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ORIGINAL ARTICLE

vlPFC–vmPFC–Amygdala Interactions Underlie Age-Related Differences in Cognitive Regulation of Emotion

Jennifer A. Silvers[1], Catherine Insel[2], Alisa Powers[3], Peter Franz[2], Chelsea Helion[4], Rebecca E. Martin[4], Jochen Weber[4], Walter Mischel[4], B.J. Casey[5] and Kevin N. Ochsner[4]

[1]Department of Psychology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095, USA, [2]Department of Psychology, Harvard University, 33 Kirkland Hall, Cambridge, MA 02138, USA, [3]Department of Psychology, Long Island University, 1 University Plaza, Brooklyn, NY 11201, USA, [4]Department of Psychology, Columbia University, 1190 Amsterdam Avenue, New York, NY 10027, USA and [5]Sackler Institute for Developmental Psychobiology, Weill Cornell Medical College, New York, NY 10065, USA

Address correspondence to Jennifer Silvers, Department of Psychology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095, USA. Email: silvers@ucla.edu; Kevin N. Ochsner, Department of Psychology, Columbia University, 406 Schermerhorn Hall, 1190 Amsterdam Avenue, New York, NY 10027, USA. Email: ko2132@columbia.edu

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Abstract

Emotion regulation is a critical life skill that develops throughout childhood and adolescence. Despite this development in emotional processes, little is known about how the underlying brain systems develop with age. This study examined emotion regulation in 112 individuals (aged 6–23 years) as they viewed aversive and neutral images using a reappraisal task. On "reappraisal" trials, participants were instructed to view the images as distant, a strategy that has been previously shown to reduce negative affect. On "reactivity" trials, participants were instructed to view the images without regulating emotions to assess baseline emotional responding. During reappraisal, age predicted less negative affect, reduced amygdala responses and inverse coupling between the ventromedial prefrontal cortex (vmPFC) and amygdala. Moreover, left ventrolateral prefrontal (vlPFC) recruitment mediated the relationship between increasing age and diminishing amygdala responses. This negative vlPFC–amygdala association was stronger for individuals with inverse coupling between the amygdala and vmPFC. These data provide evidence that vmPFC–amygdala connectivity facilitates vlPFC-related amygdala modulation across development.

Key words: amygdala, emotion regulation, fMRI, neurodevelopment, prefrontal cortex

Introduction

Behavioral research suggests that adults experience greater emotional stability than do younger individuals (Larson et al. 1980; Noftle and Fleeson 2010), with the emotional lives of children and adolescents being more volatile than those of adults. This volatility may be especially true in the domain of negative emotions, when adolescents encounter an expanding array of situations and stimuli that can elicit intensely negative responses, ranging from rejection and sadness to fear and anger (Larson and Ham 1993). Understanding how biological and environmental factors interactively tune emotion regulation in children and adolescents is essential to understand why they are at greater risk for the various psychopathologies that can take root

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during this period of life (Kessler et al. 2005; Casey et al. 2010; Lee et al. 2014; Casey 2015).

One means of studying emotion regulation is to compare reappraisal of negative emotion—which involves thinking about an emotional stimulus differently so as to change one's feelings about it—to uninstructed responding. In healthy adults, reappraisal involves interactions between dorsolateral, ventrolateral, and dorsomedial prefrontal cortex (dlPFC, vlPFC, dmPFC), the posterior parietal cortex, and the amygdala (Wager et al. 2008; Buhle et al. 2014)—suggesting that reappraisal uses PFC and parietal-supported cognitive transformations to modulate the amygdala, which appraises the motivational salience of affective stimuli.

Applying this model of reappraisal to developing populations has revealed that children and adolescents are less able to reappraise negative stimuli than adults who tend to use reappraisal more in everyday life (Garnefski and Kraaij 2006; McRae et al. 2012; Silvers et al. 2012). The neural mechanisms underlying age-related differences in reappraisal have remained elusive, however, for 2 reasons. First, prior neuroimaging studies have typically focused on *either* age-related effects related to lateral prefrontal recruitment (e.g., McRae et al. 2012) or amygdala modulation (e.g., Pitskel et al. 2011; Silvers et al. 2015)—but have not provided a concise account of how interactions between lateral prefrontal cortex and the amygdala change across development. Second, no prior reappraisal studies have tested a wide age range from childhood, through adolescence and into adulthood. Indeed, most prior work has compared just 2 age groups, such as children versus adults or adolescents versus adults. This limits the inferences that can be drawn about the nature of developmental trends. Using enhanced analytical methods in a large developmental sample, the present study sought to test 2 novel hypotheses about why age may predict an improved ability to regulate negative emotion.

First, we used mediation analyses to test the *vlPFC–amygdala pathway hypothesis*, that increasing age leads to stronger vlPFC recruitment which in turn downregulates the amygdala. This hypothesis was informed by the facts that vlPFC recruitment and amygdala downregulation frequently co-occur during reappraisal in adults (Diekhof et al. 2011; Buhle et al. 2014)—particularly during downregulation (as opposed to upregulation) of highly negative emotion (Ochsner et al. 2004, 2012; Silvers, Weber, et al. 2014) and that vlPFC is implicated in age-related changes in response selection/inhibition during adolescence (Durston et al. 2006; Houde et al. 2010; Somerville et al. 2011). Moreover, nonhuman primate anatomical work suggests that vlPFC has moderate numbers of projections to the basolateral amygdala (Ghashghaei et al. 2007) and also to ventromedial prefrontal cortex (vmPFC) (Barbas 1995), which has dense projections to the amygdala (Ghashghaei and Barbas 2002), providing 2 anatomical pathways by which vlPFC could modulate the amygdala.

Second, we identified moderators of the *vlPFC–amygdala pathway*. The goal of this analysis was to investigate whether recruiting vlPFC during reappraisal was associated with reduced amygdala responding across all individuals or whether other factors must also be at play in order for this relationship to hold. For example, if prefrontal–amygdala communication is not yet mature in a child or adolescent, vlPFC recruitment is not likely to be associated with any reduction in the amygdala response during reappraisal. Neuroimaging work has shown that vmPFC mediates the relationship between reappraisal-related lateral PFC recruitment and amygdala modulation in adults (Urry et al. 2006; Johnstone et al. 2007) and that vmPFC–amygdala functional connectivity strengthens across normative development (Gee et al. 2013; Gabard-Durman et al. 2014). In rodents, amygdala → vmPFC projections emerge prior to vmPFC → amygdala projections (Bouwmeester, Smits, et al. 2002; Bouwmeester, Wolterink, et al. 2002) and it has been proposed that in humans, a switch from positive to negative vmPFC–amygdala functional connectivity in early adolescence may index the emergence of vmPFC → amygdala projections (Gee et al. 2013). As such, negative vmPFC–amygdala functional connectivity may serve as a "key" that opens the door for vlPFC to modulate the amygdala in 1 of 2 ways. First, vlPFC could act on the amygdala *via* vmPFC. Second, earlier-developing vmPFC–amygdala connections might ready the brain for longer-reaching, later-developing vlPFC–amygdala connections. We used functional connectivity and moderation analyses to test the *vlPFC–vmPFC–amygdala connectivity moderation hypothesis*, which states that vlPFC-supported amygdala modulation is dependent on negative vmPFC–amygdala connectivity.

Materials and Methods

Participants

One-hundred and twelve healthy individuals between the ages of 6 and 23 years participated in the experiment (65 female; mean age = 15.73 years, SD = 4.36). The initial target sample size was set at 100 participants but given prior experiences with scanning developmental populations, it was anticipated that some participants' data would need to be excluded due to head motion. As such, 129 participants were scanned. The majority of these participants also participated in a separate task examining reappraisal of appetitive stimuli (Silvers, Insel, et al. 2014). Seventeen additional participants (9 females; mean age = 9.20 years, SD = 2.40) were scanned but excluded from analyses due to excessive head motion and 1 participant (female, 6.34 years) was excluded due to failure to comply with the task (i.e., not making button responses). There were 1–12 participants representing each year of age (see Supplementary Fig. 1 for a distribution). All participants could read and write in English, had normal or corrected vision, had never been diagnosed with a developmental or psychiatric disorder, had never been prescribed psychotropic medication, and had no medical conditions contraindicated for scanning. Participants were of normal intelligence, as indexed by the Wechsler Abbreviated Scale of Intelligence (mean score = 114.35, SD = 15.42), and IQ was not associated with age ($r = -0.11$, $P = 0.25$). Parents of children under 18 completed the Child Behavioral Checklist (Achenbach 2001) and reported lower than average problem behaviors (3 parents did not complete the checklist; mean t-score = 41.67, SD = 9.13, $t_{(68)} = 7.59$, $P < 0.001$). All participants aged 18 and older provided informed written consent. Participants aged under 18 provided informed written assent and their parent or guardian provided informed consent. Participants were compensated for their participation. All procedures were approved by the Institutional Review Boards at both Columbia University and Weill Cornell Medical College.

Experimental Procedures

The modal approach to examining reappraisal in adults is to compare a regulation condition (i.e., downregulation of negative affect) to a baseline condition wherein participants "respond naturally" to affective stimuli. This approach assumes that participants interpret the instruction to respond naturally in a similar manner, yet this assumption may be unwarranted when comparing children, adolescents, and adults (Church et al. 2010).

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In the present study, we opted instead to compare a reappraisal strategy, wherein participants distanced themselves so as to reduce negative affect ("Far"), to a baseline condition ("Close") that constrained affective responding by encouraging them to be psychologically close to the emotional scenes they viewed—an approach we have successfully implemented in multiple prior developmental samples (Silvers et al. 2012, 2015; Silvers, Insel, et al. 2014). For clarity of exposition, "Far" trials will be referred to as "Reappraisal" trials and "Close" trials will be referred to as "Reactivity" trials throughout this manuscript. The rationale for using this type of active baseline derived from the fact that we wanted this condition to permit assessment of age-related differences in emotional responding, and not other factors. As such, Reactivity trials reduced the likelihood of age-related variability in how participants attended to and engaged with stimuli, which could in turn lead to age-related differences in emotional responding that were not of interest. Or put another way, by instructing participants to feel psychologically close to affective stimuli, we sought to make developmental differences in emotional responding more interpretable by ensuring that stimuli would be maximally and equally likely to elicit emotional responses across all participants (1 is more likely have an emotional if an event happens proximal to and therefore is relevant to you) for reasons that were of interest (e.g., developmental changes in how the meaning of stimuli are appraised) rather than not of interest (e.g., differences in how participants might spontaneously attend to or judge stimuli in uninstructed contexts).

To assess such factors, participants completed a third-trial type, wherein they were instructed to respond naturally without any specific direction as to how to engage stimuli ("Look"). This condition was included to allow comparisons with prior adult-only studies of reappraisal that used this type of open-ended instruction and to provide a context for examining the influence on emotional responding of individual difference variables that past research indicates are most likely to occur in uninstructed viewing contexts. Data from these Look trials are not of interest here and will be reported on in another manuscript. While prior work in healthy adults has compared up- and downregulation of emotion to a condition wherein no regulation occurred, the present design ought not to be considered in this framework for 2 reasons. First, studies examining up- and downregulation of emotion often explicitly instruct individuals to increase or decrease their affective response (Ochsner et al. 2004), rather than merely giving instructions on how to change their perspective (the approach of the present study). Second, even if the present study's Reactivity and Reappraisal instructions were interpreted as eliciting the up- and downregulation of emotion, comparing Reactivity > Look and Reappraisal > Look trials across age could be deeply problematic given that people of different ages are likely to interpret "respond naturally" (i.e., Look) instructions differently. For example, it could be that children respond naturally by drawing themselves closer to emotional events, whereas adults respond naturally by distancing themselves. As such, comparing a Reactivity > Look or Reappraisal > Look contrast across age might not reveal age-related differences in up- or downregulation of emotion, but rather differences in how individuals respond naturally to affective stimuli.

The full-task design therefore included 2 factors, stimulus valence (Negative or Neutral) and regulation instruction (Reactivity, Reappraisal, or Look). Crossing of these factors yielded 6 trial types (Reactivity/Negative, Reactivity/Neutral, Reappraisal/Negative, Reappraisal/Neutral, Look/Negative, and Look/Neutral). Participants completed 15 trials of each type for a total of 90 trials over the course of 5 runs which took approximately 24 min. Look trials were modeled at the single-subject level in neuroimaging analyses and, as noted, will be characterized in a future publication. That said, for the interested reader, analyses comparing Look, Reactivity, and Regulation trials are provided in Supplementary Material. Note that data from Look trials do no change interpretation of the results from the Reactivity and Regulation trials presented here.

Prior to performing the task, participants were trained extensively on the Reactivity and Reappraisal strategies in accordance with well-validated procedures (Silvers et al. 2012). Both negative and neutral stimuli were social in nature (i.e., they contained people). Trials were presented in a randomized order such that the different trial types were intermingled.

On each trial, participants were initially presented with an instructional cue (i.e., "Close" or "Far") for 2 s followed by a photographic stimulus for 8 s. All analyses presented here were focused on the 8-s picture viewing period, wherein participants implemented the strategy they had been cued to use. Following this, participants saw a jittered fixation interval (jitter range = 2–7 s; mean duration = 3 s) and subsequently rated their current affective state (1 = Not at all bad, 5 = Very bad). Each trial concluded with a jittered fixation interval (on average, 3 s). Stimuli were drawn from the International Affective Picture System (Lang et al. 2001) (IAPS image numbers: 2102, 2104, 2210, 2214, 2235, 2270, 2305, 2372, 2383, 2393, 2394, 2495, 2514, 2515, 2560, 2575, 2579, 2593, 2594, 4621, 6312, 6350, 6838), from a set of similar pictures that had been previously used with adolescents (Silvers et al. 2012), and from freely available online sources. Each stimulus shown was unique (i.e., each image was shown only once). Parents of participants under the age of 18 prescreened 60 negative photographic stimuli prior to participation. Parents were permitted to exclude up to 10 stimuli. Excluded stimuli were replaced with a valence-matched task substitute image that the parent had approved (Silvers et al. 2012). Parents generally rejected few images (mean = 3.12, SD = 4.38) and participant age was negatively correlated with the number of pictures rejected ($r = -0.34$, $P < 0.01$). The number of images rejected did not correlate with self-reported negative affect for the Reactivity ($r = -0.10$, $P = 0.41$) or Reappraisal conditions ($r = -0.07$, $P = 0.57$), suggesting that this did not alter participants' experience. All participants aged 18 and older viewed the same stimuli. The assignment of pictures to instruction was counterbalanced between participants. The trial structure is shown in Figure 1.

Behavioral Data Analysis

Effects of valence, strategy, and mean-centered age were analyzed using a repeated-measures GLM, as implemented in SPSS 21.0. Follow-up t-tests and correlations were performed, when necessary, to clarify the nature of observed F statistics. Both linear (mean-centered age, mean = 15.73 years) and nonlinear (mean-centered age-squared) age effects were examined for behavioral analyses.

fMRI Acquisition

Whole-brain fMRI data were acquired on a 3T Siemens Magnetom Trio scanner. Structural images were acquired using a high-resolution, T_1-weighted MPRAGE sequence (TR = 2170 ms, TE = 4.33 ms, 120 1.5 mm sagittal slices). Functional images were acquired with a T_2*-sensitive EPI BOLD sequence. Thirty-four axial slices were collected with a TR of 2000 ms (TE of 34 ms, flip angle of 90°, field of view of 22.4 cm and $3.5 \times 3.5 \times 4$ mm^3

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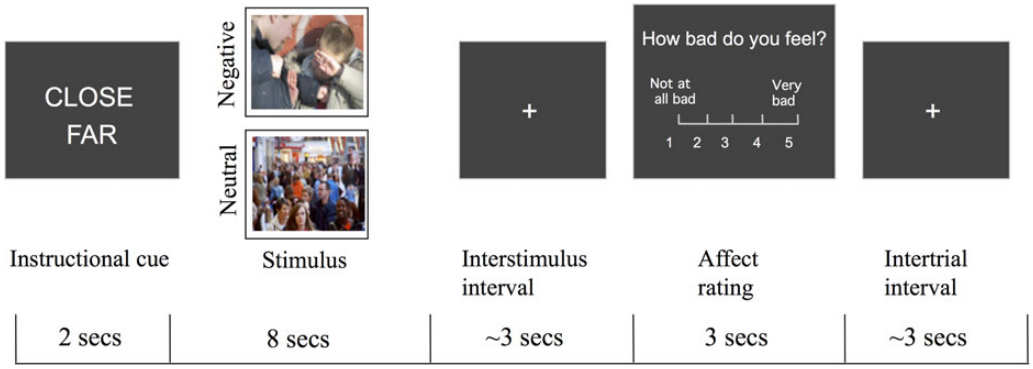

Figure 1. Trial structure for the reappraisal task.

voxels). Stimuli were presented using E-Prime and were projected onto a flat screen mounted in the scanner bore. Subjects viewed the screen using a mirror mounted on a 12-channel head coil. Extensive head padding was used to minimize participant head motion and to enhance comfort. Participants made their responses using a 5-finger-button response pad. In addition to completing the MPRAGE scan and the task described in this manuscript, most participants also completed a separate task that has been reported elsewhere (Silvers, Insel, et al. 2014). The order of the 2 tasks was counterbalanced across participants.

fMRI Analysis

Preprocessing

Preprocessing was performed using SPM8 tools (http://www.fil.ion.ucl.ac.uk/spm/) implemented in NeuroElf (http://neuroelf.net). Functional images were slice-time corrected, corrected for motion, and registered to the first functional image for each subject. Volumes (i.e., frames) with more than 1.5 mm of frame-wise head motion were censored (i.e., removed), runs were removed with more than 10% of volumes removed, and participants were removed, if more than 2 out of the 5 runs were removed. The average number of runs removed for the 112 participants included in analyses was 0.16 (SD = 0.49) and the average number of censored volumes was 0.82 (SD = 1.60). These standards for head motion have been used in prior work in similar age ranges (Somerville et al. 2013). Number of censored volumes was weakly and inversely correlated with age ($r = -0.18$, $P = 0.052$). Analyses were conducted on brain regions of interest showing age effects to examine whether a participant's number of censored volumes predicted differences in activation or functional connectivity and are reported in Supplementary Material. Structural images were spatially normalized to a standard template brain (MNI avg15T1) using unified segmentation and parameters from segmentation were used to spatially normalize the functional data for each subject (Ashburner and Friston 2005). Normalized functional images were resliced into $3 \times 3 \times 3$ mm^3 voxels and spatially smoothed with a 6-mm full-width-at-half-maximum Gaussian filter.

First-level Analyses

First-level GLM analyses were implemented in NeuroElf (http://neuroelf.net). Cue, stimulus-viewing and response portions of each trial were modeled as boxcar regressors convolved with a canonical hemodynamic response function. Separate regressors were made for each task condition and robust regression analyses were performed for each participant (i.e., a robust first-level GLM was created for each participant). Estimates of global signal in gray matter, white matter, and the ventricles, as well as 6 standard motion parameters and high-pass filters were included as additional regressors of no interest.

Second-Level Analyses

Second-level analyses were conducted in NeuroElf. A 3-way ANOVA was used to examine the effects of mean-centered age, strategy (Reactivity, Reappraisal), and stimulus valence (Negative, Neutral) on neural activation. All clusters identified with the linear age term were further interrogated to determine whether they were best fit by a linear (mean-centered age, mean = 15.73 years) versus nonlinear (mean-centered age-squared) age term. Maps were initially thresholded at $P < 0.005$, and significant voxels were subsequently identified using a joint voxel and extent threshold that corresponded to corrected $P < 0.05$ as determined by the NeuroElf AlphaSim toolbox (http://neuroelf.net/). The cluster extent threshold was 78 voxels (smoothness estimate: 10.6 mm).

The amygdala was examined as an *a priori* region of interest (ROI). Bilateral automated anatomical labeling (AAL) structural amygdala ROIs were used as a mask to examine the effects of strategy, stimulus valence and age on amygdala responses. All activations observed within these ROIs were thresholded using small-volume correction (SVC) that corresponded to corrected $P < 0.05$.

Age-Related Changes in Neural Pathways Associated with Regulation

Two hypotheses related to age-related effects associated with emotion regulation were tested.

vlPFC–amygdala pathway hypothesis: vlPFC will mediate the relationship between age and amygdala activation during reappraisal. To test this hypothesis, it was first established that age predicted reduced amygdala responses to negative stimuli during reappraisal by examining the Age × Strategy × Valence interaction. Indeed, the interaction term predicted activation in the left amygdala (MNI co-ordinates: −15, −6, −12) and follow-up correlational analyses revealed that this was driven by age predicting reduced amygdala responses on Reappraisal/Negative trials ($r = -0.34$, $P < 0.001$) but not Reactivity/Negative ($r = -0.08$, $P = 0.38$) trials. While the right amygdala was also identified by the Age × Strategy × Valence interaction, no prefrontal mediators were identified and thus it will not be discussed further (see Supplementary Material).

A mediation analysis was performed using age as a predictor (X), reappraisal-related vlPFC activity as a mediator (M), and amygdala responses as an outcome (Y). The vlPFC ROI was

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identified and tested in the following steps. First, each subject's reappraisal-related left amygdala response was calculated and correlated with neural activity in the reappraisal contrast (Reappraisal/Negative > Reactivity/Negative). Given that the goal was to identify prefrontal regions that were associated with a diminished (rather than increased) amygdala response, only brain regions showing negative correlations with the amygdala responses were examined. This correlational analysis revealed that many brain regions correlated with the amygdala response (ostensibly because of shared global signal), and thus candidate clusters were identified at a slightly more stringent peak threshold than other analyses ($P < 0.0005$, 1-tailed; 31 voxels). This analysis identified 3 prefrontal regions that were negatively associated with the left amygdala response including a cluster in vlPFC (MNI co-ordinates: −42, 39, −3). Second, ROIs identified by the correlational analysis were interrogated in SPSS to see whether they were associated with age. Third, β values from the ROIs were examined to determine whether they continued to predict changes in the amygdala response after controlling for age. In the final step of the mediation analysis, β values from the ROIs were tested using the Process toolbox in SPSS to assess whether they mediated the relationship between age and reappraisal-related amygdala activation. Significance was assessed using 1000 bootstrapping samples (Preacher and Hayes 2004).

vlPFC–vmPFC–amygdala connectivity moderation hypothesis: mature (i.e., negative) vmPFC–amygdala functional connectivity will enable vlPFC to reduce amygdala activity during reappraisal. To test this hypothesis, first support had to be found for the vlPFC–amygdala pathway hypothesis, and second, age had to predict enhanced functional connectivity between the amygdala and vmPFC during reappraisal. To assess functional connectivity, a PPI analysis was conducted. The left amygdala cluster identified in the Age × Strategy × Valence activation-based analysis was used as a seed region to examine how functional connectivity differed during regulated and unregulated responding to negative stimuli (i.e., Reappraisal/Negative > Reactivity/Negative). Given our specific hypotheses regarding amygdala–vmPFC connectivity becoming increasingly negative with age, only negative correlations between connectivity and age were examined and PPI results were masked with an anatomically defined vmPFC ROI (based on AAL's bilateral superior orbital frontal ROIs). The results of the PPI analysis were thresholded using a combined height and extent threshold corresponded to $P < 0.05$, corrected, within the 2035 voxel mask (uncorrected $P < 0.001$, 1-tailed; smoothness = 8.6 mm; 8 voxel extent). To examine which condition drove age effects in the PPI analysis, a second PPI GLM was computed with separate PPI terms for the Reappraisal/Negative and Reactivity/Negative conditions. As in the first-level activation analyses, estimates of global signal in gray matter, white matter, and the ventricles as well as 6 standard motion parameters and high-pass filters were included as additional regressors of no interest when computing the PPI.

As described in the Results, left vlPFC activation mediated the effect of age on amygdala recruitment and vmPFC–amygdala functional connectivity correlated negatively with age. We next examined whether vmPFC–amygdala connectivity moderated the influence that vlPFC exerts on the amygdala during regulation using the Process Toolbox in SPSS. Parameter estimates associated with the Reappraisal/Negative > Reactivity/Negative contrast were extracted from left vlPFC (MNI co-ordinates: −42, 39, −3) and entered as a predictor (*X*). Mean-centered PPI estimates extracted from the peak vmPFC co-ordinate identified in the PPI analysis were entered as a moderator (*M*) and β values from the amygdala were entered as an outcome (*Y*) variable. A second moderation analysis was conducted with mean-centered age added as a covariate.

Neural Correlates of Reappraisal Success

To explore what patterns of neural recruitment were associated with behavioral measures of reappraisal success (i.e., the degree to which self-reported negative affect decreased on Reappraisal versus Reactivity trials), a correlational analysis was performed. For each participant, reappraisal success was operationalized as the percent decrease in negative affect reported on reappraisal versus reactivity trials. These values were entered into a whole-brain correlational analysis with the Reappraisal/Negative > Reactivity/Negative contrast. Because reappraisal success was highly correlated with age, a partial correlational analysis was also performed wherein age was controlled for.

Results

Behavioral Results

Main Effects of Valence and Strategy on Emotional Responding

To assess whether the task manipulations were effective at eliciting expected patterns of emotion, main effects of valence and strategy were examined. As expected, participants reported less negative affect for neutral than negative stimuli ($M_{Neg\text{-}Neut} = 2.21$, $F_{1,\ 110} = 1075.08$, $P < 0.001$), and less negative affect for Reappraisal than Reactivity trials ($F_{1,\ 110} = 53.26$, $P < 0.001$). Reappraisal-related decreases in negative affect were larger for negative stimuli than neutral stimuli, as revealed by an interaction between strategy and valence ($F_{1,\ 110} = 43.03$, $P < 0.001$; Figure 2A).

Effects of Age on Emotion Regulation

To examine whether age predicted differences in how individuals regulate emotion, linear (mean-centered age, mean = 15.73 years) and nonlinear (mean-centered age-squared) age effects were examined (Fig. 2B). Both age ($F_{1,\ 110} = 9.39$, $P < 0.005$) and age-squared ($F_{1,\ 110} = 10.25$, $P < 0.005$) interacted with strategy and stimulus valence to predict negative affect. In both instances, this interaction was due to age predicting less negative affect for Reappraisal/Negative trials (age: $\beta = -0.05$, $t_{(111)} = 2.54$ $P = 0.01$; age^2: $\beta = -0.002$, $t_{(111)} = 2.76$ $P < 0.01$) but not Reactivity/Negative trials (P's > 0.37). Adding a quadratic age term (age^2) did not significantly improve model fit, as determined by the extra sum-of-squares *F*-test, and thus the linear age term was used for all analyses ($F_{1,109} = 2.99$, $P = 0.09$). A follow-up analysis using the Johnson–Neyman technique revealed that negative affect significantly differed for Reactivity/Negative and Reappraisal/Negative trials at 9.87 years suggesting that reappraisal did not significantly reduce negative affect before this age. Age did not interact with strategy (Age × Strategy interaction: $F_{1,\ 110} = 1.09$, $P = 0.30$) nor stimulus valence (Age × Valence interaction: $F_{1,\ 110} = 0.37$, $P = 0.55$) to predict self-reported negative affect.

Imaging Results

Age-independent Imaging Results

Effects of valence and strategy were examined while controlling for age. This set a standard against which age effects could be compared. Negative stimuli elicited greater recruitment than neutral stimuli in much of the brain, including regions involved in emotional responding such as the amygdala and anterior insula as well as numerous other cortical and subcortical structures

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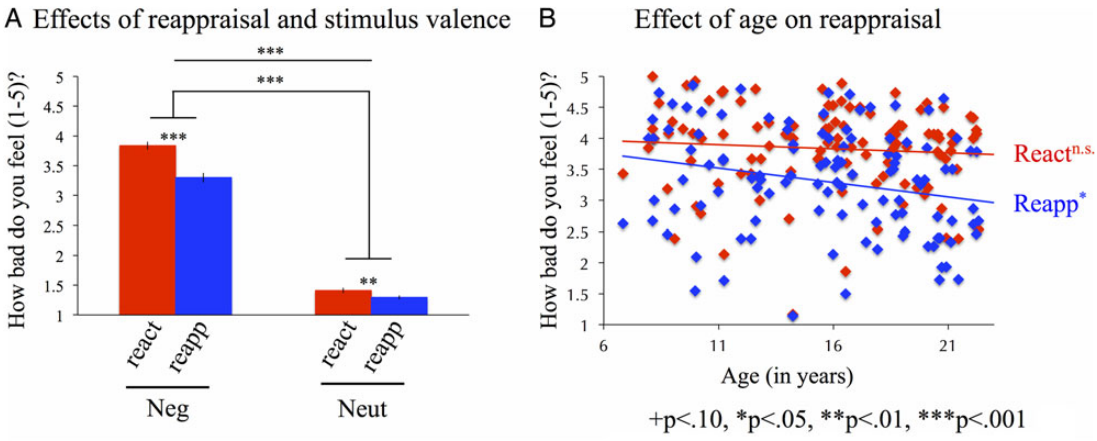

Figure 2. (*A*) Negative affect is shown as a function of strategy and stimulus valence (neg, negative; neut, neutral). (*B*) Self-reported affect on negative trials is plotted as function of age and strategy.

Table 1 Brain regions with differential recruitment as a function of stimulus valence

Region	Hemisphere	# Voxels	F	MNI co-ordinates		
				x	y	z
Negative > Neutral and Neutral > Negative[a]						
Neutral > Negative: Bilateral temporal gyri, anterior and posterior cingulate, bilateral superior temporal gyri, somatosensory cortex, superior parietal lobule, cuneus	R	24 547	407.28	51	−66	3
Negative > Neutral: Bilateral inferior frontal gyri, bilateral anterior insula, bilateral dorsal striatum, bilateral amygdala, bilateral occipital gyri, thalamus, midbrain, cerebellum						
Negative > Neutral						
dmPFC	M	1012	119.32	0	54	27
Cerebellum	L	116	37.34	−3	−54	−33
Neutral > Negative						
Middle frontal gyrus	L	412	53.89	−21	30	33
vmPFC	R	858	79.88	6	42	−6
Middle frontal gyrus	R	441	42.32	30	42	24
Inferior parietal lobule	R	352	82.45	45	−69	45

F, maximum F statistic for a given cluster. For hemisphere: R, right; L, left; M, medial. These brain regions were identified after controlling for age.
[a]A single large cluster was identified by the main effect of valence term but regions within this cluster varied according to whether they responded more strongly to negative and neutral stimuli.

(Table 1). Consistent with prior reappraisal research, the Reappraisal strategy was associated with enhanced recruitment of right dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (Table 2). The stimulus Strategy × Stimulus valence interaction revealed activation in bilateral temporoparietal junctions as well as the precuneus and posterior cingulate cortex (Supplementary Table 2).

Age-Dependent Imaging Results

Results related to vlPFC–amygdala pathway hypothesis: vlPFC will mediate the relationship between age and amygdala activation during reappraisal. Brain regions identified by the Age × Stimulus valence interaction are reported in Supplementary Table 1. In order to test the vlPFC–amygdala pathway hypothesis, it first had to be established that age predicted diminished amygdala responses to negative stimuli during reappraisal. An interaction between age, strategy, and stimulus valence was observed in the bilateral amygdala (results associated with the right amygdala are reported in Supplementary Material). In the left amygdala, age predicted decreased activation to negative stimuli for Reappraisal trials ($r = -0.34$, $P < 0.001$), but not Reactivity trials ($r = -0.08$, $P = 0.38$) (MNI co-ordinates: −15, −6, −12; Table 3; Fig. 3A). The only cluster (outside of the amygdala) that survived correction for the interaction between age, strategy and stimulus valence was a cluster that extended from the parahippocampal gyrus and the midbrain. When linear and quadratic age terms were simultaneously entered as predictors of activation in the amygdala cluster, the linear term was found to be significant ($\beta = -0.14$, $t_{(109)} = 2.08$, $P = 0.04$) and the quadratic term nonsignificant ($\beta = 0.004$, $t_{(109)} = 1.70$, $P = 0.09$). Amygdala responses were greater for Reappraisal than Reactivity trials in childhood and this pattern flipped during adolescence. Amygdala responses did not significantly correlate with self-reported negative affect for Reactivity/Negative or Reappraisal/Negative trials (P's > 0.14).

To further test the vlPFC–amygdala pathway hypothesis, a whole-brain, between-subject correlational analysis was conducted using amygdala activation as a covariate (amygdala ROI defined by Age × Strategy × Stimulus valence interaction; MNI co-ordinates: −15, −6, −12). Ventromedial and ventrolateral PFC, along with regions in temporal and occipital cortex and the

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Table 2 Brain regions showing differential recruitment as a function of strategy

Region	Hemisphere	# Voxels	F	MNI co-ordinates		
				x	y	z
More activation during regulation						
Middle frontal gyrus	R	103	19.02	33	21	39
Posterior cingulate	L	339	27.38	−3	−36	39
Superior and inferior parietal lobules	L	496	36.63	−36	−60	51
Inferior parietal lobule	R	400	33.04	48	−54	45
Precuneus	R	326	24.99	12	−63	39
Less activation during regulation						
Fusiform gyrus	R	212	20.80	39	−60	−15
Superior occipital gyrus	R	78	16.09	33	−72	21
Cuneus and left fusiform gyrus	M	656	43.34	0	−87	−6

Brain regions that showed more activation during regulation showed greater activation for Reappraisal than Reactivity trials, after controlling for age. For hemisphere: R, right; L, left; M, medial; F, maximum F statistic for a given cluster.

Table 3 Brain regions identified by the age × valence × strategy interaction

Region	Hemisphere	# Voxels	F	MNI co-ordinates		
				x	y	z
Age predicts less recruitment during reappraisal of negative emotion						
Amygdala[a]	L	3	9.62	−15	−6	−12
Amygdala[a]	R	7	13.78	33	0	−24
Parahippocampal gyrus, midbrain	L	105	20.67	−15	−36	−9

Age correlated negatively with amygdala responses on Reappraisal/negative trials but not with responses on Reactivity/Negative trials.
[a]Cluster achieved $P < 0.05$ after small-volume correction using bilateral AAL amygdala ROI masks. For hemisphere: R, right; L, left; M, medial; F, maximum F statistic for a given cluster.

cerebellum, were negatively correlated with amygdala activation for reappraisal trials (for a complete list of all brain regions identified, see Table 4). Each cluster identified by this correlational analysis was tested as a potential mediator of the relationship between age and amygdala response. Given that age linearly (and not quadratically) predicted the amygdala response, only linear age effects were examined in this analysis. Left vlPFC was the only prefrontal region that mediated the relationship between age and the amygdala response during reappraisal of negative stimuli (Reappraisal/Negative > Reactivity/Negative; Fig. 4). As reported in Supplementary Material, estimates of brain structure were unrelated to vlPFC and amygdala activation.

Age predicted greater left vlPFC recruitment (A path: $\beta = 0.009$, $t_{(110)} = 1.97$, $P = 0.05$) and vlPFC continued to predict less reappraisal-related amygdala activity after controlling for age (B path: $\beta = -0.95$, $t_{(109)} = 5.79$, $P < 0.001$). Consistent with the vlPFC–amygdala pathway hypothesis, a mediation analysis revealed that the indirect path via vlPFC accounted for 32% of the total effect of age on the amygdala response ($\beta = -0.008$, bias corrected and accelerated 95% confidence intervals = −0.03, 0.00; percent mediated = [A × B coefficients = 0.009 × −0.95]/[Total effect coefficient = −0.026] = 0.37), and that the direct effect between age and reappraisal-related amygdala activity was significantly lessened after accounting for left vlPFC as a mediator (prior to mediation [C path]: $\beta = -0.026$, $t_{(110)} = 2.95$, $P < 0.005$; after mediation [C′ path]: $\beta = -0.018$, $t_{(109)} = 2.23$, $P = 0.03$).

vlPFC–vmPFC–amygdala connectivity moderation hypothesis: mature (i.e., negative) vmPFC–amygdala functional connectivity will enable vlPFC to reduce amygdala activity during reappraisal. This hypothesis was contingent on first finding support for the vlPFC–amygdala pathway hypothesis and second, on showing that age predicted enhanced functional connectivity (using psychophysiological interaction analysis; PPI) between the amygdala and vmPFC during reappraisal. Results from the PPI analysis revealed that age predicted a switch from positive to negative connectivity between the vmPFC and the left amygdala during regulation of negative affect (Reappraisal/Negative > Reactivity/Negative PPI term; Table 5; Fig. 3B). A second GLM with separate PPI terms for the Reappraisal/Negative and Reactivity/Negative conditions revealed that age effects in vmPFC–amygdala connectivity were driven primarily by the reappraisal condition (Reappraisal/Negative: $r = -0.19$, $P < 0.05$; Reactivity/Negative: $r = 0.16$, $P = 0.10$). For descriptive purposes, absolute amygdala–vmPFC connectivity (baseline connectivity + PPI term) was calculated for each condition and means for different ages are provided in Supplementary Table 6. This supplementary analysis revealed that connectivity was positive at younger ages and slightly negative at older ages. Given that a linear, but not quadratic, age term predicted the amygdala response, only linear age effects were examined for the PPI analysis.

Consistent with our hypotheses, vmPFC–amygdala functional connectivity moderated the relationship between vlPFC recruitment and amygdala downregulation during reappraisal (R^2 improvement in model fit after including vmPFC connectivity × vlPFC recruitment interaction term = 0.03, $F_{1,108} = 4.77$, $P < 0.05$). Specifically, participants with negative vmPFC–amygdala connectivity showed a stronger inverse correlation between vlPFC and amygdala recruitment than participants with positive vmPFC–amygdala connectivity (Fig. 5). After controlling for age, the moderating effect of vmPFC connectivity was marginally significant (R^2 improvement = 0.02, $F_{1,107} = 3.66$, $P = 0.058$).

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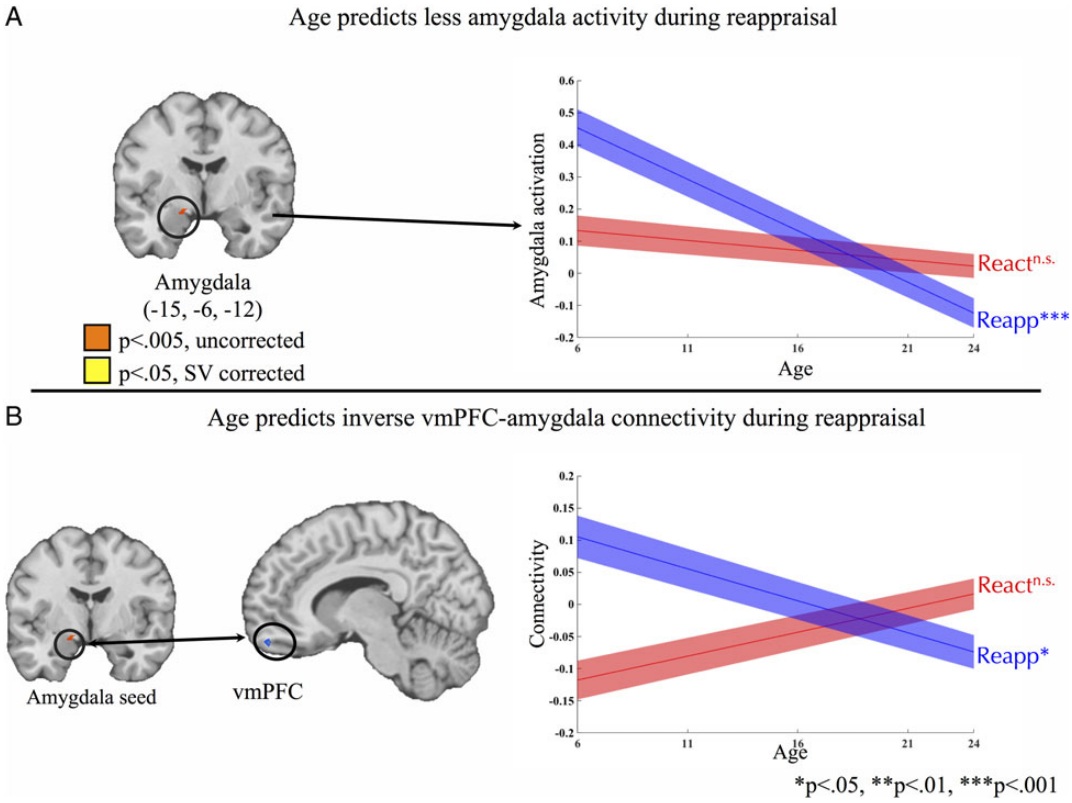

Figure 3. (*A*) Age predicted reduced amygdala responses to negative stimuli for Reappraisal trials but not for Reactivity trials. (*B*) Functional connectivity between the amygdala and vmPFC was positive in younger participants but negative in older participants during reappraisal of negative stimuli (Reappraisal/Negative > Reactivity/Negative).

Table 4 Brain regions associated with less reappraisal-related amygdala recruitment

Region	Hemisphere	# Voxels	*r*	MNI co-ordinates			Correl. age	Mediator
				x	y	z		
Middle and inferior frontal gyrus	L	71	−0.48	−42	39	−3	+	Yes
Orbital gyrus	L	35	−0.41	−21	42	−12	n.s.	
vmPFC	R	127	−0.50	3	42	−27	n.s.	
Middle temporal gyrus	L	33	−0.53	−69	−33	−18	n.s.	
Fusiform gyrus, middle temporal gyrus	L	301	−0.52	−54	−51	−15	+	
Middle occipital gyrus	R	95	−0.53	30	−99	9	+	Yes
Cuneus	L	42	−0.57	−9	−93	−18	n.s.	
Cerebellum	L	297	−0.59	−27	−39	−45	n.s.	
Cerebellum	L	43	−0.56	−21	−21	−36	+	
Cerebellum	R	33	−0.41	45	−42	−33	+	Yes

Brain regions were identified by whole-brain correlation with reappraisal-related amygdala response (Reappraisal/Negative > Reactivity/Negative). For hemisphere: R, right; L, left; M, medial. *r*, maximum *r* statistic for a given cluster. "Correl age" indicates whether age was positively (+), negatively (−) or not significantly (n.s.) associated with recruitment (assessed at $P < 0.05$). "Mediator" indicates whether neural recruitment mediated relationship between age and amygdala response during reappraisal (assessed at $P < 0.05$).

vmPFC connectivity and vlPFC recruitment were unrelated to one another, both before ($r = 0.04$, $P = 0.72$) and after controlling for age ($r = 0.11$, $P = 0.25$).

Neural Correlates of Reappraisal Success

Reappraisal success (i.e., the percent reduction in negative affect participants reported on Reappraisal/Negative trials compared with Reactivity/Negative trials) was positively correlated with the right superior parietal lobule ($r = 0.39$, MNI co-ordinates: 33, −42, 48; 213 voxels). A smaller cluster in the same right parietal region was observed after controlling for age ($r = 0.38$, MNI co-ordinates: 36, −51, 54; 132 voxels), suggesting that recruitment of this region was associated with better reappraisal success across age. This parietal cluster was partially overlapping with the right parietal region shown to be more active on Reappraisal versus Reactivity trials across age (Table 2). No other brain regions survived family wise error correction.

Discussion

The way individuals respond to emotional events changes dramatically from childhood to adulthood. The present study

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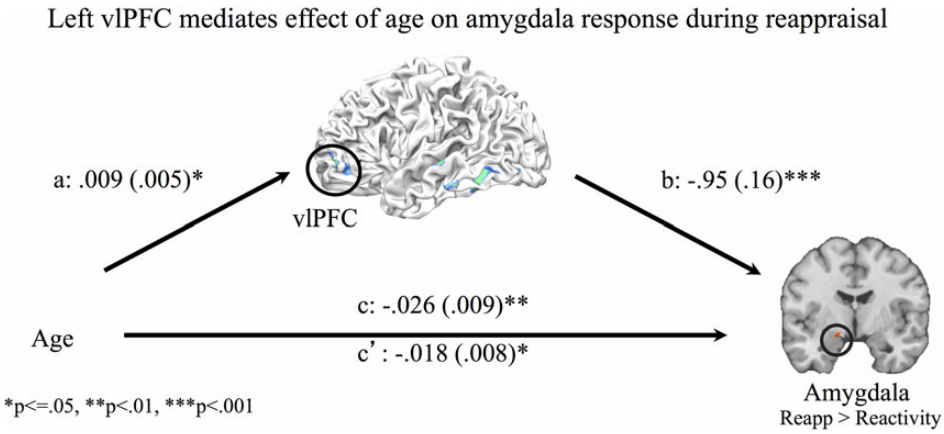

Figure 4. Left vlPFC mediated age-related reductions in the amygdala response during reappraisal (Reappraisal/Negative > Reactivity/Negative). The vlPFC ROI was defined by correlating mean reappraisal-related changes in the amygdala with activation for Reappraisal/Negative > Reactivity/Negative. Path a illustrates that age was associated with increased recruitment of vlPFC while Path b demonstrates that vlPFC recruitment predicted less amygdala recruitment on Reappraisal/Negative versus Reactivity/Negative trials while controlling for age. Path c demonstrates the total effect (combined direct and indirect paths between age and the amygdala) whereas Path c′ illustrates that the direct path between age and the amygdala response was significantly weaker after accounting for the indirect path via vlPFC.

Table 5 Ventromedial prefrontal regions showing differential amygdala connectivity during reappraisal as a function of age

Region	Hemisphere	# Voxels	*r*	Reapp	React	MNI co-ordinates		
				r	*r*	x	y	z
Amygdala connectivity correlates negatively with age								
vmPFC	R	8	−0.38	−0.19*	0.16	9	54	−21
Posterior OFC	L	9	−0.35	−0.24**	0.26**	−27	12	−15
Posterior OFC	R	9	−0.35	−0.33***	0.20*	24	12	−21

Brain regions identified within vmPFC mask showing differential amygdala connectivity (−15, −6, −15) during reappraisal of negative stimuli (Reappraisal/Negative > Reactivity/Negative) as a function of age. For hemisphere: R, right; L, left; M, medial. *r*, maximum *r* statistic for effect of age on connectivity for (Reappraisal/Negative > Reactivity/Negative). The correlation between age and connectivity for each condition is also reported, as ascertained by a second GLM that computed PPI terms for the conditions separately (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

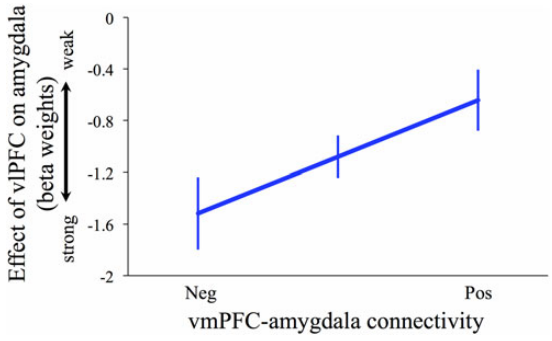

Figure 5. vmPFC–amygdala functional connectivity during reappraisal moderated the association between vlPFC and amygdala recruitment. vlPFC recruitment exerted a stronger modulatory influence on the amygdala among participants with negative vmPFC–amygdala functional connectivity than among those with positive vmPFC–amygdala functional connectivity. Predicted β estimates of vlPFC recruitment on amygdala responses are plotted as a function of vmPFC–amygdala connectivity (1 SD above and below mean-centered average).

sought to build upon prior work documenting age-related differences in the ability to implement cognitive strategies such as reappraisal by testing 2 hypotheses about the neural mechanisms underlying these age-related differences. The first was the *vlPFC–amygdala pathway hypothesis*, which posits that age-related decreases in amygdala activity during reappraisal are instantiated either directly or indirectly via recruitment of prefrontal systems involved in cognitive control. Consistent with this hypothesis, we found a mediation pathway where increasing age predicted greater downregulation of the amygdala via recruitment of left vlPFC. The second *vlPFC–vmPFC–amygdala connectivity moderation hypothesis*, posited that age-related changes in vmPFC–amygdala connectivity potentiate the effects of vlPFC recruitment on amygdala responding during reappraisal. Consistent with this hypothesis, we found that the correlation between vlPFC and amygdala activity was moderated by vmPFC–amygdala connectivity.

Together, these results suggest a model of emotion regulation whereby age-related improvements in regulatory ability are supported by changes in activation and connectivity among prefrontal–amygdala circuits. The significance of this model, and caveats with respect to our findings, are further considered below.

A Model of Negative Emotion Regulation in the Developing Brain

The present results suggest that while the magnitude of PFC and amygdala activity during reappraisal of negative emotion change across age, what changes most critically is the way these systems interact. Independent of age, participants showed

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robust recruitment of dlPFC and bilateral posterior parietal cortices. dlPFC has previously been identified in a number of neuroimaging studies of cognitive reappraisal in healthy adults, as has posterior parietal cortex (Buhle et al. 2014). Posterior parietal cortex tends to be more strongly recruited in studies using a "distancing" variant of reappraisal, such as the one used in the present study, likely because this strategy involves changes in spatial attention and perspective taking (Ochsner et al. 2012). Unlike what has been observed in prior work in adults (Buhle et al. 2014), we did not observe robust recruitment of vlPFC at the group level but instead found that vlPFC activation varied substantially across participants. Specifically, it was observed that age-related changes in the amygdala response during reappraisal are mediated by a vlPFC region implicated in semantic and cognitive control processes (Hinke et al. 1993; Huang et al. 2002; Thompson-Schill et al. 2005; Badre and Wagner 2007) that has previously been shown to support developmental changes in "cold" cognitive control processes such as response inhibition (Durston et al. 2002; Tamm et al. 2002; Velanova et al. 2008). Three prior developmental neuroimaging studies examining reappraisal of aversive stimuli obtained conflicting results about whether age predicted increased lateral prefrontal recruitment or diminished amygdala responses (Pitskel et al. 2011; McRae et al. 2012; Silvers et al. 2015). These conflicting results could be due to the fact that age-related changes in the amygdala response are influenced by individual variability in vlPFC recruitment that may not be identified as easily in standard main effect analyses, but may be more easily observed through the use of statistical mediation. No prior neuroimaging study of reappraisal of negative emotion across development has utilized as wide an age range (McRae et al. 2012: 10–23 years; Pitskel et al. 2011: 7–17 years; Silvers et al. 2015: 10–22 years) or as large a sample as in the present study (McRae et al. 2012: 38; Pitskel et al. 2011: $n = 15$; Silvers et al. 2015: $n = 56$)—factors that may have enhanced characterization of age effects in the present study.

Prior work has adopted 1 of 2 approaches when investigating prefrontal–amygdala dynamics in reappraisal. One approach has been to use correlational analyses to identify *between-participant* differences in prefrontal recruitment that predict less amygdala activation (Urry et al. 2006; Johnstone et al. 2007; Pitskel et al. 2011). Another approach has been to use functional connectivity analyses to identify prefrontal regions that dynamically track *within-participant* changes in amygdala activation (Banks et al. 2007). The present study used these 2 approaches in tandem to test *mediation* and *moderation* hypotheses about the prefrontal–amygdala pathways supporting regulatory success. Specifically, a mediation analysis revealed that left vlPFC-mediated age effects on the amygdala while a PPI analysis revealed that age predicted increasingly negative vmPFC–amygdala connectivity during strategic regulation.

Critically, by combining mediational and PPI analyses using moderation, we found that vmPFC–amygdala connectivity is a rate-limiting step for the degree to which cognitive regulation can reduce amygdala activity via vlPFC recruitment. While prior work has found age-related changes in vmPFC–amygdala connectivity during passive viewing of facial expressions (Gee et al. 2013), and other work has found age-related differences in vlPFC–amygdala connectivity during emotion regulation (Silvers et al. 2015), this is the first piece of evidence to show that vlPFC and vmPFC interactions with the amygdala during emotion regulation change across development. There are at least 2 interpretations for this finding. The first is that in older individuals, vlPFC engages vmPFC, which in turn exerts a modulatory influence on the amygdala. This possibility is appealing given vmPFC's role in regulatory processes including fear extinction and reversal learning (Milad et al. 2007; Finger et al. 2008; Schiller et al. 2008; Sehlmeyer et al. 2009; Schiller and Delgado 2010), yet the fact that vlPFC recruitment and vmPFC–amygdala connectivity were uncorrelated makes it seem less plausible. The second possibility is that increasingly negative vmPFC–amygdala coupling indexes the degree to which the amygdala is receptive to prefrontal modulation across development (Gee et al. 2013), but that vlPFC and vmPFC exert independent influences on the amygdala during reappraisal. If this were the case, vlPFC may not interact with vmPFC when modulating amygdala activity but instead vmPFC–amygdala connectivity indicates whether the amygdala can be modulated by lateral PFC cognitive control systems. An alternative possibility would be that mature vmPFC–amygdala connectivity during reappraisal can only come online once individuals start recruiting vlPFC. The results of the statistical moderation test cannot give insight into whether vlPFC is facilitating vmPFC–amygdala connectivity or whether vmPFC–amygdala connectivity is facilitating vlPFC recruitment but merely that the 2 have a significant interactive effect on amygdala responses. However, given that vmPFC matures structurally prior to vlPFC (Shaw et al. 2008) and work suggesting that maternal presence can induce vmPFC-instantiated regulation of the amygdala during childhood (Gee et al. 2014), it seems more likely that self-regulatory processes develop in a medial-to-lateral pattern in PFC and that vmPFC–amygdala connectivity must be in place before relatively distal structures like vlPFC can exert effects on the amygdala. As future work continues to explore the role of prefrontal–amygdala communication across development, it will be worthwhile to also examine how different subnuclei of the amygdala may relate to different features of affective responding and regulation. For example, it is intriguing that age predicted significant differences in reappraisal-related modulation of the dorsal amygdala, whereas regulation success (irrespective of age) was associated with differential recruitment of a more lateral portion of the amygdala.

Development of Emotion Regulation as a Function of Emotional Valence and Strategy

The present results put forth a model for how vlPFC → amygdala modulation during reappraisal of negative emotion becomes stronger across age and how this pathway is moderated by vmPFC–amygdala connectivity. These data raise important questions with regards to prescribing emotion regulatory strategies at different points in development and also whether the model holds for other types of emotional responses (e.g., positive or appetitive responses).

With regards to the first of these issues, it is striking that reappraisal did not significantly reduce negative affect in the youngest children in this sample and that left amygdala responses were actually elevated during reappraisal in children and young adolescents. These findings could be explained in 1 of 2 ways. First, it could be that prefrontal–amygdala systems that support effective reappraisal are not yet developed in children and thus children are biologically incapable of using reappraisal to strategically regulate negative affect. If vlPFC development and PFC–amygdala inhibitory connections are still under construction during childhood, it may be advisable for children to utilize regulatory strategies that do not rely heavily on vlPFC like reappraisal, such as seeking out social support from parents (Gee et al. 2014), or strategies that involve focusing attention away from the affective stimulus, such as attentional deployment (Sethi et al. 2000). Second, it could be that children

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can reappraise effectively but are simply less experienced at reappraising than are adolescents and adults. Put another way, if children are less experienced with reappraising, they may find it to be more effortful and this in part may explain why they showed elevated amygdala responses (i.e., amygdala increases could reflect greater cognitive effort or arousal). Consistent with this possibility, prior work has shown that children can reappraise when instructed to do so long before they endorse reappraisal as an effective strategy (Mischel and Baker 1975; Mischel and Mischel 1983). This would suggest that age-related amygdala effects in the present study might be driven by differences in their experience with practicing reappraising rather than differences in biology, a possibility that could be formally tested by examining whether reappraisal training leads to adult-like amygdala responses in children. Additionally, future studies might ask participants to indicate how difficult it was for them to reappraise.

With regards to the question of whether this model of emotion regulation generalizes to all emotions, there is evidence to suggest that developmental trajectories of emotion regulation differ according to emotion type. While the present model explains developmental changes in neural systems supporting the reappraisal of negative emotions, alternative and earlier-developing pathways may support regulation of other emotions. For example, seminal work by Mischel et al. revealed that children as young as 3 can be taught to reappraise appetizing food using a psychological distancing strategy similar to the one used in the present study (Mischel and Baker 1975). Moreover, children show remarkable flexibility in their ability to use this strategy with foods, such that they can cognitively transform real food into pictures in their minds eye and imagined foods into something more real (Moore et al. 1976). More recently, it has been demonstrated that children, adolescents and adults are equally skilled at reappraising appetizing food and rely on largely overlapping prefrontal regions to implement reappraisal (Silvers, Insel, et al. 2014). Taken together, this suggests that lateral prefrontal–amygdala systems involved in regulating negative affect, particularly negative affect related to social cues (Silvers et al. 2012), may be slower-developing than neural systems involved in regulating craving for simple rewards.

In sum, the present results provide a cohesive model for how age-related improvements in cognitive regulation are instantiated in the developing brain. Using a multimethod approach that combined measures of connectivity and activation, it was observed that vlPFC recruitment mediates the relationship between age and reduced amygdala activation during regulation—but that this effect is strongest in individuals with mature vmPFC–amygdala connectivity. These findings provide a framework for how vmPFC and vlPFC may work in concert to regulate affective responses across development.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

Conflict of Interest: None declared.

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