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REVIEWS

Amygdala Developmental Consequences of Childhood Maltreatment

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Childhood maltreatment is a significant social problem associated with increased risk for depression and anxiety disorders. Despite this, many adults who experience childhood maltreatment do not develop psychiatric disorders and the neurobiological correlates for risk and resilience following childhood maltreatment are not well understood. Even in the absence of psychiatric diagnosis, childhood maltreatment can be associated with sub-clinical alterations in threat detection, a likely adaptive response to the early environment. Enhanced threat sensitivity following childhood maltreatment may be mediated by alterations in the developmental trajectory of the amygdala, a region often associated with threat detection. Functional MRI studies of populations with childhood maltreatment histories suggest heightened amygdala activation to aversive stimuli. Likewise, rodent models of chronic early stress exposure suggest amygdala effects, including increased dendritic arborization and decreased expression of the serotonin transporter (5-HTT). Genetic studies have also implicated 5-HTT, reporting an increased risk for depression following childhood maltreatment in carriers of the low-expressing of the 5-HTTLPR. Neuroimaging genetic studies have found increased amygdala BOLD signal in response to emotional or threatening stimuli in the low-expressing allele carriers exposed to maltreatment. Taken together, this literature suggests that the amygdala has heightened reactivity to threatening stimuli in people exposed to childhood maltreatment, and that these effects may be mediated by genetic variations in the serotonin system. Importantly, enhanced risk for depression is an end-point outcome well downstream of a host of genetic and environmental factors that interact dynamically throughout development. Future studies should address possible mediating factors by assessing for onset and duration of maltreatment, symptom severity, as well as gene x environment effects.

Keywords: *fMRI, serotonin transporter, childhood maltreatment, amygdala, anxiety, depression*

Introduction

Childhood maltreatment is a significant social problem affecting 3.7 million children annually in the United States alone[1]. Childhood maltreatment, which can include physical, emotional, and sexual abuse, as well as physical and emotional neglect, is associated with a host of negative outcomes, including increased risk for psychiatric disorders such as major depressive disorder and anxiety disorders[2]. Even in the absence of psychiatric symptoms that meet criteria for diagnosis, populations exposed to maltreatment can experience sub-clinical alterations in emotional processing, such as increased threat sensitivity and decreased emotional regulation[3-5]. Emotional processing changes are likely adaptive responses to early environmental exposure to threat, whereby threatening experiences have become generalized to the broader social environment as a way to avoid additional harm[6]. Observed changes in threat sensitivity and emotional regulation are likely mediated by the effects of early life stress on the developmental trajectory of the amygdala, a region implicated in threat detection and fear conditioning[7], as well as anxiety and mood disorders[8]. Despite increased risk for psychiatric disorders and behavioral dysfunction in populations exposed to childhood maltreatment, a significant proportion do not develop negative outcomes later in life. What, then, are the neurobiological correlates of enhanced risk for poor outcome following childhood maltreatment? This review will examine potential gene x environment developmental effects of childhood maltreatment on the structure and function of the amygdala, as well as how altered amygdala development may mediate increased risk for psychiatric disorder.

Amygdala Alterations in Magnetic Resonance Imaging Findings of Childhood Maltreatment

Enhanced sensitivity to potentially threatening emotional

Reference	Imaging Paradigm	Maltreated/ Total	Age Range	Psychiatric Diagnoses	Maltreatment Type	Maltreatment Assessment	Amygdala Findings
Garret et al., 2012	emotional face passive viewing	30/56	10-16	None	PN, EN, PA, EA, SA	Self report	BOLD increase, neutral and angry faces
Grant et al., 2010	emotional face flanker task	10/36	18-55	MDD	PN, EN, PA, EA, SA	Self report	BOLD increase, negative affect faces
Maheu et al., 2010	emotional face directed viewing	11/30	9-18	Anxiety d/o, n=2	PN, EN	Social services documentation	BOLD increase, angry and fear faces
McCrory et al., 2011	emotional face passive viewing	20/43	10-13	None	PN, PA, EA, SA	Social services documentation	BOLD increase, angry faces
Protopopescu et al., 2005	traumatic word passive viewing	9/14	20-55	PTSD	PA, SA	Self report	BOLD increase, traumatic words
Tottenham et al., 2011	emotional face go/no-go task	22/44	7-13	Anxiety d/o, n=2; ADHD, n=5; ODD, n=1	Previous institutionalization	Social services documentation	BOLD increase, fear and distractor faces
Van Harmelen et al., 2012	emotional face passive viewing	60/135	33-41	MDD or Anxiety d/o	EN, EA	Self report	BOLD increase for all faces
Bremner et al., 1997	sMRI, hand tracing	17/34	25-52	PTSD	PA, SA	Clinician interview	No volumetric differences
De Bellis et al., 2001	sMRI, hand tracing	9/18	8-12	PTSD	SA	Social services documentation	No volumetric differences
Driessen et al., 2000	sMRI, hand tracing	21/42	22-35	BPD	PN, EN, PA, EA, SA	Self report	Volumetric decrease
Edmiston et al., 2011	sMRI, VBM	42*	12-17	None	PN, EN, PA, EA, SA	Self report	Volumetric decrease correlated with frequency
Thomaes et al., 2010	sMRI, VBM	31/59	22-47	PTSD	PA, SA	Clinician interview	No volumetric differences
Tottenham et al., 2010	sMRI, automated segmentation	34/62	5-15	Anxiety d/o, ADHD, ODD,	Previous institutionalization	Social services documentation	Volumetric increase for late adopted relative to early adopted and control
Van Harmelen et al., 2010	sMRI, VBM	84/145	35-39	MDD or Anxiety d/o	EN, PA, EA, SA	Clinician interview	No volumetric differences

Table 1: *Summary of MRI literature in populations with childhood maltreatment exposure.* fMRI, functional magnetic resonance imaging; sMRI, structural MRI; VBM, voxel-based morphometry; PTSD, post-traumatic stress disorder; MDD, major depressive disorder; ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder; PN, physical neglect; EN, emotional neglect; EA, emotional abuse; SA, sexual abuse.

*individual differences regression analysis

faces is a consistent finding in adults[9], adolescents[10], and children[11-13] exposed to childhood maltreatment. In one study, participants with maltreatment demonstrated increased sensitivity to angry faces during an emotional face-morphing paradigm. Participants viewed a set of faces that morphed along a continuum from happy to fear, happy to sad, angry to fear, or from angry to sad and were asked to identify the emotion when presented with a pair of images from each continuum. Participants with a maltreatment history overrated facial expressions as angry and identified angry facial expressions at a lower intensity than participants that did not experience maltreatment, suggesting enhanced sensitivity to potential threat, with discrimination of potential threat at a reduced sensory threshold and with decreased reaction time[14]. Furthermore, a study of adolescents exposed to childhood physical abuse suggests increased attentional allocation to threatening or aversive imagery compared to neutral or positive imagery during an emotional dot-probe task[15]. Taken together, the behavioral literature suggests that emotional stimuli are particularly salient to maltreated populations, and that social information, such as faces may be of particular importance given the social nature of early maltreatment. Although adaptive in the context of a threatening upbringing, this enhanced attention to threatening stimuli may mediate increased risk for mood and anxiety disorders later in life[15-16].

Changes in amygdala structure and function are candidate mediators of the enhanced salience of emotional stimuli secondary to maltreatment. Previous functional magnetic resonance imaging (fMRI) studies of PTSD populations exposed to trauma, although not necessarily childhood maltreatment, have implicated the amygdala in emotional processing, and have also shown correlations between increased amygdala activation and PTSD symptom severity (for review, see 17-18). Likewise, fMRI studies of adults with childhood maltreatment exposure have found heightened amygdala activation to threatening or emotional stimuli, including negatively valenced emotional faces[19-20] and traumatic reminder words[21] (**Table 1**). FMRI studies in children and adolescents report similar findings, with increased amygdala BOLD signal for negatively valenced emotional faces the most often-reported finding[22-25]. Interestingly, although all of these studies report increased BOLD signal, several have reported heightened amygdala reactivity to both neutral and emotional facial expressions[20,25]. This discrepancy could be due to a generalized enhancement in threat detection, similar to what has been reported in the behavioral literature, such that neutral faces are perceived as potentially threatening. However, there is also evidence that in typically developing children there is no heightened amygdala activation to fear faces relative to neutral faces, as there is in adults[26], suggesting that height-

ened amygdala reactivity to fear faces in maltreated child and adolescents samples may reflect an altered developmental trajectory. In addition to alterations in amygdala BOLD signal magnitude, there is also evidence for changes in amygdala BOLD signal time course. Using an emotional face block design, Garret et al. report that increases in amygdala BOLD are greatest relative to control subjects in the early rather than the late phase for angry and fearful faces, suggesting that maltreated subjects may be primed for potential threat[25]. Taken together, the fMRI literature suggests that heightened amygdala activation to emotional stimuli may underlie the increased threat sensitivity observed in behavioral studies of maltreated populations, as well as their increased risk for mood and anxiety disorders.

Volumetric MRI studies of the amygdala in childhood maltreatment have been less consistent than the fMRI literature (**Table 1**). Voxel-based morphometry studies of the amygdala in adults have found decreases[27] or no differences[28-30] in amygdala volume, but are generally confounded by the study of participants with psychiatric diagnoses, such as PTSD and Borderline Personality Disorder, that are also associated with amygdala changes. Studies of children and adolescents have also been mixed, with reports of increases[31], decreases[32], and no differences[33] in amygdala volume. Mixed findings may in part be due to the still-developing nature of limbic-prefrontal circuits in adolescence, such that early stress exposure may trigger precocious amygdala development and sensitization, followed by volumetric decreases[34]. Furthermore, the issue of risk vs. resilience confounds studies of adolescents or children with maltreatment exposure and no current psychiatric diagnosis. Some adolescents may still develop a mood or anxiety disorder in adulthood, but it is also possible that a study of young adults or late adolescents without psychiatric disorders has sampled the most resilient members of the maltreated population; the reported amygdala volume reductions could be a marker of resistance to later mood or anxiety symptoms, thereby making conclusions about the structure of the amygdala in at-risk populations difficult. However, a recent study using an individual differences approach found a negative correlation between reported maltreatment severity and amygdala volume in adolescents, particularly in emotional maltreatment, suggesting that part of the heterogeneity of previous findings may be due to maltreatment type and the limited sensitivity of group comparison studies to detect potential biologically significant thresholds in maltreatment severity[32]. An important paper by Tottenham et al. assessed a group of orphans who experienced early childhood institutionalization in Romania, followed by adoption in the United States. In this study, there were no overall differences in amygdala volume between previously institutionalized children and controls. However, further comparison of early versus late adopted subjects revealed a significant correlation between amygdala volume and age of adoption, such that later adopted children had larger amygdala volumes than early adopted children[31]. Thus, age of maltreatment onset, duration of maltreatment, and age of assessment are all potential mediators of amygdala volumetric findings; future studies with an individual difference-based approach may prove more helpful than group comparison analyses in teasing apart the relative importance of the timing, severity and duration of maltreatment on amygdala development.

Amygdala Alterations in Rodent Models of Early Life Stress

Rodent models of early life stress effects on the amygdala have been more consistent than the human subjects literature. Both juvenile and adults rodents exposed to chronic immobilization stress have increased dendritic arborization of pyramidal neurons in the basolateral amygdala, in contrast to cells in the CA3 region of the hippocampus, which typically show dendritic atrophy. These chronically stressed rodents also show increased anxiety and depressive -like phenotypes as measured in behavioral tasks such as the elevated plus maze[35] and forced swim task[36]. Other rat studies have employed maternal separation paradigms, a model of early life stress in rodents, where pups are separated from their mothers for long or short periods of time. One maternal separation study has shown that the long-separated rats exhibited down-regulation of the serotonin transporter (5-HTT) as well as of inhibitory 5-HT_{1A} receptors in the amygdala. Long-separated rats also demonstrated an anxiety phenotype compared to short-separated rats, as assessed by the open field test[37]. Other rodent studies of chronic glucocorticoid administration have suggested down-regulation of the 5-HT_{1A} receptor subtype and up-regulation of 5-HT_{2A} receptor subtype[38]. It is thought that in limbic regions, activation of 5-HT_{1A} receptors may be anxiolytic, while serotonergic innervation of 5-HT_{2A} receptors may be anxiogenic (for review, see 39). These region and receptor subtype specific alterations may explain the heightened amygdala reactivity common in populations exposed to early life stress.

Rodent models are better able to assess differential effects of chronic versus acute stress than human studies. In a rodent study employing both chronic and acute immobili-

zation stress, chronic stress was associated with increased dendritic arborization in the basolateral amygdala the day after stress termination. In contrast, after a single acute stress exposure, increased dendritic spine density was observed in the basolateral amygdala, but only after a delay period of ten days[40]. Given the role of the amygdala in fear conditioning, this is likely an adaptive mechanism, allowing for priming for future potential stressors after early environmental uncertainty. Taken together, the rodent literature suggests increases in dendritic arborization that are specific to the amygdala after early stress; these changes may be secondary to alterations in serotonin receptor subtype density caused by excessive glucocorticoid exposure. Although caution is important when making inferences about human MRI literature on the basis of rodent models, it is possible that the heterogeneity in findings in the human literature is due to varying durations between maltreatment and assessment, or differences between chronic and acute stress effects.

5HTTLPR x Stress Effects on Depression Risk

Both the serotonin-mediated anxiety phenotypes in rodent models of early stress exposure, as well as the use of selective serotonin reuptake inhibitors (SSRIs) in depression treatment, suggest a 5-HTT mediated mechanism for observed functional and structural changes in the amygdala secondary to childhood maltreatment. The serotonin transporter is involved in the regulation of synaptic serotonin via reuptake of serotonin from the synapse into the presynaptic cell. The 5-HTT gene-linked polymorphic region (5-HTTLPR) is located on the 5' regulatory area of the serotonin transporter gene and has been of particular interest in the study of increased risk for depression in the presence of early life stress[41]. The 5-HTTLPR, originally thought to have a biallelic expression, has recently been shown to have a triallellic expression, with a short and long form allele. The long form allele has an L_G and L_A form, such that the L_G form is functionally similar to the low-expressing short or "S" allele. The S or L_G alleles are dominantly expressed and result in reduced transcription of SLC6A4A and decreased presence of 5-HTT at the synaptic membrane[42].

A landmark paper by Caspi et al. employed a population-based methodology to assess for a gene x environment relationship on depression rates. Their findings suggest an increased rate of depression for adult carriers of the S allele of 5-HTTLPR who also reported exposure to stress[43]. This study is one of the first studies to demonstrate a gene x environment effect of enhanced risk for a psychiatric disorder. However, there has been much controversy surrounding the reported observation, as some studies have been unable to replicate the 5-HTTLPR x stress finding[44-47]. This may be due to differences in stress assessment between studies. For example, types of stress exposure assessments vary wildly across studies; some have employed participant interviews both with and without medical record confirmation of maltreatment, which may be subject to retrospective bias. Others have used questionnaires to asses for stress exposure, ranging from brief, four question assessments for the presence or absence of physical or sexual abuse history[45,47], to detailed multi-item questionnaires that assess for the severity, timing, and duration of a host of different early life stressors[48-49]. Importantly, many of these studies have assessed for only physical or sexual abuse, which, although associated with an increased risk for later psychopathology, may be less salient than emotional maltreatment for both increased risk of later psychopathology[3,50] and amygdala volume alterations[32]. Furthermore, later studies of the 5-HTTLPR polymorphism have employed a triallelic analysis of the polymorphism, whereas other, earlier studies employed a biallelic (short or long) analysis[48,51-53]. Although the original Caspi et al. paper employed a biallelic analysis, differences in the underlying distribution of the L_g vs. L_a allele that were not assessed may account for heterogeneity of findings in the biallelic literature. Finally, recent studies have reported a sex x genotype x environment effect on 5-HTTLPR polymorphism and increased risk for depression, with only women with the low-expressing allelic variants showing enhanced risk for depression in the presence of childhood maltreatment[54]. This may explain the failure to replicate in studies that did not consider sex difference effects. Despite the heterogeneity of findings and methods in the literature, recent meta-analysis has suggested a positive finding, although with a smaller effect size than the original Caspi report[55].

5HTTLPR x Stress Effects on Amygdala Activation

Given the controversy regarding the enhanced risk for depression in short allele carriers with early life stress exposure, more recent literature has examined the effect of gene x environment on amygdala activation using fMRI. This literature has consistently found increased BOLD signal to emotional or threatening stimuli in the low-expressing allele carriers exposed to maltreatment[55]. Other studies have found decreased functional coupling of the amygdala with prefrontal regions, such as the anterior cingulate, which are thought to down regulate amygdala activity during emotional processing[56]. These findings suggest that the amyg-

dala has a heightened reactivity to emotional or potential threatening stimuli in low expressing carriers exposed to childhood maltreatment, and/or that there is decreased functional coupling between the amygdala and prefrontal cortex in this population. Combined genetic neuroimaging studies may be more fruitful in the study of risk for psychiatric disorder. Enhanced risk for depression is an end-point outcome well downstream of a host of genetic and environmental factors that interact dynamically throughout development; diagnostic categories are heterogeneous and depressive symptoms are likely the result of multiple potential biological causes and diagnostic categories. Therefore, by examining the association between genotype and intermediate phenotypes, such as BOLD signal or well-defined clinical subgroups, studies are better able to explore possible mechanisms for enhanced risk for depression by focusing on a single (or cluster of related) biological factors.

Concluding Remarks and Future Directions

MRI findings in amygdala volume and activation following childhood maltreatment suggest that this brain region is a significant contributor to emotional and behavioral alterations observed in maltreatment-exposed adults and children, including increased risk for mood and anxiety disorders. However, this literature is varied and complex due to a variety of factors that may moderate amygdala development, including 5-HTTLPR genetic polymorphisms and sex, as well as timing, duration, and type of maltreatment exposure. Future studies should address these possible interactive effects by assessing for severity and type of maltreatment, as well as for gene x environment interactive effects. Understanding the mechanism behind observed gene x maltreatment effects for depression risk will likely involve a close examination of 5-HT system alterations across development. Importantly, a better understanding of 5-HT system changes has the chance to improve clinical treatment of adult patients with maltreatment history and depression, as some studies have suggested that these patients, as well as patients with the low-expressing 5-HTTLPR allele, may be poor-responders to SSRI treatment[57-58]. Variations in treatment response may be due to underlying differences in serotonergic system function in patient subpopulations with the 5-HTTLPR risk allele and/or with childhood maltreatment. As study of brain alterations following childhood maltreatment is necessarily difficult for ethical reasons in humans, rodent models of early life stress are particularly important in dissociating the varying developmental effects of different types of maltreatment and maltreatment duration on amygdala structure and function. Translational research to assess potential alterations in 5-HT receptor density and mechanisms underlying resultant structural and functional remodeling of limbic circuits is necessary to inform observed changes in the human behavioral, genetic, and neuroimaging maltreatment literature.

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