Early adversity and emotion processing from faces:

a meta-analysis on behavioral and neurophysiological responses

Running title: Early adversity and facial emotions

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Abstract

Background: Although the link between early adversity (EA) and later-life psychiatric disorders is well-established, it is yet to be elucidated whether EA is related to distortions in the processing of different facial expressions. We conducted a meta-analysis to investigate whether exposure to EA relates to distortions in responses to different facial emotions at three levels: (1) event-related potentials (ERPs) of P100 and N170; (2) amygdala fMRI responses; and (3) accuracy rate or reaction time in behavioral data. **Methods:** The systematic literature search (PubMed and Web of Science) up to April 2020 resulted in 29 behavioral studies (N=8555), 32 fMRI studies (N=2771), and 3 EEG studies (N=197) for random-effect meta-analyses. **Results:** EA was related to heightened bilateral amygdala reactivity to sad faces (but not other facial emotions). Exposure to EA was related to faster reaction time but a normal accuracy rate in responses to angry and sad faces. In response to fearful and happy faces, EA was related to a lower accuracy rate only in individuals with recent EA exposure. This effect was more pronounced in individuals with exposure to EA before (vs. after) the age of three years. The above findings were independent of psychiatric diagnoses. Due to the low number of eligible EEG studies, no conclusions could be made of the effect of EA on the ERPs. **Conclusions:** EA relates to alterations in behavioral and neurophysiological processing of facial emotions. Our study underlines the importance of assessing age at exposure and time since EA since some of the EA-related perturbations are mediated by these factors.

1 Introduction

Early adversity (EA) refers to encountering such stressors before the age of 18, which results in a significant biological and/or psychological strain and requires substantial adaptation from the child (1, 2). EA includes single or multiple stressors that, in turn, can be acute or chronic in nature (1, 2). Common examples of EA include emotional, physical, or sexual abuse; emotional or physical neglect; an injury or severe disease of the self or primary caregiver; criminal or violent behavior in the immediate environment; or exposure to war or natural disaster. Even 24.5−61.55% of the population is exposed to EA, with substantial variation in different types of EAs (3-5). For example, as many as 133–275 million children witness regular violence between caregivers, and at least 223 million children are exposed to sexual abuse every year (6).

Individuals exposed to EA have a several-fold higher risk for various psychiatric disorders over the lifespan (1, 7). One mechanism mediating the association between EA and these disorders could be the interpretation of others' facial emotions since it constitutes the basis for interpersonal communication and is distorted in a range of psychiatric disorders (8, 9). In distressing circumstances, children may associate a neutral facial expression with threat or distress (10). This occurs via conditional learning processes that may increase amygdala reactivity and lower behavioral reaction time to threat-related facial emotions (11). This, in turn, may enhance early detection of conflict and threat (11) and enable efficient monitoring of one's environment (12) and, in this way, increase children's adaptivity to harsh circumstances. The development of facial perception networks is suggested to have a sensitivity period in childhood (12, 13), suggesting that some of the EA-induced alterations may also remain after acute exposure to EA.

Over the decades, it has been actively discussed whether EA is related to a distorted perception of different facial emotions (11, 12). The processing of facial emotions occurs in several interconnected networks in the brain, proceeding from primary unconscious encoding to higher-level

explicit recognition (13). Three phases of this process have received particular research interest. Firstly, there is a primary visual processing and initial structural encoding of the faces that generate a complete facial representation (14-16). Those phases can be obtained as a positive event-related potential (ERP) P100 and a negative ERP of N170 (14-16). Secondly, the emotional significance of the faces is primarily assessed, which can be obtained as increased activity in the amygdala (17). When encountering threatening or otherwise emotionally salient faces, the amygdala is a significant component of enhancing physiological stress responses by activating the fight-or-flight system (13). Thirdly, the facial expressions are explicitly recognized (i.e. these emotions are consciously assigned with labels) at the behavioral level. This can be measured with behavioral tasks of recognition accuracy and reaction time in response to facial emotions.

To date, findings on EA's effect on the above neurophysiological and behavioral processing of facial emotions have been inconclusive. EEG studies have not resulted in any consistent pattern since EA has been related to the higher, smaller, or normal amplitude of N170 and P100 (18-20). A similar discrepancy exists among fMRI studies. Some fMRI studies have reported that EA is related to elevated amygdala activity in response to angry or fearful faces (11-13) or also to happy and sad faces (21), while other fMRI studies have resulted in null findings (22, 23). Behavioral studies have remained unresolved whether EA is associated with distortions in recognition accuracy or reaction time in response to facial emotions and whether these associations are emotion-specific (11, 12, 24-29). Major open questions have also been whether the heterogeneity of previous findings emerges from simultaneous psychiatric diagnoses or medications (12, 13, 30), age at exposure to EA (12), or time since EA (recent or remote EA) (30).

Here, we conducted a systematic review and meta-analysis to explore the association of exposure to EA with behavioral and neurophysiological responses to different facial emotions. We investigated whether exposure to EA is associated with distortions in responses to facial emotions at three levels: (1) P100 and N170 event-related potential (ERP) responses in EEG data (i.e., the primary

encoding of faces in the brain); (2) amygdala activity as assessed with fMRI (i.e., primary assessment of the emotional significance of faces that also has a central role in stress response); and (3) accuracy rate or reaction time in behavioral data (i.e., explicit recognition of facial emotions). Finally, by employing meta-regression, we investigated whether these associations are modified by study characteristics such as simultaneous psychiatric diagnoses or medications, age at exposure to EA, or time since EA. Given the crucial role of EA as a potent risk factor for many psychiatric disorders, we hypothesized that EA would relate to alterations in neurophysiological and behavioral responses to different facial expressions. However, due to the above heterogeneity in the previous work, we set no a priori hypotheses about the direction of these effects.

2 Methods and materials

2.1 Search and screening of articles

The article selection process is illustrated in Figure 1. The meta-analysis was conducted following the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist (https://www.elsevier.com/__data/promis_misc/ISSM_MOOSE_Checklist.pdf). We conducted a systematic literature search to identify all relevant studies published until April 10, 2020, using PubMed and Web of Science. The search terms are described in Supplementary Methods.

All identified studies were screened based on the title and abstract and defined as eligible/ineligible. Moreover, the articles' reference lists included in the review and obtained meta-analyses and systematic reviews (11, 12, 31-33) were checked to obtain additional eligible studies.

Thereafter, we assessed the full-text articles' eligibility based on the exclusion and inclusion criteria (please see Supplementary Methods). All the excluded full-text articles and the reasons for their exclusion are listed in Supplementary Table 1. At each phase of the article selection process, the inclusion/exclusion was evaluated independently by two authors (A.S./S.H./J.P./E.J./M.P./J.L.).

2.3 Data collection from the included studies

Data collection is described in Supplementary Methods. *The studies*' quality was assessed using an item-checklist modified from previous meta-analyses (see Supplementary Table 2) (34-36). We collected data on EA *quality, age at exposure to EA*, and the *timing of exposure to EA*. When the results were exclusively presented as plots, we used the WebPlotDigitizer (https://automeris.io/WebPlotDigitizer) to extract the data manually.

A majority of studies did not report age at exposure to EA or timing of exposure to EA precisely. Therefore, we could not form continuous variables for age at exposure to EA or for the timing of exposure to EA. For this reason, we had to form categorical variables. Considering the

limitations of the original articles, *age at exposure to EA* was classified as before/after the age of 3 years. This cut-off was based on two reasons. First, the psychological research literature suggests that exposure to EA may have especially adverse influences on a child's early development (due to e.g., child's misperceptions of causalities, limited verbal abilities, poor cognitive coping resources with stressful events, and limited abstract understanding of separation and death) (37-40). Second, the statistical issues (in the original studies, there were subjects exposed to EA before the age of 3 years enough for conducting group comparisons). Exposure to EA was defined to occur after the age of 3 years if the mean age of exposure to EA in the study sample had been >3 years; or if exposure to EA had been measured with a self-report questionnaire (EAs that have occurred during the first years of life cannot be recalled due to childhood amnesia) (41).

Again, considering the limitations of the original studies, the *timing of exposure to EA* could not be regarded as a continuous variable but was classified as recent/distant. Exposure to EA was defined as distant if exposure to EA had occurred >2 years ago; if the child had been moved to a favorable and stable environment (other than an institutional environment) for >2 years ago; or if the participants were adults at the time of the measurements. The cut-off of 2 years was based on the psychological literature indicating that overcoming traumatic crises typically takes at most two years (42).

(FIGURE 1 ABOUT HERE)

2.4 Statistical analyses and meta-analytical models

We analyzed the behavioral data and EEG data with R version 3.6.1 accompanied with "metafor" package (43) and the fMRI data with MetaNSUE package (https://www.metansue.com/) due to its capability to incorporate missing nonsignificant effect sizes (44, 45). We set the threshold of three studies as an absolute minimum number to perform any quantitative analysis.

Firstly, we investigated the overall effect of EA on responses to facial emotions. Specifically, we investigated 1) the mean amplitudes of P100 and N170 (EEG studies) in response to different facial expressions, 2) the mean BOLD responses to facial expressions in the amygdala (fMRI studies), and 3) the mean accuracy rate and reaction time to facial expressions (behavioral studies). When collecting statistical parameters from the included original studies, we collected all the statistical contrasts that were available related to any facial emotion. There was some degree of heterogeneity in the contrasts used in the original studies (e.g. whether facial emotions were compared to neutral faces or shapes). Thereafter, we conducted subgroup analyses separately among subjects with recent vs. distant exposure to EA. Next, we explored potential factors that could moderate the heterogeneity of the results. We examined the moderating effect of EA before vs. after the age of three years. Furthermore, we explored the moderating effects of the use of psychotropic drugs (yes/no), psychiatric diagnoses (yes/no), mean age at the time of measurement, and gender distribution of the study sample. A minimum of 10 studies was used as a criterion to conduct analyses with moderating variables (https://handbook-5-1.cochrane.org/chapter_9/9_6_4_meta_regression.htm).

We assessed heterogeneity with the I^2 value that describes the percentage of total variation across studies due to heterogeneity rather than chance (46). We used the following thresholds for interpreting I^2 values: 25% (low), 50% (moderate), and 75% (high). If a study explored the relationships of multiple early adversity types (e.g., neglect and abuse separately) with multiple outcomes (e.g., happy male face recognition and happy female face recognition separately), we used the average of these associations. We assessed the publication bias using funnel plots and Egger's test.

Since there were deflections in EA assessment (continuous vs. categorical), we were forced to convert the effect sizes using well-established formulas (47). To examine the potential

impact of the above transformations on our results, we conducted a sensitivity analysis where we only included those studies without any effect size conversion.

2.5 Amygdala activation in response to facial expressions

When investigating EA's association with amygdala fMRI responses to facial emotions, we conducted separate analyses for different facial expressions because the amygdala has divergent responses to different facial expressions (48). We included both region of interest (ROI) studies and whole-brain studies. The conversion of T-statistics of whole-brain studies is described in Supplementary Methods. Some studies with nonsignificant findings of the link between EA and amygdala activity did not report any statistics that could be converted into effect sizes. We imputed the statistics of these studies (see Supplementary Methods). Three fMRI studies (21, 49, 50) provided only EA's association with the average bilateral amygdala BOLD response. We estimated the left and right amygdala responses (see Supplementary Methods). We conducted the subgroup analyses and explored the potential moderating factors, as described earlier (see section 2.1).

3 Results

3.1 Description of the included studies

The included studies are presented in Table 1. The systematic literature search resulted in 55 studies, including 29 behavioral studies, 32 fMRI studies, and 3 EEG studies (originally published between 1983 and 2019). There were 8555 participants in behavioral studies, 2771 in fMRI studies, and 197 in EEG studies. The participants' mean age was 10.0 years in behavioral studies, 20.5 years in fMRI studies, and 6.8 years in EEG studies. 50.8% of the participants were females in behavioral studies, 49.0% in fMRI studies, and 48.7% in EEG studies. In 19 studies, exposure to EA had been recent, and in 36 studies distant, respectively. Exposure to EA had occurred after the age of 3 years in 39 studies and before the age of 3 years in 11 studies. Twenty-four studies reported that subjects exposed to EA had psychiatric diagnoses. GAF was reported only in two datasets. An estimate of full-scale intelligence quotient (IQ) was reported in 20 datasets (mean IQ=109.3). The studies' quality scores ranged between 1–12 (mean=7.6) (see Supplementary Table 2). For a further description of the included studies, please see Supplementary Results.

(TABLE 1 ABOUT HERE)

3.2 Meta-analysis of the behavioral studies

Figure 2 presents the findings of recognition accuracy and reaction time in response to facial emotions. The forest plots are available in Supplementary Figures 1-8.

3.2.1. Recognition accuracy of facial emotions

Exposure to EA had a negative effect on the recognition accuracy of happy (g=-0.15) and fearful (g=-0.31) faces (Figure 2a). These effects were moderately (I^2=69.5% for happiness) or highly heterogeneous (I^2=84.8% for fear).

Further, the timing of exposure to EA related to EA's effect on recognition accuracy of happy and fearful faces as recent but not distant exposure to EA had a negative effect on recognition accuracy of happy (g=-0.27) and fearful faces (g=-0.52) (test of moderators: Q=2.2, p=0.138 for happiness; and Q=4.3, p=0.039 for fear). Recent EA's relationship on recognition accuracy of happy and fearful faces was not affected by publication bias (in Egger's test, p=0.33 for happy; p=0.83 for fearful faces) and was moderately or highly heterogenous (I^2=62.1 for happiness; I^2=86.9% for fear). Sensitivity analyses indicated that exclusion of those studies where we used any effect size conversion resulted in similar effect sizes as above: recent EA was related to the recognition accuracy of happy (g=-0.32; p=0.029) and fearful faces (g=-0.6438, p=0.0026).

Next, we used meta-regression to explore this heterogeneity (Figure 2b) and found that age at exposure to EA moderated the association of recent exposure to EA with a recognition accuracy of happy (Z=2.07, p=0.039) and fearful faces (Z=2.15, p=0.0315). That is, recent EA had a stronger negative effect on recognition accuracy of happiness and fear if exposure to EA had occurred before (vs. after) the age of three years. There were no moderating effects for participants' age, sex distribution, use of psychotropic drugs, psychiatric diagnoses, or study quality (all p-values >0.05).

Exposure to EA was not associated with the recognition accuracy of sad or angry faces (Figure 2a). Further, the timing of exposure (whether recent or distant) did not moderate these associations (p-values >0.05).

3.2.2. Reaction times to facial emotions

Exposure to EA related to shorter reaction times to angry (g=-0.29) and sad faces (g=-0.29) when compared to controls (Figure 2a). These relationships were homogenous (I^2<0.1%) and were not

affected by publication bias (in Egger's test, p=0.446 for angry faces and p=0.695 for happy faces). Sensitivity analyses showed that exclusion of those studies where we used any effect size conversion had no effect on our findings: EA was related to reaction time to angry faces (g=-0.28; p=0.0312) and sad faces (there were no studies with effect size conversion). Exposure to EA was not associated with reaction time to happy or fearful faces.

(FIGURE 2 ABOUT HERE)

3.3 Meta-analysis of the fMRI studies

Exposure to EA was related to the greater left (r=0.18) and right (r=0.25) amygdala BOLD response to sad faces (Figure 3). Exposure to EA was not related to the amygdala BOLD response to happy, fearful, angry, or angry/fearful faces. There was a minor between-study heterogeneity for the left (I^2=1.16%) and right amygdala responses (I^2=4.55%). Sensitivity analyses showed that the exclusion of a study where we estimated the left and right amygdala responses from the average bilateral amygdala response did not affect our results. When investigating responses to sad faces, we found potential publication bias for the studies on the right amygdala (p=0.046) but not the left amygdala BOLD response (p=0.96). Finally, we conducted sensitivity analyses by limiting our analysis to the studies using group comparison (exposed vs. non-exposed to EA) rather than continuous EA assessment. In this analysis, we found a positive relationship of exposure to EA with the right amygdala BOLD response (p=0.016) but not with the left amygdala (p=0.13). The forest plots of the results are available in Supplementary Figures 9-13.

(FIGURE 3 ABOUT HERE)

3.4 Meta-analysis of the EEG studies

We did not conduct any meta-analysis on the effect of EA on N170 response since there were only two eligible original studies available. In addition, there were three studies (i.e., the minimum of studies that can be analyzed in a meta-analysis) assessing EA's relationship with happy and angry facial expressions in P100. When analyzing these very few studies, we found no association of exposure to EA with P100 response to angry or sad faces. Forest plots available in Supplementary Figures 14-15. Due to the low number of original studies, we did not conduct subgroup or sensitivity analyses. Overall, no firm conclusions could be made on the effect of EA on P100 or N170 responses.

4 Discussion

4.1 Summary of the main findings

In response to angry and sad faces, EA was related to faster reaction time but a normal accuracy rate independently of the timing of exposure to EA. In response to fearful and happy faces, EA was related to a lower accuracy rate recently after exposure to EA (but not thereafter) and in a more pronounced way if recent exposure to EA had occurred before (vs. after) age of 3 years. Regarding fMRI activity in the amygdala, EA was associated with heightened bilateral amygdala reactivity to sad faces (but not other facial emotions) independently of the timing of exposure to EA. These associations were found to be independent of sex, age at measurement time, psychiatric diagnoses, exposure to psychotropic drugs, or quality of measurement of EA. Hence, although there was substantial variation in participants' age in the original studies, our findings may not be explained by age differences. No significant publication bias was obtained. As there were very few eligible original EEG studies, no conclusions could be made on the association of EA with P100 or N170 responses to facial emotions.

Overall, EA is not related to distortions in the primary facial encoding but heightened amygdala reactivity to sad faces. Most evident distortions across different facial emotions were obtained in behavioral reactivity to facial emotions (i.e., explicit recognition of facial emotions). Age at exposure to EA and time since EA appear to play essential roles in EA's effect on recognition of facial emotions.

4.2 Behavioral and neural alterations related to early adversity

Since EA was related to normal accuracy rates but shorter reaction times in response to angry faces, exposure to EA appears to be related to rather sophisticated abilities to recognize angry faces. The

fast and accurate recognition of anger may have evolutionary functions. For instance, these behavioral alterations may enhance the early detection of conflict and threat (11) and enable efficient monitoring of one's environment (12). Importantly, faster recognition of anger persisted even after the cease of acute exposure to EA. This might indicate that facial perception networks' development has a sensitivity period in childhood, as suggested in previous studies (12, 13). This persisting response may protect against exposure to other EA types in the upcoming years, which is essential as EAs commonly accumulate within individuals (5, 10, 12).

Previous investigations have discussed the role of age at exposure to EA for alterations in facial emotion recognition (12). Our findings indicate that exposure to EA before (vs. after) the age of three years may result in greater inaccuracy in recognizing responses to fear and happiness in individuals with recent exposure to EA. During the first years of life, children are particularly vulnerable to exposure to EA. Firstly, children younger than three years commonly have a self-focused attribution style and are prone to misperceive causal relationships (37, 40). For example, they may blame themselves for their parents' hostile behavior or suppose that sudden life events result from their behavior (37, 40). Secondly, very young children do not have sophisticated abilities in symbolic play or verbal processing of life events, which reduces possibilities for adaptive coping with traumatic events (39, 40). Thirdly, the first years are crucial for attachment development that may become disturbed by parental neglect or abuse (37, 40). Finally, very young children cannot separate between temporary separations and death, causing challenges to cope with separation from a close other (37). Nevertheless, it is necessary to consider that specific types of EAs (e.g. witnessing domestic violence) may negatively influence a child's development independently of age at exposure (51).

There have been inconclusive views on whether distortions in facial expression recognition are stable or normalize over age or whether there is a delay in EA's effect on facial emotion recognition (10, 30). Our findings showed that normalization over age occurs: behavioral

alterations in responses to fear and happiness may not be evident after acute EA exposure. This may be explained by the maturation and plasticity-related "catch-up" of the brain (52) that may be especially evident in the first years after acute exposure to EA (53).

It is widely known that EA is related to a wide variety of psychiatric disorders (1, 7). A debated and unsolved question has been whether psychiatric diagnoses are causes or consequences of altered recognition of facial emotions or whether facial processing alterations are the substrates of psychiatric diagnoses (13, 54). Our results showed that distortions in facial emotion recognition due to EA's could result independently of psychiatric diagnoses. However, the link between EA and psychiatric disorders appears to be mediated by a variety of factors. Previous studies have elucidated the role of emotion regulatory strategies, cognitive patterns (e.g. attention-related processes), alterations in serotonergic systems, sleep disturbances, immune system abnormalities, or epigenetic effects that could drive, in part, the link between EA and psychiatric disorders (55, 56). Our study adds to the literature by underlying the role of EA-related aberrant emotion processing, which might also be a potential precursor of psychiatric disorder, given that many psychiatric disorders are related to dysfunctions in emotion recognition from faces (57, 58).

EA has been suggested to relate to elevated amygdala responses to threatening emotions (11-13). Our meta-analysis, however, showed that EA relates to heightened bilateral amygdala activity to sad faces. There is evidence that amygdala responses to sad stimuli are higher without cognitive reappraisal and involvement of the dorsolateral prefrontal cortex (59). In addition, individuals with complicated or recent grief have elevated amygdala reactivity to sadness (60) and stronger connections between the amygdala and regions involved in autobiographic memory (61). Thus, EA-related amygdala responses to sad faces may be related to impaired emotion-regulation functioning or personal grief processes. Finally, it is necessary to consider that although the amygdala exhibits activity to different facial emotions (62), the responses may be generally weaker to sadness than fear (48).

In addition, EA was related to normal accuracy rates but shorter reaction times in response to sad faces, indicating that EA appears to be related to rather sophisticated abilities to recognize sad faces. Importantly, faster recognition of sadness persisted even after the cease of acute exposure to EA. From an evolutionary viewpoint, sadness promotes recognition of what has been lost, searching for compensatory factors, and preventing further losses (63). Additionally, sadness may include experiences of unfairness or protest that result in a high level of arousal (64). Finally, individuals exposed to EA may experience sadness as a forbidden emotion that results in elevated reactivity of the amygdala to sad faces. This is because individuals with EA are especially vigilant to emotions that they have been only rarely exposed to in the past (11, 12).

Finally, only very few eligible EEG studies investigate whether exposure to EA is related to P100 and N170 responses to facial emotions. Thus, a more substantial number of studies are required to draw any conclusions on whether exposure to EA is associated with the altered primary encoding of faces in the brain.

4.3 Methodological considerations

It is necessary to consider that there may exist adversity-specific influences on responses to facial emotions (11). In this meta-analysis, we did not investigate whether different types of EAs have different effects on facial emotion processing due to several reasons. Firstly, adversities are known to accumulate within individuals, and, therefore, differentiating between the effects of specific EAs might not be possible or justified (5, 10, 12). Secondly, several studies have focused on only one sort of EA, without excluding the presence of other types of EAs (65, 66). Thus, it was not possible to clearly differentiate between the effects of different EAs on a child's development (and to adjust the analyses for the effects of other EAs). Thirdly, there were no original studies to comprehensively analyze the effect of different EAs on neural and behavioral responses to different facial emotions. Lastly, different types of EAs have also been pooled in previous meta-analyses (67).

The original studies' data enabled us to investigate whether exposure to EA before vs. after the age of three years has different influences on facial emotion recognition. However, the role of age at exposure to EA could not be investigated more precisely. Further, we could not examine the role of EA duration on responses to facial emotions since the duration of EA was reported only in a few original papers. Consequently, we highly agree with the previous recommendations that age at exposure to EA and EA duration should be reported more precisely (10, 12). However, it may be challenging to isolate the specific point of exposure to EA because, in many cases, individuals are exposed to chronic or several EAs that occur during partly overlapping time periods (10).

In the past years, it has been actively debated whether basic emotions have discrete neural "fingerprints" or whether emotions should be investigated using a more dimensional approach instead. Several studies have indicated that facial expressions are categorically represented in the brain (68), different basic emotions have specific neural signatures (59, 69), and infants have differential responses to discrete emotions (70). Importantly, however, not all studies have supported the theory of discrete emotions (71). In this meta-analysis, we could investigate only responses to discrete facial emotions because most of the original studies had used facial emotion tasks measuring responses to discrete emotions. Future studies could investigate the influence of EA on facial emotion processing using other approaches than tasks measuring discrete emotions.

4.4 Conclusions

Our study suggests that EA relates to alterations in behavioral and neurophysiological processing of facial emotions that might be independent of psychiatric diagnoses. Due to the very low number of eligible EEG studies, no conclusions could be made of the effect of EA on P100 and N170 responses (i.e. the primary encoding of faces). However, we found that EA relates to higher amygdala reactivity to sadness but not to other facial emotions. Most evident EA-related distortions across facial emotions were obtained at the behavioral level, i.e., in the accuracy and reaction time when explicitly

recognizing facial emotions. Lastly, our study underlines the importance of considering age at exposure and time since EA in future studies since some of the EA-related perturbations are mediated by these factors.

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Disclosure of competing interest

The authors report no financial relationships with commercial interests.

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Table 1. Descriptive information of the included studies.

First author (year of publication)	Type of study	Sample size in total sample; in case group	Mean age (SD) in total sample	Female (%) in total sample	Psychiatric diagnoses in case group	Recent vs. distant EA	Early adversity		Emotions under investigation
							Type	Assessment method	
Aas (2017) (72)	fMRI; Behavioral	101; 48	31.3 (10.2)	44.6	Yes	Distant	Emotional, physical, and sexual abuse; physical and emotional neglect	The Childhood Trauma Questionnaire	Fear, happiness
Ardizzi (2015) (73)	Behavioral	62; 31	7.7 (1.7)	50.0	No	Recent	Living on the street	A semi-structured interview; Records of Sanitary, Educational and Charitable Institutions	Anger, fear, happiness, sadness
Ardizzi (2013) (74)	Behavioral	41; 19	15.8 (1.3)	0.0	No	Recent	Social deprivation and neglect; living on the street and in the jail	NA	Anger, fear, happiness, sadness
Baumgartner (2010) (65)	Behavioral	174; NA	6.1 (NA)	41.3	No	Recent	Victimization to bullying	Questionnaire filled by teachers	Anger, fear, happiness, sadness
Benedetti (2011) (75)	fMRI	40; NA	36.0 (9.7)	40.0	Yes	Distant	Adverse family environment (e.g. abuse, violence, aggression.)	The Risky Families Questionnaire	Fear
Bick (2017) (24)	Behavioral	80; 36	12.8 (0.6)	51.9	No	Distant	Early institutionalization	Records of Child-Protective Services	Anger, fear, happiness, sadness
Bogdan (2012) (76)	fMRI	279; NA	13.6 (1.0)	50.2	No	Recent	Emotional, physical, and sexual abuse; emotional and physical neglect	The Childhood Trauma Questionnaire	Fear
Brañas (2019) (77)	Behavioral	62; 32	31.1 (8.2)	46.8	Yes	Distant	Emotional neglect; physical, sexual, and psychological abuse	Semi-structured Interview	Anger, fear, happiness

Camras (1983) (78)	Behavioral	34; 17	5.0 (NA)	35.3	No	Recent	Physical abuse and neglect	Records of Child Abuse Preventive Services Programs	Anger, fear, happiness, sadness, surprise, disgust
Cisler (2019) (79)	fMRI	88; 29	14.7 (1.7)	100.0	Yes	Distant	Direct physical or sexual assault	The Childhood Trauma Questionnaire; the trauma assessment section of the National Survey of Adolescents	Fear
Clark (2017) (49)	fMRI	53; 31	47.5 (10.9)	39.6	No	Distant	Physical and sexual abuse, neglect, family conflict, victimization to bullying	The Early Life Stress Questionnaire	Fear
Crozier (2014) (80)	fMRI	74; 29	12.3 (2.5)	52.7	Yes	Recent	Physical, sexual, emotional abuse; physical or emotional neglect	Records of the Child Protective Services; Positive forensic investigation	Fear
Curtis (2013) (81)	EEG	45; 25	1.3 (0.1)	55.6	No	Recent	Maternal maltreatment	Records of the Child Protective Service and Preventive Services	Anger, happiness
Curtis (2011) (18)	EEG	71; 46	3.5 (0.2)	45.1	No	Distant	Maternal maltreatment (physical neglect, physical or sexual abuse)	Records of the Child Protective Service and Preventive Services	Anger, happiness
Dannlowski (2012) (82)	fMRI	145; NA	33.8 (10.4)	48.3	No	Distant	Emotional maltreatment	The Childhood Trauma Questionnaire	Fear
Dannlowski (2013) (83)	fMRI	150; NA	34.5 (10.6)	47.3	No	Distant	Emotional maltreatment	The Childhood Trauma Questionnaire	Happiness, sadness
De Bellis (2012) (84)	fMRI	16; 5	13.6 (3.2)	50.0	Yes	Recent	Physical abuse and neglect	Reports of the Child Protective Services	Sadness
Demers (2018) (85)	fMRI	80; 41	30.1 (3.5)	48.8	No	Distant	Emotional maltreatment, physical neglect,	Records of Department of Human Services; The	Fear

							physical abuse or sexual abuse	Maternal Maltreatment Classification Interview	
Dunn (2018) (25)	Behavioral	6506; NA	8.0 (NA)	50.5	No	Distant	Adverse family environment (e.g. physical, sexual, or emotional abuse; parent legal problems)	Questionnaires filled by mothers	Anger, fear, happiness, sadness
English (2018) (86)	Behavioral	126; NA	19.0 (NA)	100.0	No	Distant	Emotional maltreatment	The Childhood Trauma Questionnaire	Anger, fear
Fonzo (2013) (87)	fMRI; Behavioral	33; 16	39.3 (8.5)	100.0	Yes	Distant	Emotional, physical, or sexual abuse; emotional or physical neglect	The Childhood Trauma Questionnaire	Anger, fear, happiness
Ganzel (2013) (88)	fMRI	14; NA	13.1 (2.2)	28.6	No	Distant	Traumatic life events (e.g. interpersonal violence, accidents, natural disaster, violence)	The PTSD section of The Composite International Diagnostic Interview (CIDI)	Fear
Gard (2017) (89)	fMRI	310; NA	20.0 (NA)	0.0	No	Distant	Adverse family environment (e.g. harsh parenting, neighborhood deprivation)	Observation; interviews of parents; questionnaires presented to parents); the US Census data	Anger, fear, surprise
Garrett (2012) (90)	Behavioral	46; 23	14.4 (1.9)	54.3	Yes	Recent	Interpersonal trauma (sexual or physical abuse; witnessing violence)	Records of Social Service Departments and Mental Health Clinics	Anger, fear, happiness, sadness
Gee (2013) (91)	fMRI	92; 40	11.6 (3.1)	56.1	No	Distant	Early institutionalization	Records of Child-Protective Services	Fear, happiness
Grant (2011) (92)	fMRI	26; 10	34.3 (10.0)	53.8	Yes	Distant	Emotional maltreatment	The Childhood Trauma Questionnaire	Sadness
Hart (2018) (26)	fMRI; Behavioral	47; 20	17.5 (2.0)	23.4	Yes	Distant	Physical, sexual, or emotional abuse; emotional or physical neglect	The Childhood Trauma Questionnaire; The Childhood Experience of Care and Abuse	Anger, fear, happiness, sadness

								Interview; Records of Social Services	
Herringa (2013) (22)	fMRI	28; NA	26.6 (2.6)	0.0	Yes	Distant	Emotional, physical, or sexual abuse; physical or emotional neglect	The Childhood Trauma Questionnaire	Anger, happiness
Holz (2017) (93)	fMRI	181; NA	25.0 (NA)	59.1	No	Distant	Adverse family environment (e.g. parental delinquency or marital discord)	Standardized interview of parents	Fear
Keding (2016) (23)	fMRI; behavioral	53; 25	14.2 (3.1)	58.5	Yes	Distant	Pediatric PTSD	The Kiddie Schedule for Affective Disorders and Schizophrenia; The UCLA PTSD Reaction Index	Anger, happiness
Lee (2015) (94)	fMRI	45; NA	16.1 (0.5)	0.0	No	Recent	Verbal abuse	Verbal Abuse Questionnaire	Happiness, sadness, contempt
Leist (2009) (95)	Behavioral	23; NA	16.6 (0.6)	26.1	Yes	Recent	Emotional maltreatment, neglect, physical abuse	The Maltreatment Classification System	Anger, fear, sadness, disgust
Lieslehto (2017) (96)	fMRI; Behavioral	104; NA	22.8 (0.8)	57.0	No	Distant	Emotional, physical, or sexual abuse; emotional or physical neglect	The Trauma and Distress Scale	Fear, happiness
Maheu (2010) (97)	fMRI; Behavioral	30; 11	13.5 (2.5)	73.3	Yes	Distant	Caregiver deprivation, emotional neglect	Records of Social Services; a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children	Anger, fear, happiness
Marusak (2019) (66)	Behavioral	34; 17	9.0 (1.4)	44.1	Yes	Distant	Pediatric cancer	Medical Records	Anger, happiness
Masten (2008) (27)	Behavioral	46; 29	11.6 (1.7)	54.3	Yes	Recent	Emotional or physical neglect; emotional,	Records of Child-Protective Services	Fear, happiness

							physical, or sexual abuse; violence		
McCrory (2011) (98)	fMRI	43; 20	12.3 (1.3)	41.9	No	Recent	Family violence (exposure to physical abuse and/or intimate-partner violence)	Records of the Social Services; Standardized Clinical Interview of the Parents	Anger, sadness
Neukel (2019) (28)	fMRI; Behavioral	53; 27 (fMRI) / 46; 26 (beh)	39.4 (6.1)	100.0	No	Distant	Physical and sexual abuse	The Childhood Experience of Care and Abuse Interview	Happiness, sadness
Nicol (2015) (99)	fMRI	20; NA	35.8 (8.6)	85.0	Yes	Distant	Emotional, physical, and sexual abuse; emotional and physical neglect	The Childhood Trauma Questionnaire	Fear
Peters (2019) (100)	fMRI	132; 50	25.6 (8.9)	68.8	Yes	Distant	Emotional, physical, and sexual abuse; emotional and physical neglect	The Childhood Trauma Questionnaire	Anger, fear, happiness, sadness
Pollak (2001) (29)	Behavioral	42; 28	8.7 (1.6)	31.0	No	Recent	Physical abuse and neglect	Records of Child Protective Services; Clinical and Medical Records	Anger, fear, happiness
Pollak (2000) (101)	Behavioral	48; 33	4.4 (0.6)	40.0	No	Recent	Physical abuse and neglect	Records of the Child Protective Services; Clinical and Medical records	Anger, fear, happiness, disgust
Schermerhorn (2019) (102)	Behavioral	99; NA	10.5 (0.9)	44.6	No	Recent	Interparental conflict	The Children's Perceptions of Interparental Conflict Scale	Anger, happiness
Scrimin (2009) (103)	Behavioral	203; 101	11.9 (1.2)	42.4	No	Recent	Predisaster traumatic events and terrorism-related exposure	Assessment of trained certified psychologists; school teachers and school psychologist	Anger, fear, happiness, sadness
Shenk (2013) (104)	Behavioral	106; 50	17.0 (1.2)	100.0	No	NA	Sexual or physical abuse; physical neglect	Child Protective Services (CPS) agency investigation	Anger, fear, happiness, sadness

Suzuki (2014) (105)	fMRI	115; NA	9.9 (1.3)	51.3	Yes	Recent	Traumatic life events (e.g. physical and sexual abuse, accidents, natural disaster)	The Preschool Age Psychiatric Assessment; The Child and Adolescent Psychiatric Assessment	Fear, happiness, sadness
Suzuki[1] (2015) (106)	Behavioral	40; 18	45.6 (12.9) / 51.5 (11.4)	57.1 / 72.2	Yes/no (two samples)	Distant	Emotional, physical, or sexual abuse; emotional or physical neglect	The Childhood Trauma Questionnaire	Anger, fear, happiness, sadness
Taylor (2006) (107)	fMRI	30; 15	27.0 (NA)	60.0	No	Distant	Adverse family environment (e.g. physical or verbal abuse, violence)	The Risky Families Questionnaire	Fear
Tottenham (2011) (108)	fMRI; Behavioral	44; 22	10.1 (2.4)	65.9	Yes	Distant	Early institutionalization	Local International Adoption Consultation Services	Fear
van den Berg (2019) (50)	fMRI	171; NA	35.1 (16.6)	57.3	Yes	Distant	Abuse or neglect by parents	Adapted versions of the Conflict Tactics Scales; the Childhood Trauma Questionnaire	Anger, happiness, fear
van Harmelen (2013) (21)	fMRI	135; 75	36.4 (2.1)	65.9	Yes	Distant	Emotional neglect; emotional, physical, or sexual abuse	The NEMESIS Trauma Interview	Anger, fear, happiness, sadness
Veague (2014) (109)	Behavioral	44; NA	26.8 (6.2)	100.0	Yes	Distant	Physical, sexual, or emotional abuse	The Childhood Maltreatment Interview Schedule	Anger, fear, happiness
Wagner (1999) (110)	Behavioral	41; 21	33.5 (7.4)	100.0	No	Distant	Physical or sexual abuse	The Childhood Maltreatment Interview Schedule	Anger, fear, happiness, sadness, contempt, disgust, surprise
Williams (2009) (111)	fMRI	39; 14	30.5 (11.3)	40.0	No	Distant	Traumatic life events (e.g. abuse, neglect,	The Early Life Stress Questionnaire	Fear

							illness/death, natural disasters)		
Woods (2009) (112)	Behavioral	200; 42	9.9 (0.5)	NA	No	Recent	Victimization to bullying	Self-report Questionnaire	Anger, fear, happiness, sadness
Young (2017) (20)	EEG	81; 44	12.7 (0.6)	48.1	No	Distant	Early institutionalization	Records of Child-Protective Services	Anger, fear, happiness

NA=Information not available in the original publication. [1] This study included two datasets.

Figure 1. The article selection process was modified from the PRISMA. EA=Early adversity.

Figure 2. (a) The effect of exposure to EA on recognition accuracy and reaction time in response to facial emotions (27, 17, 25, and 25 datasets for happiness, sadness, anger, and fearfulness, respectively). Asterisks refer to statistical significance ($p<0.05$). The effect of recent exposure to EA on reaction time to sad faces was not analyzed due to the low number of original studies. **(b)** The effect of age at exposure to EA (before vs. after the age of three years) on recognition accuracy of happy and fearful faces in studies exploring recent EA. The size of the circle reflects the sample size of the original study. Abbreviations: EA=early adversity; SDM=standardized mean difference; CI=confidence interval.

Figure 3. The effect of exposure to EA on the amygdala BOLD response to facial emotions (15, 10, 10, 10, and 16 datasets for happiness, sadness, anger, and fearfulness, respectively). Asterisks represent statistical significance ($p<0.05$). Abbreviations: EA=early adversity; CI=confidence interval. Subgroup analyses with fewer than three studies were not conducted.