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Child Maltreatment and Emotion Regulation Networks

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Abstract

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Child maltreatment has been strongly associated with a variety of later life psychopathology. Investigations into mechanisms of this association have explored neurodevelopmental disruptions in brain networks associated with emotion regulation. Using fMRI, we investigated differences in neural function in a sample of 58 adolescents with and without exposure to childhood maltreatment during a task in which participants viewed negative emotional stimuli both passively and while attempting to modulate emotional response using cognitive reappraisal. As has been shown elsewhere in adults, effortful regulation engaged a network of brain regions including Inferior Frontal Gyrus (IFG) and superior temporal gyrus in down-regulating the amygdala. Ventro-Medial PFC (vmPFC) was not functionally coupled with amygdala or IFG activation during effortful regulation, suggesting that adolescents instead use prefrontal structures to support down-regulation of the amygdala through medial and lateral temporal cortex. Maltreatment was associated with greater functional connectivity between IFG and these temporal areas.

Introduction

As many as 1 in 4 children in the United States will experience some form of physical or sexual abuse by age 18 (Finkelhor, Turner, Shattuck, & Hamby, 2013; Finkelhor, Ormrod, Turner, & Hamby, 2005), and exposure to these and other forms of childhood maltreatment has been linked to substantially higher risk of psychopathology during childhood as well as later in life (Cohen, Brown, & Smaile, 2001; McLaughlin et al., 2012). Developing our understanding of the neurodevelopmental mechanism of this association is critical to our ability to develop research informed interventions and preventative treatments.

One hypothesized mechanism for this risk is that adaptation to threatening environments may lead to neurodevelopmental disruptions in emotion regulation systems. These disruptions may serve to facilitate rapid identification and response to potentially threatening stimuli – a pattern of emotion regulation and response that may be maladaptive later in life (Sheridan & McLaughlin, 2016; Maughan & Cicchetti, 2002). This hypothesis is supported by evidence that areas of the brain implicated in neural response to salient cues, notably the amygdala, respond more strongly in maltreated children to facial displays of anger (McCrary et al., 2011; McCrary et al., 2013), as well as a number of studies showing that greater physiological and behavioral responses to stressful life events in maltreated youth mediate the relationship between early life maltreatment and later psychopathology (Maughan & Cicchetti, 2002; Glaser, van Os, Portegijs, & Myin-Germeys, 2006; Kim & Cicchetti, 2010; McLaughlin, Hatzenbuehler, Mennin, & Nolen-Hoeksema, 2011).

Neural correlates of emotion regulation, particularly deliberate or effortful emotion regulation, in children are still being explored. One view is that, during effortful regulation, more generalized cognitive control regions such as dorsolateral prefrontal cortex (dlPFC) engage the ventromedial prefrontal cortex (vmPFC), which in turn inhibits amygdala response. This view is supported by anatomical studies showing connections between the vmPFC and the amygdala (Ghashghaei, Hilgetag, & Barbas, 2007), as well as imaging work showing that

the vmPFC is critical for fear extinction and reversal learning (Milad et al., 2007; Milad & Quirk, 2012). Research on children has shown that stronger inverse coupling between vmPFC and amygdala explains the reduction of children's affective response during an emotion regulation task as they grow older (Silvers et al., 2016). Another view is that cognitive control areas modulate the amygdala through recruitment of areas in the lateral temporal cortex associated with semantic and perceptual representations, possibly modifying representations of the emotional significance of stimuli (Ochsner & Gross, 2005, 2007; Ochsner, Silvers, & Buhle, 2012). A recent meta-analysis of emotion regulation studies in adults provided strong evidence for this network's primacy in effortful emotion regulation rather than a ventro-medial cortical network (Buhle et al., 2014). However, given that pre-frontal cortex is still developing in children through the age of 18 (Lenroot & Giedd, 2006) and previous research showing vmPFC network activity during regulation in children (Silvers et al., 2016), network recruitment during effortful emotion regulation may differ in children.

Research investigating the effects of childhood maltreatment on neural correlates of effortful emotion regulation processes remains limited. McLaughlin, Peverill, Gold, Alves, and Sheridan (2015) demonstrated that maltreated children show heightened response in multiple nodes of the salience network (including the amygdala) during passive viewing of negative images, but showed similar levels of amygdala activity during effortful regulation coupled with heightened response from cognitive control regions in dlPFC. This could indicate that maltreated children are just as able to modulate their emotional response during effortful regulation, but require more cognitive resources to do so. One important limitation of this study is that it did not investigate functional connectivity between brain regions, which limited the ability of the study to make inferences about neural network activity. Studies of resting state connectivity in maltreated children have shown decreased connectivity between vmPFC and amygdala relative to non-maltreated controls (Herrington et al., 2013). As this is one circuit that has been implicated in effortful emotion regulation, reduced connectivity

may indicate differences in network recruitment during emotion regulation, possibly leading to the previously observed pattern of less efficient regulatory activity.

The present study used psychophysiological interaction analyses to examine functional connectivity in a sample of maltreated and non-maltreated adolescents during an emotion regulation task. We investigated what brain networks functionally down-regulate the amygdala during effortful regulation in adolescents, and hypothesized that adolescents may continue to rely on a vmPFC network during effortful regulation. We further investigated how exposure to maltreatment affected emotion regulation network function, and hypothesized that maltreated children would show greater reliance on a network involving the temporal cortex rather than the vmPFC.

Methods

Sample

Fifty-eight adolescents aged 13-19 years ($M = 16.78$, $SD = 1.48$) participated in the study, 60% of the sample were female. Twenty-one participants (13 female) with a history of physical or sexual abuse were recruited from a previous study (McLaughlin et al., 2015). Control participants with the same age, sex, and handedness with no maltreatment exposure were matched to each maltreated participant. Additional participants were then recruited to the control group. Final groups were found to differ slightly in age and by race. Additionally, Maltreated participants were more likely to exhibit psychopathology, both internalizing and externalizing, and showed lower levels of parental education. For additional details, see table 1, which compares participants whose violence scores lie above and below a validated threshold (Walker et al., 1999). Data from some a portion of the sample were presented previously in (McLaughlin et al., 2015).

Participants were excluded if they were currently taking psychiatric medication (with the exception of stimulants used to treat ADHD, which were discontinued 24 hours before

Table 1: Sample Description

		Malt.		Cont.		All		χ^2	<i>p</i>
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
Sex	Male	8	38	15	41	23	40	.03	.855
	Female	13	62	22	59	35	60		
Race	White	2	10	14	38	16	28	12.88	.012*
	Black	8	38	10	27	18	31		
	Latino	5	24	6	16	11	19		
	Asian	0	0	5	14	5	9		
	Other	6	29	2	5	8	14		
		<i>M</i>	<i>sd</i>	<i>M</i>	<i>sd</i>	<i>M</i>	<i>sd</i>	<i>t</i>	<i>p</i>
Age		16.25	1.43	17.08	1.45	16.78	1.48	- 2.1	0.041*
Physical Abuse		10.57	4.65	5.24	0.72	7.17	3.82	5.21	< 0.001*
Sexual Abuse		10.33	6.18	5.00	0.00	6.93	4.48	3.95	< 0.001*

scanning), if they had braces, claustrophobia, an active substance use disorder, pervasive developmental disorder, were non-English speaking, or if there were active safety concerns.

Behavioral Measures

The Childhood Trauma Questionnaire (CTQ) and the Childhood Experiences of Care and Abuse (CECA) interview were used to assess abuse history. The CTQ assesses frequency of physical, sexual, and emotional abuse during childhood. The CTQ has excellent psychometric properties including internal consistency, test-retest reliability, and convergent and discriminant validity with interviews and clinician reports of maltreatment (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). The CECA assesses many aspect of caregiver ex-



Figure 1: Schematic Diagram of the task with cue, stimulus, rating, and ITI stages. (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015)

periences, including physical and sexual abuse, and has demonstrated excellent inter-rater reliability for maltreatment reports and high agreement between siblings on reports of maltreatment (Bifulco, Brown, Lillie, & Jarvis, 1997). a composite maltreatment score was then calculated for each participant from the sum of the physical and sexual abuse scales of the CTQ.

fMRI Task

Participants were asked to complete an event-related task designed to elicit emotional reactivity and both automatic and effortful emotion regulation behaviors in response to both positive and negative affective stimuli (the present analysis will only examine responses to negative trials). This task has been widely used in fMRI studies of emotion regulation and has been used in the past with children (Buhle et al., 2014; Ochsner et al., 2004; McRae et al., 2012). Prior to stimulus presentation, participants were shown an instruction to “look,” “decrease,” or “increase” their response to the stimulus. A positively, negatively, or neutrally valenced picture was then presented from the International Affective Picture System (IAPS)

(Lang, Bradley, Cuthbert, et al., 2005). Participants were then asked to rate the strength of their affective response on a 5-point Likert scale (see fig. 1 for task design).

Prior to the scan session participants completed a training session in which they were instructed in how to respond to each cue, observed examples, and practiced. For “look” trials, participants were asked to observe the stimulus without engaging in active strategies to modify their response. For “decrease” and “increase” trials, participants were asked to engage in specific cognitive reappraisal strategies such as imagining that the image was close to them or far away or to modify the salience of the image (eg. they could imagine the image was in their neighborhood or that it was from a movie and not actually real). Participants were given the ‘increase’ instruction only to positive and neutral pictures and the ‘decrease’ instruction only to neutral and negative pictures.

Image Acquisition

Scanning was performed on a 3T Siemens Tim Trio scanner at the Harvard Center for Brain Science using a 32-channel head coil (for detailed imaging parameters see McLaughlin et al., 2015).

Image Processing

Pre-processing was conducted using FreeSurfer, FSL, and ART. T1-weighted scans were processed using FreeSurfer version 5.3 (Fischl et al., 2002). Preprocessing and statistical analysis of fMRI data was performed in GNU make (Askren et al., 2016). Preprocessing included spatial realignment, slice-time correction, and spatial smoothing (6-mm full width at half maximum), implemented in FSL. Data were inspected for artifacts using artifact detection software (ART). Volumes with motion > 2 -mm or > 3 -SD change in signal intensity were excluded from analysis, and 6 rigid-body motion regressors were included in person-level models. Person- and group-level models were estimated in FSL. A component-based

anatomical noise correction method was used to reduce noise associated with physiological fluctuations (Behzadi, Restom, Liao, & Liu, 2007). Following estimation of person-level models, the resulting contrast images were normalized into standard space, and anatomical co-registration of the functional data with each participant's T1-weighted image was performed using surface-based registration in FreeSurfer, which provides better alignment than other methods in children. Normalization was implemented in Advanced Normalization Tools (ANTs) software (Ghosh et al., 2010).

Analysis Plan

Regressors were created by convolving a boxcar function of phase duration and amplitude 1 with the standard (double-gamma) hemodynamic response function for each phase of the task (instruction cue, stimulus, and rating) separately for neutral, negative, and positive stimuli for look, decrease, and increase trials. Positive trials were not analyzed. We applied the standard analysis approach used in other studies utilizing this task (Buhle et al., 2014) to create a contrast modeling regulation of emotional responses to negative stimuli (decrease negative > look negative).

Functional connectivity between brain regions was conducted using psycho-physiological interaction (PPI) models (Cisler, Bush, & Steele, 2014; McLaren, Ries, Xu, & Johnson, 2012). Physiological regressors were constructed, one per model, based on time series extracted from a-priori regions of interest in the left and right amygdala and inferior frontal gyrus (IFG). The amygdala was selected as it reflects salience-related arousal in the brain and has shown modulation in previous studies on this task. Masks for left and right amygdala were calculated based on BOLD signal response across the sample in the look negative > look neutral contrast at $p > .05$, masked by the amygdala ROI from the Harvard Subcortical Atlas in FSL at 50% certainty. The IFG was selected due to its role in cognitive inhibition and its association with effortful regulation in meta-analyses using this task (Buhle et al.,

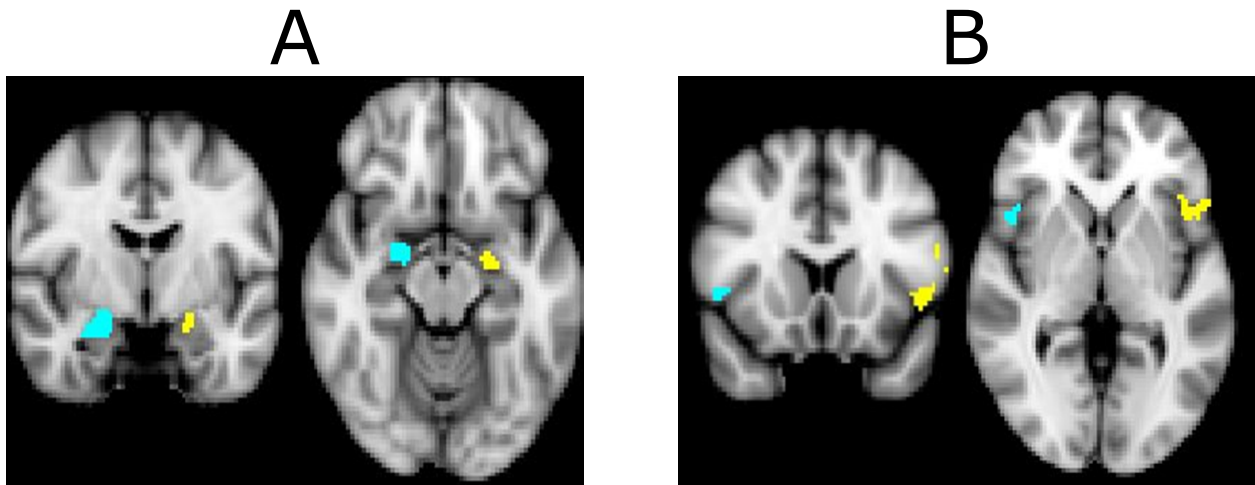


Figure 2: Left and Right seeds for amygdala (A) and IFG (B).

2014). To create the left and right IFG masks, each subject's IFG was calculated in Freesurfer, normalized, and intersected with a mask calculated from Buhle et al. (2014)'s meta-analysis thresholded at $p = .01$ (See fig. 2). For each subject, an estimate was made of the interaction effect of each physiological regressor with the decrease > look negative task-related regressor, producing an estimate of functional connectivity between brain regions attributable to the regulation contrast specifically. Finally, group level random effects models were constructed to establish group-level averages while controlling for parental education, race, internalizing and externalizing psychopathology, and maltreatment as well as to estimate effects of maltreatment while controlling for other study variables.

Results

Sample Functional Connectivity During Regulation

During effortful regulation (decrease negative > look negative) several brain regions including right IFG, insula, and superior temporal gyrus were negatively associated with right amygdala activity, but no clusters showing significant functional connectivity with left amygdala (see

table 2, fig 3).

During effortful regulation (decrease negative > look negative) Left Lateral Occipital Cortex and Precentral Gyrus were associated with activity in Left IFG. Activity in Right Insula, Precuneus, and bilateral juxtapositional lobule cortex was inversely correlated to Left IFG. Right IFG activity was correlated to Bilateral Occipital Fusiform Gyrus and inversely correlated to activity in Left Juxtapositional Lobule Cortex (see table 2, fig 3).

Effects of Maltreatment

Maltreatment was associated with increases of functional connectivity between left IFG and the right inferior temporal gyrus as well as the right cerebellum and left central opercular cortex during effortful regulation. There were no associations between maltreatment and functional connectivity in other seed regions during effortful regulation (see table 2, figure 3).

Discussion

Our first hypothesis concerned operation of emotion regulation networks in an adolescent sample. Effortful regulation engaged a network of brain regions including IFG and superior temporal gyrus in down-regulating the amygdala. These areas have been shown elsewhere to be active in adults during similar re-appraisal tasks (Buhle et al., 2014). The vmPFC showed negative functional connectivity to amygdala during passive viewing of negative stimuli, but was not functionally coupled with amygdala or IFG activation during effortful regulation. This suggests that effortful regulation in adolescents does not rely on prefrontal support of automatic regulation networks involving the vmPFC, and instead recruits prefrontal structures to support down-regulation of the amygdala through medial and lateral temporal cortex as has been shown in adults. Therefore no support was found for hypothesis 1 as the network of brain regions recruited by adolescents to down-regulate the amygdala was broadly similar

Table 2: Functional Connectivity during Effortful Regulation (Decrease > Look Negative)

Seed Region	Region of Peak Activation	Cluster Size	X	Y	Z	Z-score
L. Amygdala		(No significant clusters)				
R. Amygdala	R. Insula	793	38	-2	4	-3.27
L. IFG	L. Lateral Occipital Cortex	4224	-38	-80	-6	4.35
	Precentral Gyrus	602	-40	2	28	3.64
	Bilat. Juxtapositional Lobule	4212	2	-4	50	-4.02
	R. Insula	1792	38	6	10	-4.1
	Precuneus	1089	14	-66	26	-3.58
R. IFG	Bilat. Occipital Fusiform Gyrus	8337	-20	-82	-12	4.47
	L. Juxtapositional Lobule	655	-4	-10	58	-3.29
L. IFG	R Inf. Temporal Gyrus	1045	54	-2	-36	3.58
\times Maltreatment	R. Cerebellum	613	16	-46	-30	3.76
	L. Central Opercular Cortex	522	-44	-10	8	3.72
R. IFG \times Maltreatment		(No significant clusters)				

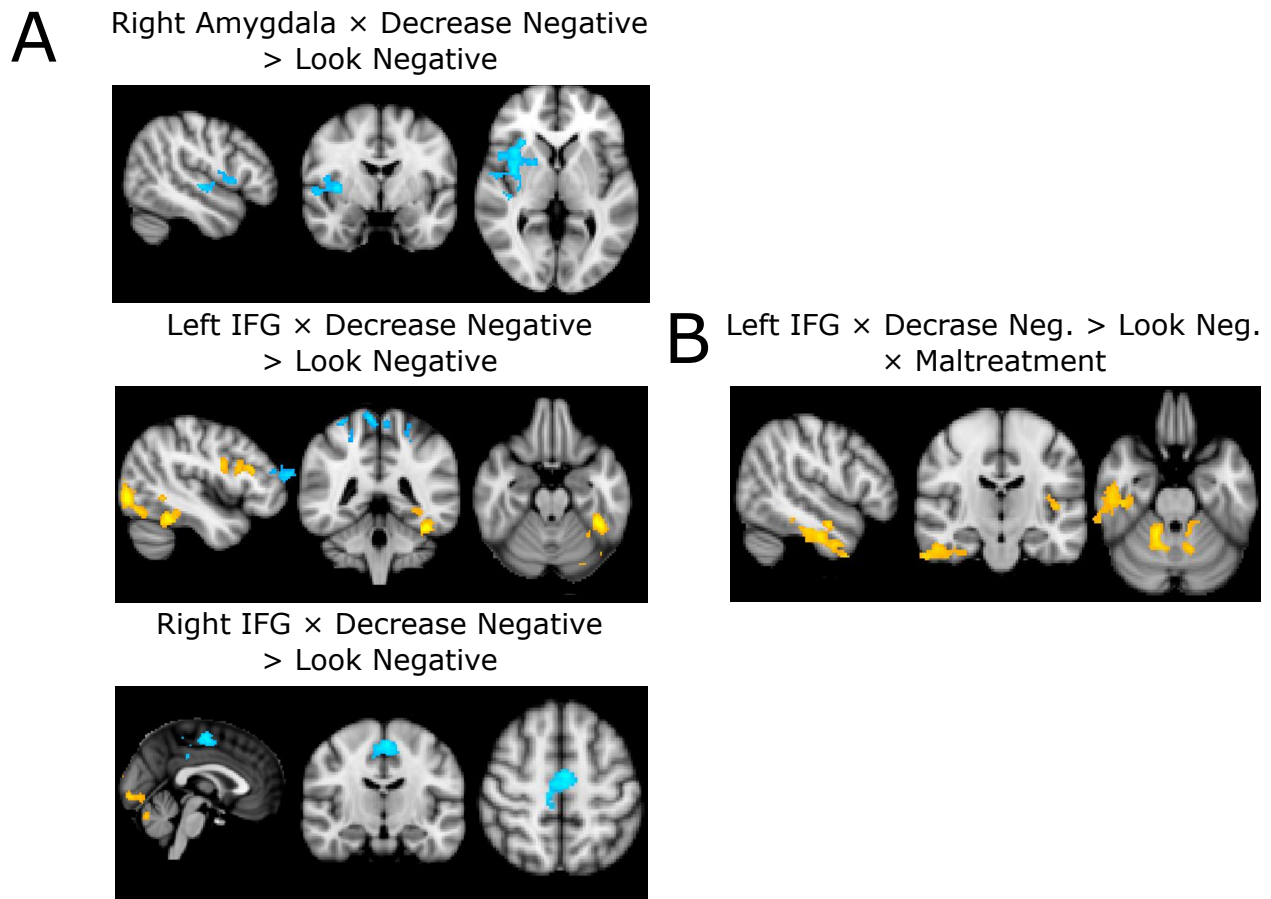


Figure 3: Whole brain results A) across sample, B) effects of maltreatment. Volumes without significant clusters not portrayed. All resulted corrected for family wise error.

to findings from the literature in adults.

Maltreatment was associated with greater functional connectivity between IFG and temporal areas. Our second hypothesis that maltreated children would rely more heavily on this network than control children was therefore supported. This greater reliance on temporal cortex to support reappraisal than in control children may be related to stronger baseline reactivity in amygdala (McLaughlin et al., 2015) and/or reduced effectiveness of ‘automatic’ emotion regulation networks in maltreated children (Herrington et al., 2013).

Taken together, our findings strongly support the criticality of the lateral temporal cortex in effortful emotion regulation processes at least as early as adolescence. Furthermore, we demonstrated increased connectivity within this network in maltreated children, perhaps illustrating an important developmental consequence of early life maltreatment on the neurodevelopment of emotion regulation. Although maltreated children show similar levels of amygdala response as controls during effortful regulation (McLaughlin et al., 2015), they may require more cognitive resources than controls to effect this regulation and their regulatory processes may be more vulnerable to disruption under cognitive load.

This research suggests the importance of further work examining factors affecting the development of the vmPFC to amygdala inhibitory pathway including psycho-educational approaches, possibly leading to the development of interventions designed to encourage this function. Another possible area of research is the nature of the lateral temporal effortful regulation network and its relevance to effortful emotion regulation strategies other than reappraisal.

Our study was not without limitations. Our sample size was small given the power requirements of the PPI analysis we performed. This increases the possibility of false negatives in our analysis, which may account for the lack of bilateral findings in many of our contrasts. Additionally, PPI cannot establish direction of connectivity. It is possible that co-activation could be explained by activation/inhibition in a direction opposite to that hypothesized or indirectly through other brain regions not examined. We rely on existing anatomical and cognitive neuroscience research to make inferences about the nature of the observed connectivity. Finally, although our task has been extensively used in similar studies, it is by no means a perfect experimental model of cognitive reappraisal, whose neural correlates may differ in important ways from the task performed in our experiment. Further research on these processes should use expanded sample sizes and utilize multiple experimental tasks to address these shortcomings.

This study represents a valuable contribution to the field. The analysis of functional connectivity strengthens existing findings about differences in emotion regulation function between maltreated and non-maltreated children. These findings will open up new avenues for research both on the nature of emotion regulation processes and on potential treatment methodologies targeting maltreated youth.

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