Neural Response to Social Rejection in Children With Early Separation Experiences

Vanessa B. Puetz, MSc, Nils Kohn, PhD, Brigitte Dahmen, MSc, Mikhail Zvyagintsev, MD, PhD, André Schüppen, Dipl.-Inform., Robert T. Schultz, PhD, Christine M. Heim, PhD, Gereon R. Fink, MD, Beate Herpertz-Dahlmann, MD, Kerstin Konrad, PhD

Objective: Nonhuman and human studies have documented the adverse effects of early life stress (ELS) on emotion regulation and underlying neural circuitry. Less is known about how these experiences shape social processes and neural circuitry. In this study, we thus investigated how ELS affects children's perception of, and neural response to, negative social experiences in a social exclusion paradigm (Cyberball). **Method:** Twenty-five foster or adopted children with ELS (age 10.6 ± 1.8 years, 13 male and 12 female) and 26 matched nonseparated controls (age 10.38 ± 1.7 years, 12 male and 14 female) took part in a Cyberball paradigm during functional magnetic resonance imaging (fMRI). **Results:** During peer rejection, children with ELS reported significantly more feelings of exclusion and frustration than nonseparated controls. On the neural level, children with ELS showed reduced activation in the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (dlPFC), and reduced connectivity between dlPFC-dACC, areas previously implicated in affect regulation. Conversely, children with ELS showed increased neural activation in brain regions involved in memory, arousal, and threat-related processing (middle temporal gyrus, thalamus, ventral tegmental area) relative to controls during social exclusion. The number of separation experiences before entering the permanent family predicted reductions in fronto-cingulate recruitment. The relationship between early separations and self-reported exclusion was mediated by dlPFC activity. **Conclusion:** The findings suggest that ELS leads to alterations in neural circuitry implicated in the regulation of socioemotional processes. This neural signature may underlie foster children's differential reactivity to rejection in everyday life and could increase risk for developing affective disorders. J. Am. Acad. Child Adolesc. Psychiatry, 2014; 53(12):1328–1337. **Key Words:** early life stress, social exclusion, fMRI, adoption, PPI

Early life stress (ELS), such as early caregiver separation, constitutes a major threat to children's socio-affective and neural development.[1-3] Such adversity can increase the risk of developing psychiatric disorders over the course of the lifetime, with disorders emerging earlier and with greater severity, increased comorbidity, and poorer responses to treatment.[4] However, there is still limited understanding as to how early life adversity might heighten developmental vulnerability to psychiatric disorders.

Brain imaging studies have documented long-lasting changes in brain structures and functions associated with memory,[5] executive control,[6,7] reward,[8] sensory,[9] and affective processing[10-15] in individuals with a history of early life adversity. Negative experiences related to caregiver separation, such as frequent change of caregivers, are known to potentiate negative outcomes on the behavioral and neural level and can persist even after years in a stable environment.[10,16] These data suggest that ELS can lead to altered maturation of prefrontal brain regions involved in the control of stress and emotion regulation. This might mediate an increased reactivity to stressful situations and altered social perception in everyday social interactions throughout development. However, positive environmental changes potentially attenuate psychosocial and physiological dysfunction,[16-18] suggesting that

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the negative neural and behavioral outcomes associated with ELS may be malleable to intervention.

One of the most distressing social experiences is the feeling of being rejected by loved ones[19] or even strangers.[20,21] This feeling affects adults, adolescents, and children,[22-24] and youths who experience early adversity are at highest risk for being rejected by their peers.[25] Indeed, children who have experienced early adversity are less popular and more frequently rejected by their peers from an early school age through to late adolescence.[25] Interestingly, the effects of ELS on children's risk for victimization and rejection might be mediated by deficits in emotion regulation.[26] In addition, negative self-referential processing and cognitive biases (interpretive or attentional) have been implicated in maladaptive responses to peer rejection in depressed youth.[27]

Factors such as maternal warmth, parental support, and attachment quality[28] strengthen emotion-regulation skills and may serve as protective factors against social rejection and its negative consequences. Children with ELS who have experienced the most fundamental rejection experience early in life often grow up devoid of such protective factors, which might affect the neural substrates underlying the ability to regulate the distress of exclusion, namely, the prefrontal cortex (PFC) and the dorsal anterior cingulate cortex (dACC). In line with this suggestion, recent studies have provided compelling evidence for this claim by showing marked alterations in the synaptic organization and function of fronto-cingulate circuits in maternally deprived animals and children with ELS.[15,29,30] Importantly, dysfunction of fronto-cingulate circuitries in emotion regulation have been implicated as a vulnerability factor in the development of affective disorders such as depression and anxiety,[31-33] all of which are highly prevalent in children with ELS.[34,35] However, no study to date has investigated the neural underpinnings of social rejection in children who have experienced ELS through permanent separation from their biological caregivers. Accordingly, in the present study, we aimed to investigate the neural mechanisms underlying the experience and processing of social rejection in children with ELS using an established social rejection paradigm, Cyberball,[21] during functional magnetic resonance imaging (fMRI). This paradigm reliably activates a cerebral network consisting of the anterior cingulate cortex (ACC), which is involved in emotion regulation (ventral ACC) and conflict detection (dorsal ACC)[36]; the insula, which is involved in the representation of visceral states and safety signals[37]; and the medial and lateral prefrontal cortices, which are involved in the regulation of stress and negative emotions.[38]

We investigated whether children with an ELS experience would show altered perception of social exclusion; whether children with ELS would exhibit reduced recruitment of fronto-cingulate circuitries typically involved in the registration and regulation of exclusion-related distress; and whether neural response patterns would potentially mediate differential perception of social exclusion. Finally, we investigated a potential association between children's neural response to rejection by risk and protective factors.

METHOD

Participants

Twenty-five children who were permanently separated from their biological parents and subsequently adopted or placed into German foster families that provided permanent long-term care participated in this study. The children with ELS were separated before their third year of life (mean age at separation: 1.59 years, SD $\pm$ 1.05 years; mean time spent in permanent foster/adoption family: 9.14 years, SD $\pm$ 2.27 years). Detailed information on the children's lives before separation was collected via a semi-structured biographical interview[39] conducted with the children's current caregivers and an inspection of all available medical records. Information about the reason for separation was obtained through caregiver reports based on the youth welfare offices' documentation. More than half of the children in the ELS sample (n = 16; 64%) had experienced emotional and/or physical neglect.

Twenty-six controls who grew up with their biological parents and were comparable with respect to age ($t[49] = -0.45$, $p = .66$), sex ($\chi^2[1] = 0.07$, $p = .78$), IQ ($t[49] = 1.03$, $p = .31$]), handedness ($LR[1] = 0.22$, $p = .70$), parental socioeconomic status ($U[49] = 238.5$, $z = -1.32$, $p = .18$), and had never been in contact with social services were recruited to participate in the study. The number of close friends, as evidenced by parental ratings, did not differ between the groups ($\chi^2[2] = 4.39$, $p = .11$), indicating that both groups were comparable in terms of current social integration. In the group of children with ELS, number of separation experiences varied between 1 and 4 before permanent placement and was not associated with type of maltreatment ($r_s = -0.14$, $p = .24$). Table 1[40-43] summarizes demographic data for ELS and control children, and Table 2 summarizes biographical and clinical information for children with ELS.