J Psychopathol Behav Assess (2015) 37:634–644
DOI 10.1007/s10862-015-9492-z

An fMRI Pilot Study of Cognitive Reappraisal in Children: Divergent Effects on Brain and Behavior

Lea R. Dougherty[1] · **Sarah L. Blankenship**[1] · **Philip A. Spechler**[1] · **Srikanth Padmala**[1] · **Luiz Pessoa**[1]

Published online: 19 May 2015

Abstract Although neuroimaging studies in adults demonstrate that cognitive reappraisal effectively down-regulates negative affect and results in increased prefrontal and decreased amygdala activity, very limited empirical data exist on the neural basis of cognitive reappraisal in children. This study aimed to pilot test a developmentally-appropriate guided cognitive reappraisal task in order to examine the effects of cognitive reappraisal on children's self-reports of affect and brain responses. Study 1 (N=19, 4–10 years-old) found that children successfully employed guided cognitive reappraisal to decrease subjective ratings of negative affect, supporting the effectiveness of the guided cognitive reappraisal task. Study 2 (N=15, ages 6–10 years-old) investigated the neural responses to guided cognitive reappraisal and found that the neural responses showed increased activation in the amygdala and ventromedial prefrontal cortex during the cognitive reappraisal condition compared to the no regulation condition. In addition, amygdala activity was positively correlated with ventromedial prefrontal cortex activation during cognitive reappraisal. Findings suggest that the neural networks supporting cognitive reappraisal in children involve similar brain regions but brain responses deviate from findings in adults. Our findings suggest that the neural networks supporting emotion regulation are still developing during middle childhood, and future research is necessary to delineate age-related development of the neural network involved in cognitive reappraisal.

Keywords Emotion regulation · Cognitive reappraisal · Children · fMRI · Amygdala · Prefrontal cortex

Emotion regulation is broadly defined as the ability to modify one's emotional experiences and expressions (Gross 1998). Emotion regulation strategies are adaptive in that they enable individuals to respond appropriately to emotional content in their environments and social relationships. Deficits in the ability to regulate one's emotions are linked to a wide range of cognitive, academic, interpersonal, and physical health problems (Graziano et al. 2007; Gross 1998; Gross and John 2003). Furthermore, maladaptive emotion regulation is a core feature of numerous psychiatric disorders and has been implicated in the etiology and maintenance of psychopathology, including anxiety and mood disorders in children and adults (Beauregard et al. 2006; Carthy et al. 2009; Monk 2008; Pitskel et al. 2011; Southam-Gerow and Kendall 2002). Given the far-reaching significance of emotion regulation across the lifespan, investigations of the neural bases of emotion regulation are critical in order to understand how emotion regulation abilities develop and lead to negative outcomes.

While a number of emotion regulation strategies exist (e.g., distraction, response modulation), the majority of research has focused on cognitive reappraisal, the deliberate reinterpretation of emotional material to decrease its emotional salience and, ultimately, the emotional response (Gross 1998; Ochsner and Gross 2005). Cognitive reappraisal has been shown to have lasting effects on decreasing negative affect based on self-report and physiological measures of emotion (e.g., Gross and John 2003; McRae et al. 2012; Ray et al. 2010; Wolgast et al. 2011) and, as such, is a core skill taught in

Electronic supplementary material The online version of this article (doi:10.1007/s10862-015-9492-z) contains supplementary material, which is available to authorized users.

✉ Lea R. Dougherty
ldougher@umd.edu

[1] Department of Psychology, University of Maryland, College Park, MD 20742, USA

cognitive behavioral therapy for mood and anxiety disorders. The neural networks supporting reappraisal have been well-documented in the adult literature and appear to be comprised of prefrontal cortices and subcortical areas. Specifically, brain responses observed during cognitive reappraisal in adults include: increased activation in dorsolateral prefrontal cortex (PFC), ventromedial PFC, and lateral temporal cortex, and decreased activation in the amygdala (for review, see Buhle et al. 2014; Kohn et al. 2014; Ochsner et al. 2012). It has been suggested that the increased activation in frontal regions and the decreased activation in the amygdala reflect a top-down cognitive control mechanism whereby prefrontal regions down-regulate emotion processing regions such as the amygdala. Evidence of a negative correlation between ventromedial PFC and amygdala activation during emotional down-regulation in adults is consistent with this hypothesis (Banks et al. 2007; Urry et al. 2006).

In contrast to the adult literature on emotion regulation, very little research has investigated the neural basis of emotion regulation in children. Nevertheless, the capacity for emotion regulation may begin as early as infancy (Dennis et al. 2009; Manian and Bornstein 2009), with evidence suggesting children as young as 3 years are aware that certain contexts warrant differential emotional responses and can alter their behavioral responses based on contextual demands (Dennis et al. 2009). Self-report evidence suggests that cognitive emotion regulation strategies are used to down-regulate emotions during middle childhood and adolescence, making cognitive reappraisal a particularly relevant strategy to investigate during these ages (Gullone et al. 2010; Stegge and Meerum Terwogt 2007). Moreover, the first signs of psychopathology typically emerge during childhood and adolescence, making it imperative to study emotion regulation, and more specifically, reappraisal, within a neurodevelopmental framework.

In the first functional magnetic resonance imaging (fMRI) study of the neural basis of reappraisal in children, Levesque et al. (2004) instructed 8–10 year-old girls to down-regulate their emotional response to a sad film clip and observed significant activation in lateral PFC, orbitofrontal cortex, medial PFC, right anterior cingulate cortex, and ventrolateral PFC in response to reappraisal versus passive viewing. Unfortunately, down-regulation of amygdala activation was not examined. Pitskel et al. (2011) instructed 7–17 year-olds to attend to, increase, or decrease feelings of disgust before viewing neutral and disgusting images selected from the International Affective Picture System (IAPS; Lang et al. 2008). Children were provided with specific strategies to increase (e.g., "pretend it's in front of you") and decrease (e.g., "pretend its fake") their affective response. Similar to findings in adults (Urry et al. 2006), the authors reported that down-regulation of disgust resulted in an inverse relationship between left amygdala and medial PFC activity, reinforcing the idea of a down-regulating effect driven by prefrontal control regions. In addition, left amygdala activation decreased with age, suggesting that the network supporting reappraisal undergoes developmental change.

In a recent developmental study, McRae et al. (2012) investigated reappraisal networks in children (10–13 years), adolescents (14–17 years), and young adults (18–22 years) and found developmental changes in the neural mechanisms supporting cognitive reappraisal. Similar to the paradigm used by Pitskel et al. (2011), at the beginning of each trial, children were provided with a reappraisal instruction to attend to or decrease negative affect followed by the presentation of a negative or neutral IAPS image. During reappraisal, activation in the left inferior frontal gyrus and a left ventrolateral PFC region increased linearly with age while activation in the posterior cingulate, medial PFC, and anterior temporal cortex showed quadratic changes with age, with adolescents showing greater activation than adults or children during reappraisal. Interestingly, down-regulation of the amygdala was not observed in any age group during reappraisal; however, several prefrontal regions did show significant activation during reappraisal, but this effect was not observed in children ages 10–13 years. These findings suggest that cognitive reappraisal mechanisms may differ across development.

While there have been recent attempts to investigate the development of reappraisal networks in younger individuals, the existing literature is inconclusive. Some studies suggest children are capable of successfully down-regulating amygdala activity (Pitskel et al. 2011), while others indicate they are not (McRae et al. 2012). Even more, there is still a dearth of research investigating emotion regulation networks during early to middle childhood (6–10 years), a period of ongoing neurodevelopment and reorganization in regions implicated in emotion regulation. The prefrontal cortex undergoes developmental changes into adulthood (Gogtay et al. 2004), and the amygdala reaches its peak volume around age 10 (Uematsu et al. 2012). Recent evidence also suggests that during fearful face processing, amygdala-prefrontal functional connectivity undergoes a developmental change around age 10 where a shift from positive to negative connectivity between these regions occurs (Gee et al. 2013). Taken together, evidence of the protracted development of regions implicated in emotion regulation and the connectivity between these regions suggests that early to middle childhood is a period of interest in understanding the development of emotion regulation networks.

The current study aimed to pilot a developmentally-appropriate guided cognitive reappraisal task (Dennis and Hajcak 2009) modified for functional magnetic resonance imaging (fMRI) use in order to examine the neural basis of cognitive reappraisal during early to middle childhood (6–10 years). Given the current state of the literature, we tentatively hypothesized that (1) guided cognitive reappraisal would effectively down-regulate negative affect, as assessed via children's self-reports; and (2) guided cognitive reappraisal would be associated with increased prefrontal and

decreased amygdala activation. We also hypothesized that ventromedial PFC would show inverse coupling with amygdala activity during reappraisal. However, these hypotheses are tentative as recent findings by McRae et al. (2012) suggest that children at this age, in contrast to adults, may not have the control mechanisms necessary to down-regulate amygdala activation using reappraisal strategies.

Method

Overview

Study 1 examined the behavioral effects of cognitive reappraisal on regulating negative affect. Using a self-report measure of affect, we assessed the degree to which directed reappraisal stories up-regulated or down-regulated children's emotional responses to negatively valenced pictures. Study 2 examined changes in functional brain activity associated with the cognitive reappraisal paradigm used in study 1.

Study 1: Behavioral Study of Cognitive Reappraisal

Participants Participants were recruited via a commercial mailing list and print advertisements distributed throughout local schools, community centers, daycare and healthcare providers in the greater Washington, DC area. Interested parents of child participants were interviewed on the telephone to determine study eligibility. Eligible participants were between the ages of 4 and 10 years old, native English speakers, and free from any cognitive or developmental disorders based on parent-report. A total of 19 children were recruited for the behavioral study (12 females; Age M=6.7 years, SD=1.1, range=4–10). The study was approved by the human subjects review committee, and informed consent was obtained from parents. Child assent was obtained from children 7 years and older.

Emotion Regulation Task The emotion regulation task was based on a directed reappraisal paradigm developed for children ages 5–10 years-old that has been shown to modulate brain responses to emotional stimuli as measured by event related potentials (see Dennis and Hajcak 2009). In the current study, participants were presented with 45 negative pictures (e.g., frightening animals, negative facial expressions) and 15 neutral pictures.[1] Developmentally appropriate negative- and neutral-valenced images were selected from the International Affective Picture System (IAPS; Lang et al. 2008) and the Emotional Picture Set (EmoPicS; Wessa et al. 2010). The negative pictures were divided into three conditions: negative-attend, negative-decrease, and negative-increase. All neutral pictures were presented in the neutral-attend condition. Each picture was preceded by a brief story containing an implicit instruction to attend, decrease, or increase their affective response to the upcoming picture. Participants were instructed to "match the story to the picture" and were trained in a practice session before the main experiment. The decrease stories provided a directed reappraisal of the negative-valenced picture to down-regulate negative affective responses. For example, prior to the presentation of a picture of a crying father and son, the participant heard the following directed reappraisal: "This family just won a big prize and is so happy they are crying". Conversely, the increase stories provided a directed reappraisal to up-regulate the negative affective response from the picture (e.g., "This family just lost their home in a fire and is sad and crying"). The attend conditions (negative-attend and neutral-attend) provided an objective description of the picture, absent of any regulatory cues or affective language (e.g., "This is a picture of a man holding a small boy in his arms"). See Online Resource 1 for a complete list of stimuli and associated stories.

The stories paired with negative pictures were counterbalanced across participants such that all negative pictures were balanced across each negative condition (i.e., decrease, increase, attend). Neutral pictures were always paired with an "attend" story. None of the images or stories was repeated during the session. The stories were recorded by a female staff member using an external microphone attached to a computer using the open-source program Audacity (http://audacity.sourceforge.net/). Each story had a spoken duration of approximately 5 s (s) (M=4.52, SD=0.50). Our final stimuli set consisted of 60 story-picture pairs (15 per condition). Both the behavioral and fMRI versions (described below) of the experiments were programmed using Presentation software (Neurobehavioral Systems, Albany, CA, USA).

We assessed children's self-reported affect following the presentation of each picture using an abbreviated version of the self-assessment manikin (SAM) valence rating system (Lang et al. 2008). The 5-point valence scale depicts five characters who range from unhappy (1) to happy (5) with three being neutral. Participants were told to "point to the picture of SAM that best shows how you feel". Children's responses were hand recorded by the experimenter. The abbreviated SAM has been shown to assess self-reported affective responses in children as young as 5 years (Dennis and Hajcak 2009).

The experiment was divided into three "runs" of approximately 5–6 min each in duration. Each run consisted of 20 trials (5 per trial type). All four experimental conditions were intermixed in a pseudorandom fashion. Each picture was presented for 2.5 s (visual angle=9.5° × 9.5°), preceded by the story lasting approximately 5 s during which a fixation mark was presented on a blank screen. A 2 s delay period was included between each story and picture (see Fig. 1). The picture

[1] **IAPS**:1050,1120,1201,1300,1302,1321,1525,1930,1932,2120,2130,2457,2458,2703,2780,2810,2900,3022,3230,3280,6300,6312,6370,7380,9050,9250,9321,9421,9440,9480,9490,9561,9582,9594;**EmoPicS**:208,209,210,211,212,216,225,235,246,251,329

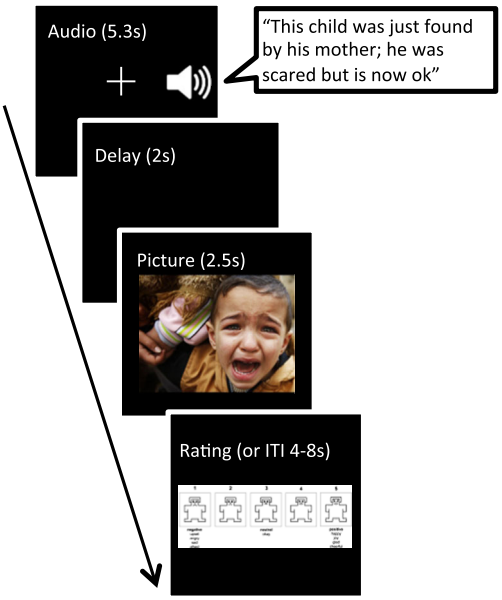

Fig. 1 Experimental paradigm: Each trial began with an auditory story lasting 5.3 s, followed by a delay lasting 2 s, and followed by a negative or neutral-valenced picture lasting 2.5 s. Study 1 concluded each picture display with a subjective report of affect prompt. Study 2 did not collect subjective reports; each picture was followed by a 4–8 s jittered inter-trial interval (ITI)

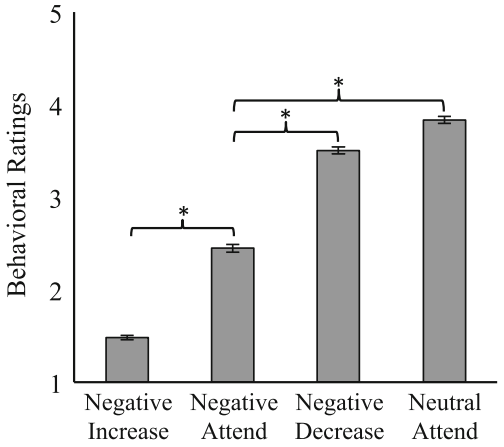

Fig. 2 Mean affect ratings as a function of condition in Study 1. Affect ratings ranged from from 1 (*negative*) to 5 (*positive*). *Error bars* represent standard error of the mean. *Asterisks* represent significance at a threshold of $p<.001$

disappeared to a blank screen for 500 ms followed by a SAM rating prompt. After recording the participant's response, the experimenter initiated the next trial.

Before the start of the experimental runs, participants were introduced to the task in a practice run. The practice run consisted of 8 trials (2 per trial type) using a separate set of stimuli and stories. As in the main experimental runs, all four experimental conditions were intermixed in a pseudorandom fashion. None of the stories or pictures from the practice run was included in the main runs. The participants were instructed to match the story to the picture, and the experimenter probed the child to confirm that s/he understood the task and the rating scale before proceeding to the experimental task.

Data Analysis Plan

First, to assess self-reported emotional reactivity to negative stimuli, self-reported SAM ratings of negative-attend vs. neutral-attend conditions were compared using a paired *t*-test. Second, we investigated the effects of directed reappraisal to up- and down-regulate negative-valenced pictures by comparing SAM ratings of negative-increase vs. negative-attend and negative-decrease vs. negative-attend conditions, respectively, using separate paired *t*-tests.

Results

Self-Report Ratings As seen in Fig. 2, self-reported affect was sensitive to condition. Lower SAM ratings are indicative of stronger negative affect. Self-reported affect was rated higher in negative affect in the negative-attend condition ($M=2.53$, $SD=0.80$, range: 3.87–1.20) than the neutral-attend condition ($M=3.74$, $SD=0.73$, range: 5.00–2.13), $t_{18}= -4.60$, $p<.001$, indicating an increase in negative affect in response to negative vs. neutral stimuli. As evidence for the down-regulation of negative affect as a function of cognitive reappraisal, self-reported affect was rated lower in negative affect in the negative-decrease condition ($M=3.50$, $SD=0.74$, range: 4.67–1.47) than the negative-attend condition, $t_{18}=4.76$, $p<.001$. In contrast, self-reported affect was rated higher in negative affect in the negative-increase condition ($M=1.55$, $SD=0.50$, range: 2.93–1.00) than the negative-attend condition, $t_{18}= -7.30$, $p<.001$.

Study 2: fMRI Study of Cognitive Reappraisal

Methods

Participants Novel participants were recruited in the same manner as the behavioral study. Potential participants were excluded if they were left handed; below 6 or above 10 years of age; non-native English speakers; had a current or past diagnosis of neurological or psychiatric disorder based on parent-report; had a history of head trauma; currently used psychotropic medication; or had any MRI contraindication (e.g., metal in the body, orthodontic braces). From a total of 21 participants, 15 children were included in the final analysis. Two children were excluded due to excessive motion inside the scanner (cumulative motion relative to reference volume exceeding 6 mm in any direction); two children were excluded due to an inability to tolerate the scanning environment; one child was excluded due to technical difficulties; and one child's scan was terminated prematurely due to too much motion. Of the 15 children, children's mean age was 7.94 years ($SD=1.21$, range=6–9 years), and 8 children were female (53 %). Lastly, two participants included in the

analysis only provided usable data for 2 of the 3 runs due to excessive head motion in one of the runs. The study was approved by the human subjects review committee, and informed consent was obtained from parents. Child assent was obtained from children 7 years and older.

Emotion Regulation Task The fMRI paradigm used the same stories and pictures from the behavioral paradigm described in Study 1 with the addition of 6 new neutral stimuli[2] to balance the number of trials per condition. Three conditions were included in the fMRI task: neutral-attend, negative-attend, and negative-decrease. The negative-increase condition was not included to minimize the time children spent in the scanner and increase the number of trials per condition. In addition, self-report SAM ratings were not obtained in the fMRI version given concerns about excessive head movement while providing behavioral responses.

Prior to scanning, eligible participants prepared for the MRI and practiced the behavioral task outside and inside a mock scanner 1 h before the MRI scan. The practice sessions consisted of 9 trials (3 per trial type presented in pseudorandom fashion). None of the stories or pictures from the practice run was included in the fMRI task. After successful completion in the mock scanner session, participants participated in the MRI session. The fMRI task consisted of 3 runs, and each run included 21 trials (7 per trial type presented in pseudorandom fashion). Each trial was nearly identical to the version used in the behavioral experiment with the exception of no rating period after picture presentation and a longer inter trial interval of 4–8 s used to jitter the stimulus onset times to aid in the estimation of fMRI responses.

MRI Data Acquisition MRI data were collected using a 3 Tesla Siemens TRIO scanner (Siemens Medical Systems, Erlangen, Germany) with a 12-channel head coil (without parallel imaging). Each scanning session began with a high-resolution MPRAGE anatomical scan (TR=1900 ms, TE=2.52 ms, TI=900 ms, 1 mm cubic voxels, 250 mm field of view). Subsequently, during each functional run, 170 EPI volumes were acquired with a TR of 2000 ms and TE of 24 ms. Each volume consisted of 36 oblique slices with a thickness of 3 mm and an in-plane resolution of 3 mm × 3 mm (FOV=192 mm). Slices were positioned approximately 30° relative to the plane defined by the line connecting the anterior and posterior commissures, helping to decrease susceptibility artifacts in regions such as the ventromedial prefrontal cortex, temporal cortex, and amygdala.

Imaging Analysis Preprocessing of the data was conducted using the AFNI software package (Cox 1996), with the exception of the skull-stripping of the anatomical data, which was processed using statistical parametric mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK). The first 3 volumes of each functional run were discarded to account for equilibration effects. The remaining volumes were slice-time corrected using a Fourier interpolation, such that all slices were realigned to the first acquisition slice to account for timing differences. Six-parameter rigid-body motion correction within and across runs was performed using Fourier interpolation (Cox and Jesmanowicz 1999) so that all volumes were spatially registered to the first volume. Prior to spatial normalization to standard space, the anatomical and functional data were coregistered. We spatially normalized the anatomical data to the MNI anatomical template for children ages 4.5–8.5 years using a 12-parameter affine transformation. The rationale and production of this atlas can be found in Fonov et al. (2011). The same transformation was then applied to the functional data. All volumes were spatially smoothed using a Gaussian filter with a full-width at half maximum of 6 mm (i.e., two times the voxel dimension). Finally, the signal intensity of each voxel was scaled to a mean of 100 (on a per run basis), which allowed the interpretation of the estimated regression coefficients in terms of percent signal change.

Voxelwise Analysis The central goal of the voxelwise analysis was to define regions of interest (ROIs). Each participant's fMRI data were analyzed using a linear model framework with AFNI. Constant, linear, and quadratic terms were included for each run separately (as covariates of no interest) to model baseline and drifts of the MRI signal. To account for the signal variance related to head motion, six estimated motion parameters were included as nuisance regressors in the model. Further, we excluded the current and previous TR data whenever frame-to-frame movement within a run was more than half a voxel size (i.e., 1.5 mm) in any direction. Specifically, collapsing across conditions, there was an average of .99 %/4.87 TRs (range: 0–5 %; 0–24 TRs) of data lost per participant due to motion, and the number of excluded volumes (i.e., TR) did not differ across condition, $F(2, 28)=.08$, $p=.92$; hence, minimal data was lost due to motion. No assumptions were made about the shape of the hemodynamic response function. All trials from three conditions were pooled together resulting in a total of one main event type in the design matrix. Trials were pooled together in order to define ROIs in an unbiased manner (see below). Responses were estimated on each trial starting from trial onset to 24 s post-onset using cubic spline basis functions. This method is closely related to the use of finite impulses ("stick functions"), the commonly employed technique that can be considered the simplest form of basis expansion. Cubic splines allow a smoother approximation of the underlying responses, instead of the discrete approximation obtained by finite impulses. As an index of picture related activation, we averaged the estimated responses at time points 12, 14, and 16 s post-trial onset (i.e., approximately 4, 6, 8 s post-picture onset). We used the average of these time points, as picture-related response would be maximal at these time points, while the effect of story-related response would be minimal. We further confirmed that these three time points had maximal picture-related responses in early visual cortex and minimal story-related responses in early

[2] **IAPS**: 2250,2342,2411;**EmoPicS**:268,302,339

auditory cortex. Nevertheless, given our design, we cannot rule out some contribution of story-related response on subsequent picture related activation.

Group Analysis Whole-brain voxelwise random-effects analyses were restricted to gray-matter voxels based on the MNI pediatric gray matter template (Fonov et al. 2011). The template was resampled to match the resolution of the functional data. To assess picture related processing (vs. baseline), a one sample *t*-test (vs. zero) was run on the estimated response strength index of picture related activation. We did not analyze auditory story related responses because our primary goal was to investigate how the responses to the pictures were modulated by the preceding auditory stories.

ROI Analysis To enhance statistical power, we focused our analysis on a priori ROIs commonly implicated in the context of emotion regulation: the ventromedial PFC, dorsolateral PFC, and amygdala (Table 1). The left and right amygdala ROI were anatomically defined initially in the talairach space using the maximum-probabilistic atlas containing subcortical regions ("DD_Desai_MPM") provided in the AFNI package (Destrieux et al. 2010). The ROIs were transformed into the MNI space using the 3dWarp command and then aligned to the MNI template for children using the Nudge tool in the AFNI package. The ROIs were then resampled to match the resolution of the functional data. We then selected those voxels activated during the voxelwise analysis with a threshold set at $p=.05$ (uncorrected). The other ROIs were functionally defined based on the voxelwise analysis with a threshold set at $p=.05$ (uncorrected) and a minimum cluster extent of 10 voxels. We adopted the selection criterion of picture-related processing (pooled over all three conditions) to determine ROIs, because it was statistically independent of the central goal of our analysis: to examine the emotion regulation (i.e., negative-decrease vs. negative-attend) and the emotional reactivity (i.e., negative-attend vs. neutral-attend) contrasts (Kriegeskorte et al. 2009; Vul et al. 2009). A representative time series for each ROI was then created by averaging the time series of all gray matter voxels inside the ROI. Then, for each ROI, we ran the analysis on the representative time series data to estimate the hemodynamic response function of three main event types: neutral-attend, negative-attend, and negative-decrease. For each condition, as an index of picture related activation, we averaged the estimated responses at time points 12, 14, and 16 s post-trial onset (i.e., approximately 4, 6, 8 s post-picture onset).

First, to assess emotional reactivity, in each ROI we contrasted the response indices of negative-attend and neutral-attend conditions using a paired *t*-test. Second, to assess emotional down-regulation, in each ROI we contrasted the response indices of negative-decrease and negative-attend conditions using a paired *t*-test. For the sake of completeness, additional voxelwise analyses were also performed and followed the same emotional reactivity and emotional regulation contrasts as in the ROI analysis. Results from these supplementary voxelwise analyses are reported in Online Resource 2.

Association Between Brain Responses in Amygdala and Ventromedial PFC Because previous studies have highlighted the importance of the functional relationship between the amygdala and ventromedial PFC during emotion regulation (e.g., Banks et al. 2007; Urry et al. 2006), we investigated the association between brain responses in the amygdala ROIs and the ventromedial PFC ROI. For each participant, we created the emotion down-regulation index (negative-decrease minus negative-attend) for each ROI, separately. Then, across participants, we investigated the linear relation of the down-regulation index between each amygdala ROI and ventromedial PFC ROI using robust regression. We employed iterative reweighted least squares, the robust fit function from Matlab (Mathworks, Natick, MA, USA), given that standard Pearson correlation is sensitive to even a few influential data points (Wilcox 2005).

Results

ROI Results We focused our analysis on a priori regions that were previously implicated in the cognitive reappraisal literature. First, we compared the negative-attend vs. neutral-attend pictures to investigate children's emotional reactivity to negative stimuli. We observed significant differential activation in the right amygdala and right dorsolateral PFC and marginally significant activation in the left dorsolateral PFC (Table 2). In

Table 1 Peak coordinates in MNI space and number of voxels [k] in each ROI

ROI	x	Y	z	*K*
Left dorsolateral PFC	56	−31	13	75
Right amygdala	−16	5	−14	72
Left amygdala	−20	−2	−17	52
Ventromedial PFC	2	−22	−26	18
Right dorsolateral PFC	−52	−19	28	12

PFC prefrontal cortex

Table 2 ROI paired *t*-test results

ROI	Negative-attend vs. Neutral-attend	Negative-decrease vs. Negative-attend
Right amygdala	$t_{14}=2.23$, $p=.043$	$t_{14}=2.98$, $p=.010$
Left amygdala	$t_{14}=1.59$, $p=.134$	$t_{14}=1.81$, $p=.092$
Left dorsolateral PFC	$t_{14}=2.14$, $p=.051$	$t_{14}=0.99$, $p=.341$
Right dorsolateral PFC	$t_{14}=2.34$, $p=.035$	$t_{14}=1.52$, $p=.151$
Ventromedial PFC	$t_{14}=0.10$, $p=.924$	$t_{14}=2.54$, $p=.024$

PFC prefrontal cortex

these regions, as expected, activation during negative-attend pictures was greater than during the neutral-attend pictures (Fig. 3a–d). To investigate children's emotion regulation, we contrasted negative-decrease vs. negative-attend pictures. We observed significant differential activation in the right amygdala and ventromedial PFC (Table 2). In the right amygdala, responses during negative-decrease pictures were *higher* compared to negative-attend pictures (Fig. 3a). Negative-decrease condition showed stronger responses compared to negative-attend condition in ventromedial PFC (Fig. 3e).

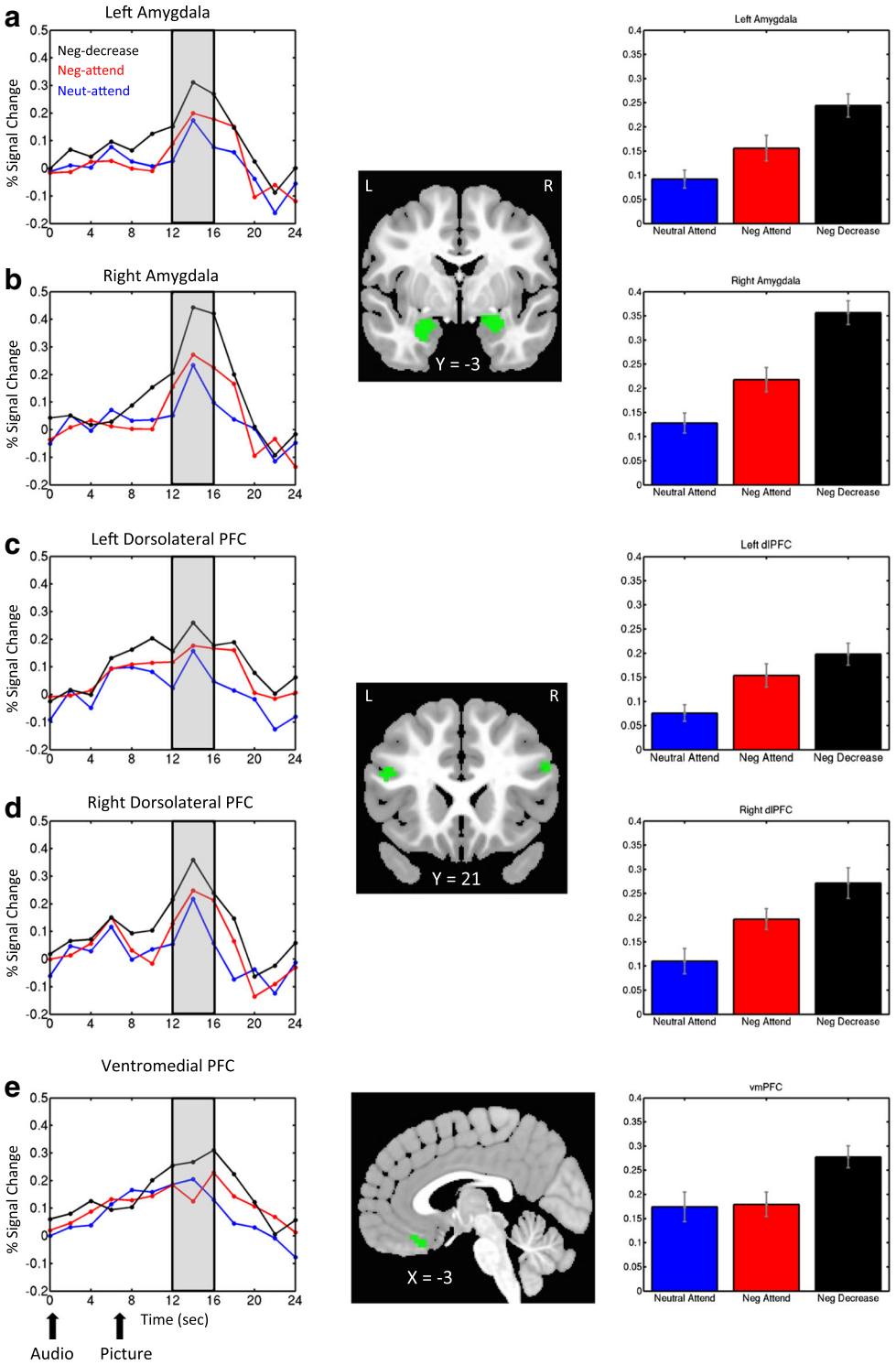

Fig. 3 Visualization of the ROIs on pediatric MNI atlas. *Graphs* display the average deconvolved responses (*left*) and response indices (*right*) as a function of trial type in bilateral amygdala (**a**,**b**), bilateral dorsolateral PFC (**c**,**d**), and ventromedial PFC (**e**) . *Shaded regions* indicate the time points used to index responses to pictures. *Error bars* denote the standard with-in subject error term (Cousineau 2005). PFC=prefrontal cortex. *Arrows* in Fig. 3e indicate the onset times of the auditory story and picture phases

Associations Between Brain Regions Given the importance of the functional link between amygdala and ventromedial PFC during emotion regulation, particularly cognitive reappraisal, we evaluated the association between responses in these regions. A robust regression analysis using the emotion regulation index revealed a positive correlation between responses in the right amygdala and ventromedial PFC (robust R^2=0.54, p=.036; Fig. 4a). The association between responses in the left amygdala and ventromedial PFC was not detected (robust R^2=0.40, p=.144; Fig. 4b).

Discussion

The current pilot study examined the neural basis of cognitive reappraisal during middle childhood (6–10 years) using a developmentally-appropriate directed reappraisal task. We found that children can successfully use guided cognitive reappraisal to decrease subjective ratings of negative affect. In contrast to the behavioral data, children's brain responses demonstrated *increased* activation in the amygdala and ventromedial PFC during the reappraisal condition compared to the no regulation condition. These findings suggest that the neural networks supporting reappraisal at this age involve similar brain regions identified in adults but brain responses seem to deviate from findings in adults.

Our behavioral results indicate that children are capable of using guided reappraisal to decrease subjective measurements of negative affect, confirming our hypothesis that negative-decrease (reappraised) images would receive lower self-reported ratings of negative affect than negative-attend images. These results are consistent with previous research that indicates that reappraisal is effective at down-regulating negative affect in children, adolescents, and adults (Banks et al. 2007; McRae et al. 2010, 2012; Ray et al. 2010).

Our neuroimaging results revealed that similar to adults, children's emotional reactivity (negative-attend – neutral-attend) engaged bilateral amygdala and dorsolateral PFC, supporting children's increased neural responses to negative stimuli. In addition, both the ROI and supplemental whole brain voxelwise analyses showed that the brain regions involved in cognitive reappraisal in adults (Buhle et al. 2014; Kohn et al. 2014; Ochsner et al. 2012), which include the amygdala and PFC, were also activated during cognitive reappraisal in children ages 6–10 years. However, contrary to the extant adult literature that suggests that prefrontal cortices down-regulate amygdala activity during reappraisal, children's brain responses did not show decreased activation in the amygdala. In the current study, reappraisal (negative-decrease – negative-attend) elicited a significant *increase* in activation in the right amygdala and ventromedial PFC. Interestingly, Levesque et al. (2003, 2004) reported that during reappraisal children displayed more distributed regions of prefrontal activation in comparison to adults. In addition, McRae et al. (2012) showed that while adolescents and adults displayed a reappraisal effect in regions of PFC, 10–13 year-old children did not show this effect. Similar to these neuroimaging findings, DeCicco et al. (2012) found that the amplitude of the late positive potential (LPP), an event-related potential responsive to reappraisal in adults, was not reduced during reappraisal in 5–7 year-old children. Further, there is evidence that reappraisal is also ineffective at down-regulating physiological responses to negative stimuli at age 10 (de Veld et al. 2012), while in adults the opposite is found (Ray et al. 2010). Taken together, these findings suggest that the neural networks underlying cognitive reappraisal undergo significant developmental change across childhood.

We observed *greater* amygdala activity following reappraisal (negative-decrease condition) compared to the negative-attend condition. This effect was, of course, unexpected and further experiments are needed to clarify it. However, it is intriguing to note that, during reappraisal, amygdala

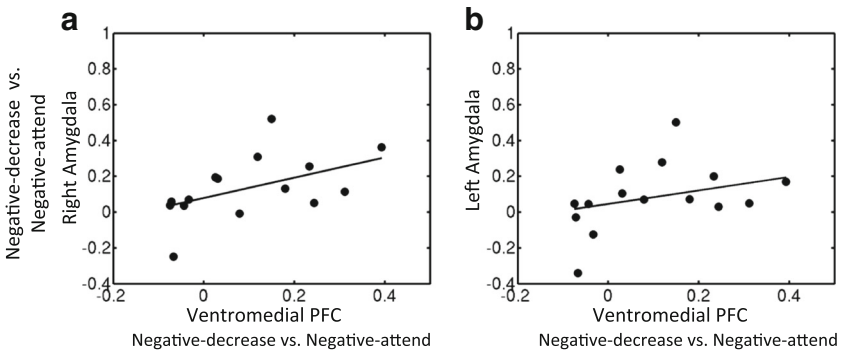

Fig. 4 Relationship between brain regions during down-regulation using robust regression. Across participants a significant linear relationship was observed involving fMRI interactions scores ([negative-decrease vs. negative-attend]$_{Amygdala}$ – [negative-decrease vs. negative-attend]$_{ventromedialPFC}$) between Right amygdala and ventromedial PFC (**a**); a linear relationship was not significant between Left amygdala and ventromedial PFC (**b**). *PFC* prefrontal cortex

activity was *positively* correlated with ventromedial PFC activation. This positive relationship may be related to the observation of increased amygdala responses following reappraisal. It is possible that the greater recruitment of prefrontal regions during cognitive reappraisal simultaneously recruits subcortical areas, such as the amygdala. Naturally, our finding is in contrast to a robust body of literature in adults that shows an inverse relationship between ventromedial PFC and amygdala during reappraisal (for review, see Kohn et al. 2014). But our findings may be related to evidence that amygdala-prefrontal functional connectivity during fearful face processing undergoes a developmental shift around age 10 from positive to negative connectivity (Gee et al. 2013).

Of particular interest is the apparent discrepancy between our behavioral and neuroimaging findings: while 6–10 year-old children were capable of using reappraisal to decrease subjective ratings of image valence, the observed decrease in subjective ratings of negative affect was not reflected in decreased amygdala activity. Other investigations have reported a discontinuity between subjective ratings of affect and neural responses in children. For example, McRae et al. (2012) reported that reappraisal elicited a reduction in negative affect based on behavioral ratings in children ages 10–13 years old, while there were no effects of reappraisal on amygdala and prefrontal cortex responses.

As the first fMRI investigation of reappraisal in this age range, our findings suggest that the neural circuitry supporting emotion regulation has not fully developed to a mature, adult-like network. By extending the current literature to a younger age group, we were able to begin identifying the developmental trajectory of emotion regulation networks and shed light on the reason for potential inconsistencies in the literature. Given methodological limitations of such a young sample, we employed an age-appropriate paradigm utilized in an ERP investigation of reappraisal in this age whereby reappraisals were orally presented to the children instead of requiring participants to self-generate their own reappraisals (Dennis and Hajcak 2009). This paradigm limited the cognitive load for our young participants, reduced the risk for motion artifacts, and provides consistency between two modes of reappraisal investigations at this age.

The study also had limitations. First, given that this study was a pilot study, our sample size was small, which limited our statistical power and ability to use a whole-brain search space. As suggested by Levesque et al. (2003, 2004), children show more distributed loci of activation in PFC and whole-brain analyses may be more sensitive to these differences, which may be overlooked in a ROI-based analysis. Second, given evidence of gender differences in emotion regulation (e.g., Dennis and Hajcak 2009; McRae et al. 2008) and brain changes occurring during early to middle childhood, larger samples would allow for investigations of gender and age differences in reappraisal circuitry. Third, due to concerns about excessive head motion and task length for children in this age range, children did not complete a SAM rating following each trial while in the scanner. It will be important for future research to examine whether child affect ratings vary as a function of children's brain responses. Fourth, even though the guided reappraisal task allowed us to investigate cognitive reappraisal in young children, the paradigm deviates from the self-generated reappraisals adult studies employ. It is possible that self-generated reappraisals would engage different neural networks. Future research will need to compare the neural processes underlying guided reappraisals and self-generated reappraisals across development. Lastly, our small sample size and lack of correction for multiple comparisons in ROI analysis makes it difficult to draw firm conclusions from this study alone; nevertheless, future research can build upon the present study to investigate the neural basis of emotion regulation in children and its role in developmental psychopathology.

In sum, our findings suggest that while children are capable of using reappraisal to decrease subjective ratings of negative affect, neural responses in the amygdala revealed a divergent pattern with increased activation during the reappraisal condition. In light of the developmental literature, the discrepancy between behavioral and neuroimaging findings may be attributable to immature connectivity between PFC and amygdala which purportedly subserves top-down regulation of the amygdala during reappraisal. This literature, in accordance with our current findings, suggest that neurodevelopmental changes occur during middle childhood through adolescence, which equip children with the ability to employ reappraisal to down-regulate neural responses to negative content. Future research is necessary to delineate age-related development of the neural network involved in cognitive reappraisal. Our findings suggest that the neural networks supporting emotion regulation are still developing during middle childhood. Failure to employ top-down regulation of amygdala activity during this age may result in prolonged neurophysiological responses and could indicate a mechanism by which childhood is marked by a particular vulnerability to emotional events.

Acknowledgments This research was supported by the University of Maryland (UMD) Maryland Neuroimaging Center Seed Grant Program (LRD, LP), UMD College of Behavioral and Social Sciences Dean's Research Initiative Award (LRD), the UMD Research and Scholars Award (LRD) and in part by the National Institute of Mental Health R01 MH071589 (LP). The authors wish to thank the children and families for their participation in the study and the Maryland Neuroimaging Center.

Conflict of Interest Lea R. Dougherty, Sarah L. Blankenship, Philip A. Spechler, Srikanth Padmala and Luiz Pessoa declare that they have no conflict of interest.

Experiment Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience, 2*, 303–312.

Beauregard, M., Paquette, V., & Lévesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Neuroreport, 17*(8), 843–846.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., & Ochsner, K. N. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex, 24*, 2981–2990.

Carthy, T., Horesh, N., Apter, A., & Gross, J. J. (2009). Patterns of emotional reactivity and regulation in children with anxiety disorders. *Journal of Psychopathology and Behavioral Assessment, 32*, 23–36.

Cousineau, D. (2005). Confidence intervals in within-subject designs: a simpler solution to Loftus and Masson's method. *Tutorial in Quantitative Methods for Psychology, 1*, 4–45.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29*(3), 162–173.

Cox, R. W., & Jesmanowicz, A. (1999). Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine, 42*, 1014–1018.

de Veld, D. M. J., Riksen-Walraven, J. M., & de Weerth, C. (2012). The relation between emotion regulation strategies and physiological stress responses in middle childhood. *Psychoneuroendocrinology, 37*, 1309–1319.

DeCicco, J. M., Solomon, B., & Dennis, T. A. (2012). Neural correlates of cognitive reappraisal in children: an ERP study. *Developmental Cognitive Neuroscience, 2*, 70–80.

Dennis, T. A., & Hajcak, G. (2009). The late positive potential: a neurophysiological marker for emotion regulation in children. *The Journal of Child Psychiatry, 50*, 1373–1383.

Dennis, T. A., Cole, P. M., Wiggins, C. N., Cohen, L. H., & Zalewski, M. (2009). The functional organization of pre-school age children's emotion expressions and actions in challenging situations. *Emotion, 9*, 520–530.

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage, 53*, 1–15. doi:10.1016/j.neuroimage.2010.06.010.

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage, 54*, 313–327. doi:10.1016/j.neuroimage.2010.07.033.

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., Hare, T. A., Bookheimer, S. Y., & Tottenham, N. (2013). A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *The Journal of Neuroscience, 33*, 4584–4593.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences, 101*, 8174.8179.

Graziano, P. A., Reavis, R. D., Keane, S. P., & Calkins, S. D. (2007). The role of emotion regulation and children's early academic success. *Journal of School Psychology, 45*, 3–19.

Gross, J. J. (1998). Antecedant- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology, 74*, 224–237.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology, 85*, 348–362.

Gullone, E., Hughes, E. K., King, N. J., & Tong, B. (2010). The normative development of emotion regulation strategy use in children and adolescents: a 2-year follow-up study. *Journal of Child Psychology and Psychiatry, 51*, 567–574.

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). Neural network of cognitive emotion regulation—an ALE meta-analysis and MACM analysis. *NeuroImage, 87*, 345–355.

Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S., & Baker, C. I. (2009). Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience, 12*, 535–540.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8*. Gainesville: University of Florida.

Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.-M., Bourgouin, P., & Beauregard, M. (2003). Neural circuitry underlying voluntary self-regulation of sadness. *Biological Psychiatry, 53*, 502–510.

Levesque, J., Joanette, Y., Mensour, B., Beaudoin, G., Leroux, J. M., Bourgouin, P., & Beauregard, M. (2004). Neural basis of emotional self-regulation in childhood. *Neuroscience, 129*, 361–369.

Manian, N., & Bornstein, M. H. (2009). Dynamics of emotion regulation in infants of clinically depressed and nondepressed mothers. *Journal of Child Psychology and Psychiatry, 50*, 1410–1418.

McRae, K., Ochsner, K. N., Mauss, I. B., Gabrieli, J. D., & Gross, J. J. (2008). Gender differences in emotion regulation: an fMRI study of cognitive reappraisal. *Group Processes and Intergroup Relations, 11*, 143–162.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D. E., Gross, J. J., & Ochsner, K. N. (2010). The neural bases of distraction and reappraisal. *Journal of Cognitive Neuroscience, 22*, 248–262.

McRae, K., Gross, J. J., Weber, J., Robertson, E. R., Sokol-Hessner, P., Ray, R. D., Gabrieli, J. D. E., & Ochsner, K. N. (2012). The development of emotion regulation: an fMRI study of cognitive reappraisal in children, adolescent and young adults. *Social Cognitive and Affective Neuroscience, 7*, 11–22.

Monk, C. S. (2008). The development of emotion-related neural circuitry in health and psychopathology. *Development and Psychopathology, 20*, 1231–1250.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *TRENDS in Cognitive Science, 9*, 242–249.

Ochsner, K.N., Silvers, J.A., & Buhle, J.T. (2012). Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences,* E1–24.

Pitskel, N. B., Bolling, D. Z., Kaiser, M. D., Crowley, M. J., & Pelphrey, K. A. (2011). How grossed out are you? The neural bases of emotion regulation from childhood to adolescence. *Developmental Cognitive Neuroscience, 1*(3), 324–337.

Ray, R. D., McRae, K., Ochsner, K. N., & Gross, J. J. (2010). Cognitive reappraisal of negative affect: converging evidence from EMG and self-report. *Emotion, 10*, 587–592.

Southam-Gerow, M. A., & Kendall, P. C. (2002). Emotion regulation and understanding implications for child psychopathology and therapy. *Clinical Psychology Review, 22*, 189–222.

Stegge, H., & Meerum Terwogt, M. (2007). Awareness and regulation of emotion in typical and atypical development. In J. J. Gross (Ed.), *Handbook of emotion regulation* (pp. 249–268). New York: Guilford Press.

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala

and hippocampus from infancy to early adulthood in healthy individuals. *PLoS ONE, 7*(10), 1–10.

Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., Jackson, C. A., Frye, C. J., Greischar, L. L., Alexander, A. L., & Davidson, R. J. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *Journal of Neuroscience, 26*(16), 4415–4425. doi:10.1523/JNEUROSCI.3215-05.2006.

Vul, E., Harris, C., Winkielman, P., & Pashler, H. (2009). Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Perspectives on Psychological Science, 4*, 274–290.

Wessa, M., Kanske, P., Neumeister, P., Bode, K., Heissler, J., & Schönfelder, S. (2010). EmoPics: Subjektive und psychophysiologische Evaluationen neuen Bildmaterials für die klinisch-bio-psychologische Forschung. *Zeitschrift für Klinischer Psychologie und Psychotherapie, Supplement, 1/11*, 77.

Wilcox, R.R. (2005). Outlier detection. *Encyclopedia of statistics in behavioral science*.

Wolgast, M., Lundh, L., & Viborg, G. (2011). Cognitive reappraisal and acceptance: an experimental comparison of two emotion regulation strategies. *Behaviour Research and Therapy, 49*, 858–866.