappraisal is consistent with past functional neuroimaging studies that have implicated this region in the generation and maintenance of a cognitive strategy to reframe negative emotional stimuli (Ochsner *et al.*, 2002; Ochsner and Gross, 2005). The specificity of the results to the left hemisphere is consistent with previous studies that have found activation of the left PFC to be negatively correlated with activation in the amygdala in rodents (2003), as well as in humans when engaging in cognitive reappraisal (Ochsner *et al.*, 2002), implicating the left PFC in the modulation of activity in neural regions underlying emotion responding.

The finding that greater 'cortical thinning' of the left dlPFC and vlPFC was related to increased cognitive reappraisal is also consistent with past findings regarding cortical development in relation to cognitive development (Tamnes *et al.*, 2010b, 2013). However, research

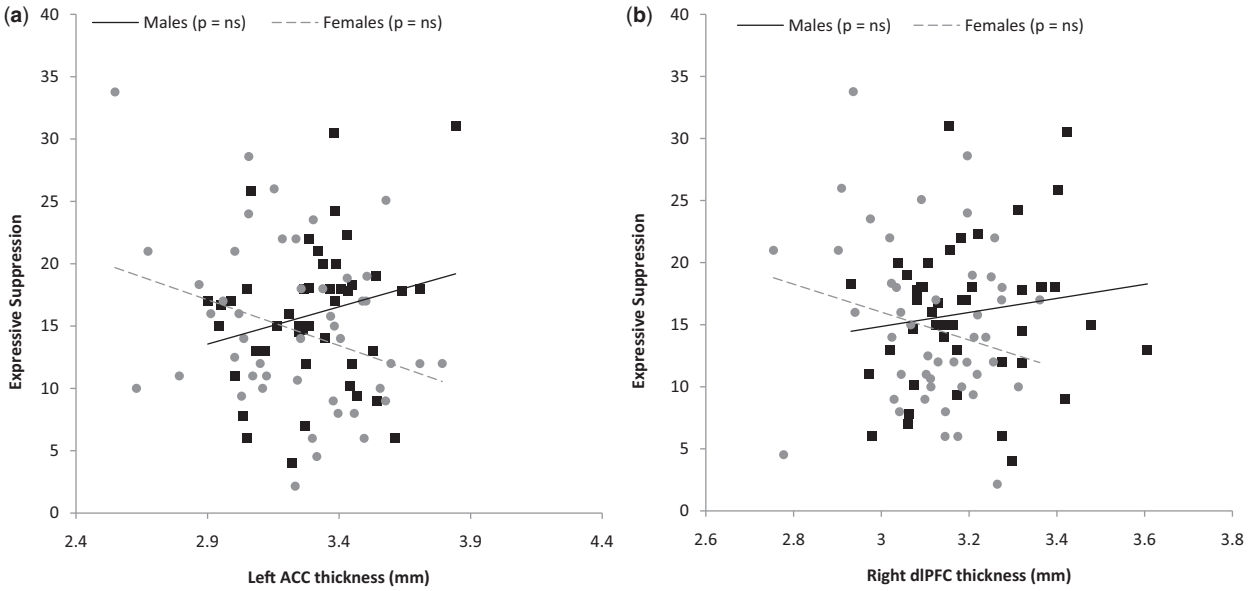

Fig. 3 Mean Expressive Suppression scores at time 3 in relation to (**a**) left ACC and (**b**) right dlPFC thickness (mm) at time 1, in males and females.

Table 5 Cortical development (annualized percentage change) for ROIs in males and females

	Mean (SD)			Sex differences (*t*-test)
	Total sample	Females	Males	
Right ACC	−0.914 (1.431)	−0.925 (1.519)	−0.903 (1.459)	0.071
Left ACC	−0.342 (1.421)	−0.214 (1.302)	−0.475 (1.539)	−0.877
Right dlPFC	−2.536 (1.121)	−2.691 (0.881)	−2.354 (1.316)	−0.563
Left dlPFC	−2.320 (1.464)	−2.235 (1.205)	−2.408 (1.702)	1.451
Right vlPFC	−0.916 (1.378)	−1.155 (1.396)	−0.667 (1.329)	0.6
Left vlPFC	−1.819 (1.505)	−1.155 (1.395)	−1.722 (1.678)	1.719

investigating cortical development in relation to functional outcomes is in its infancy and is characterized by inconsistent findings. Indeed, the study by Tamnes *et al.* (2010b) mentioned earlier also found that less reduction in cortical thickness was associated with better performance of the Stroop task. In comparison, Fjell *et al.* (2012) failed to identify any relationship between ACC thickness and performance on the Flanker task in adolescents. Whether these findings relate to task-specific developmental effects, the age range or the cross-sectional nature of the studies remains to be clarified. The lack of significant findings relating cross-sectional measurement of cortical thickness during early adolescence with cognitive reappraisal in our study suggests that longitudinal within-subject change (i.e. developmental trajectories) may be more informative than absolute thickness values during adolescence.

Although the exact mechanisms mediating the relationship between cortical development and regulatory abilities remain unknown, it has been hypothesized that normative cortical thinning is reflective of neurobiological processes that improve neuronal efficiency, stability and temporal precision of neuronal firing patterns (Lewis, 1997; Rutherford *et al.*, 1998). Potential mechanisms include synaptic pruning, changes in axonal caliber, proliferation of glial cells and increased myelination of previously unmyelinated tissue at the periphery of the brain (Bourgeois and Rakic, 1993; Huttenlocher and Dabholkar, 1997; Sowell, 2004; Paus *et al.*, 2008).

Our findings also shed light on the importance of examining sex differences in emotion regulation during adolescence, consistent with previous research by our research group that identified sex differences in the ability to engage in cognitive strategies during adolescence (Yücel *et al.*, 2012). It is currently uncertain why thinning of the lateral PFC was adaptive in females alone. Pubertal effects may have played a role; given that female brains tend to mature earlier than male (Lenroot *et al.*, 2007), it may be that the developmental processes occurring during early- to mid-adolescence is more important in predicting cognitive reappraisal in females, whereas brain development in later years may be more important in predicting cognitive reappraisal in males. This notion is also supported by the non-significant trend observed for the interaction between baseline left dlPFC thickness and sex in predicting cognitive reappraisal. Although greater thickness was related to superior reappraisal in females, the opposite relationship was present in males. This effect may reflect females having reached their peak thickness during the baseline assessment, but males experiencing delayed maturation. Future research should therefore study cortical development across a longer period of time and examine non-linear trajectories of change.

Sex differences in cognitive reappraisal have also been identified in past functional neuroimaging studies. Although both males and females have been found to engage in cognitive reappraisal to a comparable level of success (Gross and John, 2003; McRae *et al.*, 2008), they have been found to exhibit differential activation of cognitive control networks within the PFC during reappraisal. McRae *et al.* (2008) found that women showed greater activation than men in the superior and inferior frontal gyri, ACC and ventral-striatal regions when engaging in cognitive reappraisal to regulate their emotional reaction to negatively valenced pictures. Similarly, Koch *et al.* (2007) found that females activated the OFC and the amygdala to a greater extent when performing a working memory task during conditions of induced negative mood, whereas males exhibited greater activation of posterior brain regions. These findings suggest that women may preferentially recruit prefrontal regions during cognitive reappraisal, thus potentially explaining the importance of structural maturation of these regions in females.

It is interesting to note that we identified the opposite relationship between the development of the PFC and a more maladaptive form emotion regulation, expressive suppression. Specifically, females with greater cortical thinning had lower expressive suppression scores at

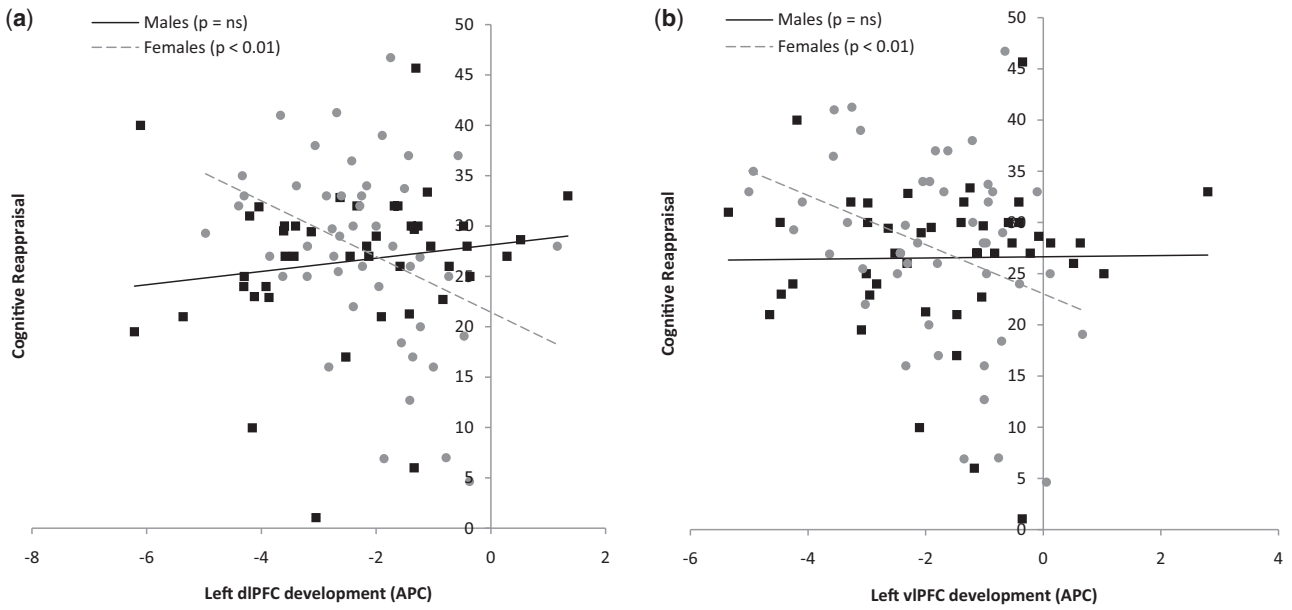

Fig. 4 Mean Cognitive Reappraisal scores at time 3 in relation to (**a**) left dlPFC and (**b**) left vlPFC development, in males and females. Cortical development is calculated as APC, with negative scores indicating reductions over time and positive scores indicating increase over time.

time 3. It is difficult to speculate why females who experience less thinning engage in greater expressive suppression during late adolescence. However, the findings do suggest that normative cortical thinning of the PFC may be important for the emergence of adaptive forms of emotion regulation in females, whereas aberrations from this process (i.e. less thinning or thickening) may result in the emergence of less adaptive regulation, as expressive suppression has been related to greater experience of negative emotions, poorer interpersonal relationships and lower levels of well-being (Gross and John, 2003). Interestingly, greater cortical thinning of the PFC was related to the emergence of expressive suppression in males. Although expressive suppression is not considered to be adaptive in males, they have been found to be less emotionally expressive than females (Kring and Gordon, 1998). Therefore, our finding suggests that sex differences in emotional expressivity may potentially be biologically driven. However, past research indicates that other factors, such as the socialization process and associated gender roles, are also likely to impact on such sex differences. Furthermore, the ROIs in this study were chosen based on the literature on neural correlates of cognitive reappraisal, as it was the main focus of this study. However, expressive suppression is thought to have different neural correlates, such as the orbitofrontal and dorsomedial prefrontal cortices (Goldin *et al.*, 2008; Giuliani *et al.*, 2011b; Kühn *et al.*, 2011; Hermann *et al.*, 2013). For these reasons, it is difficult to speculate on potential neural underpinnings of sex differences in the emergence/use of expressive suppression in adolescents without further study of relevant brain regions and the impact of social factors.

Limitations

These findings must be considered within the context of the study's limitations. The availability of neuroimaging data from only two time points limits modeling of development to linear patterns, despite past research identifying non-linear trajectories of development. Furthermore, the time period studied for cortical development was restricted to early to middle adolescence; consequently, we were not able to model the entire period of protracted adolescent development. The temporal gap between measurement of cortical development and cognitive reappraisal abilities, and the lack of ERQ data from time 1 and 2, limited our ability to assess causality. Future research would therefore benefit from longitudinal assessment of the ERQ occurring concurrently with MRI scans.

Another limitation was that scans at T1 were acquired from a different scanner to those at T2, thus confounding time and site. In addition, FreeSurfer's preferred voxel dimension of 1 mm^3 was not used for baseline images. Past research suggests that different scanners may increase variability in cortical thickness estimates. However, this increase is small compared with variability in cortical thickness estimates produced from the same scanner (Han and Fischl, 2007). Our reliability analysis also suggested that between-scanner variance was no greater than previous estimates of within-scanner variance. Furthermore, it is highly unlikely that between-scanner variance would be significantly and meaningfully related to our psychological outcome. Nevertheless, future research would benefit from acquiring both longitudinal scans from the same machine, as well as using the preferred voxel dimension of 1 mm^3 at both time points. We also chose an ROI approach given the extensive research conducted on neural correlates of cognitive reappraisal to date. However, future studies could employ whole brain analyses to further explore the cortical networks underlying emotion regulation.

CONCLUSIONS

The findings from this study highlight the relationship between maturation of the lateral PFC and cognitive reappraisal abilities in adolescents. Greater thinning of the left dlPFC and left vlPFC during adolescence predicted cognitive reappraisal abilities in females, whereas no relationship was observed between cognitive appraisal and absolute cortical thickness. This highlights the importance of studying neural correlates of emotion regulation using a longitudinal framework during this developmental period.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

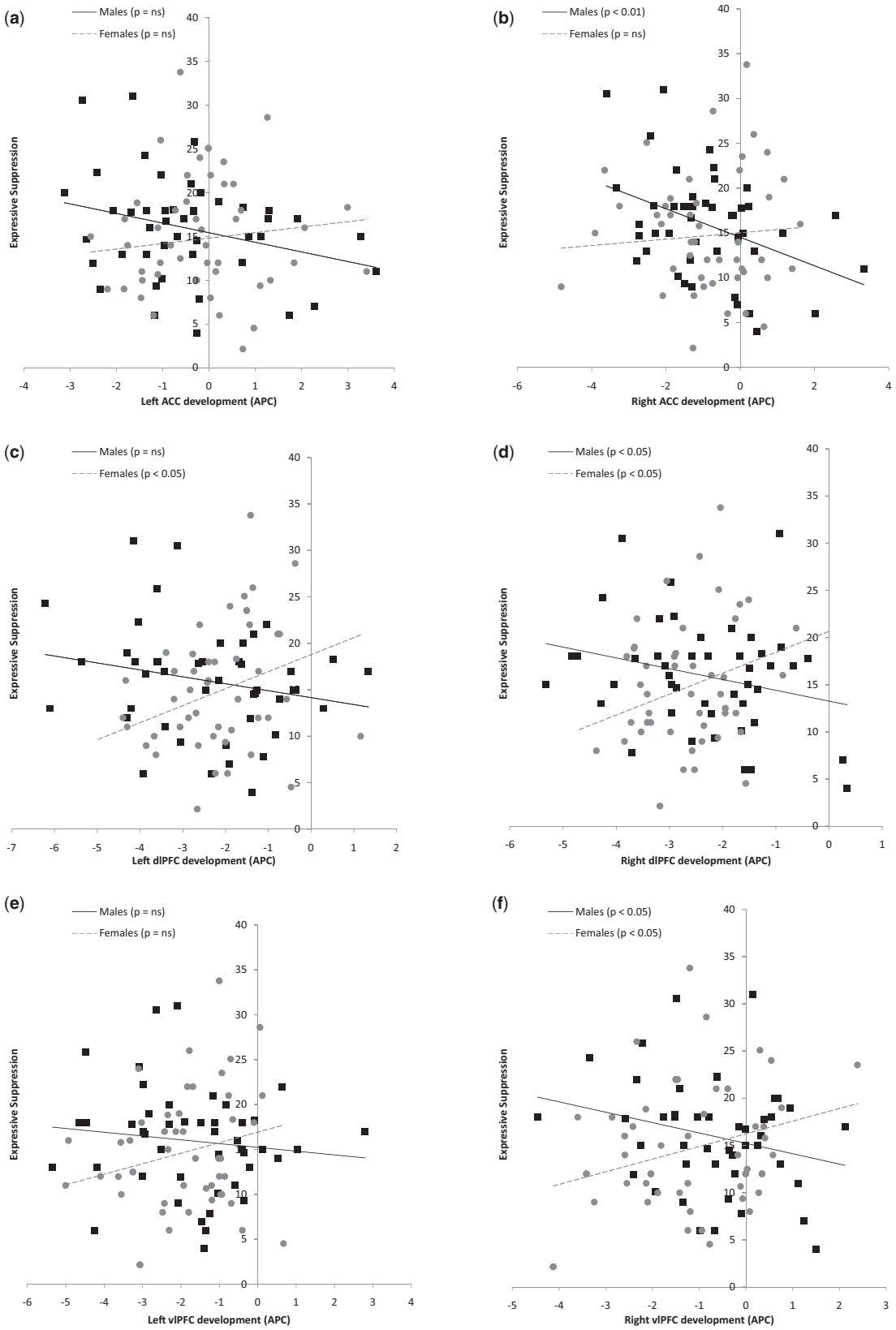

Fig. 5 Mean Expressive Suppression scores at time 3 in relation to (**a**) left ACC, (**b**) right ACC, (**c**) left dlPFC, (**d**) right dlPFC, (**e**) left vlPFC and (**f**) right vlPFC development, in males and females. Cortical development is calculated as annualized percentage change (APC), with negative scores indicating reductions over time and positive scores indicating increase over time.

Conflict of Interest

None declared.

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