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Commentary: Childhood Maltreatment, Cortical and Amygdala Morphometry, Functional Connectivity, Laterality and Psychopathology.

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As readers of the journal *Child Maltreatment* undoubtedly know, maltreatment is distressingly prevalent. Further, maltreatment is the most important preventable risk factor for psychopathology and a root cause of chronic medical illness (Shonkoff, Boyce, & McEwen, 2009). According to the Adverse Childhood Experience (ACE) study, and similar efforts, child maltreatment (CM) and household dysfunction account for 45% of the population attributable risk (PAR) for childhood onset mental illnesses (Green et al., 2010), 30% and 54%, of the PAR for anxiety disorders (Green, et al., 2010) and depression (Dube, Felitti, Dong, Giles, & Anda, 2003) as well as 56%, 64%, and 67% of the PAR for illicit drug use problems, addiction to illicit drugs, and parenteral drug use, respectively (Dube et al., 2003). These are the most prevalent adult psychiatric disorders and leading causes of disability worldwide.

Hence, there is a pressing need to understand how CM gets ‘under the skin’ to markedly increase risk in some individuals as well as a comparable effort to identify factors associated with better than expected outcomes in other individuals. This special issue of *Child Maltreatment* provides a series of sophisticated studies on the neurobiological impact of CM. This is a remarkable milestone. Twenty or so years ago there were only three laboratories focused on using brain imaging to study the consequences of CM (Carrion et al., 2001; M D. De Bellis, Keshavan M.S., Clark D.B., & al, 1999; Teicher et al., 1997). Now it appears that almost every major medical center or psychology department has one or more investigators working diligently in this domain. This dramatic increase in interest likely stems from the compelling series of discoveries made to date and both the large effect sizes and general reproducibility of the key findings (Teicher & Samson, 2016; Teicher, Samson, Anderson, & Ohashi, 2016).

From this issue we have selected four articles to comment on. The articles by Oshri et al., (in press) and Peveril, Sheridan, Busso & McLaughlin (in press) are amygdala centric and provide important new information on the impact of CM on the morphology and functional connectivity of this highly stress susceptible structure. These studies make use of state-of-the art techniques to provide new findings regarding the specific amygdala nuclei altered as well as the specific prefrontal components functionally interconnected with the amygdala that appear to be targeted by abuse. The article by Demers et al., (in press) presents data from a longitudinal study that illustrates the potentially disruptive effects of CM on the association between maternal relationship quality, frontal cortical development and

symptomatology. Finally, the De Bellis et al., (in press) study addresses the pressing question, which we have labeled the 'ecophenotype hypothesis', that postulates that maltreated and non-maltreated individuals with the same primary DSM diagnosis are clinically and neurobiologically distinct (Teicher & Samson, 2013), and provides new evidence for a specific prefrontal cortical neurobiological abnormality in the maltreated subtype.

More specifically, Oshri et al., (in press) made excellent use of the high-resolution segmentation algorithms provided in version 6 of FreeSurfer (Saygin et al., 2017) to assess the association between ACEs, volume of specific amygdala nuclei and their relationship to current psychiatric symptoms in N=119 emerging adults of African American ancestry. Interestingly, they found that higher ACE scores were related to reduced volume of the right, but not the left, amygdala and appeared to specifically target six component nuclei within the right amygdala (i.e., lateral, basal, accessory basal, cortical and paralaminar nuclei and corticoamygdaloid transition zone). Furthermore, as volumes of the discrete nuclei were highly correlated they cleverly used structural equation modeling techniques and found that volumetric measures for individual nuclei could be meaningfully grouped into two oblique factors – a central medial regional component (consisting of the central, cortical and medial nuclei) and a basolateral regional component (consisting of the six remaining portions). Greater ACE scores were associated with reduced volume in both components of the right amygdala. However, only the right basolateral component was associated with increased symptoms and partially mediated the association between ACE scores and ratings of anxiety, depression and alcohol use problems.

These findings are consistent with two earlier reports showing a specific right-sided reduction in amygdala volume in maltreated individuals involving basolateral and superficial-cortical nuclei (Van Dam, Rando, Potenza, Tuit, & Sinha, 2014; Veer et al., 2015), though the current study provides a more definitive segmentation analysis. There are a number of important implications from this study and the two facets that we wish to draw attention to are the directionality and laterality of the findings. In general, studies on the association between CM and morphology of stress-susceptible structures are rather consistent, though this is not the case regarding potential direction of impact on amygdala volume. In the supplement of our last review (Teicher, et al., 2016) we found that 21/40 studies reported no significant influence of CM on amygdala volume. However, there were 13 studies reporting a statistically significant decrease and 6 reporting a statistically significant increase.

Studies reporting significantly larger amygdala volumes in maltreated participants were distinctly different from those observing significantly smaller volumes. Two studies with larger volume findings reported results from institutionally-reared children, one reported results from children with chronically depressed mothers, and two reported results from a longitudinal sample in which most participants had disturbed attachment bonds in infancy. Hence, increased amygdala volumes were observed primarily in individuals with early exposure to emotional or physical neglect. In contrast, studies reporting significant smaller amygdala volumes predominantly evaluated adults or older adolescents (8/13 studies) with exposure to multiple forms of CM across development. Ten of the thirteen studies also

focused on subjects with current psychopathology. Hence, studies reporting significantly smaller amygdala volumes had, on average, older participants, greater degrees of psychopathology and exposure to multiple types of abuse during childhood.

We have proposed that CM does not damage the brain but induces phenotypic adaptations in structure, function and connectivity which in our evolutionary past enhanced childhood survival and reproductive success, though such changes may now prove maladaptive (Teicher, 2002; Teicher, et al., 2016). These adaptations likely result from modification to developmental processes taking place at the time of exposure, particularly the overproduction of dendrites, axonal terminals, synapses and receptors during early to middle childhood and the pruning of these processes during adolescence and early adulthood (Petanjek et al., 2011). Hence, early maltreatment may amplify overproduction in specific regions leading to enlargement or thickening while later exposure may augment pruning leading to volume loss or thinning. Inconsistencies in amygdala volume probably reflect important differences in timing of exposure to adversity. We have postulated that early exposure to stress seems to produce a significant but modest enlargement of the amygdala. However, it also sensitizes the amygdala so that later exposure to subsequent stressors produces a graded reduction in volume (Teicher & Samson, 2016; Teicher, et al., 2016). Consequently, assessing the potential impact of CM without regard to timing of exposure may result in increased, decreased or non-significant findings depending on the percentage of subjects with primarily early exposure versus subjects with both early and later exposure. Oshri et al., (in press) in selecting a low-income (46% below poverty level), rural, African-American sample, may have enhanced the likelihood of recruiting maltreated individuals with both early and later childhood exposure, so their finding of reduced volume makes good sense.

An interesting question not addressed in this study is the relationship between amygdala volume and function. We recently reported (N=202), that similar to volume, that prepubertal versus postpubertal exposure to maltreatment appeared to be associated with opposite effects on amygdala function. Early exposure was associated in adulthood with a blunted response to threatening faces while postpubertal exposure was associated with an augmented response, and that in general a smaller amygdala was associated with an enhanced response and diminished ability to discriminate between threatening and neutral stimuli (Zhu et al., 2019).

Another important finding in Oshri et al., (in press) was that the relationship between ACE score and amygdala measures were entirely right sided, which is not unusual, but quite important. In general, studies observing an overall decrease in volume were more likely to report right sided differences while studies observing an overall increased were more likely to report left hemisphere differences, though many studies observe bilateral effects (Teicher, et al., 2016). We found, in a collaborative venture with Karlen Lyons-Ruth, who has followed a high-risk sample from infancy to 30 years of age, that the key determinant of right amygdala volume was severity of maltreatment at 10–11 years of age (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014) while left amygdala volume was predicted by quality of the attachment bond at 18 months of age (Lyons-Ruth, Pechtel, Yoon, Anderson, & Teicher, 2016). This hemispheric difference in amygdala sensitivity to experience has important

implications. The amygdala plays a key role in the evaluation of salience and this is no more in evidence than in the detection and response to threats (Ohman, 2005). We have proposed that a child faces two fundamentally different types of threats. Perhaps the most critical in early life is the threat of insufficient care or abandonment and we have postulated that the left amygdala may have an especially important role in detecting and responding to this type of threat (Lyons-Ruth, et al., 2016). Conversely, the right amygdala may have an especially important role in detecting and responding to abusive and other hazardous situations. This hypothesis is consistent with hemispheric differences in the behavioral expression of emotion, with the left anterior hemisphere specialized for processing positive or approach-related emotions and the right anterior hemisphere specialized for processing negative or withdrawal-related emotions (Davidson, Ekman, Saron, Senulis, & Friesen, 1990). Clearly, an approach response makes much more sense in the context of an early abandonment threat, while a withdrawal or flight response may be optimal when facing a threat to our bodily integrity. Their finding of a specific association between the volume of the right basolateral amygdala component and ratings of anxiety, depression and alcohol use problems, is consistent with the role of the right amygdala. It is important to keep in mind though that left-right differences in hemispheric emotional processing apply to populations, and as with handedness there is a substantial percentage of individuals with reversed emotional laterality (Schiffer et al., 2007).

The well analyzed and sophisticated study by Peveril et al., (in press) also reported an important lateralized consequence of CM on the amygdala and its functional connectivity with the ventromedial prefrontal cortex (vmPFC). They selected a sample of N=59 adolescents from a longitudinal study of CM to participate in a functional neuroimaging task in which they viewed neutral, negative, and positive images from the International Affective Picture System. During part of this task they were instructed to “look” at the image without trying to modify their emotional response and during another part were instructed to regulate their emotional response using cognitive reappraisal strategies they learned prior to scanning. This study focused on the passive viewing phase. In a previous report they found in a subsample that passively viewing negative versus neutral images enhanced BOLD fMRI activity in the amygdala, thalamus, anterior insula, putamen, and vmPFC bilaterally, and this differential negative > neutral response was enhanced in most of these regions (except vmPFC) in youths reporting exposure to physical or sexual abuse (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015).

In the current study they focused on the effects of abuse, as a specific form of threat and adversity, on the connectivity between the vmPFC and the amygdala, as the vmPFC appears to play an important role in the ‘top-down’ regulation of amygdala response. This role emerges over the course of development and appears to be paralleled by an important switch in the nature of the functional connectivity between these regions. Gee, Humphreys, et al., (2013) found that prior to 10 years of age that temporal fluctuations in BOLD response in these two regions were positively correlated but shifted to a negative (reciprocal) pattern after age 10, and this was accompanied by a steady decline in amygdala reactivity. Interestingly, children raised in institutional care (Gee, Gabard-Durnam, et al., 2013), or with insensitive parents (Thijssen et al., 2017), showed an earlier developmental shift to a negative connectivity pattern, which makes adaptive sense.

Briefly, Peveril et al., (in press) first found using psychophysiological interaction (PPI) models that the task-related contrast (look negative > look neutral) revealed a functional connectivity relationship between the left amygdala and the right vmPFC, encompassing the medial orbitofrontal cortex (mOFC) and the subgenual anterior cingulate cortex (sgACC). Second, no regions were identified that displayed this type of functional connectivity pattern with the right amygdala. Third, the functional connectivity relationship between the vmPFC and the amygdala was negative. Fourth, history of abuse (and severity of abuse) were associated with greater negative task-related functional connectivity between the left amygdala and both the mOFC and sgACC clusters within the right vmPFC. Fifth, more negative task-related functional connectivity between left amygdala and both mOFC and sgACC was associated with higher levels of externalizing psychopathology. Sixth, task-related functional connectivity between left amygdala and mOFC was associated with current internalizing symptoms. Finally, functional connectivity between left amygdala and sgACC predicted externalizing psychopathology two years later but did not mediate the relationship.

This study provides important new findings on potential neurobiological mechanisms leading to abuse-related abnormalities in affective regulation. Indeed, the enhanced negative coupling between right vmPFC and left amygdala may be a critical contributor to the mood lability and affective instability seen in maltreated individuals. The challenge in fully interpreting this study, as implied in their discussion section, is in understanding the finding that the abuse-associated increased in negative functional connectivity between vmPFC and amygdala was associated with higher levels of externalizing and internalizing symptoms. In general, negative functional connectivity between these regions is viewed as prefrontal regulatory control dampening amygdala response (Gee, Humphreys, et al., 2013). However, in order to explain the association between higher negative functional connectivity and greater symptoms scores Peveril et al., (in press) proposed that enhanced negative connectivity was not indicative of increased inhibitory control but represented *reduced* regulatory response from vmPFC when amygdala activity is high. Though conceivable, reduced regulatory control would more likely be associated with a reduction in the absolute strength of the correlation rather than in a stronger reciprocal relationship.

We suspect that a focus on laterality may provide a more physiologically sound explanation for their findings. In Gee, Humphreys, et al., (2013) the positive to negative shift in functional connectivity was observed between vmPFC bilaterally and the right amygdala, which is more strongly associated with fear and enhanced psychiatric symptomatology than the left. In Peveril et al., (in press) functional connectivity was enhanced between vmPFC and the left amygdala. Hence, it is conceivable that abuse specifically targeted and enhanced vmPFC inhibitory regulation of the left amygdala, without affecting right amygdala regulation, leading to a relatively stronger right-sided fear-based withdrawal response. This fits with the large N observation from Dannlowski et al., (2012) that maltreatment was specifically associated with increased right but not left amygdala BOLD response to passive threat in adulthood. In this way it is possible to understand the relationship between increased negative connectivity and higher symptoms scores without needing to propose that enhanced negative coupling involves a reduction in regulatory control.

Demers et al., (in press) in a novel longitudinal study used path analysis to ascertain whether documented CM moderated the influence of maternal relationship quality during adolescence on adult prefrontal cortical (PFC) volume and measures of internalizing and externalizing symptoms and adaptive competence. The sample consisted of N=88 adults (48 maltreated) averaging 30 years of age, who participated in a research summer camp for low-income, high-risk children (6 –12 years of age) and were reassessed in adolescence (13–15 years) and adulthood. During adolescence the majority lived in female-headed single parent households, and mother was implicated as a perpetrator in 90% of participants with documented maltreatment. FreeSurfer (V5.1.0) was used to measure PFC volume in adulthood, which was computed by summing individual volume measures for superior frontal, rostral and caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral and medial orbitofrontal, precentral, and paracentral cortex bilaterally.

The key findings were that adult bilateral frontal lobe volume was predicted by the interaction of maternal relationship quality during adolescence and number of types of CM experienced. However, the potential growth promoting influence of high adolescent maternal relationship quality was only clearly evident in the non-maltreated participants. Further, greater frontal lobe volume predicted fewer internalizing symptoms and greater adaptive competence, but did not predict externalizing symptoms, though again these predictions only held in the non-maltreated participants. This is likely the first study to provide a neurobiological model that effectively links maternal relationship quality in adolescence to adult symptomatology and adaptive competence. Finding that this was mediated through the slowly maturing PFC makes sense, though it is surprising that this influenced could be observed in such a coarse measure as total bilateral frontal lobe volume. It would have been interesting, albeit statistically problematic, if they had drilled down to assess whether left or right frontal lobe volume was more predictive and identified the cortical subregions most specifically involved.

Although this was a very well-designed longitudinal study, with carefully matched maltreated and non-maltreated groups, it was limited, as they acknowledged, by the collection of maternal relationship quality only in adolescence and neuroimaging data only in adulthood. Hence, they were not able to conclude whether maternal relationship quality was actually exerting key influence on PFC morphometry during adolescence or at earlier ages. In their introduction the strongly emphasized the possibility that the key determinant was the quality of the early attachment bond (Demers, et al., in press) and cited studies suggesting that the cortex is especially sensitive to early stress. However, the studies cited with data on early exposure (Hodel et al., 2015) only assessed cortical volume at 12–14 years of age, and the cited studies on parenting quality and more general measures of brain development only assessed subjects in infancy (Sethna et al., 2017) or early childhood (Kok et al., 2015; Thijssen, et al., 2017). In terms of adult PFC volume, we provided retrospective data suggesting that it was most susceptible to maltreatment at 14–16 years of age (Andersen et al., 2008). More definitively, the Avon Longitudinal Study assessed exposure to childhood adversity (including interpersonal loss, family instability, abuse and emotional cruelty) at 8, 21, 33, 47, 61, and 73 months, and conducted brain imaging at 18–21 years of age in N=494 males (Jensen et al., 2015). Volumes were measured in 30 cortical regions and they found that exposure during the first 6 years was only associated with alterations in gray

matter volume in the right caudal anterior cingulate and right precuneus, neither of which are included in their frontal lobe volume measure. Hence, although PFC development and connectivity will be influenced to some degree by early exposure it is likely that peripubertal and adolescent exposure will play a disproportionate role in shaping the slowly maturing prefrontal cortex.

There were, however, a number of potentially problematic observations in this study. The first was that there was no significant difference between maltreated and non-maltreated participants in the adolescent ratings of maternal relationship quality, though mothers were perpetrators of abuse for 90% of the maltreated group. This suggests that either a substantial amount of healing took place within these relationships or that the maltreated group was ratings their relationship with their mothers in a more idiosyncratic manner. This, in turn, may explain why there was a significant association between maternal relationship quality and frontal lobe volume in the non-maltreated group but not in the maltreated participants. The lack of association may also be an artifact of sample size as the total N=88 was barely sufficient for a model with 16 paths and 10 parameters, and underpowered for any of the subgroup analyses The second curious observation was that there was no overall group difference in frontal lobe volume, though reduced cortical volume is one of the most consistent findings in maltreated individuals (Lim, Radua, & Rubia, 2014; Teicher & Samson, 2016) and maltreatment was associated with reduced volume within the study. The authors suggest that some unspecified factor may be influencing or helping to stimulate frontal lobe volume in the maltreated group. Scatter plots showing the relationship between frontal lobe volume, maternal relationship quality and number of types of maltreatment would have been helpful.

The most problematic observation is that they found in their model an extremely strong positive association between intracranial volume (ICV) and both internalizing and externalizing symptoms, suggesting that adults with larger head sizes were more symptomatic, which is rather unlikely. A quick check in our data set (N=336) showed no significant association between ICV and symptoms of depression, anxiety or anger-hostility. In their model, they were endeavoring to predict internalizing and externalizing symptoms using both frontal lobe volume and ICV, which are highly correlated and we suspect led to a problem with multicollinearity (Petraitis, Dunham, & Niewisrowski, 1996). A potential solution would be to perform the path analysis using frontal lobe volume adjusted for ICV and to omit the collinear ICV measure, which would also simplify the model.

De Bellis et al., (in press) in a very nice introduction laid out a pressing problem in the substance use disorder (SUD) field, which is that studies exploring the neurobiology of SUD, or the impact of drugs and alcohol on the developing brain, almost never consider the potential confounding or interactive effects of CM. Indeed, besides this new De Bellis study, we were only aware of one other study to do so (Van Dam, et al., 2014). This is an enormous problem as CM is the most important risk factor for alcohol use disorder (AUD) and other SUDs (M. D. De Bellis, 2002; Dube, Felitti, Dong, Chapman, et al., 2003), and it produces effects on brain development that often parallel those produced by AUD/SUD.

De Bellis et al., (in press) addressed this issue by recruiting three groups of participants in this pilot study: adolescents (13–18 years) with adolescent-onset AUD without child maltreatment (AUD-MAL) (n=28, n=22 neuroimaging); adolescents with adolescent-onset AUD and a child protective services CM history (AUD+MAL) (n=17, n=9 neuroimaging) that occurred prior to AUD; and healthy adolescents (n=31, n=28 neuroimaging), without exposure to traumatic events, any axis I disorder or history of AUD/SUD. Participants were required to have been abstinent from drugs or alcohol for at least 21 days. Subject selection was followed by comprehensive clinical and substance use assessment, neuropsychological testing and morphometric analysis using FreeSurfer (V5.1.0) of PFC regions of interest, amygdala, hippocampus, parahippocampus gyrus, and corpus callosum.

Briefly, they found that both the AUD-MAL and the healthy control group performed significantly better than the AUD+MAL group in sustained attention. The control group performed significantly better than AUD+MAL group in Reading and Math Fluency, and there were no group differences in Fine Motor, Visual-Spatial, Memory/Retrieval, and Executive Function domains. Neuroimaging revealed that the left pars triangularis, a portion of the inferior frontal gyrus, was larger in the AUD+MAL compared to AUD–MAL and control groups, and that the anterior corpus callosum was smaller in the AUD+MAL group than in the AUD–MAL group. Further, total hippocampal volume showed an inverse association with age in the AUD+MAL that was not present in the AUD–MAL (non-significant decrease) or healthy controls (trend level increase).

This study is of particular interest as it helps to underscore what we believe to be an evolution in our thinking regarding the relationship between CM and psychopathology. Very gradually, following Kempe's publication of the battered-child syndrome (Kempe, Silverman, Steele, Droegemueller, & Silver, 1962), there emerged a dawning awareness in psychiatry and clinical psychology of the potential importance of CM. Initially, CM was viewed as a complicating factor associated with comorbid PTSD or personality disorders that resulted in a more difficult course and poorer outcomes. This was shortly followed by epidemiological studies indicating that CM was a key risk factor associated with a substantial portion of the population attributable risk for the most prevalent psychiatric disorders (Dube, Felitti, Dong, Chapman, et al., 2003; Green, et al., 2010). What we now suspect is that CM is a primary etiological factor that produces pathophysiologically distinct clinical outcomes with unique neurobiological signatures. We have labeled the maltreated variant an '*ecophenotype'* and proposed that maltreated and non-maltreated individuals with the same primary DSM disorder are clinically, neurobiologically and genetically distinct (Teicher & Samson, 2013). In general, the ecophenotype has an earlier onset, more severe course, more comorbidities and poorer response to first line treatments. The clearest differences however are neurobiological, with the ecophenotype showing alterations in the morphometry of stress-susceptible structures not apparent in the non-maltreated variant (Chaney et al., 2014; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; Malykhin, Carter, Hegadoren, Seres, & Coupland, 2012; Opel et al., 2014; Sheffield, Williams, Woodward, & Heckers, 2013; Vythilingam et al., 2002; Wang et al., 2014). In these studies, there were no morphological differences between the non-maltreated subtype and healthy controls, suggesting their underlying pathophysiology in non-maltreated individuals may be more molecular or functional than structural. The current neuroimaging findings from De Bellis et

al., (in press) add additional support to this hypothesis as the AUD+MAL group had morphometric abnormalities not apparent in healthy controls or in the AUD–MAL group.

The most striking morphometric difference in the AUD+MAL group was increased size of the left inferior frontal gyrus pars triangularis. This is intriguing as we recently reported that the left pars triangularis appears to play a particularly important role in susceptibility / resilience to the adverse psychiatric consequences of CM (Ohashi et al., 2019). Briefly, we found (N=342) that psychiatrically symptomatic and asymptomatic adults with CM histories had the same array of abnormalities in structural brain network architecture. However, the asymptomatic group differed from both the symptomatic CM group and healthy control group in having reduced nodal efficiency (ability of a brain region to propagate information throughout the network) in 9 brain regions including right amygdala and left pars triangularis. In particular, low nodal efficiency of the left pars triangularis appeared to protect maltreated individuals from symptoms of anxiety, depression and number of drug use issues (Ohashi, et al., 2019). The left pars triangularis includes a portion of Broca's area and we suspect may be the source of the hypercritical 'voice' that maltreated individuals often have in their head. In the asymptomatic maltreated participants the left pars triangularis had fewer connections to right temporal lobe and limbic system, and we proposed that diminishing the impact of these 'voices' may enable the asymptomatic participants to more effectively compensate for abnormalities in network architecture and morphometry (Ohashi, et al., 2019). The enlarged left par triangularis observed by De Bellis et al., (in press) in the AUD+MAL group, on the other hand, may render these individuals more susceptible.

Overall, it is encouraging to see the field expanding and thriving in this manner. Understanding how CM alters trajectories of brain development is critically important in our efforts to prevent psychopathology, to foster neurobiological substrates of resilience and to develop more effective treatments. Each of these studies adds an important new element to a fascinating evolving picture.

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