

# The Role of the Social Environment on Adaptive Neuroplasticity in Early Development

Lead Guest Editor: Andrea Guzzetta

Guest Editors: Pier F. Ferrari, Lynne Murray, and Rosario Montirosso





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


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## Editorial

# The Role of the Social Environment on Adaptive Neuroplasticity in Early Development

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Adaptive neuroplasticity is the ability of the brain to reorganize neural connectivity in response to experience. It is potentially more efficient during early development, allowing children to be more fast-paced, for example, in learning a new language or in achieving new, complex, motor skills required, for example, for proficient playing of musical instruments. At the same time, deprivation or perturbation of experiences during early life can impact the development of functions relating to the nature of the deprivation (e.g., see [1]).

In this very critical phase for infant neurodevelopment, social interactions, such as in the caregiver-infant dyad, seem to play a particularly important role in modulating infant experiences. The objective of this special issue was, therefore, to examine the scientific evidence for cerebral plasticity in relation to social interactions with the environment during early development, focusing on risk factors for atypical neurodevelopment and on the role of specific sensory, motor, and social experiences.

The topics covered by this special issue were the objectives of a very stimulating workshop held in Erice, Sicily, and hosted at the Ettore Majorana Foundation and Centre for Scientific Culture in October 2017. This special issue represents the fruitful results of the scientific exchanges and stimulating ideas circulating among scholars and participants during the meeting.

The fundamental role of early social experience was addressed by C. A. Nelson III et al. by reviewing current

knowledge concerning the effects of psychosocial deprivation in rodents, nonhuman primates, and institutionalized infants. More specifically, the authors summarized the results of two randomized controlled trials from institutionalized children in Romania who were followed up after adoption out of the institutional setting into families. They discussed how deprivation can have a range of short- and long-term psychodevelopmental and behavioral consequences, with clear differences in brain structure, and changes in cellular and molecular level markers according to the timing and duration of institutional deprivation.

Even when interactions between the caregiver and infant are possible from the start of the postnatal period, there are nevertheless several factors that can interfere and negatively affect newborn development. One of them is the presence of perinatal adverse events, putting the infant at risk of neurodevelopmental disorders. F. Festante et al. reviewed the studies reporting on the quality of early parent-infant interactions in dyads where the infant was at high risk of neuromotor disorders, such as cerebral palsy, showing that both infant and maternal behaviors within early interactions are markedly compromised. Abnormalities in infant behavior tended to persist beyond the first semester of life, with infants being less engaged in the interaction, while early intrusive maternal behaviors later evolved into more controlling and attention-directing behaviors. The role of mother-infant interactions in populations at risk was indirectly confirmed by the study of G. Sgandurra et al. who showed

how an early intervention that involves parents, as in the Car-Tot model, seems to be effective in reducing maternal distress, as compared to standard care for preterm infants. This is consistent with the findings of C. Vandormael et al. who reviewed current knowledge on the effects of preterm birth on the development of language skills, showing how environmental and neurophysiological factors can influence preterm neuroplasticity with potential short- and long-term effects on language development.

The ability of the infant to express social signals seems particularly relevant in the development of the dyadic interaction. By studying infants with cleft lip, in comparison to typical infants, L. Murray et al. showed, through microanalytic video analysis, a lower rate of maternal mirroring of infant expressions by mothers of infants with cleft lip. Interestingly, this was associated with reduced maternal gaze to the infant's mouth, suggesting a high sensitivity of parent-infant interactions to specific variations in interactants' appearance and behavior. Some of the consequences of infant impaired ability to express emotions due to facial palsy were explored by Y. Nicolini et al. who tested the hypothesis that, in children with Moebius syndrome, the impaired motor expression of a given emotion is directly linked to the autonomic responses associated with that same emotion. By means of functional infrared thermal imaging, they were able to demonstrate how the impairment of facial movement attenuates the intensity of emotional experience, probably due to the weakening of action-perception cortical mechanisms and the diminished activation of autonomic responses typically associated with the facial expression of emotions. The role of empathy during development is confirmed by the study from A. Milone et al. who explored the relationship between empathy and callous-unemotional traits in children with a diagnosis of conduct disorders, showing a significant correlation of callous-unemotional traits with both cognitive and emotional dimensions of empathy.

As one of the objectives of this special issue was to expand our understanding of the role of specific sensory experiences on early neuroplasticity, we welcomed contributions exploring the mechanisms of sensory processing or the effects of early sensory deprivation. In a review paper, O. Chorna et al. examined the recent literature on fetal and neonatal processing of a complex, but specific, sensory stimulation, that is, music. In particular, the authors examined the behavioral, neurophysiological, and neuroimaging literature describing fetal and neonatal music perception and processing, concluding with recommendations for music stimulation within the framework of early socioemotional development. New evidence of the effects of early auditory deprivation and visual deprivation on neural processing and function was explored in two separate studies. J. Andin et al. reported fMRI evidence of different patterns of activation of parietal numerical processing regions in adult deaf singers as compared to typically hearing adult controls, shedding light on the possible underpinnings of the poorer numerical abilities reported in congenitally deaf individuals. Z. Zhou et al. reported effects of early visual deprivation on the microstructure and functional brain connectivity in early blind adolescents compared to normal-sighted controls, thus

providing new insights into the mechanisms underlying the neural reorganization of the brain in adolescents with early visual deprivation.

Expanding our knowledge of the role of the social environment on adaptive neuroplasticity in early development in a multilayer perspective (i.e., from biomarkers to behavior) can support collaborations between basic researchers and clinical contexts. Indeed, improved understanding of some of the mechanisms involved provides potential directions for promoting the translation of the principles of neuroplasticity into implementation for more effective early interventions, in order to reduce the impact of neurodevelopmental disability across a range of clinical conditions.

## Conflicts of Interest

I confirm that there is no conflict of interest regarding the publication of this article.

A. Guzzetta  
L. Murray  
R. Montirosso  
P. F. Ferrari

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- [1] T. L. Lewis and D. Maurer, "Multiple sensitive periods in human visual development: evidence from visually deprived children," *Developmental Psychobiology*, vol. 46, no. 3, pp. 163–183, 2005.

## Review Article

# Parent-Infant Interaction during the First Year of Life in Infants at High Risk for Cerebral Palsy: A Systematic Review of the Literature

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**Introduction.** Perinatal adverse events put neonates at high risk for short and long-term disabilities, including cerebral palsy (CP). The most recent guidelines about early intervention in infants with brain damage have emphasized the importance of family involvement from the very first phases of development. Early parent-infant interactions are pivotal in promoting infant cognitive and social developmental trajectories. However, little is known about the extent to which severe adverse perinatal events can affect the quality of early parent-infant interactions. **Patients and Methods.** We systematically searched five databases (PubMed, PsycINFO, EMBASE, CINAHL, and Cochrane Library) for the publications assessing parent-infant interactions in infants at high neurological risk within 1 year of age. Articles were selected if they involved direct comparison between high-risk populations and healthy controls or low-risk populations, and if quantitative or semiquantitative tools were used to assess the parent-infant interaction. Measures of parent-infant interaction included infant interactive behaviors, parental interactive behaviors, and dyadic interactive patterns. **Results.** The search yielded 18 publications that met the inclusion criteria. The articles represent a high level of heterogeneity in terms of infant neurological risk, infant age, and tools assessing interactive behaviors. Both infant and maternal behaviors within the investigated interactive exchanges were reported to be compromised, leading to subsequent overall impairment of the dyadic patterns. **Conclusion.** While the studies reviewed here provide general and important information, the review did not yield a clear picture of early dyadic interactions in high-risk infant populations. Further observational studies are warranted in order to provide a more accurate knowledge of the early dyadic exchanges between infants at high neurological risk and their parents, as they might provide a critical opportunity for early family centered rehabilitative interventions.

## 1. Introduction

The role of parent-infant interaction during early development has been studied extensively in the past decades. Newborn's brain is known to be prone to interactive exchanges at birth or even before [1, 2]. Neonatal imitative processes, occurring from the very first hours of life [2], represent the first signs of reciprocity between parents and infants that, within the first months of life, evolve towards actual *protoconversations*, characterized by reciprocal multimodal exchanges and rhythmic vocal, facial, and gesture imitations [3–5]. Murray and colleagues have recently suggested the existence of a functional

architecture of mother-infant engagements, active from the very first weeks of life and apt to support the development of infant intersubjective skills [6]. Authors reported that the occurrence of mirroring or marking maternal responses to infant social expressions predicts the increase of such infant behaviors over time. More importantly, they stressed the importance of contingency more than frequency of maternal responses, thus suggesting that infants are able to capitalize on relatively limited exposure to specific parental behaviors, already at very early developmental stages.

Primary dyadic interactions support infants' cognitive, motor, and social skills maturation [7, 8]. Studies in typically

developing infants have widely demonstrated that the quality of early dyadic interactions can strongly influence later infants' developmental outcomes [9–12]. For instance, Feldman and Greenbaum [10] reported that maternal affective attunement and dyadic synchrony within the interaction of 3-month-old infants and their mothers were predictive of infants' quality of play, verbal IQ, and regulation capacity at 2 years of age. The contingency within interactive exchanges at 3 months of age has been reported to be a precursor of infants' attachment style at 1 year [13], while maternal sensitivity to infant distress has been described as a predictor of a secure attachment [14]. Accordingly, studies focusing on clinical populations showed that the occurrence of either parents' adverse conditions (e.g., maternal depression, anxiety or early traumatic experiences, and poor socioeconomic family) or infant pathological conditions (e.g., preterm birth, autism, and cleft lip palate) can be associated with poor infant affective, social, and cognitive outcomes, likely due, at least partly, to a disruption of the quality of early dyadic interactions [7, 15–17].

So far, little attention has been given to the quality of early dyadic interaction in infants at high risk of neuromotor disabilities, and more specifically of cerebral palsy (CP), as studies on term infants with brain damage are very scarce, while the majority of the studies on preterm infants have focused on low-risk prematurity [18, 19].

CP is the most common physical disability in childhood [20]. Despite the progressive improvements in perinatal and neonatal care, extreme prematurity as well as perinatal insults are still associated with major neonatal morbidities with long-term sequelae such as neurodevelopmental delay, neurosensory disorders, and cerebral palsy [21–25]. More specifically, in populations of very or extremely premature infants or of full-term infants with a history of perinatal asphyxia, the prevalence rate of CP is still consistently above 10% in high-income countries [26–30]. Scientific evidence is rapidly growing in support of the importance of an early diagnosis of CP for the improvement of long-term outcomes [31]. This is essential for a prompt referral to early intervention programs aimed at promoting and maximizing neuroplasticity, minimizing further medical complications [31], and providing emotional support for parents [32–34].

The most recent guidelines about early intervention in infants with brain damage have greatly emphasized the importance of family involvement from the very first phases of development [35]. Indeed, review studies in infants at very high risk of CP indicate that early interventions focusing on parents' empowerment and supporting early parent–infant relationships may have a greater impact on later cognitive and neuromotor outcomes compared to those with an exclusive focus on infant functional impairment [36, 37]. A deep knowledge of general and detailed aspects of parent–infant interaction in populations at high risk of CP would be therefore essential to inform new strategies for early clinical support in both infants and parents. Unfortunately very little is known about how the parent–infant dyad is affected by the occurrence of severe perinatal events. In order to contribute to bridging this knowledge gap, we systematically reviewed the existing literature on early dyadic interactions between parents and infants at high risk of neurological impairments.

The main objective of this paper was to review the current knowledge on the influence of severe adverse perinatal events on the quality of early parent–infant interaction, focusing on infant behavior, parental behavior, and dyadic interactive patterns. We specifically focused on papers evaluating dyadic interactions occurring within the first year of life, as the optimal time window of the emergence and early development of infant and parental interactive patterns.

## 2. Methods

**2.1. Literature Search and Selection of Studies.** A systematic literature search was performed in February 2018, through the following electronic databases: PubMed/MEDLINE, PsycINFO, EMBASE (OVID), CINAHL, and Cochrane Library. No publication date limits were applied to the searches.

The following search strategy, including both MeSH headings and keywords, was used: (Parent-child relations (Mesh) OR Mother-Child OR Father-Child OR Parent-Child OR Mother-Infant OR Father-infant OR Parent-infant) AND (Interaction\* OR Relation\* OR Attachment\* OR Bond\* OR Intersubjectiv\* OR Transact\*) AND (Brain injuries (Mesh) OR Brain damage\* OR Brain Injury\* OR Brain lesion\* OR Brain malformation OR Asphyxia OR Hypoxia OR Ischemia OR Encephalopathy OR Hypoxic Ischemic Encephalopathy OR Cerebral stroke OR Leukomalacia OR Hemorrhage OR Haemorrhage OR High-risk) AND (Infant (Mesh) OR Infant OR Newborn\* OR Neonate\* OR baby OR Preterm OR Premature).

The list of records was first checked for duplicates using EndNote (EndNote X8.2, bld 13302). Subsequently, two authors (FF and CA) independently reviewed the remaining records for suitability by title and abstract. Finally, full-text articles addressing the topic of interest were screened in order to exclude those not meeting inclusion criteria. Secondary searches involved checking of publication reference lists and manual searches of relevant journals.

Agreement for articles inclusion was reached upon discussion between authors (FF, CA, and AG).

**2.2. Inclusion Criteria.** Article selection was restricted to peer-reviewed research articles published in English and to human studies. Articles were selected if they met all of the following criteria: (1) the study involved direct comparison between at least one population of infants at high risk for neurological impairment and either healthy controls or low-risk populations, (2) mother–infant and/or father–infant and/or both parents–infant interactions were assessed, (3) quantitative or semiquantitative tools were used to assess the interaction, (4) the study included assessments within the first year of the infant's life.

High risk for neurological impairment was defined by one or more of the following conditions: gestational age (GA) at birth under 30 weeks, birth weight (BW) below 1500 g, perinatal asphyxia or hypoxic ischemic encephalopathy, cerebral stroke, periventricular leukomalacia, severe intraventricular hemorrhage (grade III or IV), or any type of documented brain damage occurring within the first month of life. Populations were defined as at high risk for



neurological impairments if at least 50% of the participants met the above criteria.

No limitations for article inclusion were applied to parent-infant interaction assessment methods, which could include feeding sessions, face-to-face interactions, and free or structured play sessions, either toy-centered or non-toy-centered. Similarly, early interaction scoring modalities including scoring scales, manuals, or checklists were included provided that a clear description of the analyzed parental and/or infant interactive dimensions (e.g., maternal intrusiveness, infant engagement, and dyadic synchrony) were reported.

**2.3. Data Extraction.** Descriptive information of all included articles was systematically extracted and gathered in an electronic database. These included authors, year, study design, sample size, inclusion and exclusion criteria for clinical and/or control samples, age of infants at the time/s of the parent-infant interaction assessment, assessment methods (e.g., place, duration), scoring modalities (e.g., behavioral annotation), and main findings relative to the early parent-infant interaction. Additional parental, neonatal, or developmental outcome measures and any other results relevant to the current report were scored and gathered, if reported. The quality of the included studies was assessed by using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Case-Control Studies [38], which was chosen based on the study design of the included articles. Two authors (OC and FF) independently evaluated the items of the tool as “yes,” “no,” “not applicable,” “cannot determine,” or “not reported.” The comprehensive evaluation of all items was then used to rate the global quality of each study as “good,” “fair,” or “poor.”

**2.4. Measures of Parent-Infant Interaction.** Measures of parent-infant interaction were grouped into three categories. (i) Infant interactive behaviors included all behaviors originated by the infant as either initiations or responses within the assessed interactions, such as activity (e.g., movements, vocalizations, or expressive language) and engagement (e.g., facial expressions or eye contact). (ii) Parental interactive behaviors included all dimensions originated by the parent as either initiations or responses within the assessed interactions, such as sensitivity, vigilance, intrusiveness, and emotional involvement (e.g., kinesthetic or proximal stimulation, smiling, vocalizations, time spent looking at infant, and proximity to infant). (iii) Dyadic interactive patterns included all behaviors of the dyad observed as a single entity within the assessed interactions, such as synchrony, reciprocity, and coregulation (e.g., timing, rhythmicity, and fluency of interactive exchanges).

### 3. Results

The flow chart in Figure 1 summarizes the whole selection process and exclusion criteria at each selection step. Database and secondary searches yielded 2910 articles. After duplicates removal, titles and abstracts of 2673 articles were

screened. Then, 82 full-text articles were scored, of which 18 met all predetermined inclusion criteria and were included in the present review. Overall, the quality of the studies was evaluated as fair or good with the exception of one paper whose quality was rated as poor. Details of the studies, including the quality rating, are summarized in Table 1.

**3.1. Level of Neurological Risk of the Study Populations.** All studies included preterm populations, while few of them involved mixed populations of preterm and full-term infants at high risk of neurological impairments. The severity of infant risk status was varied among the selected articles. In 8 articles, the high-risk population presented intraventricular hemorrhage (grades III–IV), periventricular leukomalacia, severe perinatal asphyxia, seizures, meningitis, or other severe medical conditions [39, 45, 46, 49–51, 55, 58], while in the remaining studies, the high-risk population included infants on the basis of intrauterine growth retardation (IUGR), birth weight, or prematurity with or without mild or moderate medical complications [41, 42, 53, 60, 62, 64, 65, 67, 69, 70].

Seven of the 18 studies explicitly excluded infants with severe brain lesions or perinatal asphyxia from their high-risk samples [50, 51, 60, 62, 67, 69, 70]; however, the resulting populations still met at least one of our inclusion criteria for high neurological risk (i.e., BW or GA) and were therefore retained in the current review.

**3.2. Parent-Infant Interaction Assessment Modalities.** The time duration for observation of early parent-infant interaction was also heterogeneous, varying from few minutes long video-recorded sessions (from 3 to 20 minutes) [39, 49, 51, 53, 58, 62, 64, 67, 69] to much longer (up to 120 minutes) live observations [41, 42, 46, 50]. A wide variety of parent-infant interaction coding modalities was used, including microanalytic coding systems [42, 45, 49, 58, 60, 70], rating scales [46, 53, 55, 62, 64, 65, 67, 69], and scoring checklists [39, 41, 51]. Only one study used a mixed coding system which included both microanalytic and global rating scores [50]. Assessment details are summarized in Table 2.

The timing at which parent-infant interaction assessments were performed was equally distributed over the first year of the infant life, with about half of the included studies collecting data within the first semester of life [39, 42, 51, 53, 58, 60, 62, 64, 67, 69] and half focusing on older infants, from 6 to 12-month-old infants [41, 45, 46, 49, 50, 55, 65, 70]. Most of the studies involved a cross-sectional design [39, 41, 45, 46, 53, 58, 60, 64, 67, 69, 70], while few of them implemented a longitudinal design, with data collection at multiple time points [42, 50, 51, 65]. Three studies [49, 55, 62] evaluated mother-infant interaction over a longer period of time, which was beyond the first year of life. For these studies, however, only assessments that occurred within the first year of life were considered in the present review.

Finally, all studies focused on mother-infant interaction. Feldman [64] was the only study that, in addition to the mother-infant interaction, also included father-infant and triadic early interactions. The authors found no differences between father-infant and mother-infant interactions;



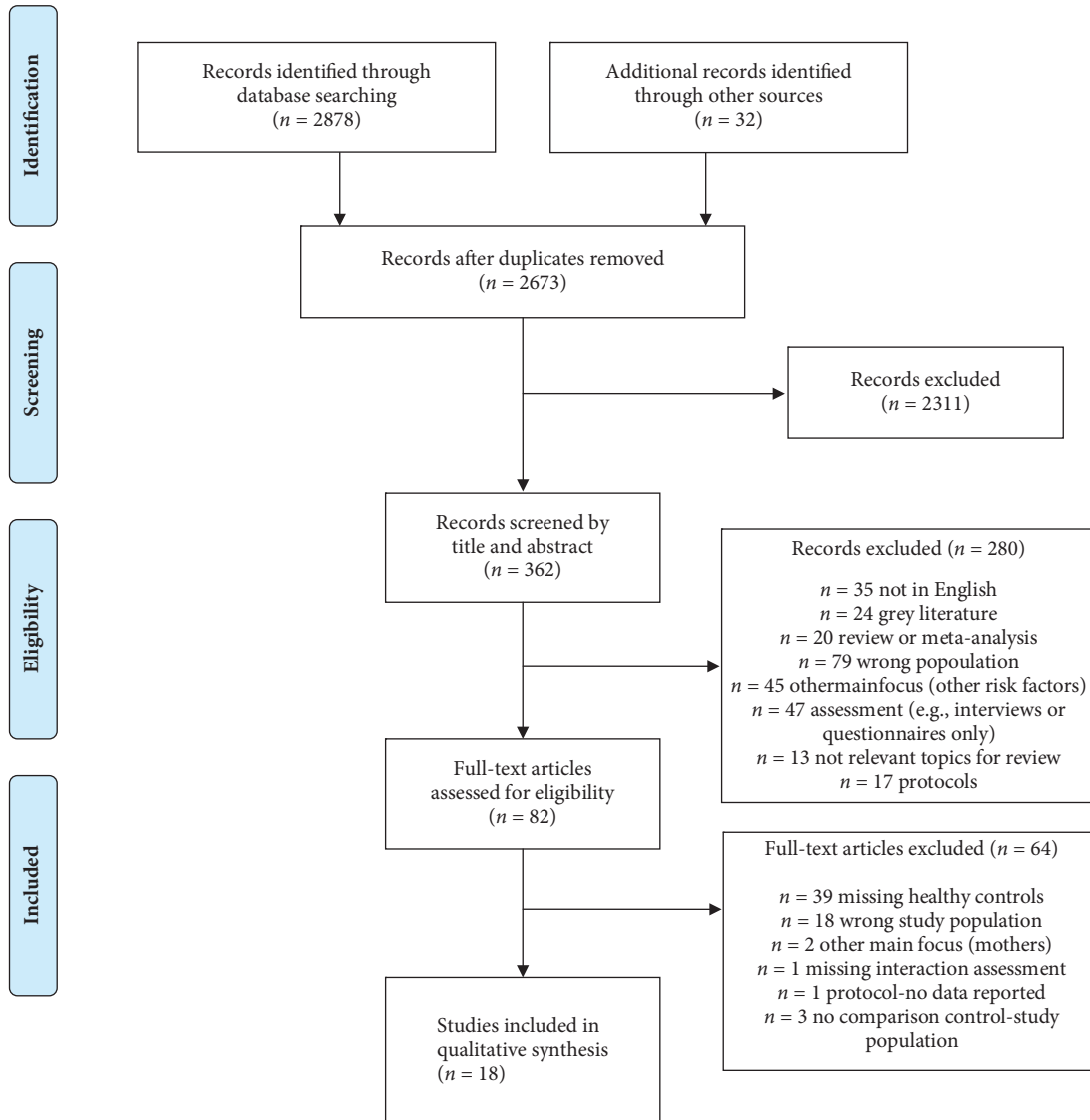


FIGURE 1: PRISMA flow chart. Flow chart of literature search and study selection.

therefore, we abstain from discussing this topic further in this review.

**3.3. Comparison of Interactive Patterns between High-Risk and Non-High-Risk Dyads prior to 6 Months.** Overall, all of the included studies described compromised dyadic interactive patterns between mothers and infants who experienced adverse perinatal events, compared to those occurring within control populations. While most of the studies focused on interactive behaviors considering mother and infant as discrete interacting units, few studies analyzed the quality of early interactive exchanges from a dyadic perspective. Due to the variety of the interaction assessments and the scoring modalities utilized within the included studies, a wide range of parental and infant dimensions were analyzed. However, a categorization of common terms used within the selected publications is included for our reporting purposes (see bold text in the following section). Therefore, below, we report the

findings in three sections, divided into groups of behaviors or behavioral dimensions.

**3.3.1. Infant Interactive Behavior.** Within the first semester of life (corrected age for prematurity), infants at high risk were generally described as less active, less engaged in the interaction, and more fretful than controls. Minde and colleagues [42] reported that preterm infants were less alert and focused, as revealed by the fact that they spent less time with their eyes open during feeding sessions at one month of age, although they became more physically active by the third month of life. Davis et al. [53] described preterm infants at risk as less responsive to their caregivers compared to typically developing infants, during feeding. Schmücker et al. [58] and Feldman [64], instead, found that high-risk preterm infants were less optimally engaged in dyadic interaction with their mothers, as they showed less facial expressions and more negative engagement cues,

TABLE 1: Characteristics of the included studies.

Study	At high-risk sample	Control sample	Exclusion criteria	Timing of assessment	Method	Main results	Study quality*
Greene et al. [39]	16 PT, with RDS (S-PT)	14 PT, healthy (H-PT)	Not defined	At 3 months (CA)	(i) Free play interaction	(i) Infant—look/gaze at mother: H-PT, H-FT > S-PT, S-FT	Good
	16 FT, with birth asphyxia (S-FT)	16 FT, healthy (H-FT)			(ii) Video recording: 15 min (iii) At the laboratory (iv) Checklist by Lewis [40]	(ii) Mother—vocal responsivity: H-PT, S-PT > H-FT, S-FT (iii) Mother—proximal and kinesthetic stimulation: S-FT > S-PT, H-FT, H-PT (iv) Mother—affection and distal stimulation: S-FT < S-PT, H-FT, H-PT <i>Other measures:</i> S-FT, S-PT lower scores in orientation cluster at NBAS	
Lasky et al. [41]	40 PT, BW <1500 g and/or requiring mechanical ventilation (PT)	25 FT, healthy (H-FT)	Not defined	At 12 months (CA)	(i) Free interaction in 5 different situations: waiting, physical exam with a nurse present, physical exam with the nurse absent, the nurse return, and blood drawing (ii) Live observation: 5, 2, 2, 2, and 4 min, respectively (iii) At the hospital (iv) Checklist by Lasky et al. [41]	(i) Mother—restrain infant, positioning near infant, looking at the infant, not smiling at infant during blood draw: H-FT > PT <i>Other measures:</i> Bayley Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI): PT < H-FT	Good
Minde et al. [42]	20 PT, BW <1500 g (PT)	20 FT, healthy (H-FT)	No physical malformation	At 1, 2, and 3 months (CA)	-Visit 1 and 2: routine feeding, visit 3: face-to-face play sequence. -Live observation, visits 1-2: duration not reported, visit 3: 10 min -At home -Scoring of infant and maternal behaviors (as in Minde et al. [43])	(i) Feeding 4 weeks: Infant—alert/focused: H-FT>PT Mother—look en face: PT>H-FT Mother—vocalize to others: PT>H-FT Mother—touch: PT<H-FT Mother—smile: PT<H-FT (ii) Feeding 8 weeks: Infant—leg movements: H-FT>PT Mother—vocalize to others: PT>H-FT Mother—vocalize to baby: PT>H-FT Mother—touch: PT<H-FT Mother—smile: PT<H-FT (iii) Play 12 weeks: Infant—head/mouth movements: PT>H-FT Mother—look: PT>H-FT Mother—vocalize to baby: PT>H-FT Mother—smile: PT<H-FT <i>Other measure:</i> “Sicker infants” defined according to a morbidity scale by Minde et al. [44] display more behavioral disorganization during feeding, cry more, and have their eyes open.	Good

TABLE 1: Continued.

Study	At high-risk sample	Control sample	Exclusion criteria	Timing of assessment	Method	Main results	Study quality*
Landry et al. [45]	20 high-risk (HR) PT with IVH III-IV, RDS, or BPD (HR-PT)	20 low-risk (LR) PT with transient to moderate RDS and/or IVH I-II (LR-PT)	Not defined	12 months (CA)	-Free play interaction -Video recording—10 min -At the laboratory -Coding of mothers' attention-directing and infants' exploratory strategies [45]	-Mother—attention-directing behaviors: HR-PT>LR-PT, H-FT; -Mother—questions: H-FT>LR-PT=HR-PT <i>Other measures:</i> mothers of HR-PT used questions more often with infants with higher MDI, while they use attention-directing gestures with infants with lower MDI	Good
	37 High-risk (HR) infants with intracranial hemorrhage and/or perinatal asphyxia and/or seizures and/or meningitis and/or BW < 1500 (HR)	37 healthy (H) infants matched for age, sex, and race	Not defined	At 8 months (CA)	-Interactions during a feeding episode, a session in which the mother is asked to teach the child an age-appropriate task and a free play session. -Live observation: 120 min in total -At home -NCAFS, NCATS, and HOME scale (including an interview to the mother) [47, 48]	(i) Dyads—scores at NCAFS and NCATS: HR<H <i>Other measures:</i> a strong association between NCAFS and risk status was reported	Poor
Landry et al. [49]	11 PT with IVH III or IV (HR-PT)	16 PT with RDS or IVH I and II (LR-PT)	Other medical complications	At 12 months (CA)	-Toy-centered play interaction -Video recording: 10 min -At the laboratory -Coding of mother's attention-directing and infant's exploratory strategies [45]	-Infant—exploratory play in response to mother's structured strategy: LR-PT>H-FT -Infant—exploratory play: HR-PT<H-FT, and LR-PT -Infant—exploratory play in response to unstructured versus structured strategies: H-FT>LR-PT, HR-PT -Infant—exploratory play in response to structured versus unstructured strategies: LR-PT>H-FT, HR-PT	Fair
	89 PT with BPD, IVH III or IV, and/or PVL (HR-PT)	123 PT with IVH I or II, transient RDS (LR-PT)	Sensory impairments, meningitis, encephalitis, congenital abnormality of the brain	At 6 and 12 months (CA)	-Toy play session and naturalistic observation of daily activity -Live observation—10 min and 60 min -At home -Mixed rating scale and microanalytic coding system [45, 50]	(i) Daily activities and toy play at 6 and 12 months: Mother—interactive behaviors: HR-PT=LR-PT-H-FT <i>Other measures:</i> 6 months (i) MDI, daily living, receptive language: FT, LR-PT>HR-PT (ii) Expressive language: HR-PT<H-FT (iii) Positive correlation between mother attention maintaining behavior and infant	Fair
Smith et al. [50]	128 FT: healthy (H-FT)	128 FT: healthy (H-FT)					

TABLE 1: Continued.

Study	At high-risk sample	Control sample	Exclusion criteria	Timing of assessment	Method	Main results	Study quality*
Schermann-Eizirik et al. [51]	67 PT, GA < 32 was required IC** (VPTIC)					mental age and receptive language score (during daily activity and toy play): HR-PT, LR-PT>H-FT	Good
	75 PT, GA < 36 was required IC** (PTIC)	70 FT, healthy (H-FT)	Chromosomal abnormalities and severe cerebral malformations.	At 2, 4, and 6 months (CA)	-Interaction during undressing of the infant and face-to-face situation -Video recording—variable time, 3 min -At the laboratory -Mother-infant interaction coding [52]	(iv) Positive correlation between mother attention maintaining behavior and infant expressive language score (during daily living activity): HR-PT, LR-PT>H-FT	
	66 FT, required IC** (FTIC) **IC, intensive care for CPAP or parenteral nutrition o severe asphyxia					(v) Positive correlation between mother—attention maintaining behavior and infant expressive language score (during toy play):HR-PT>LR-PT, H-FT	
Davis et al. (2003) [53]	50 PT, BW < 1500 g, with neurobiological risk (defined by NBR5) (HR-PT)	Normative data	No congenital anomalies	Within the 6 <sup>th</sup> month	-Interaction during feeding -Video recording—20 min -At home -NCAFS [47]	2,4,6 months: -Mother—interactive behaviors: VPTIC, PTIC=H-FT -Infant—interactive behaviors: VPTIC, PTIC=H-FT -Dyad—positive interaction: VPTIC, PTIC=H-FT 2 months: -Mother—interactive behaviors: FTIC=FT -Infant—interactive behaviors: FTIC=FT 4 months: Mother—sensitivity/involvement: FTIC<FT Infant—interactive behaviors: FTIC<FT Dyad—positive interaction: FTIC<FT (iv) 6 months: Mother—sensitivity/involvement: FTIC<FT Infant—interactive behaviors: FTIC=FT	Fair
						(i) Total feeding score: HR-PT<normative data	
						(ii) Mother—interactive behaviors: HR-PT=normative data (iii) Infant—responsivity to caregiver: HR-PT<normative data <i>Other measures:</i> mothers who coped better had more responsive children at three months after discharge, according to the Coping Health Inventory for Parents [54]	

TABLE 1: Continued.

Study	At high-risk sample	Control sample	Exclusion criteria	Timing of assessment	Method	Main results	Study quality*
Muller-nix et al. [55]	28PT, high-risk (HR) PT, defined by PERI [56] (HR-PT)	19 low-risk (LR) PT, PT, defined by PERI (LR-PT) 25 FT, healthy (H-FT)	Infant malformation, chromosomal abnormalities, foethopathy	At 6 months (CA)	-Mother-child toy-play interaction -Video recording: 10 minutes -Context not specified -CARE index [57]	(i) Mother—sensitivity: HR<LR<FT (ii) Infant—interactive behaviors: HR-PT=LR-PT-H-FT <i>Other measures:</i> Mother—posttraumatic stress symptoms: HR-PT>FT More stressed mothers were less sensitive and more controlling in dyadic play	Fair
Schmücker et al. (2005) [58]	79 PT, BW < 1500 g, and/or with IVH, PVL, SGA or required more than 28 days on mechanical ventilation (HR-PT)	35 FT, healthy (H-FT)	Not defined	At 3 months (CA)	-Interaction during diaper change and free play -Video recording—10 minutes -At the laboratory -Microanalytic coding system to rate early mother-child interaction [59]	-Infant-vocalize: HR-PT>H-FT -Infant-vocally responsive: HR-PT>H-FT -Infant—facially responsive: HR-PT<H-FT Mother—facially responsive: HR-PT<H-FT <i>Other measures:</i> The higher the neurobiological risk of the infant, the more mothers were judged to lack sensitivity	Fair
Feldman (2006) [60]	17 PT, BW: < 1000 g, GA < 30 ws (HR-PT)	25 PT BW= 1700-1850 g, GA = 34-35 ws (LR-PT) 29 FT: GA > 2500 g > 36 ws, (H-FT)	IVH III and IV, asphyxia, metabolic and genetic diseases.	At 3 months (CA)	-Face-to-face interaction -Video recording: 5 min -At home -Scoring with Monadic Phase Manual [61]	-Mother-infant synchrony: H-FT>HR-PT, LR-PT HR-PT=LR-PT -Mother-infant degree of synchrony (coherence): FT>LR-PT>HR-PT -Infant—negative emotionality: HR-PT, LR-PT>H-FT <i>Other measures:</i> Biological rhythm analysis revealed that sleep-wake cyclicity, vagal tone, orientation, and arousal modulation are each uniquely predictive of mother-infant synchrony at 3 months	Good
Feldman and Eidelman [62]	18 PT, SGA, BW: < 1000 g (SGA < 1000) 28 PT, AGA, BW: < 1000 g (AGA < 1000)	22 PT, SGA, BW: > 1000 g (SGA > 1000) 52 PT, AGA, BW: > 1000 g (AGA > 1000)	IVH IV, asphyxia, metabolic or genetic or syndromic disease, SNC infections	At 3 months (CA)	-Mother-infant interaction -Video recording: 10 min -At home -CIB [63]	Mother-intrusiveness: (SGA < 1000) > (SGA > 1000) > (AGA < 1000), (AGA > 1000) Infant—negative engagement: (SGA < 1000) = (SGA > 1000) = (AGA < 1000) = (AGA > 1000)	Good

TABLE 1: Continued.

Study	At high-risk sample	Control sample	Exclusion criteria	Timing of assessment	Method	Main results	Study quality
Feldman [64]	34 PT, BW < 1500 g (HR-PT)	38 FT: healthy (H-FT)	Maternal and/or paternal depression and anxiety	At 4 months (CA)	- Interaction mother-infant father-infant, triadic interaction - Video recording: 5 min each - At home - Coding Interactive Behavior (CIB) Manual [63]	<i>Other measures:</i> At 12 months, SGA < 1000 showed poorer cognitive development at MDI. SGA < 1000 scored significantly lower on orientation and motor maturity compared with other groups - Mother—intrusiveness: HR-PT>H-FT - Mother—sensitivity: HR-PT<H-FT - Infant—negative emotionality: HR-PT>H-FT - Dyad—reciprocity: HR-PT<H-FT <i>Other measures:</i> (i) Family cohesion: HR-PT<FT - Family rigidity: HR-PT>FT Mother of IUGR infants showed the highest intrusiveness scores and IUGR infants showed the highest negative emotionality. Family also showed the highest rigidity	Good
	21 PT, IUGR, <1500 g (HR-PT)						
Korja et al. [65]	30 PT, BW <1500 g; GA: <32 WS (PT)	36 FT: healthy (H-FT)	Major congenital anomalies	At 6 and 12 months (CA)	- Free play mother-infant interaction (toy optional) - Video recording: 5 min - At the laboratory - PC-ERA [66]	- 6 months: Infant—intrusive behaviors: PT=H-FT Mother—intrusive behaviors: PT=H-FT - 12 months: Infant—quality of play and attention: PT<H-FT Infant-sober and withdrawn: PT<H-FT Mother—intrusive behaviors: PT=H-FT <i>Other measures:</i> duration of holding at 5 months (CA) was positively associated with the good quality of mother–infant interaction at 6 and 12 months in PTFTs cried (combined fussing and crying) more often and were held more than H-FT	Good
	29 PT, BW: <1000 g (HR-PT)						
Agostini et al. [67]	40 PT, BW: <1500 g (PT)	80 FT healthy (H-FT)	Infant chromosomal abnormalities, CP, malformations and foetopathy	At 3 months (CA)	- Face-to-face interaction - Video recording: 5 min - At the laboratory - Global rating scale (GRS) [68]	- Mother—sensitivity: HR-PT=PT=H-FT - Mother—intrusiveness: HR-PT>H-FT - Mother—remoteness: PT, HR-PT<H-FT - Infant—interactive behaviors: HR-PT=PT=H-FT <i>Other measures:</i> In H-FT mothers, higher degree of remoteness was associated to the presence of depressive symptoms	Good
	32 PT, BW: <1000 g (HR-PT)						
Neri et al. [69]	32 PT, BW: <1000 g (HR-PT)	20 FT, healthy (H-FT)	Infant chromosomal abnormalities,	At 3 months (CA)	- Face-to-face interaction - Video recording: 5 min	- Mother—sensitivity: PT>H-FT - Mother—intrusiveness: HR-PT>H-FT - Mother—remoteness: HR-PT<H-FT	Good

TABLE 1: Continued.

Study	At high-risk sample	Control sample	Exclusion criteria	Timing of assessment	Method	Main results	Study quality*
	45 PT; BW <1500 g (PT)		cerebral palsy, malformations and foetopathy		-At the laboratory -Global rating scale (GRS) [68]	-Infant—communicative dimension: PT>FT <i>Other measures:</i> Mother—signs of depression: HR-PT, PT>H-FT	
						-Dyad—frequency of symmetric coregulation patterns: HR-PT<H-FT -Dyad—frequency of unilateral coregulation patterns: HR-PT>H-FT -Infant—emotional Involvement: HR-PT<H-FT -Mother—frequency of high positive affective intensity: HR-PT<H-FT Infant—frequency of neutral affective intensity: HR-PT>H-FT Infant—frequency of high positive affective intensity: HR-PT<H-FT Infant—frequency of low positive affective intensity: HR-PT>H-FT Infant—duration of neutral affective intensity: HR-PT>H-FT Infant—duration of high positive affective intensity: HR-PT<H-FT Infant—duration of low positive affective intensity: HR-PT<H-FT Infant—duration of neutral affective intensity: HR-PT>H-FT Infant—duration of low negative affective intensity: HR-PT>H-FT	
Sansavini et al., 2015 [70]	20 PT; GA <28 ws (HR-PT)	20 FT; >37 ws (H-FT)	Major cerebral damage, PVL, IVH > II grade, hydrocephalus	At 12 months (CA)	-Mother-child toy-play interaction -Video recording: 10 minutes -At the laboratory -R-RCS for dyadic coregulation and Lunkenheimer's coding system for coding affective intensity [71, 72]	Fair	

AGA = appropriate for gestational age; BPD = bronchopulmonary dysplasia; BW = birth weight; CA = corrected age; CIB = coding interactive behavior; FT = full-term infant; GA = gestational age; H-FT = healthy full term; H-PT = healthy preterm; HOME = Home Observation Measurement of the Environment; HR-PT = high-risk preterm; IUGR = intrauterine growth retardation = IVH: intraventricular hemorrhage; LR-PT = low-risk preterm; MDI = Bayley Mental Developmental Index; NBAS = Neonatal Behavioral Assessment Scale; NBRS = Neurobiological Risk Score; NCAFS = Nursing Child Assessment Feeding Scale; NCATS = Nursing Child Assessment Teaching Scale; PC-ERA = Parent-Child Early Relational Assessment; PDI = Bayley Psychomotor Developmental Index; PT = preterm infant; PTIC = preterm who required intensive care; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; S-FT = sick full term; S-PT = sick preterm; SGA = small for gestational age; VPTIC = very preterm who required intensive care. \* Assessed through National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Case-Control Studies [38].



TABLE 2: Assessment and scoring scales used in the studies.

Assessment and scoring scales	Description	Reference	Studies
<i>Global scales</i>			
Global rating scales (GRS)	Assessment of the quality of mother-infant interaction. Maternal behavior is rated on 4 dimensions: sensitivity, intrusiveness, remoteness, and signs of depression. Infant behavior is rated on 3 dimensions: communicative, inert, and distressed. One dimension assesses the quality of the overall interaction between mother and infant. A 5-point Likert-type scale is used to rate each dimension, with 1 being the poorest and 5 being the optimal rating.	Gunning et al. Murray et al. [15, 73]	Agostini et al. [67]; Neri et al. [69]
NCAST Feeding (NCAFS) and Teaching (NCAST) PCI Scales	The NCAST-PCI evaluates 149 items related to maternal and infant behaviors. It comprises two scales: NCAFS and NCATS. Infant and parent items are coded as yes or no; items are then added to provide a total score. Each scale includes 4 subscales, measuring maternal behaviors and 2 subscales, measuring infant's behaviors. Maternal subscales are sensitivity to cues, responsivity to child's distress, social-emotional growth fostering, and cognitive growth fostering. Infant subscales are clarity of cues and responsiveness to parent.	Barnard et al. [47]	Davis et al. [53] Farel et al. [46]
Coding Interactive Behavior (CIB)	Global rating system of parent-child interaction in different play or interaction situations, including 42 codes: 21 for parents, 16 for infants, and 5 for dyads. Each score is rated with a Likert-type scale, where 1 corresponds to the poorest and 5 to the optimal rating. Five composite scales are included: maternal sensitivity, maternal intrusiveness, child's social involvement, and dyadic reciprocity.	Feldman [63]	Feldman and Eidelman [62]; Feldman [64]
Parent-Child Early Relational Assessment (PC-ERA)	Semistructured assessment to evaluate affective and behavioral quality of parent-infant interaction during 4 situations: feeding, administration of a structured task, free play, and a separation-reunion task. Three parental subscales (29 items) are coded: positive affective involvement and verbalization, negative affect and behaviors, and intrusiveness, insensitivity, and inconsistency. Three Infant subscales (28 items) are coded: positive affect, social and communicative competence; quality of play, interest and attentional skills; dysregulation and irritability. Two dyadic subscales (8 items) are coded: mutual enjoyment and reciprocity, tension and disorganization. A 5-point Likert-type scale is used to rate each item.	Clark [66]	Korja et al. [65]
CARE-Index	Assessment of the quality of adult-infant interaction. Three adult behaviors are scored: sensitivity, control, and unresponsiveness. Four infant behaviors are scored: cooperativeness, compulsiveness, difficultness, and passivity. The scores range from 0 to 14, with 0 score being the worst score.	<a href="http://www.patcrittenden.com">http://www.patcrittenden.com</a> , Crittenden 1979-2004 [57]	Muller-nix et al. [55]
HOME	Inventory designed to identify the presence of risk for developmental delay due to lacking of appropriate quantity and quality of stimulation from home environment. Forty-five binary items, organized in six subscales, are scored using a combination of semistructured mother interview relative to children routine activities, observation of mother-infant interaction during play and interview and assessment of kinds of play materials available to the child. Six subscales are coded: emotional and verbal maternal responsivity,	Bradley and Cadwell [48]	Farel et al., [46]



TABLE 2: Continued.

Assessment and scoring scales	Description	Reference	Studies
	maternal avoidance of restriction and punishment, maternal involvement with the child, organization of the environment, provision of appropriate play materials, and variety in daily stimulation.		
<i>Microanalytic</i>			
Coding system of Minde (1980)	Microanalytic system recording the occurrence of the 10 maternal and 11 infant behaviors. Infant behaviors: arm, head, leg, hand to mouth; eyes open; scan; grimace; cry; vocalize; smile; yawn. Maternal behaviors: look; look <i>en face</i> ; verbalize to baby and to others; instrumental and noninstrumental touch; hold; feed; smile; standing further than 1 meter away from the baby.	Minde et al. [43]	Minde et al. [42]
Microanalytic coding system to rate early mother-child Interaction by Jorg (1994)	Microanalytic system which rates interactive behaviors at fixed time intervals of 1, 15, and 30 seconds. In particular, maternal behaviors rated per second are direction of gaze, vocalization, facial expression, content of interaction, and proximity; infant behaviors rated per second are direction of gaze, vocalization, and facial expression; joint mother-child behaviors rated every 15-30 seconds are appropriateness of stimulation, maternal responsiveness, and child responsiveness.	Jorg et al. [59]	Schmücker et al. [58]
Coding system of Landry (1986)	This coding system is based on the recording of the occurrence of mothers' attention-directing strategies and infants' responses. The variables scored are maternal attention-directing attempt, verbal technique-question, verbal technique-imperative, verbal technique-attention verbs, nonverbal techniques attention directing-gesture, nonverbal techniques attention directing-demonstrate, nonverbal techniques attention directing-give, initial focus of attention-maintain, initial focus of attention-introducing, initial focus of attention-redirecting, infant response-no response, infant response-look, infant response-manipulate.	Landry [45]	Landry [45]; Landry [49]
Monadic Phase Manual	Coding system in which the stream of affective behavior of each partner is coded using 6 expressive modalities for the parent, which are vocalization, direction of gaze, head orientation, facial expression, body position, and specific handling of the infant and 5 for the infant which are vocalization, direction of gaze, head orientation, and facial expression. Combination of expressive modalities, checked second by second, is transformed in one of the following seven adult monadic phases: avoid, avert, monitor, elicit, set, play, and talk. Six infant monadic phases are also coded: avoid, avert, monitor, set, play, and talk.	Tronick et al. [61] Feldman [74]	Feldman [60]
Revised relational coding system (R-RCS)	This coding scale assesses dyadic coregulation based on 5 patterns: symmetrical, asymmetrical, unilateral, disruptive, and unengaged. One additional pattern, no code, can be used for missing information.	Fogel et al. [71]	Sansavini [70]
Lunknenheimer's coding system	This scale codes parent and infant positive and negative affective intensity in 30 s intervals. An ordinal 3-point scale (non, low, high) is used to code affective behaviors based on a combination of voice tone, facial expression, eye contact, and body language.	Lunknenheimer et al. [71]	Sansavini [70]

TABLE 2: Continued.

Assessment and scoring scales	Description	Reference	Studies
<i>Checklist</i>			
Checklist by Lewis	<p>Checklist sheet for recoding 13 infant and 12 maternal behaviors. Behavior are coded within 10-second periods: occurrence, initiation, or response. Two principal types of summary variables are computed from discrete infant and maternal behaviors: general behavior and responsivity.</p> <p>Maternal general behaviors: frequency of general stimulation; frequency of proximal stimulation, frequency of distal stimulation, frequency of kinesthetic stimulation, frequency of positive affect expression, and frequency of vocal stimulation. Infant general behaviors: frequency of fret/cry, frequency of vocalization, and frequency of look/gaze at mother.</p> <p>Maternal responsivity: proportion of general responsivity, proportion of proximal responsivity, proportion of distal responsivity, and proportion of vocal responsivity. Infant responsivity: proportion of general responsivity.</p>	Lewis et al. [40]	Greene et al. (1983) [39]
Checklist by Lasky et al., 1984	<p>Observational method based on rating the presence of maternal and infant behaviors in 5 different situations. 10 behaviors initiated by the infant and 12 behaviors initiated by the mother are checked.</p>	Lasky et al. [41]	Lasky et al. [41]
Checklist by Bohlin et al., 1989	<p>Observational method based on a 5-point scale (higher score indicating higher frequency or better performance) rating of maternal, infant, and dyadic items. Maternal items are grouped into three variables: sensitivity, intrusiveness, and involvement. Infant items are grouped into two variables: infant interactive behaviors. The dyadic variable corresponds to a global evaluation of quality of positive interaction.</p>	Bohlin et al., [52]	Schermann-Eizirik et al. [51]
<i>Other</i>			
Mixed rating scale and microanalytic coding system	<p>Five-point rating scale to code a composite measure labeled “warm sensitivity” which comprises three maternal behaviors: positive affect, warm concern/acceptance, and flexibility/responsiveness combined to a microanalytic coding scheme developed to quantify maternal attention-directing events defined as verbal and nonverbal behaviors (frequency of events is considered for analysis).</p>	Landry et al., [45] Smith et al., [50]	Smith et al. [50]

respectively, compared to controls. Interestingly, however, Schmücker and colleagues [58] also reported that preterm infants were more vocally active and responsive than full-term infants were, thus indicating that the extent of responsiveness to the caregiver can be different depending on the communicative channel.

Two studies explored populations of full-term infants at high neurological risk, reporting abnormal infant behaviors within the parent-infant interaction [39, 51]. Specifically, Greene and colleagues [39] found that healthy infants looked significantly more at their mothers than sick infants, with sick full-term infants, corresponding to the group at highest neurological risk, having the lowest scores compared to healthy controls. Similarly, results by Schermann-Eizirik and colleagues [51] revealed that, unlike preterm born infants, full-term infants who required

intensive care at birth, thus supposedly corresponding to the most impaired infants, differed from healthy full-term controls in their interactive patterns, with the first group showing significantly less interactive behaviors than the second one.

Finally, more recent studies investigating early mother-infant interactions within the first trimester of life showed no significant differences in terms of negative engagement or interactive patterns between preterm infants and full-term controls [62, 67]. Only one study [69] reported more communicative behaviors in very low birth weight (VLBW) infants compared to full-term ones.

**3.3.2. Parent (Mother) Interactive Behavior.** Consistent with the results on infant behaviors during the first months of life, mothers of high-risk infants were described as less sensitive,

more vigilant or intrusive, and less emotionally involved than mothers of healthy or low-risk infants.

At 3 months of age, Greene and colleagues [39] reported that, compared to healthy infants, high-risk infants, and specifically high-risk full-term infants, received more proximal and kinesthetic stimulation, but less distal and affective behaviors from their mothers during free play interactions. At the same infant age, other studies [62, 64, 67] reported that mothers of high-risk infants had more intrusive and less remote behaviors during face-to-face interaction than mothers of controls. Similarly, Minde and colleagues [42] reported that during feeding sessions (1 and 2 months) and play interactions (3 months), mothers of premature infants at higher risk provided more compensatory care (e.g., vocalization and face-to-face look), but less affect (e.g., smiling) to their infants compared to full-term mothers.

More inconsistent results were found about maternal sensitivity. In fact, while some studies [53, 58, 67] failed to find differences between study and control mother groups in the sensitivity dimension, others showed that mothers of high-risk infants were less sensitive than mothers of controls were [51, 60]. In particular, Schermann-Eizirik and colleagues [51] did not find differences in interactive behaviors between mothers of preterm infants, some of whom required intensive care, and mothers of healthy full-term infants. However, they observed significantly less sensitivity and less interactive involvement in mothers of high-risk full-term infants compared to mothers of healthy full-term infants at 4 and 6 months. Only one study reported enhanced sensitivity in mothers of high-risk infants, which was, however, associated with a higher level of intrusiveness [69].

Taken together, all these studies support the idea that mothers of high-risk infants are particularly focused on close monitoring and stimulating their infants rather than interacting with them in an affectionate or social manner.

**3.3.3. Dyadic Interactive Patterns.** Among the studies included in the current review, some approached a dyadic perspective, in addition to analyzing discrete maternal and infant dimensions, and focused on compromised patterns of synchrony [60], reciprocity [64], and positive exchanges within the dyad [51]. Two studies focused on the dyadic synchrony and reciprocity in the first semester of life and revealed that dyads at risk were less synchronized than control dyads were, showing less reciprocal rhythmic and fluent exchanges [60, 64]. The study by Schermann-Eizirik and colleagues [51] revealed that high-risk dyads showed less positive exchanges compared to control dyads.

**3.4. Comparison of Interactive Patterns between High-Risk and Non-High-Risk Dyads from 6 to 12 Months.** Studies focusing on older infants evaluated more heterogeneous and difficult-to-compare interactive parameters, such as play, social, and communication skills. Consequently, also the results of these studies were more heterogeneous than were those observed during the first semester of life.

**3.4.1. Infant Interactive Behavior.** During toy-centered play sessions, both Muller-Nix et al. [55] and Landry et al. [45]

found no significant differences between the study and control groups in infant play-interactive patterns, at 6 and 12 months, respectively. Conversely, significant differences in play-strategies between 12-month-old high-risk and control infants were found by Landry et al. and by Korja et al. [49, 65]. Results by Landry and colleagues [49] revealed that high-risk infants showed, in general, less exploratory capacities compared to low-risk and healthy full-term infants and, more specifically, that high-risk infants were more dependent on mothers' structuring strategies than controls were. Similarly, Korja et al. [65] described 12-month-old preterm infants as less skilled in play, less attentive, and more apathetic, passive, and avoiding than controls during free play interactions.

A different approach was used by Farel and colleagues [46] who investigated interactive behaviors during feeding at 8 months of age and found that high-risk infants showed less clarity of cues and less responsiveness to their mothers than did controls. Finally, Smith and colleagues [50] found that high-risk infants had significantly lower expressive language abilities than controls during daily activity.

**3.4.2. Parent (Mother) Interactive Behavior.** As far as maternal behaviors are concerned, results of studies focusing on older infants highlighted two main altered dimensions. Consistent with studies focused on younger infants, mothers of high-risk older infants seemed to be more stimulating and less sensitive toward their infants than did mothers of control infants. For example, Landry et al. [45] found more attention-directing behaviors in high-risk mothers than in mothers of controls, while Farel and colleagues [46] found that mothers of high-risk infants reached lower scores in fostering cognitive growth behaviors than control mothers did.

Less affective behaviors were found in mothers of high-risk infants by Lasky et al. [41], Muller-Nix et al. [55], and Sansavini et al. [70]. Lasky and colleagues [41] reported that mothers of preterm infants restrain their infants less during a stressful clinical examination, maybe because they were more used to this kind of procedure. Muller-Nix et al. [55] found a negative gradient of maternal sensitivity, with mother of high-risk infants being less sensitive than mothers of low-risk infants that, in turn, were less sensitive than mothers of full-term infants. The study by Sansavini and colleagues [70], instead, revealed that mothers of extremely small for gestational age infants showed lower positive affect compared to mothers of full-term infants.

Finally, two studies [50, 65] found no differences in maternal interactive behaviors between high-risk and control infant populations. However, both studies, differently from the other studies analyzing multiple discrete maternal dimensions, only reported a global score of maternal behaviors. Thus, whether significant differences would have been found, should single discrete maternal behaviors be analyzed, remains unanswered.

**3.4.3. Dyadic Interactive Patterns.** Among the studies focusing on dyadic interactive patterns at later infants' ages, Farel and colleagues [46] showed that high-risk dyads reached significantly worse total interactive scores, during feeding at 8

months, compared to control dyads. Korja and colleagues [65] found no differences in dyadic mutuality, flatness, and disorganization and tension between 12-month-old high-risk and control infants. Finally, the study by Sansavini and colleagues [70] reported that extremely low gestational age (ELGA) dyads showed less frequent symmetrical coregulation and more frequent unilateral coregulation, specifically meaning that mothers observe, initiate, and demand doing something, while infants do not respond to them.

**3.5. Coding Systems Used in Multiple Studies.** In order to evaluate if similar patterns of mother-infant interaction could be inferred, we compared the quantitative results of those studies using the same coding systems. Only four scales were applied in more than one study (see Table 2).

The scale by Gunning et al. [68] and Murray et al. [15, 73] was used in two studies, in populations with the same characteristics and at the same age of assessment [67, 69]. Consistent results were reported in “intrusiveness” and “remoteness” dimensions, describing mothers of high-risk infants as more intrusive and less remote than mothers of controls, while inconsistent results were reported for the “sensitivity” dimension.

The NCAST scale was also used in two studies [46, 53]. The authors reported similar results in the feeding subscale, with a higher score in populations considered at high risk compared to control groups or normative data. However, investigated populations differed in clinical risk and age at the time of the mother-infant interaction assessment.

The CIB was used in other two studies [62, 64]. They both found significant differences in the “intrusiveness” dimension, with mothers of the risk group reported to be more intrusive than mothers of the control group. However, the population characteristics of the two studies and the age at the time of the mother-infant interaction assessment differed between the two studies.

Finally, two studies by Landry et al. [45, 50] used the same coding system which was developed by the authors. Comparison of the data was however not feasible, as the results in one paper [45] were only related to mother behaviors, while the results of the other [49] were only related to infant behaviors.

No further quantitative comparisons, nor meta-analysis, were feasible with the selected articles, due to the heterogeneity of the publications and because the assessment tools and the dimensions analyzed were not consistent across the reports.

## 4. Discussion

In the last thirty years, extensive research has provided evidence that early interactive exchanges are fundamental in fostering later social and cognitive development, as they steadily drive, throughout early infancy and toddlerhood, emerging infant social abilities toward intentional and more complex relational capacities [3–6, 9, 10, 71]. The occurrence of adverse perinatal events, however, negatively impacts the overall infant neurodevelopment with consequent detrimental effects also on infant social and relational

dimensions [7, 8, 11, 15, 17]. The extent to which severe neonatal complications, such as the extremely preterm birth or low birth weight or the occurrence of neonatal brain insults, might affect early interactive exchanges between infants and their primary caregivers is, however, mostly uncharted. Our main objective was to review the studies that included the emerging behavioral interactive patterns of parent-infant dyads in infant populations at high neurological risk compared to control populations. We specifically focused on parent-infant interactions occurring over the first year of life, as it represents one of the most critical stages in infants’ neurodevelopment and therefore is considered an optimal timeframe for early intervention on infants experiencing consequences of brain damage including developmental delays.

Most of the 18 studies resulting from our systematic search revealed that both infant and maternal behaviors within early interactions are compromised, which results, in turn, in a more general impairment of dyadic patterns. During the first six months of life, infants at high neurological risk are described as less engaged and active than control infants, which makes them less responsive social partners, unable to communicate cues that are sufficiently clear to their caregivers [47, 58, 60]. The most likely explanation of this finding is that these altered behaviors are primarily dependent on infants’ neurophysiological immaturity and medical conditions, which necessarily affect their propensity to interact. This is consistent with the findings by Feldman [60] who evaluated neonatal biological rhythms and their relationship with mother-infant synchrony at 3 months of age. The author found that immature or dysregulated endogenous rhythms, due to perinatal events, limit the capacity of arousal modulation and negatively affect infant emotionality. During the same timeframe, i.e., the first semester of life, mothers of high-risk infants are more intrusive and overstimulating but, at the same time, less sensitive and affective [51, 60]. Authors have generally interpreted these behaviors as the result of major maternal concerns relative to the health status of their infants. In this view, mothers tend to be more focused on infants’ caretaking while lacking emotional involvement [39, 58].

It is of interest that the abnormalities observed in infant behavior tend to persist beyond the first semester of life, with infants being less engaging in the interaction and less focused during play sessions, while the intrusive maternal behaviors observed in early interactions evolve into more controlling and attention-directing behaviors in the second semester of life [45, 49]. This has been interpreted as a process by which mothers become more conscious of their infants’ compromised motor, cognitive, and communicative skills and shift from early concerns to the adoption of more suitable strategies to optimize their interactions with infants, such as directing their attention. Taken together, these results suggest that communicative patterns between mothers and infants at risk are less fluent and more disorganized compared to those typically observed in healthy populations and that the resulting quality of interaction is significantly impaired on the short and long terms.

Findings from the current review do not provide an exhaustive characterization of early mother-infant



relationships in populations at very high risk of developing CP. In fact, many of the studies excluded infants with major neurological complications, thus leaving low birth weight and extreme prematurity as the primary selection criteria. While this selection approach limited the heterogeneity of the investigated samples, it clearly reduced the overall level of neurodevelopmental risk of the populations defined as at high risk. In spite of this important limitation, the available data support the concept that illness, rather than prematurity per se, gives the greatest contribution to the disruption of early infant interactive behaviors and, in turn, of maternal responses. In particular, our findings show that infants with more severe illness, either born prematurely or at term, have less optimal interactive approaches toward their mothers, as opposed to those with lower levels of neurodevelopmental risk [39, 41, 42, 45, 46, 50, 51, 58]. Similarly, maternal behaviors are directly related to infants' medical status with greater levels of infant risk associated with greater alterations of maternal interactive behaviors [42, 50, 51, 58]. In general, mothers of infants who faced major neurological complications at birth were also more depressed, distressed, and anxious, as revealed by postnatal interviews or questionnaires, and these emotional states seem to influence mothers' interactive behaviors toward a less efficient perception of their infants' cues [55, 58, 67, 69]. However, some inconsistency was found in relation to this aspect. Some other studies have found weak or no significant impact of maternal emotional states on the mother-infant interaction in high-risk populations, differently from the control population in which they seemed to play a bigger role [42, 53, 58]. Specifically, more negative emotional states were associated to poorer or more negatively affected maternal interactive patterns. Finally, few and discordant results were identified on the extent to which maternal emotional state compared to infants' risk can alter the interactive patterns [55, 58, 64, 69]. Further investigations are therefore needed to disambiguate such aspects and, more importantly, to provide deeper insights on the maternal emotional state following the occurrence of perinatal adverse events and on the extent to which they can influence maternal interactive patterns over time.

It is of interest that the studies included in this work cover a time span of over thirty years. However, only older studies focused on very high neurological risk populations, while most recent ones mainly focused on prematurity. Two main considerations can be made. First, it is plausible that since first attempts at investigating early interactions in such complex populations have not been fully successful, subsequent attempts have mainly deviated toward more homogeneous populations including only premature infants. On the one hand, this approach has led to more consistent and reliable knowledge on early interactive exchanges in premature populations. On the other hand, however, this has also left many unanswered questions about the role of neurological illness in early mother-infant interactions. Second, the survival rate of infants at high risk for neurological impairments as indicated by current guidelines was significantly lower in the past decades, while it has significantly increased following advances in perinatal and neonatal care. Currently, more than ever, there is a critical need for the prompt referral of

high-risk infants to diagnostic-specific early intervention, promoting early social interactions.

It is important to underline that findings were not consistent across studies. Inconsistent results were found in relation to maternal dimensions, in particular maternal sensitivity [55, 64, 67, 69], as well as to infant dimensions, in particular communicative patterns [58, 62, 69]. A number of factors might support these inconsistencies. Firstly, methods and scoring modalities used to investigate the interaction were very heterogeneous, varying from short video sessions to very long live observations and from microanalytic to global rating scoring systems. Different observational approaches and analyzed dimensions may result in heterogeneous pictures of dyadic exchanges. Secondly, studies were conducted at different infants' ages, albeit within the first year of life. Consequently, observational analyses were quite different across studies and specifically aimed at capturing the most appropriate interactive behaviors at different developmental stages. The last and the most important factor is that all articles included in this review focused on infant populations at high risk or neurologically impaired, but inclusion selection criteria were relatively variable, namely, varying from prematurity only to severe brain lesions. Therefore, not unexpectedly the extent of the interaction impairment was proportional and strictly related to the severity of infant medical risk.

Few studies have reported that early coping maternal behaviors influence later interaction maternal status [53]. Our results show that mothers of older infants demonstrate adaptive interaction strategies based on the impairment level of their infants. In particular, mothers of infants who clearly showed developmental delays as revealed by outcome measurements chose alternative strategies to properly communicate with their infants (i.e., g attention-directing gestures vs questioning) [49, 50]. These findings might indicate a natural maternal attitude to adapt their behaviors based on infant needs over time [45, 49, 53]. Clearly, further investigations are needed in order to extend these results also in view of early interventions aimed at fostering such attitude as early as possible which would be of crucial importance.

In conclusion, results from this work extend previous research which has mainly focused on preterm populations, providing more information relative to early interactions involving infant population with or at high risk for neurological impairments. In fact, while our findings confirm that premature infants displayed behaviors similar to those previously observed in healthy populations, extremely preterm infants and full-term infants with severe illness showed markedly more impaired interactive patterns. Similarly, when maternal behaviors were taken into account, results showed that mothers of high-risk infants were more likely to show altered interactive patterns. However, while the studies reviewed here provided important information, the review did not yield a clear picture of early dyadic interactions in high-risk infant populations. Therefore, further investigation focusing on less heterogeneous populations (e.g., targeting infants with severe perinatal insults only versus controls) and embracing a longitudinal and comprehensive perspective, including, for instance, the systematic

evaluation of maternal mental states and their impact on the interaction, are necessary to better characterize the extent to which early parent-infant interactions are impaired following severe perinatal insults. This is an essential step in order to determine the specific impact of addressing the promotion of positive parent-infant interactions as part of early intervention in infants at high neurological risk.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Festante F and Antonelli C contributed equally to this work.

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## Research Article

# Empathy in Youths with Conduct Disorder and Callous-Unemotional Traits

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Previous studies indicated that a lack of empathy could be considered the core feature of callous-unemotional (CU) traits in children and adolescents. The present study is aimed at exploring relationships among CU traits, cognitive and emotional dimensions of empathy, emotion recognition (basic, social, and complex emotions), and history of maltreatment in a sample of youths with conduct disorder diagnosis. The sample consisted of 60 Italian male patients (age range 11-17 years, mean age  $13.27 \pm 1.90$  years) referred to the Department of Child and Adolescent Psychiatry (Pisa, Italy). In the whole sample, the levels of CU traits were significantly negatively associated with both cognitive and emotional dimensions of empathy; in addition, the CD patients with high levels of CU traits show significantly lower levels of empathic concern compared to those with low levels of CU traits. Clinical implications of the findings are discussed.

## 1. Introduction

Empathy is a multidimensional construct whose development begins early in life. Several studies on the development of empathy, in fact, indicated that early environments assume an important role in sustaining the neurobiological underpinnings of both cognitive and affective aspects of empathy [1]. For instance, sensitive, responsive, and supportive caregiving may influence the development of typical levels of empathy [2, 3]. Although most of previous studies on the relations between early environment and empathy development have not focused on specific components (cognitive and affective) of empathy in isolation, those that have distinguished between cognitive empathy and affective empathy have indicated that sensitive parenting may sustain the development of capacities in both domains [4]. Such caregiving has been found to promote young children's proclivity to take others' perspectives and to predict increased

empathic concern and perspective taking in adolescence [5]. It has likewise been shown to predict increases in children's levels of prosocial behavior toward peers [6]. Previous studies argued that eye contact with attachment figures was critical for both emotional development and for the development of social cognition, including cognitive empathy [7, 8]. In other terms, these authors argued that reduced eye contact with attachment figures might contribute to the development of a lack of empathy. The implementation of eye gaze/emotional engagement strategies represents one of the targets of some parent training to implement child's emotional engagement, parent-child interaction, and empathy development.

In this framework, also, early negative experience such as maltreatments can influence the development of empathy; however, on this topic, the findings are still unclear.

In fact, from one side, some authors emphasized the existence of a trauma-based pathway to psychopathy in

adults documenting a link between early affective deficits, CU traits, and exposure to maltreatment. Other studies highlight in children exposed to maltreatment a highly faster and more accurate emotional recognition. For instance, Dadds et al. [9, 10] indicated that also early experience of maltreatment may lead to deficit in emotion recognition skills, a measure of both domains of empathy, affective empathy and cognitive empathy. These controversial data show that pathways to high CU traits are complex, involving genetic aspect and environmental factors and both can influence the characteristic features associated with the traits (e.g., Dadds et al., 2017).

Callous-unemotional (CU) traits designate a specifier for children with conduct disorder (CD) diagnosis in the DSM-5 [11]. This specifier is used in CD patients, who show persistently over 12 months, in more than one setting, two or more of these clinical characteristics: lack of remorse or guilt, lack of empathy, unconcerned about performance, and shallow or deficient affect. CU traits are considered the precursors of the affective dimension of psychopathic personality and delineate a subtype of CD youths with a severe persistent and pervasive form of antisocial behavior with specific neurological, cognitive, emotional, and social characteristics [12–15]. Previous studies revealed an increasingly complex picture of the characteristics of CU traits; however, several studies indicated that a lack of empathy could be considered the core feature of CU traits [16]. Anastassiou-Hadjicharalambous and Warden [17] revealed deficits in patients with CD but low CU traits for both affective and cognitive aspects of empathy. In contrast, patients with CD and high CU trait children showed relative competency in cognitive, but deficits in affective, aspects of empathy. This finding suggested an affective-specific plausible dissociation of affective and cognitive aspects of empathy in patients with CD and high levels of CU traits. Dadds et al. [18] found that only deficit in affective empathy is persistent in adolescence and adulthood, even if some studies showed that in boys with CD and CU, both cognitive and affective were impaired [18, 19]. Bons et al. [20] demonstrated a different empathic profile in adolescent boys and in girls with high CU traits: boys and girls showed impairment in affective empathy, but girls showed also a similar impairment pattern in cognitive empathy too. The authors concluded that their work marked that adolescents with higher levels of psychopathic traits have not been characterized by an absolute stable pattern of empathy deficit but rather a relative deficit. Except this study (see also Jones et al. [21]), empirical data on the relations between deficits in empathy's components and levels of CU traits in CD patients are scarce. To the best of our knowledge, most of studies that have investigated the relations between CU traits and lack of empathy were conducted in a community or at-risk samples rather than in clinical samples of youths with CD diagnosis, even though the lack of empathy is a criterion for the CU specifier of CD diagnosis. In order to fill in this gap in the CU-based research, the current study is aimed at exploring the empathy characteristics in a sample of Italian youths with a CD diagnosis.

In recent years, the distinction between affective empathy and cognitive empathy has been receiving growing attention by clinical and cognitive scientists. Affective empathy is the capacity of sharing emotions with someone else; it involves the anterior insular, the cingulate cortex, and the amygdala [22]. Cognitive empathy is the capacity to understand the mental state of someone else, without a reflection of the other's affective state. Cognitive empathy includes the ability of decoding and labeling emotions. Some studies show a close relation between cognitive empathy and the theory of mind (ToM) and abilities or recognizing beliefs, desires, and intentions of someone else [23, 24]. Cognitive empathy reflects the functioning of parts of the dorsolateral prefrontal cortex, posteromedial cortex, superior temporal sulcus, and temporal-parietal junction [22].

A previous remarkable study investigated the relations between CU traits and the levels of cognitive empathy and affective empathy, in a community sample of Australian children, 3 to 13 years [18]. They found that CU traits are related to lower levels of affective empathy, independently to the participants' age. Conversely, previous studies that investigated specifically the relations between CU traits and the levels of cognitive empathy and/or ToM have generally indicated that high levels of youth CU traits are not related to impairment in cognitive empathy [21, 25, 26]. To summarize, the lack of affective empathy seems to be a primary deficit associated to the levels of CU traits in youth; conversely, the cognitive empathy abilities seem to be intact in youth with high levels of CU traits. Moul et al. [27] describe this youth as “a child who understands the emotional states and thoughts of others (intact cognitive empathy), but is unmoved by this understanding (poor affective empathy)”.

Several studies investigated problems in empathy using emotion-recognition paradigms [28]. Usually, in emotion-recognition tasks, participants are presented with images of faces expressing an emotion (happiness, sadness, angry, and fear) and asked to categorize emotions. Other tasks, such as the Reading the Mind in the Eyes task [29], use images of the eye region of more nuanced emotions (playful, comforting, irritated, and bored). Importantly, all these types of tasks measure the levels of both cognitive empathy and affective empathy. Using emotion recognition tasks, Sharp and Vanwoerden [30] showed a relation between CU traits and deficits in recognition of complex emotions rather than basic emotions. Sharp and Vanwoerden [30] concluded that the deficits of CU youths in emotion recognition are related to lower levels of cognitive empathy. Other previous studies that have used emotion recognition tasks indicated that in youth with elevated levels of CU traits, both cognitive and affective were impaired [19, 31]. Overall, findings from studies with emotion recognition tasks indicated that deficits in cognitive empathy might be more pronounced and pervasive among individuals with CU traits than previously thought.

The current study focused on the relationships among CU traits, cognitive and emotional dimensions of empathy, emotional recognition (basic, social, and complex emotions), and history of maltreatment in a sample of youths with CD diagnosis. Research based on the subgrouping of children

with conduct problems characterized by high versus low levels of CU traits has been particularly informative with regard to such theoretical accounts in recent years, providing compelling support for the notion that distinct deficits in empathy map onto these subgroups. Furthermore, to address the call of this special issue, we investigated how early difficulties in parent-infant relationship (history of maltreatment) might be associated to the levels of youths' empathy. Overall, we aim

- (1) to explore relationships among CU traits, cognitive and emotional dimensions of empathy, emotional recognition (basic, social, and complex emotions), and history of maltreatment in a sample of youths with CD diagnosis
- (2) to examine the difference between CD patients with low and high CU traits on the different components of empathy

## 2. Method

**2.1. Participants.** The sample consisted of 60 male patients (age range 11-17 years, mean age  $13.27 \pm 1.90$  years) consecutively referred to the Department of Child and Adolescent Psychiatry of Scientific Institute "Stella Maris" (Pisa, Italy). All patients were diagnosed according to a systematic evaluation, including a structured clinical interview according to DSM-5 criteria, the Schedule of Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version K-SADS-PL [28], administered by trained child psychiatrists. Inclusion criteria for the participation in the current study were (1) DSM-5 diagnosis of conduct disorder according to K-SADS-PL, (2) a total WISC-IV IQ score above 80, and (3) no psychotic status or associated neurological disorders. The current sample and samples used in our previous studies did not overlap. All subjects participated voluntarily in the study after a written informed consent was obtained from parents or legal caregivers. The entire study protocol, which includes a wide range of neuropsychological tasks and psychopathological questionnaires, was approved by the local Ethical Committee.

## 2.2. Measures

**2.2.1. Psychopathic Traits.** The antisocial process screening [32] was used in the current study to evaluate the levels of CU traits. The APSD is a 20-item rating scale, used in this study in its combined version (APSD parent version and APSD youth version) taking the highest score of each item. The APSD items are rated on a three-point Likert scale as not at all true (0), sometimes true (1), or definitely true (2). Factorial analysis using a nonclinical sample of 1120 children and adolescents identified a subdimension of the APSD related to callous-unemotional traits (defined by 6 items). The APSD has been shown to have reasonable reliability and validity in previous studies [33]. There is substantial support for the validity of the APSD in distinguishing subgroups of antisocial youth with more severe and aggressive behavior and characteristics similar to adult

psychopathy [13, 34]. Our group translated the APSD in Italian language, using the back translation method. In the current sample, the reliability of the CU subscale of the APSD is excellent (Cronbach = .86).

**2.2.2. Empathic Concern and Perspective Taking.** The Interpersonal Reactivity Index (IRI) [35] is a self-reported questionnaire that assesses perceived individual differences in the tendency to be empathetic. In this study, we used the Italian version of IRI [36].

IRI consists of 28 Likert-type items on a response scale with five alternatives ranging from 1 (does not describe me well) to 5 (describes me very well). The scale allows a multidimensional assessment of empathy measured by two cognitive subscales (perspective taking and fantasy) and two affective subscales (empathic concern and personal distress). Previous studies demonstrated the IRI reliability, and the IRI reliability has been found to be good in the current sample (Cronbach's alpha range from 0.70 to 0.80). The IRI scales showed high convergent validity with other questionnaires used to assess empathy as Empathy Questionnaire for Children and Adolescent [37], Jefferson Scale of Empathy [38], Empathy Quotient [36, 37], and Basic Empathy Scale [33]. In this study, we use two subscales: perspective-taking (PT) and empathic concern (EC). The subscale PT evaluates the propensity to adopt the views of others, in the everyday life, and the subscale EC investigates the tendency to experience feelings of compassion and concern for people having negative experience. Therefore, the scores of each subscale range between -14 and +14 points where higher scores indicate more empathic abilities. For the study, we used the Italian version of IRI by Albiero et al. [39]; the reliability of the scale is satisfactory with a good internal consistency [39].

**2.2.3. Emotion Recognition.** In this study, we used the child's eye test (CET) [29] adapted from the adult version "Reading the Mind in the Eyes Test" developed by Baron-Cohen et al. This test was originally developed as a sensitive measure used to evaluate the theory of mind that consists the ability to make inferences regarding others' emotions (affective or emotional ToM) or beliefs and motivations (cognitive ToM). In recent years, CET was used in literature to test the ability to recognize basic and/or complex emotions. The test includes 28 photographs of the eye region of the face and requires participants to choose which of the four words best describes what the person in the picture is thinking or feeling. Three of the four words are foil mental state terms, while the fourth is defined as "correct." The position of the four words is randomized for each item. Written instructions were given to each participant before starting the test. In the present study, the 28 items were divided into three subcategories, conveying basic emotions (e.g., happiness and sadness corresponding to Ekman's basic emotions, demonstrated to be cross-culturally recognized from the face and proposed to rely on innately specified mechanisms; 10 items), social emotions (e.g., guilt, arrogance, admiration, and flirtatiousness, which depended on the complex social context for their specification, 9 items), and complex mental

states (e.g., interest, thoughtfulness, and boredom, which have been shown to depend most critically on information signaled by the eye region of the face; 9 items). For the total score and each subscale, correct responses are summed so that higher scores indicate better emotion recognition.

**2.2.4. History of Maltreatment.** Maltreatment scores were collected using the maltreatment index clinician-child report (MI) [40]. The MI is based on the Maltreatment Classification System by Barnett et al. and uses a 4-point Likert scale (1 = never) to rate the veracity of three statements pertaining to emotional abuse, physical abuse, and neglect. MI ratings were produced by taking the highest score in the clinician or patient report. The rate of MI rating agreement was .84 ( $k$  Cohen). For the statistical analyses, we combined physical and emotional maltreatment into a combined physical/emotional maltreatment (active maltreatment).

**2.3. Statistical Analyses.** With regard to the first aim, associations among measures of components of empathy, CU traits, and history of maltreatment were explored using Pearson's correlations. With regard to the second aim, the CD patient group was divided in two subgroups using the cutoff for the CU subscale as reported in the APSD manual [32]. Specifically, we divided the sample in CD youths with high levels of CU traits ( $\geq 9$ ) and CD youth with low levels of CU traits ( $< 9$ ). The group differences on main study variables were analyzed by Student's  $t$ -test. All statistical analyses were performed using SPSS v.25.0.

### 3. Results

Descriptive statistics for all variables are presented in Table 1. The levels of CU traits were significantly negatively associated with empathic concern ( $r = -.29$ ,  $p < .05$ ) and negatively associated with perspective taking abilities ( $r = -.27$ ,  $p < .05$ ). The levels of CU traits were not associated with abilities in emotion recognition and history of maltreatment.

**3.1. Empathic, Emotional, and Behavioral Profiles of CD Patients with High CU Traits.** As shown in Table 2, the  $t$ -test revealed a significant difference between subjects with and without elevated levels of CU traits only on empathic concern ( $t = 2.10$ ;  $p = .04$ ). In particular, the CD patients with high levels of CU traits show significantly lower levels of empathic concern compared to those with low levels of CU traits.

### 4. Discussion

Empathy is a multidimensional construct that includes two distinct but interrelated abilities. Cognitive empathy is the ability to understand and identify another's affective state, while affective empathy refers to share another person feelings [18, 41, 42]. Impaired empathy is a core feature in children and adolescents with CD and high CU traits, but there is limited and controversially research-concerning individuation of specific empathy deficits in CD youths. Therefore, many authors stressed the need to analyze

empathy as a psychological process involved in CD youths and to develop more specific assessment [43].

One of the aims of our work was to analyze the differences in empathic concern (an aspect of affective empathy) and perspective taking (an aspect of cognitive empathy) in a clinical sample of CD patients subgrouping in CD with or without CU traits. The findings showed a specific impairment of affective empathy in patients with CD and CU traits: they lack in the ability to experience feelings of compassion and concern for people having negative feelings. No significant difference was detected in perspective taking (an aspect of cognitive empathy) between CD youths with or without high CU traits. These findings are partially in agreement with previous research into CU traits and their correlations with impaired imbalance dimensions of empathy. In community children, Anastassiou-Hadjicharalambous and Warden [44] found that CU traits are associated with deficits in both cognitive empathy and affective empathy. Similarly to our findings, Dadds et al. [18] found that typically, development children with higher levels of CU traits had lower parent-reported affective empathy level, whereas Muñoz et al. [45] in a preadolescent community sample showed that the group highest in CU traits was lowest only in affective empathy and Seara-Cardoso et al. [46] found that the affective/interpersonal component of psychopathy is associated with weaker affective empathy in an adolescent community sample. Finally, Pardini et al. [47] found that adolescents with elevated levels of CU traits showed low levels of affective empathy while controlling for delinquency and conduct problems and Jones et al., [21] using a sample of children and adolescent boys with conduct problems, found that CD children with high levels of CU traits are impaired in affective empathy but not in cognitive empathy. In a recent work, with a sample of adults from the community, authors found that both components of empathy negatively correlated with CU traits. However, the negative correlations observed between self-reported affective empathy and CU traits are significantly larger than the correlations between CU traits and cognitive empathy [48].

Several studies indicated that CD children and adolescents with CU traits had deficits in emotion processes and in orienting to affective stimuli; furthermore, they showed low fearful inhibition and are under arousal in the sympathetic autonomic nervous system. These CU characteristics may determine deficits in affective empathy as well as in cognitive empathy. Our findings are partially in line with the well-studied subject [15]; in our sample, cognitive empathy deficits are not restricted to CD children with high-level CU traits. These findings have important clinical implications, since they suggest that CD with CU traits is primarily characterized by low levels of affective empathy.

Differences in our emotion recognition task did not mark CD patients with elevated levels of CU traits. Furthermore, in our sample, correlations between CU traits and emotional recognition impairment were not significant for basic, social, and complex emotions.

In several studies, the ability to recognize fear and sadness was individuated as uniquely an impairment in adults with psychopathy traits, which explains their tendency



TABLE 1: Descriptive statistics and correlation matrix.

	M	SD	2	3	4	5	6	7
APSD CU	7.82	2.38	-.29*	-.27*	-.13	-.06	-.19	.11
Empathic concern	3.23	.81	—	.37**	.09	.07	-.03	-.08
Perspective taking	2.35	.62	—	—	.36*	-.02	.05	-.13
CET—basic	6.16	1.57	—	—	—	.39*	.03	.14
CET—social	5.41	1.46	—	—	—	—	.33*	.13
CET—complex	5.52	1.48	—	—	—	—	—	.09
Active maltreatment	2.88	.43	—	—	—	—	—	—

\*\*Significant for  $p < .001$ ; \*significant for  $p < .05$ .

TABLE 2: Empathic, emotional, and behavioral profiles of the CU groups.

	Low CU ( $N = 40$ )		High CU ( $N = 20$ )	
	M	Ds	M	Ds
Empathic concern	3.38 <sup>a</sup>	.79	2.81 <sup>b</sup>	.77
Perspective taking	2.68	.62	2.55	.80
CET—basic	5.97	1.87	6.36	1.50
CET—social	5.15	1.48	5.00	1.90
CET—complex	5.76	1.71	5.18	1.60

Different letters indicate statistically significant differences between groups.

toward aggression [49–52], but other studies have found either no deficits or superior recognition of these emotions [45, 46, 50, 53–55]. Impairments in the recognition of fear and sadness was previously described in adolescents with high levels of CU traits, but these findings were not confirmed in other studies [53, 55, 56]. Sharp et al. [56] explain discrepant findings with a unique association between CU traits and specific deficit in recognizing complex emotions and weaker associations with basic emotion recognition. Conversely, our findings did not show correlation between the levels of CU traits and recognition of both basic and complex emotions. Moreover, the levels of basic and complex emotion recognition did not discriminate the CD youths with high levels of CU traits from those with low levels of CU traits.

Marsh and Blair [57] highlighted that methods and measures for indexing ER, typically using static images on a computer screen, may only partially tap the ER impairment or do so with variable validity and reliability. Furthermore, Schwenck et al. [58] and Dawel et al. [28] indicated that ER deficits in psychopathy are pervasive across emotions and modalities and age group but revealed that important limitations in current data were that age was confounded with the sample source and that there were insufficient studies reporting results for the affective subfactor of psychopathy.

Finally, Dadds et al. [43] showed that the simple manipulation of asking a youth to look at the eyes results in increased emotion recognition. These evidences suggest that the attention to the eye region of others might improve the

emotion recognition ability also in children with high levels of CU traits. Given that, we could also postulate that the characteristics of the CET stimuli help the subjects with CU traits in recognizing emotions.

Finally, in our research, the active maltreatment, evaluated using MI, did not correlate to the measures of adolescents' empathy profile and CU traits. The experience of maltreatment in childhood clearly contributes to the development of externalizing behavioral problems, empathy components, and CU trait dimension. However, the direction of influence between maltreatment and CU traits may operate through a complex interplay of heredity and environmental factors in which high CU traits can elicit harsher parenting and maltreatment [59] as well as the result from it [9].

Our study also provides some useful clinical implications. CU traits are predictors of poor response to treatment [60]. Battagliese et al. [61] indicated several treatment models for reducing aggressive behavioral problems in children and adolescents; however, only pilot studies are aimed at reducing CU traits in children and adolescents [62–65]. These models focus on the improvement of empathic behavior in children, as well as on parenting skills.

Recently, Dadds et al. [66] tested the efficacy in reducing the levels of CU traits of a specific parent training model. Although the results of this study were promising, however, the authors suggested that intervention for CU traits will need to be strengthened involving more therapeutic sessions (in terms of dose of intervention). Furthermore, they suggested augmenting behavioral with biological intervention such as oxytocin.

One of the limits of the present study is represented by the sample size, which is small and made up of males only. In particular, the sample size could significantly influence the results, which appear to be not conclusive. Further and well-oriented studies in a large sample size are needed to confirm the results.

Moreover, it could be very interesting to include females in the sample in order to explore the dimension of empathy also in females with CD.

## Data Availability

The dataset used to support the findings of this study are available from the corresponding author upon request.

## Ethical Approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki declaration of 1975, as revised in 2008.

## Conflicts of Interest

Dr. G. Masi was on the advisory boards for Eli Lilly, Shire, and Angelini. He has received research grants from Eli Lilly, Shire, Lundbeck, Humana, and FB Health and has been a speaker for Eli Lilly, Shire, Lundbeck, FB Health, and Otsuka. None of the other authors have conflicts of interest to declare.

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## Research Article

# Autonomic Responses to Emotional Stimuli in Children Affected by Facial Palsy: The Case of Moebius Syndrome

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According to embodied simulation theories, others' emotions are recognized by the unconscious mimicking of observed facial expressions, which requires the implicit activation of the motor programs that produce a specific expression. Motor responses performed during the expression of a given emotion are hypothesized to be directly linked to autonomic responses associated with that emotional behavior. We tested this hypothesis in 9 children ( $M_{\text{age}} = 5.66$ ) affected by Moebius syndrome (MBS) and 15 control children ( $M_{\text{age}} = 6.6$ ). MBS is a neurological congenital disorder characterized by underdevelopment of the VI and VII cranial nerves, which results in paralysis of the face. Moebius patients' inability to produce facial expressions impairs their capacity to communicate emotions through the face. We therefore assessed Moebius children's autonomic response to emotional stimuli (video cartoons) by means of functional infrared thermal (fIRT) imaging. Patients showed weaker temperature changes compared to controls, suggesting impaired autonomic activity. They also showed difficulties in recognizing facial emotions from static illustrations. These findings reveal that the impairment of facial movement attenuates the intensity of emotional experience, probably through the diminished activation of autonomic responses associated with emotional stimuli. The current study is the first to investigate emotional responses in MBS children, providing important insights into the role of facial expressions in emotional processing during early development.

## 1. Introduction

Moebius syndrome (MBS) is a rare congenital syndrome affecting approximately 1 in 50000 to 1 in 500000 live

births [1], with no gender predominance [2]. The disorder presents with varying phenotypes and severity and is characterized by unilateral or bilateral facial paralysis, as well as impaired bilateral movement of the eyes. This is due

to maldevelopment of the VI and VII cranial nerve nuclei early in prenatal life [3–7]. The VI and VII cranial nerves control, respectively, the abduction of the eyes and the muscles used to generate facial expressions, lip speech, and eye closure. V, IX, X, and XII cranial nerves can also be affected [8–10]. Other congenital abnormalities are sometimes associated with the syndrome, including sensorineural hearing loss, craniofacial malformations, limb anomalies, Poland syndrome (underdevelopment of the pectoralis muscle and hand malformation), hypoglossia, and poor coordination [10, 11]. Most patients are of normal intelligence, while approximately 9–15% present mild mental retardation, and another 0–5% are diagnosed with autistic-like behaviors [12–14].

One of the most prominent features of MBS patients is their inability to smile or produce any facial movement, which limits their capacity to communicate emotions through the face [15–19].

Evidence has shown that the motor component of emotional facial expressions is associated with an involuntary autonomic nervous system (ANS) response [20]. It has been proposed that the coding of emotional stimuli in macaque monkeys is mediated by the activity of brain networks including both cortical motor and specific limbic regions [21]. Human neuroimaging studies have demonstrated that, in addition to motor regions, the observation and direct experience of an emotion activate specific brain areas (i.e., the anterior insula, the anterior cingulate cortex (ACC), and the amygdala) [22], which are important not only in the control of the motor components of emotions but also in orchestrating the complex visceromotor responses associated with an emotional state (increase/decrease in heart rate (HR), changes in blood pressure, pupil dilation, piloerection, metabolic changes, etc.) [21, 23–25]. Emotional processing therefore relies on a complex network of brain regions in which some structures, such as the insular cortex, the amygdala, and the ACC, could coordinate the autonomic responses typical of the limbic system with the motor modifications associated with the expression of an emotion [26, 27]. This tight connection between motor and autonomic responses is therefore of utmost importance when investigating disturbances involving the motor commands controlling emotional expressions.

Several studies posit that the same motor regions involved in the generation of a particular facial expression of emotion are also implicated in recognizing that emotion in others [28–30]. The neuronal basis of this process is underpinned by a mirror mechanism, implemented by a parietal-premotor cortical network known as the “mirror neuron system” (MNS) [31, 32]. The MNS in humans has been proposed to support not only the understanding of others’ action intentions [33–35] but also the recognition of others’ emotions through activation in the observer of a neural motor representation similar to that expressed by the observed individual [25–27, 34–40]. Emotion recognition therefore occurs via unconscious mimicking of the observed expression, which requires the implicit activation of those motor programs responsible for the production of a particular facial expression and associated physiological

responses (also named *reverse simulation model*) [41–44]. According to embodied simulation theories [41, 45–49], the perception of an emotional facial expression is accompanied by the simulation of that specific emotional state in the motor, somatosensory, affective, and reward systems of the perceiver [44, 50, 51].

In light of these premises, facial motor impairment in MBS patients could impact several processes related to emotions. A few studies have shown that adult Moebius patients can recognize others’ emotions to some degree, but the results are mixed. This is likely due to certain methodological limitations including patient sample size, lack of clinical evaluation, nonobjective assessment (i.e., self-evaluation), and variations in the measures and tasks used [52–55]. In addition, previous studies have centered on adults, who may have developed alternative strategies throughout their lifespan in order to cognitively recognize facial expressions. These supportive strategies, whereby specific facial cues of emotion expression (e.g., the mouth corners turned up or down) are extracted [56, 57], could have positively affected their ability to discern different emotions later in life. Finally, the above-mentioned studies focused on Moebius patients’ emotion recognition abilities without investigating the autonomic component of emotional processing.

Bearing in mind that the motor and autonomic components associated with an emotional expression interact with each other, one could say that the congenital absence of facial muscle activity and relative proprioceptive feedback could result in a dysfunctional autonomic response to emotional stimuli and difficulties in recognizing others’ emotions [52, 55]. MBS patients therefore represent an interesting population to investigate this.

The measurement of the autonomic component of emotional processing during childhood would enable the constraints linked to cognitive processing of emotional information to be bypassed. In this sense, the lack of facial expressivity in Moebius children makes them an ideal subgroup to study emotional processing during the early phases of development, when complex cognitive strategies have yet to emerge.

We hypothesized that the lack of facial motor activity in MBS children during the decoding of emotions could induce an altered autonomic response while watching emotional videos, as well as difficulties in deciphering emotional facial stimuli. To this end, we monitored participants’ autonomic response during observation of emotional stimuli using functional infrared thermal (fIRT) imaging, a dynamic and noninvasive method of measuring skin temperature distribution [58]. Facial skin thermal patterns depend on subcutaneous vessels transporting blood heat. These vessels regulate blood flow via local vascular resistance (vasodilation and vasoconstriction) and arterial pressure [59]. Therefore, by recording the dynamics of facial cutaneous temperature, it is possible to assess ANS activity and infer the subject’s emotional state [60–64].

fIRT has been shown to be effective in detecting several affective states, including extreme stress [63], startle [65], fear [66], arousal [67], and happiness [68]. For example, fear experienced during a threatening and distressing situation

[62, 69–71], as well as the experience of stress [71, 72] or guilt [61], is related to a decrease in nasal tip temperature due to subcutaneous adrenergic vasoconstriction [73]. On the contrary, social interaction [62, 74] and sexual arousal [75] produce an increase in nasal tip temperature, caused by the vasodilation effect of the parasympathetic nervous system on the autonomic state of the individual. Crucially, due to its low invasiveness and versatility, fIRT results are particularly suitable for use with younger individuals, as well as clinical populations [61, 62, 76, 77].

In the present study, we expected to observe a weaker thermal modulation in MBS participants compared to control subjects, and we hypothesized that the motor impairment of MBS patients would result in an impaired autonomic response during emotion observation.

## 2. Materials and Methods

**2.1. Participants.** We recruited 9 children (5 males) with MBS aged 4 to 8 years (mean age 5.66, SD = 1.78). Moebius participants exhibited unilateral or bilateral facial paralysis, as well as related neurological symptoms (see Table 1); all were referred to as cognitively able in the study, and all were attending mainstream schools at a level appropriate to their age. Moebius children were recruited through the clinical center at the University of Parma, which specializes in the diagnosis of MBS and therapeutic intervention. Only patients without cognitive disability or diagnosis of autism were included in the experiments. We also recruited 15 healthy children (control group) (9 males) in the same age range (mean age 6.6, SD = 1.79). All participants were informed that they would be videotaped by means of a thermal camera and a webcam. All parents gave their informed written consent after full explanation of the procedure, which is in accordance with the 1964 Declaration of Helsinki. The study was approved by the Ethics Committee of the University of Parma.

**2.2. Materials.** Thermal IR imaging was performed by means of a digital thermal camera FLIR T450sc (IR resolution:  $320 \times 240$  pixels; spectral range:  $7.5\text{--}13.0\ \mu\text{m}$ ; thermal sensitivity/NETD:  $<30\ \text{mK}$  at  $30^\circ\text{C}$ ). The frame rate was set to 5 Hz (5 frames/sec). A remote-controlled webcam (Logitech webcam C170) was used to film the participants' behavior, so as to record their level of attention while watching video stimuli.

**2.3. Procedure and Stimuli.** Prior to testing, each participant was left to acclimatize for 10 minutes to the experimental room and to allow their skin temperature to stabilize. The recording room was set at a standardized temperature ( $23^\circ\text{C}$ ) and humidity (50–60%) and was not subject to direct sunlight, ventilation, or airflow. During an initial neutral interaction, the experimenter asked the child to answer questions related to personal data (e.g., name and age). The child was then invited to watch a series of video stimuli displayed on a computer monitor ( $32.5 \times 22.7\ \text{cm}$ ) placed 60 cm far from the chair where the child was sitting. According to other thermal imaging studies using video stimuli [60, 78, 79], our sequences included 6 different video clips (neutral

baseline-happiness-neutral baseline-sadness-neutral baseline-fear), with each emotional video preceded by a neutral video. Stimuli were comprised of short clips taken from the Internet in which the main character of the scene was in a happy, sad, or scary situation. The emotional video clips varied in their duration (mean = 81.38 sec; SD = 43.49), while neutral video clips (ones with no emotional content) lasted about 30 sec (mean = 28.83 sec; SD = 3.69) (Figure 1). Chosen stimuli represented the kind of videos that children of this age are familiar with.

Video clips were validated before the experiment in order to ensure that they were easily comprehensible and represented the specific emotion deemed appropriate for the age range of interest here. To do this, we presented neutral (baseline), happy, sad, and scary videos to a separate group of 16 children (8 males) with a mean age of 7.5 years; participants were asked to categorize the video clip as evoking feelings of “happiness,” “sadness,” “fear,” or “neutral baseline.” The average percentage of correct recognition was 95.83%. Based on our validation study, we randomly presented two video sequences from a list of six. The choice to present two sequences only was based on expected fatigue, habituation, and difficulty in sustaining children's attention for long periods of time.

During the experimental session, thermal and video cameras were placed above the monitor, one meter away from the participant. Cameras were automatically calibrated and manually fixed to capture a frontal view of the child's face. Facial thermal images and videotapes were recorded during each video presentation.

At the end of each short video clip, participants were asked a series of questions concerning (1) the emotional state of the main characters depicted in the video cartoon and (2) the child's own emotional involvement while watching each video clip. Unfortunately, in most cases, the children did not reply to the questions and therefore it was not possible to apply statistical analyses. To overcome the difficulty of this assessment, we also administered the Italian standardized version (see [80]) of the *Test of Emotion Comprehension* (TEC-1) [81], so as to obtain an index of the individual's capacity to discriminate different emotions. MBS children were administered component I of the TEC-1, which assesses emotion recognition by means of facial expression discrimination (Figure 2). Four simple drawings were presented on an A4 sheet of paper, which included four out of five possible emotions depicted by cartoon facial expressions. The children were asked to indicate which of the facial expressions was happy, sad, angry, scared, or “just alright” (i.e., neutral component). Figure 2 illustrates the items used to assess children's emotion recognition. Five successive items were used to test children's recognition of emotions. Depending on the participant's own gender, a corresponding version of the drawings (i.e., female or male) was presented. Component I of the TEC-1 was also used to test the emotion recognition ability in 15 healthy subjects in the same age range as Moebius participants. The full experimental session, including both emotional sequences and TEC-1, lasted a maximum of 45 minutes.

TABLE 1: Moebius subjects' medical cases. The term "laterality" refers to the kind of facial paralysis that can be unilateral or bilateral; the sixth and seventh cranial nerves are usually involved, but other nerves may also be affected. "Associated pathologies" linked to Moebius syndrome can involve possible hand and foot anomalies, muscle hypotonia, hypoacusis, swallowing and speech problems, and Poland syndrome.

ID no.	Sex	Laterality	Cranial nerves involved	Additional functional deficits and associated pathologies
1	M	Unilateral left	VI, VII	—
2	M	Bilateral	VI, VII, III, IV	Strabismus, hypotonia, hypoacusis of the right ear, speech deficit (articulation-phonetic disorders), right plagiocephaly, psychomotor delay, epileptic seizures, cardiac crisis
3	F	Bilateral	VI, VII, XII	Foot malformations
4	F	Unilateral left	VI, VII, XII	Speech deficit, club feet
5	M	Bilateral	VI, VII, XII	Club foot, brain stem atrophy with enlargement of the fourth ventricle, hand deformities
6	F	Unilateral right	VI, VII, XII right	Micrognathia, tongue hypoplasia
7	F	Bilateral	VI, VII	Bilateral mixed hypoacusis, hypotonia, delayed growth, laryngomalacia, palatal schisis, coloboma of the right optic nerve
8	M	Bilateral	VI, VII, XII left	Respiratory difficulties, micrognathia, hypotonia, psychomotor delay, club foot
9	M	Bilateral	VII	No ocular deficits, speech delay

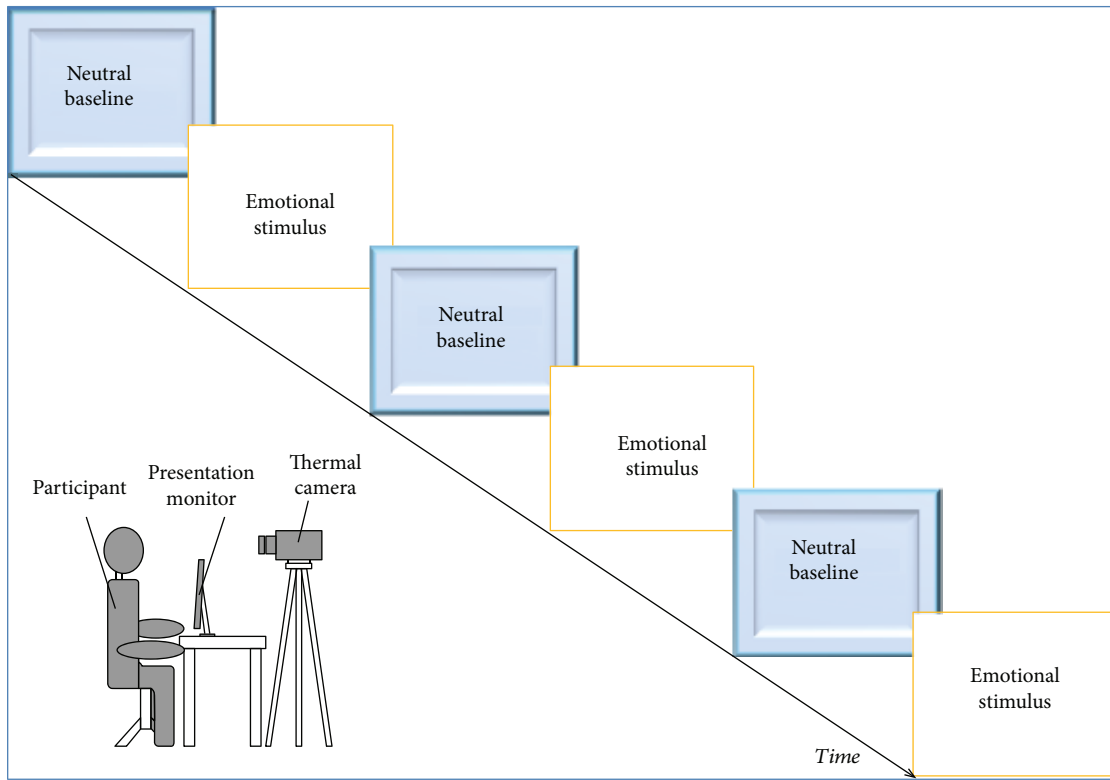


FIGURE 1: Experimental paradigm. Schematic overview of the experimental paradigm.

**2.4. Data Analysis.** A quantitative analysis was carried out to measure temperature variations of participants' nasal tips. Elliptic regions of interest (ROIs) with identical shape and dimensions ( $A = 297$  pixels;  $\text{MajorAxisLength} = 20.35$  pixels;  $\text{MinorAxisLength} = 18.64$  pixels) were utilized. We focused on this ROI for two main reasons. First, given the relatively low incidence of MBS, the specific age sample of interest, and the pioneering nature of the current study, we decided to include patients with unilateral or bilateral facial

paralysis. The nasal tip is a nonlateralized ROI, so its temperature should not be modulated by the lateralization of nerve impairment. Second, the nasal tip has been shown to be particularly sensitive to emotional state transitions [62, 65, 70, 82]. This area of the face is indeed highly innervated by adrenergic fibers, resulting in a privileged window on a participant's autonomic state. More specifically, sympathetic nervous responses to emotional and distressing stimulation produce a decrease in nasal tip temperature whereas



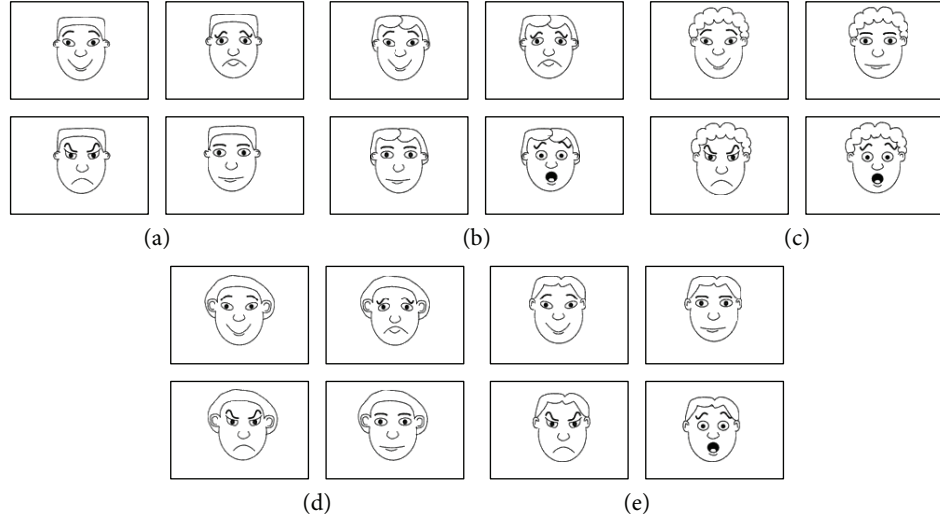


FIGURE 2: Example of cartoon pictures presented during TEC-1 (component I, emotion recognition).

parasympathetic responses result in a temperature increase in this ROI [62, 65, 68, 71, 77, 82, 83]. Thermal signals were extracted through the use of the software Morphing GUI, developed with customized MATLAB algorithms (The Mathworks Inc., Natick, MA). This analysis procedure is more extensively described in [84]. Due to the high computational load associated with the morphing procedure, we decided to downsample the collected dataset. Given the slow nature of thermal responses, such a processing choice did not affect the precision of temperature change detection [62, 84]. For each video stimulus presented to the child, three thermal images were extracted (one frame at the beginning, one in the middle, and one at the end of each video) and morphed. These particular frames were selected in order to minimize the effect of the respiratory cycle on the thermal imprinting of the subject [71]. The three frames selected within each condition (emotional or neutral) were averaged. In order to interpret any affective response, the selection of an appropriate baseline represents the starting point for defining the directionality of the physiological change during emotional arousal [76]. For this reason, we selected video clips with no emotional content (see Procedure and Stimuli) to eliminate the interindividual variability in the subjects' temperature and to minimize the effect of participants' circadian variations on our data. We followed a typical procedure for thermal data analysis [62]: subtraction of the mean thermal value of each neutral condition from the mean thermal value of its following experimental condition (happiness, sadness, and fear). In this way, we obtained a dataset of thermal variation for each emotional condition relative to the neutral condition. The thermal variations for the two trials belonging to the same condition were then averaged to obtain a mean value for each emotion (happiness, sadness, and fear) (see Figure 3(a)). This was used as the variable of interest in our statistical analyses, including the comparison of MBS participants and the control group.

During TEC-1 administration, participants' answers were noted on the answer sheet by the experimenter and

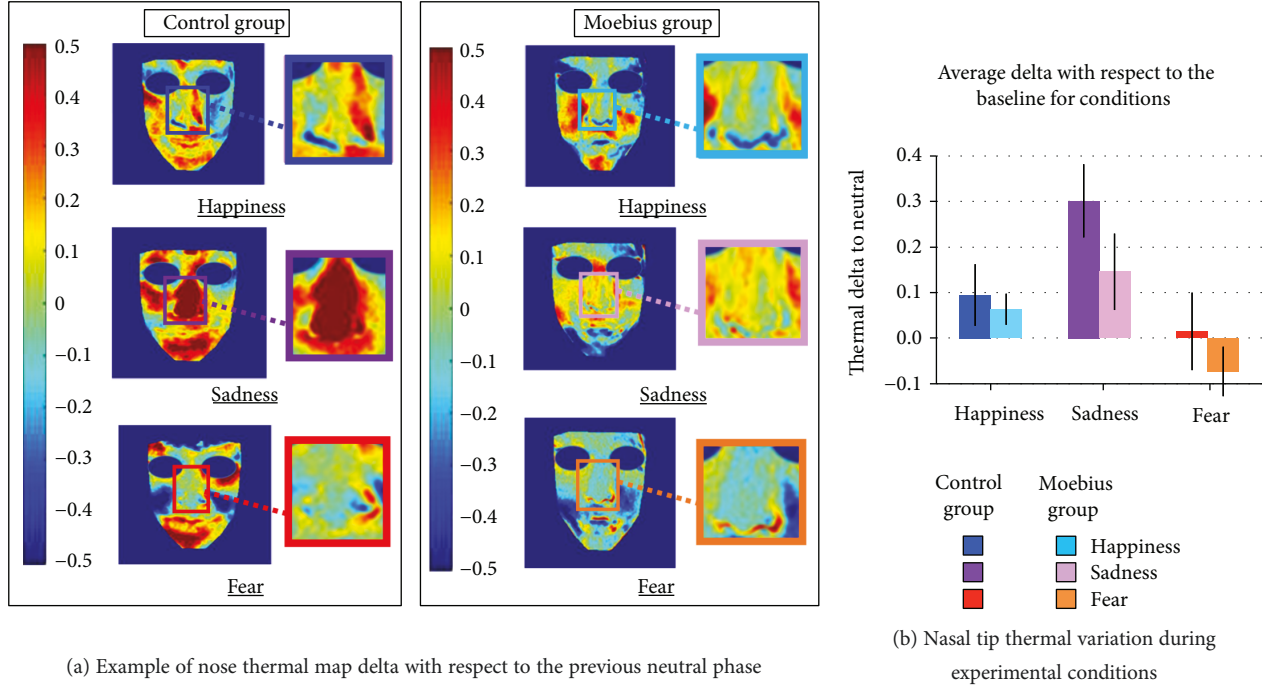
subsequently coded (1 point for each correct answer and 0 for each wrong answer).

**2.5. Statistical Data Analysis.** A repeated measures ANOVA ( $6 \times 2$ ) was performed on the neutral baseline temperature values in order to confirm that baseline temperature did not significantly differ between the Moebius and control groups ( $p > 0.05$ ). A repeated measures ANOVA ( $3 \times 2$ ) was performed on the mean nasal tip values (emotion compared to neutral baseline) for all participants [76]. The emotion condition (happiness, sadness, and fear) was set as a within-subjects factor, while the group (Moebius and controls) was set as a between-subjects factor [85, 86]. Bonferroni post hoc tests (Bonferroni corrected) followed the two-way ANOVA. Assumptions of residual normality and homogeneity of variance were investigated using Shapiro-Wilk and Levene's tests, respectively. Normality and equal variance were confirmed. If data violated the sphericity assumption, Greenhouse-Geisser ( $\epsilon < 0.75$ ) or Huynh-Feldt ( $\epsilon > 0.75$ ) corrected values were reported.

A nonparametric Mann-Whitney  $U$  test for independent samples was used to compare Moebius and control group answers from the TEC-1. One Moebius subject did not complete the TEC-1 and was excluded from the analysis. Finally, we correlated the thermal values for each emotion condition with the TEC-1 scores. Data were analyzed by means of Statistica 8.0 (StatSoft, Tulsa, OK, USA).

### 3. Results

**3.1. Thermal Data: Group Temperature Variations in relation to Conditions.** A repeated measures ANOVA ( $3 \times 2$ ) was performed on the resampled variations of mean nasal tip temperatures. We did not find any differences between the two groups ( $p = 0.432$ ). The results highlighted a significant effect of emotion condition ( $F_{(1.53,33.71)} = 10.99$ ;  $p \leq 0.001^*$ ;  $\eta^2 = 0.325$ ); post hoc tests showed that nasal tip temperature during the sadness condition significantly increased



(a) Example of nose thermal map delta with respect to the previous neutral phase

(b) Nasal tip thermal variation during experimental conditions

FIGURE 3: (a) Thermal modulation in an example control participant and Moebius patient during the “happiness,” “sadness,” and “fear” conditions. In the figure, the inlays present the entire nasal area, but elliptic nasal tip ROIs were used for analyses ( $A = 297$  pixels;  $\text{MajorAxisLength} = 20.35$  pixels;  $\text{MinorAxisLength} = 18.64$  pixels) [62, 65]. The control participant shows stronger thermal variation during the sadness condition than the Moebius patient. (b) Mean temperature values during each of the experimental conditions, baseline-corrected with respect to the neutral condition. Both control and Moebius participants show a significant nasal tip temperature increase during the “sadness” condition ( $*p \leq 0.001$ ). Means and standard errors (SE) are reported for each condition in both control and Moebius groups.

TABLE 2: Descriptive statistics for each group and condition.

	Group	Happiness	Sadness	Fear
Mean	Control	0.199	0.364	0.216
	Moebius	0.144	0.212	0.118
Std. error mean	Control	0.033	0.075	0.042
	Moebius	0.030	0.057	0.023
Standard deviation	Control	0.128	0.290	0.163
	Moebius	0.090	0.171	0.069
Variance	Control	0.016	0.084	0.026
	Moebius	0.008	0.029	0.005

compared with that during the happiness ( $p = 0.013$ ) and fear ( $p \leq 0.001^*$ ) conditions (for descriptive statistics, see Table 2). No significant difference was observed between the fear and happiness conditions ( $p = 0.133$ ) (Figure 3(b)). The group  $\times$  emotion condition interaction was not statistically significant ( $p = 0.447$ ).

As shown in Figure 3(a), during all of the experimental conditions, Moebius participants exhibited a less appreciable thermal modulation compared to control participants while watching emotional stimuli. To measure any possible differences in the intensity of thermal modulation between the two groups, we considered the absolute value of change in temperature from baseline. As previously suggested, control participants exhibited a larger thermal response than Moebius participants during each experimental phase (Figure 4(a)).

A one-way ANOVA performed on the absolute value of the change in temperature from baseline revealed a significant effect of the group ( $F_{(1,22)} = 4.732$ ;  $p = 0.041$ ;  $\eta^2 = 0.177$ ), with control participants having higher absolute changes in temperature ( $0.261 \Delta T$ ) than Moebius participants ( $0.149 \Delta T$ ) (Figure 4(b)).

**3.2. Test of Emotion Comprehension (TEC-1).** Mann-Whitney  $U$  tests were performed to assess if control and Moebius participants’ scores significantly differed during the *Test of Emotion Comprehension* (TEC-1) administration. The results showed that the Moebius group had a lower level of facial emotion recognition (mean = 2.63; SD = 1.69) than the control group (mean = 4.80; SD = 0.41) ( $p = 0.002$ ) (Figure 5). The autonomic responses and TEC-1 scores were not significantly correlated ( $p > 0.05$ ).

## 4. Discussion

The purpose of our study was to detect psychophysiological responses in children affected by MBS by means of a fIRT camera. Moebius and control participants were asked to observe two sequences of emotional cartoon video stimuli representing three main emotions: happiness, sadness, and fear. Changes in nasal tip temperature were measured during the observation of the stimuli, and the results showed a significant difference between emotional conditions. Both MBS and control participants showed an increase in nasal tip temperature during the “sadness” condition [73], but

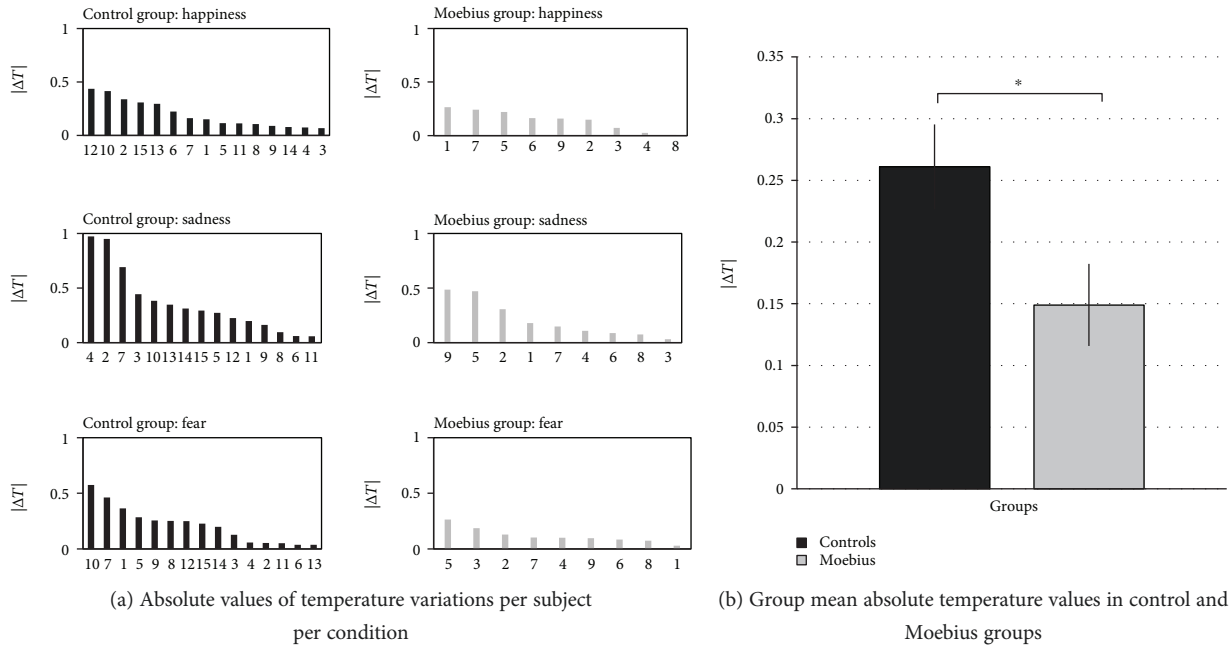


FIGURE 4: (a) Absolute value of the change in temperature from baseline per participant during each of the experimental conditions. Moebius participants exhibit a lower thermal modulation compared with control participants. (b) Group mean absolute temperature values in control and Moebius participants. Control participants have significantly more intense thermal modulation compared with Moebius participants. Means and standard errors (SE) are reported for both control and Moebius groups.

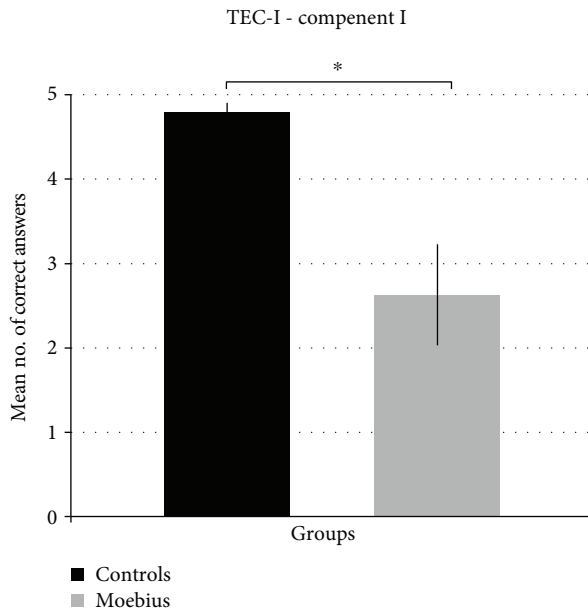


FIGURE 5: Mean number of correct answers from both control and Moebius participants. During the emotion recognition task (TEC-I), control participants performed better than Moebius participants. Means and standard errors (SE) are reported for both control and Moebius groups.

Moebius participants were characterized by a less pronounced change in nasal tip temperature across all three of the experimental conditions. Recent studies investigating the ANS response specificity in emotion found a dual sympathetic-parasympathetic coactivation in response to “sadness” [73].

Several studies using video clip stimuli to induce feelings of sadness have found that crying is associated with sympathetic activation, while parasympathetic activation is typical of sadness without crying. Specifically, an activating sadness response (crying) appears to be typified by increased cardiovascular sympathetic response and changed respiratory activity, while a deactivating sadness response (noncrying) is distinguished by a decrease in sympathetic activation. Furthermore, noncrying sadness is characterized by decreased HR associated with decreased electrodermal activity [73]. These results are in line with our thermal findings. Although nasal tip temperature increased in both groups during the sadness condition, Moebius patients exhibited a generally weaker thermal response. The reason why it was not possible to highlight a significant differential response to emotional conditions between MBS and control participants is probably due to the interindividual variability of participants’ thermal response to each emotion. For this reason, we considered the absolute values of participants’ thermal responses (independently of the direction of thermal variation with respect to a neutral baseline) in order to identify differences between groups. Our data revealed a weaker, nonspecific thermal response of Moebius children while watching emotional stimuli, with respect to control participants.

The diminished temperature changes observed in Moebius patients could be ascribed to a minor modulation of the autonomic system in response to emotional stimuli. This differential intensity of thermal change could be interpreted in terms of the tight link between an action-perception mechanism, which contributes to sensorimotor simulation and to the process of recognition of others’ emotions, and



coordinated changes in the autonomic system which control visceral responses associated with emotions [23, 31, 87].

Neuroimaging studies have shown that the observation and production of emotional facial expressions activate similar networks of brain areas [26, 38]. More specifically, in addition to the temporo-parietal-frontal areas, which are the core of the action-observation network, other regions such as the amygdala, the ACC, and the anterior insula show an overlapping activation during both imitation and observation of emotional facial expressions [26]. These regions are involved not only in processing the emotional content of a stimulus but also in coordinating the physiological responses associated with the emotion [21, 22, 25, 38]. Electrical stimulation of the anterior insula in the monkey has revealed that this region is composed of several sectors which generate different autonomic responses and facial motor patterns when stimulated [21]. This strengthens the proposal of a strict link between the production of emotional facial expressions and the physiological modifications associated with experience of them. Our results suggest that the autonomic response related to the observation of emotional stimuli is reduced in children with congenital facial palsy. Previous brain imaging studies have provided support for the crucial role of corticolimbic circuits in the regulation of emotions [88]; however, so far, none has investigated the effects of the lack of peripheral feedback on autonomic responses to emotional stimuli.

Although this was not the main purpose of our study, we also wanted to assess children's explicit comprehension of the emotions expressed by video cartoons. The difficulty in acquiring these behavioral measures (e.g., participants' identification of the emotion depicted by the characters of the videos and participants' feelings during the presentation of the cartoons) led us to administer a less complex task in order to assess children's ability to explicitly recognize basic emotions. We therefore examined the emotion recognition ability in Moebius children by means of a standardized test, TEC-1. Compared to control participants, Moebius participants showed impairments on the emotion recognition task, with lower scores than healthy children of comparable age. These findings suggest that the impairment of facial muscles involved in the emotional display could affect not only the autonomic response but also facial expression recognition [47, 89, 90]. These results, though preliminary, are also compatible with the reverse simulation model, which proposes that the preservation of cortical control of the facial muscles is necessary to fully comprehend the emotional state of the other [35].

A few reports have tested the capacity of Moebius patients to recognize emotions, and the results are inconsistent [51, 53–55]. Most of these studies tested a small group of adult patients, with significant interindividual variability. One study utilized a considerable number of adult patients [54], and the authors did not find any evidence of facial emotion recognition deficits. However, it must be noted that this study suffers from some critical methodological limitations, such as the indirect assessment of participants' performance and of their neurological deficits.

Our study is the first to use a relatively large sample of very young patients to investigate the effects of facial muscle

paralysis on both autonomic responses and emotion recognition. The investigation of these issues early in development is critical for the detection of emotional processing mechanisms at a stage where more complex cognitive strategies might not yet compensate for their deficits. In this regard, a large amount of literature has focused on how and when children's decoding of facial emotions develops [91, 92]. In the early stages of postnatal development, infants discriminate between different facial expressions and respond appropriately to different emotions displayed by their caregiver [93]. Furthermore, even if the debate revolving around the existence, prevalence, and meaning of neonatal imitation is still underway (see [94, 95], but also see a reexamination of this study [96] by Meltzoff and colleagues, which led to opposite results), much of the literature suggests that newborns are capable of mimicking certain facial expressions, such as smiles, indicating an early capacity to match own and others' facial expressions [96–99].

Considering that MBS facial paralysis is present since birth, we can hypothesize that MBS patients will exhibit mild deficits in the development of a fully functional MNS during the early stages of life. According to a theoretical developmental account [100, 101], after birth, facial expression synchronization with caregivers is critical to creating a link between the "self" and the "other" and to ensuring the shaping of the mirror mechanism supporting social communicative functions. Indeed, neonates are able to engage in reciprocal and emotional face-to-face interactions with their mothers. These exchanges, including facial and vocal expressions and gestures, are present immediately after birth and in the first month of life [102] and can be important for the development and function of the MNS [97, 103–105]. Recent studies have shown that based on such mother-infant face-to-face exchanges, the capacity of neonates to develop social expressiveness is related to their ability to produce appropriate emotional facial expressions and is correlated with the mother's skill in mirroring or marking such expressions [102, 105]. We do not know how this type of early experience could impact brain and emotional development, and this requires further investigations related to brain activity in cortical motor regions during mother-infant interactions in early development. However, children with MBS, due to their inability to express emotions through the face, might experience reduced quality of social interactions. It has been suggested that Moebius children might receive diminished facial responses from other individuals who, not perceiving a clear facial response during interactions, are less encouraged to socially engage and interact with them facially [106]. These hypothetical reduced inputs from both caregivers and other children, especially during early developmental periods, could have occurred from birth through childhood, resulting in an overall lower exposure to facial stimuli and consequent biased responses compared to healthy control participants.

Despite our findings that Moebius children have some deficits in recognizing emotions, they are still capable of understanding the emotional content of complex stimuli. The ANS response results, showing a similar, though less intense, thermal response in Moebius children compared with control

participants, suggest that several cognitive processes may be used by Moebius subjects in order to understand the emotional content of complex stimuli. It is possible that although subtle aspects of emotion recognition are impaired as a consequence of altered facial mimicry, brain plasticity during development and the exploitation of other cognitive strategies could be employed by Moebius patients to compensate for the early deficits.

At this point of the discussion, it should be mentioned that the role of the MNS in action understanding has been debated and discussions are still ongoing (see [107, 108], but also see [32, 109]). According to Hickok [110], action understanding and motor system function could be dissociated. In contrast to this view, a meta-analysis found impairments in recognizing actions associated with lesions in MNS regions [111]. These results are further supported by a study by Michael and colleagues [112] where participants received theta-burst stimulation to temporarily create a lesion on the premotor cortex, causing clear impairments in understanding actions performed by others. Our study does not allow us to support the hypothesis that facial mimicry is the only process involved in emotion understanding; in fact, other mechanisms could be exploited when automatic peripheral facial feedback is absent. However, a diminished autonomic response in Moebius patients makes us propose that, in line with embodied theories [48], facial mimicry could represent a key mechanism for emotional processing.

A few methodological limitations of our study should be mentioned. Cartoon stimuli differed in length because of our specific aim to present participants with an authentic content able to induce a particular emotion. Since emotional content is the actual variable expected to influence thermal values, the differential duration of the stimuli alone would not have affected the thermal results, given the slow dynamic of thermal response. This is further confirmed by our main result showing a difference between the experimental and control groups that was independent of stimuli duration.

Additionally, Moebius patients' impaired ocular abduction could be considered one limit of the current study; however, as discussed by Carta and colleagues [113], these patients compensate for their lack of lateral version with large movements of the head.

It has also to be pointed out that the extreme rarity of the syndrome, the limited age range taken into account, and the exclusion of patients with autism or mental retardation let us to include only a limited number of participants (9 participants), which did not permit further analysis. Despite the challenges involved in acquiring a sample large enough to study this syndrome, it would be worthwhile for future studies to explore the emotion recognition ability at different ages and/or gender differences.

Lastly, although fIRT is at the forefront of the techniques allowing ANS recording in a naturalistic setting, the thermal signal as a result of perspiration and muscle activity and the time course of metabolic responses are rather sluggish. Nevertheless, the reliability and feasibility of fIRT have been confirmed by several comparisons with other standard methods of ANS measurement such as electrocardiography (ECG) and skin conductance or galvanic skin response (GSR) [70].

As this technology is still in development, there is a need to determine if heat patterns indicate discrete emotions [114] or dimensional responses [115]. It would therefore be useful to integrate this method with other techniques to compare ANS measurements within the same experimental paradigm.

## 5. Conclusions

MBS patients' decreased capacity to activate a motor simulation process during the decoding of emotions could have led to a diminished thermal variation and ANS response during the observation of complex emotional stimuli. It is possible that patients' impairments in mimicking could have affected not only their cognitive emotion recognition processes but also the way in which they are related to ANS changes associated with emotions. If the absence or reduction of motor representations resulted in deficiencies in their early facial expression recognition mechanism (as a consequence of having limited control of facial muscles), MBS individuals might learn during development to cognitively deduce the emotional states of others by using a number of visual cues related to the face and the environmental context [116, 117]. By exploiting such cues, MBS patients can extract regularities and develop conceptual knowledge of an emotion [89]. Further studies are crucial in order to address the relationship between the level of emotion recognition deficits and the magnitude of the autonomic response, in order to better understand their possible causal relationship.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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## Review Article

# Neuroprocessing Mechanisms of Music during Fetal and Neonatal Development: A Role in Neuroplasticity and Neurodevelopment

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The primary aim of this viewpoint article is to examine recent literature on fetal and neonatal processing of music. In particular, we examine the behavioral, neurophysiological, and neuroimaging literature describing fetal and neonatal music perception and processing to the first days of term equivalent life. Secondly, in light of the recent systematic reviews published on this topic, we discuss the impact of music interventions on the potential neuroplasticity pathways through which the early exposure to music, live or recorded, may impact the fetal, preterm, and full-term infant brain. We conclude with recommendations for music stimuli selection and its role within the framework of early socioemotional development and environmental enrichment.

## 1. Introduction

The human brain is both wired with innate music abilities and shaped by music experience, starting in utero and continuing across the lifespan [1]. A growing body of literature from music therapy, music cognition, musicology, neurosciences, and affective and behavioral sciences target fetal and neonatal life, shedding light on the emergence and early development of sound and music perception. However, the great variability present in the literature in terms, for example, of type of music exposure, means of music administration, or age at exposure, has not yet allowed a clear understanding of how music experience impacts and shapes the human infant brain in the context of early neuroplasticity.

Human neural processing of music involves an extremely complex and widespread bilateral network of cortical and

subcortical areas, integrating several auditory, cognitive, sensory motor, and emotional functions [2, 3]. Although part of the mechanism underlying music processing might be explained by simple sound processing, music perception is more than the sum of its basic acoustic features. In addition to auditory signal transduction, it triggers a sequence of cognitive, motor, and emotional processes that involve a number of brain areas, unilaterally (e.g., pitch and melody processing are more lateralized to the right hemisphere), as well as bilaterally, involving a number of “musical subfunctions” (for review see [4]).

The wide effects of music on brain function, encompassing auditory perception, language processing, attention and memory, emotion and mood, and motor skills, have suggested the use of music as a therapeutic tool in neuropsychiatric patients, including young infants at neurodevelopmental risk. Indeed, several systematic reviews and

meta-analyses have examined the therapeutic role of music in preterm infants at neurodevelopmental risk, with inconclusive results, mainly due to the variation in study quality and methodology [5–10]. In most cases, the effects of the intervention were assessed in relation to cardiorespiratory parameters, growth and feeding outcomes, length of stay, effects on behavioral state, or pain. Much less is known on the effect of music intervention on direct measures of brain function and structure or on short- and long-term neurodevelopmental outcomes.

In this viewpoint review, we will firstly summarize current knowledge on the emergence and development of music processing during fetal and early postnatal life. Then, we will review the effects of music exposure in fetuses, preterm, and term newborns, with a specific emphasis on the effects of music on brain structure and function. Finally, in the light of these findings, we will discuss the possible role of music in early intervention programs, within the framework of early socioemotional development and environmental enrichment.

## 2. Emergence and Early Development of Music Processing in Fetuses, Preterms, and Term Newborns

**2.1. Evidence of Music Processing through Behavioral Techniques.** Studies measuring fetal movement or heart rate response to sound have shown that, although yet not fully mature, the developing auditory system enables responses to sound in utero from around 25 weeks of gestation. Fetuses respond first to low frequency 250 or 500 Hz tones, at around 25–27 weeks, and then to the 1000 or 3000 Hz tones by 29–31 weeks [11]. Fetal sound sensitivity, which refers to the intensity required to elicit a motor response (fetal movements quantified by ultrasound) at different frequencies, matures rapidly between 24 and 35 weeks of gestation [12]. High-intensity music to fetuses was shown to induce heart-rate accelerations and increased motor responses, whereas low-intensity music showed opposite effects [13]. An interesting study by Kisilevsky et al. [14] assessed the maturation of fetal response to music by evaluating fetal heart rate and fetal movement and suggested that a change in processing of complex sounds (such Brahms' Lullaby) might occur at around 33 weeks. At around term, by monitoring fetal cardiac responses, it was possible to show that near-term fetuses have very precise modulations of physiological behaviors related to specific aspects of the musical stimulus, such as sound intensity, frequency, and spectra [15–19] and can also process some fast and slow amplitude temporal variations in auditory streams [20].

A number of behavioral experiments appear to support the ability of newborns to process music per se. For example, preterm infants and term born neonates entrain to live-sung consonant lullabies, including synchronization of their sucking, mouth protrusions and tongue movement, respiration, and vocalizations which match the music contours [21]. There is compelling evidence that the ability of newborns to respond to music, and process it, is influenced by the

sound exposure during the last trimester of gestation in the womb [22]. Newborn infants prenatally exposed to music and with minimal or no exposure to it after birth, already show, in the first days of life, physiological responses to music including reactions to basic rhythmic and pitch patterns. These fetal memories can affect different psychobiological domains, and their impact is carried into the newborn period [23, 24].

**2.2. Evidence of Music Processing through Neurophysiological Techniques.** Fetal auditory-evoked responses have been evaluated with magnetoencephalography (MEG) studies and identified from 27 weeks gestation, showing a continuous decrease in latency with age until term [25, 26]. In these studies, pure tones, single tones, or syllables have been the stimuli of choice while to date no MEG studies have used music. A recent study used seven different amplitude-modulated tones with carrier frequency of 500 Hz for the evaluation of the fetal (31–40 weeks) brain response to envelope slopes and intensity change at the onset of the sounds [27]. The authors found significant differences between the response latency to low, middle, and high rates of amplitude modulation, supporting fetal ability to differentiate between intensity changes of sounds and not only frequency changes.

In preterm infants, brainstem auditory-evoked responses appear at around 27 to 29 weeks of gestation, showing synchronous eighth-nerve activity and brainstem responses [28–31]. In keeping with fetal MEG studies, the absolute latencies decline progressively with advancing age and with an inverse relationship to the intensity of the auditory stimulus. In the following weeks, initial cortical-evoked potentials are noted and seen as a pattern of intermittence of low- and high-voltage activity. Low voltage is asynchronous and also referred to as “relative quiescence” while high voltage is already present simultaneously in the corresponding areas of both hemispheres and therefore, synchronous, beginning at the occipital lobe and moving forward to the temporal regions. Auditory-evoked potentials in premature neonates at 33 week gestation have shown early cortical activity with nearly mature biomechanical function of the cochlear signal. The lack of electrical activity in the olivocochlear system in premature neonates before 32 weeks gestation might indicate that before that stage the immature auditory pathways cannot relay the information from the periphery to the cortex [32, 33].

In healthy full-term infants, the innate ability to detect the beat in a music sound sequence has been investigated with EEG on day 2 or 3 of life. The stimulus used was a 2-measure rock drum accompaniment pattern composed of snare, bass, and hi-hat spanning 8 equally spaced (isochronous) positions. The authors concluded in favor of the existence of beat detection abilities, based on the expectation of pattern downbeat, as measured by peak amplitude measurements 200 ms before and 600 after the stimuli presentation [34].

**2.3. Evidence of Music Processing through Neuroimaging Techniques.** Few functional MRI (fMRI) studies have assessed fetal and neonatal response to sound. Studies

evaluating fetal response to sound have demonstrated fetal hearing functional response to pure tones from 33 weeks of gestation in the left temporal lobe, localized between the sylvian sulcus and the superior temporal sulcus, consistent with the location of the primary auditory cortex [35]. Therefore, sound processing can already be observed beyond the reflexive subcortical level at the beginning of the third trimester. In full-term newborns, fMRI has revealed a bilateral BOLD (Blood Oxygen Level Dependent) response in the superior temporal regions to an auditory stimulation by a tonal sweep [36].

As far as music processing is concerned, two studies have evaluated near-term fetal response to music by fMRI. One used as stimulus is a Spanish guitar music, showing temporal activations in 4 of 7 participants and frontal activation in 1 participant [37]. The second one used as stimulus is a mother's voice singing a nursery rhyme, showing a significant temporal lobe activation in 2 of 3 fetuses [38].

In another study, one to 3-day old term born western neonates showed right lateralized auditory cortex activity as well as neural responses within the limbic system to altered musical stimuli when excerpts of western tonal music were used. In this study, western tonal music evoked predominantly right-hemispheric activation in primary and higher order auditory cortex. However, when altered versions of the same excerpts are presented, activation diminished in the right auditory cortex, instead emerging in the left superior and middle temporal regions, left inferior frontal cortex, and the limbic structures [39].

### 3. Effects of Music Exposure in Fetuses, Preterms, and Term Infants

Several studies have explored, in fetuses and newborns, the effects of the experimental manipulation of music stimuli to test the specific influence of music as compared to other or no stimuli, either between groups of otherwise matched subjects or within the same subjects at different times (intervention studies). The majority of them have focused on infants at neurodevelopmental risk, in particular preterm infants, as shown by the relevant number of systematic reviews and meta-analyses that addressed the question on the effects of music intervention in neonatal intensive care unit (NICU) populations [5–10]. In most cases, the effects of the intervention as to infant parameters were assessed in relation to physiological indexes such as heart rate or respiratory rate, to growth/feeding outcomes and length of stay, to impact on behavioral state, or to pain attenuation. In spite of the numerous studies available, systematic reviews of the literature failed to provide conclusive results on the benefit of music intervention in infants at neurodevelopmental risk, possibly due to the high study heterogeneity. Indeed, the reviewed studies have shown important differences in methodological aspects such as type and complexity of music exposure (e.g., vocal, instrumental, solo, or ensemble/orchestral), means of music administration (e.g., live or recorded music played in the environment; live or recorded music directed to/provided for each infant), and age or age range of the exposition. Much less attention has been given to the

effects of music intervention on more direct measures of brain function and structure, which is the focus of this part of the present review.

*3.1. Effects of Music Exposure as Assessed by Neurophysiological Techniques.* Few studies investigated through neurophysiological techniques the effects of fetal exposure to music. In one study, fetal exposure to a simple recorded lullaby presented 5 times per week starting from the 29<sup>th</sup> week of pregnancy until birth was compared to controls. The exposure group had significantly stronger amplitude event-related potential (ERP) responses at birth and 4 months that also correlated with the amount of prenatal exposure [40]. This indicates that prenatal music exposure has an effect on the neural responsiveness to sounds several months later, supporting a sustained effect of fetal memory through early infancy.

In preterm-born infants, amplitude-integrated EEG (aEEG, a restricted channel, compressed display EEG) has been utilized to investigate the effect of recording music on sleep-wake cycles, reporting positive effects of music exposure on quiet sleep in hospitalized premature infants [41, 42]. More recently, aEEG was used to study the effect of Brahms' Lullaby on the sleep-wake cycle of low-risk preterm infants between 33 and 37 weeks of gestation, reporting fewer interruptions of quiet sleep and increased postconceptional age sleep patterns as the result of music exposure [43]. The results, however, were called to be read with caution due to the potential conceptual flaws in the interpretation of the findings presented by the authors [44].

Additionally, ERP responses have been used as a biomarker of infant speech-sound differentiation during the neonatal period; at the same time, cortical responses to speech sounds were shown to be a feasible measure of the effect of infant vocal music exposure in the NICU. Specifically, infants were exposed to their mother's *a cappella* lullabies recording versus standard female *a cappella* lullabies recording, contingent to infant suck response for 20 minutes twice per day for 2 weeks. Infants in both groups had an increase in speech sound differentiation response on ERP. However, those that listened to their mother's voice had greater increase in spoken (standard) speech sound differentiation [45].

Clinical compatibility of care and research is an important factor to consider in data collection with vulnerable populations such as preterm infants; therefore, recommendations are consistent in encouraging the utilization of multichannel methods for a comprehensive view of the maturation process of preterm born infants, especially since the feasibility of acquiring electrophysiology data at bedside has been well established [46–48].

*3.2. Effects of Music Exposure as Assessed by Neuroimaging Techniques.* To the best of our knowledge, no studies have investigated the effects of music exposition through neuroimaging techniques during fetal life.

In preterm infants, cranial ultrasonography was utilized for the evaluation of the effect of music on development. A study using cranial ultrasonography evaluated the effect of a



musical intervention during neonatal stay of extremely premature infants until they reached term [49]. Infants exposed to maternal sounds (speech, filtered reading, and singing voice, as well as heart beat), for about a month of cumulative daily 3 hours of stimuli, had a significantly larger auditory cortex bilaterally, but not in frontal horn neither in corpus callosum, as compared to control newborns receiving standard care in the NICU. However, the magnitude of the right and left auditory cortex thickness was significantly correlated with gestational age but not with the duration of sound exposure.

Only one study explored music processing in preterm infants at term-equivalent age using fMRI [50]. The authors showed that very preterm infants at term-equivalent age already distinguish between a known music and the same melody played on a different tempo. In this study, authors used psychophysiological analysis to show that, unlike preterm infants without previous music listening or full-term newborns, preterm infants who listened to music from 33 weeks of gestation until term equivalent age show an increased functional connectivity between the primary auditory cortex and the thalamus and the middle cingulate cortex and the striatum, when listening again to the known music. These brain regions have been linked to tempo, familiarity, pleasantness, and arousing music processing, suggesting that these abilities might be modulated by music exposure during the week preceding term equivalent age.

#### **4. Music and Musicality in the Frame of Early Social and Emotional Development**

Findings summarized in the previous sections of this review support the view that, starting from the very early phases of development, listening to music is far from a simple auditory experience, as it triggers a series of cognitive and emotional components with distinct and interconnected neural substrates [51]. Human brain imaging studies have shown that neural activity associated with music listening extends well beyond the auditory cortex involving a widespread bilateral network of frontal, temporal, parietal, and subcortical areas related to attention, motor functions, memory [52–54], and limbic and paralimbic regions related to emotional processing [55–57]. Music can therefore be a useful tool for infant multisensory stimulation [58–60].

Experiments on adult rodents proved that enriched environment, including auditory enrichment, stimulates cortical plasticity [61, 62]. In humans, imaging studies on adults suffering from traumatic brain injury, stroke, and degenerative diseases have shown that they benefit from the exposure to music with an enhanced memory functioning, attention focusing, motor regulation, and emotional adjustment [63–65]. Särkämö and colleagues [66] further showed that music listening after middle cerebral artery stroke induced a larger increase of grey matter volume in frontolimbic network, including orbitofrontal cortex.

Development of neural networks in the perinatal period is highly dependent on the intrinsic and extrinsic multisensory activity driving maturation of neuronal circuits. In particular, music during prenatal and early postnatal period in

rats has been shown to modulate brain development in improving learning capacities [67–69]. As prematurity affects socioemotional development and its neural correlates, musical intervention, as framework for brain plasticity, has shown major impact on the reward system [70]. Music induces activity in limbic (e.g., amygdala and hippocampus) and paralimbic structures (e.g., orbitofrontal cortex, parahippocampal gyrus, and temporal poles), regions implicated in emotion generation and regulation and might therefore influence the maturation of socioemotional development [71]. Previous studies showed that full-term infants in the first days of life already show neural emotional responses to musical stimuli [39]. Recently, preterm infants were shown to benefit from enrichment of their environment in the form of audio recordings of maternal sounds with an increased cortical thickness in primary auditory cortex [49]. But, to what extent music during the early postnatal period in preterm infants can influence socioemotional development and the underlying corticolimbic network formation?

Early social interactions in a specifically structured context, such as music and singing, can be a tool for early social and emotional intervention in a broad sense. Beyond the enrichment of auditory skills, through the organization of primary and secondary auditory brain regions, early experiences in music and singing might be also a way to sensitize newborns to the dynamics of social interactions. Actually, when parents interact with their newborns, they provide a dynamic structure in which microevents produced by parents (e.g., silence and prosodic accents) are contingent to the specific reactions of their newborns. For example, it has been shown that when preterm newborns produced a motor action such as open eyes or mouth corners elevation (interpreted as a smile by the mothers), the mothers modulated their voice in a dynamic way, thereby establishing a dyad contingency [72]. In this early face-to-face interaction, when infants open the eyes or smile, the maternal voice is perceived by adult naïve listeners as more emotional and more smiling than it is in the absence of any infants' facial display. When mothers sing or speak directed to their preterm infants, their vocal act is not only related to preterm infant behavior but also bears modulated emotional content [73]. It is likely, given the fact that music and singing induced brain activations in a widespread neural network including the reward and habits system, i.e., the basal ganglia, the orbitofrontal regions, and deeper structures including the amygdala and the hippocampus [74], that early interactions have an impact on the development and the organization of these neural networks involved in social interactions and emotion regulation. Moreover, it has also been shown that human voice induces a specific set of brain activations localized in the middle superior temporal sulci and gyri in adults, i.e., the so-called voice sensitive areas [75]. These regions have also been shown being sensitive to the emotion conveyed by the voice [76, 77].

Therefore, early exposure to human voice (often emotional in the context of early interactions between preterm babies and parents) in a structured context such as in singing might be served in neural organization during early stages of development and might have a long-term impact on the relevance and importance of human voice in social interactions.



These voice-sensitive regions (i.e., superior temporal sulcus and superior temporal gyrus) are in close interactions with frontal areas and especially important for the acoustical invariance extractions. Therefore, premature infant exposure to voice during live interactions in early period may be a way to establish the precursors of the acoustical invariance extractions for the categorization of specific emotions inferred from human voice [78]. These abilities are fundamental in social interactions and especially important in the social exchanges between parents and fragile infants.

## 5. Where to from Here? Possible Role of Music in Early Intervention Programs

From the standpoint of the neurodevelopmental role of music in the NICU, the primary aspect for this mechanism is the environmental enrichment of sensory experiences of the preterm-born infant. Even in the absence of overt neural injuries and its severe developmental consequences, most infants born prematurely experience neurodevelopmental differences, many of which are believed to be a consequence of their stressful, atypical early sensory extrauterine hospitalization experience [79–81]. Many NICU environmental guidelines have been published and implemented in units caring for preterms; however, the simulation of the intrauterine environment is not feasible under current medical conditions. Therefore, the goal of environmental improvement is the inclusion of positive experiences to aide parent-infant bonding, infant sleep, and enriched awake hour interactions in the context of the medical reality.

Some of the most commonly reported music types that have been used in NICU studies are lullabies [59, 60, 82, 83]. Lullabies can have different structures and forms according to the different cultures they belong to, but they share several similarities that result from the intended audience and function of the songs [84]. The most frequently used lullabies present slow tempo and frequent repetitions, with few dynamic changes, with a limited pitch range and a high degree of continuity. These essential characteristics are shared by the other music pieces, such as Brahms or Mozart lullabies, which are also frequently used in studies. In addition, the reported music presented to preterm babies includes consistent consonance.

Unfortunately, except from studies with live music, the recorded music used in research with infants is rarely described in detail. While the intensity and duration descriptions are often accurate and report, respectively, the range levels in decibels and the precise duration in seconds, other musical components lack accurate descriptions. Further, the same music stimulus (i.e., a composition extract) can be performed in different tempos, instrumentation, and arrangement, but this is rarely described.

In general, independent from the musical piece, the recorded music chosen for preterm infants show a high degree of similarity in the structure such as slow tempo, high levels of consonance, high number of repetitive elements, few sudden dynamic, pitch or timbre changes, and a limited pitch range [85, 86]. The main difference between the chosen extracts can be the presence or absence of vocals, even

if previous studies did not find specific differential effects [85]. Further research is warranted to determine if the vocal component of the presented music, which makes the piece more comparable to the natural condition of maternal singing, can constitute a valuable variable in the efficacy of music exposure.

*5.1. Recommendations for the Application of Music for NICU Neonate Population.* The role of all developmental therapists, including those directly providing, or training parents to provide music to infants in the NICU, is first and foremost to provide parent support. This includes reading the infant cues and modeling appropriate interactions with the infant, especially in cases of severe medical fragility, high parental stress, and grief during the NICU stay. Therefore, recommendations are for live experiences actively involving parents as the most beneficial form of intervention for the overall neurodevelopment of infants and family support. In this respect, it is important to consider the variability in the hospital policies for parental visits to the NICUs, as some still do not allow 24/7 access to the infants even for parents. Visits are also based on maternity and paternity leave allowances and capabilities of parents to visit from remote locations. Therefore, recorded maternal/paternal voices and therapist provided experiences can be effective options in such circumstances.

Training of therapists providing or supporting music experiences for patients and families in the NICU is highly variable based on the country program structures and requirements [87, 88]. However, it is recommended that developmental specialists providing music experiences in the NICU or consulting music research with infants should be trained, at minimum, in infant development, music, physiology, medical terminology, and psychology.

At term and postterm, medically and neurologically stable infants (including infants maintained in the hospital) are able to tolerate and may benefit from continually more complex musical stimuli with increasing age, including vocal and instrumental (also orchestral) music. However, the exposure should be intentional. Since neonates have little awake time, the usage of this time to actively engage is recommended. Layering recorded music with movement/dance, tactile/massage, and visually stimulating (nonscreen) multi-sensory input is appropriate and recommended in later stages of development, when the repertoire of activities and infant's "readiness" for more complex sensory processing are expanded. Specifically, it is the opinion of the authors based on the previously published evidence, that music intervention provided in the NICU should be consistent with the following recommendations.

The effects of a music interventions—both live or recorded, administrated by parents or trained specialists—on very preterm infants with severe health complications or with very immature brains are currently unknown. Most of the studies in the previously reported systematic reviews and meta-analyses evaluating the effects of music interventions are limited to stable preterm infants. Thus, we recommend considering the stability and the age as key criteria for beginning a music intervention. Moreover, music experience for

preterm and full-term infants has to be accurately planned with a trained developmental specialist. Similar to all of the early interventions delivered in the NICU, the music administration should consider infant needs and behavioral state. There is no evidence demonstrating that a specific music (i.e., Mozart Sonata) is beneficial per se for every infant and without an individualized and intentional professional intervention [89].

Every music intervention should respect the sound level guidelines for NICUs. The guideline was published by the American Academy of Pediatrics recommending for the combination of continuous background sound and operational sound to not exceed an hourly equivalent continuous sound level of 45 decibels [90].

The types of music that have been tested and most frequently reported in the previously mentioned systematic reviews include a limited pitch and dynamic range, an absence of sudden change (increase or decrease) in intensity, a slow tempo, and frequent repetitions.

Live music, directed to an individual infant [91], either administered by singing parents or supported by professionals, is primarily suggested as an early music intervention in the frame of environmental enrichment and infant emotional development [91, 92]. A recorded music administration should follow the principles of increasing in structure complexity and individualization to infant's reactions. With the increase of age, following a careful individual observation, the administered music can present further degrees of acoustical complexity, such as multiple instrumentation, a moderate degree of variation or length.

## 6. Conclusions

The neuroprocessing mechanisms of music stimuli during fetal and neonatal developmental stages warrant much more vigorous research with neuroimaging, neurophysiology, and behavioral techniques. The combined inclusion of these methods in robust randomized controlled trials is needed to evaluate both (i) the neuroprocessing mechanisms of music stimuli and its similarities or differences with auditory processing of other stimuli, such as language or voice, and (ii) the effects of music experiences and interventions on the developmental trajectories of the most vulnerable neonatal population: preterm-born infants cared for in NICUs. Robust clinical trials with specific attention to the differences between a live or a recorded music administration are needed. Similarly, studies are needed to investigate the specific effects of different types of administered music, instrumental versus vocal music and maternal singing versus other voices or music. Current evidence is, however, already available to support the utilization of music interventions in the context of environmental enrichment and family centered care for hospitalized infants.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

O. Chorna and M. Filippa contributed equally to the manuscript.

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## Review Article

# Language in Preterm Born Children: Atypical Development and Effects of Early Interventions on Neuroplasticity

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Predicting language performances after preterm birth is challenging. It is described in the literature that early exposure to the extrauterine environment can be either detrimental or advantageous for neurodevelopment. However, the emphasis mostly lies on the fact that preterm birth may have an unfavorable effect on numerous aspects of development such as cognition, language, and behavior. Various studies reported atypical language development in preterm born children in the preschool years but also in school-aged children and adolescents. This review gives an overview of the course of language development and examines how prematurity can lead to atypical linguistic performances. In this paper, we mainly focus on environmental and neurophysiological factors influencing preterm infant neuroplasticity with potential short- and long-term effects on language development. Further research, however, should focus on examining the possible benefits that early exposure might entail.

## 1. Introduction

Preterm (PT) birth is a phenomenon that affects a large and variable group of newborns due to its many underlying causes. According to a 2010 estimation by the World Health Organization, approximately 15 million babies are born PT, worldwide, each year [1]. Considering this large number, a broad amount of studies have been performed to examine the consequences of prematurity on development. Within the neuroconstructivism framework approach, the basis of cognitive development can be characterized by mutually induced changes between the neural and cognitive levels. Thus, PT infants' neurodevelopment is constrained by underlying brain structures which are, in turn, affected by experience-dependent processes [2]. This led to a definition of atypical rather than delayed development in the PT population (for a review, see [3]). In particular, in the first weeks of life, sensory development and behavior of the PT infant are negatively affected by neonatal characteristics and morbidities, the stressful environment of the neonatal intensive care unit (NICU), and social factors which may influence later

neurodevelopment leading to complications such as motor delays, global cognitive impairment, visual perception problems, executive functioning deficits, and learning difficulties in school [4–6]. More specifically, children born PT show an increased risk for behavioral and attention difficulties [7, 8]. Furthermore, many studies have found a higher degree of language and social communication problems in PT-born children compared to full terms [9–12]. Deficits in expressive language, receptive language, word retrieval and short-term auditory memory were found [13]. In a meta-analysis performed by van Noort-van der Spek et al., which comprised of 17 studies on language development in PT children, it was discussed that even in the absence of major disabilities, very PT (VPT) survivors show difficulties in simple and complex language functions. This latter, involving higher-order cognition and highlighting the central role of cortico-cortical white matter tracts connectivity, might be a more useful indicator of the developing brain plasticity and of language functioning in PT children than simple language function. For complex language functions, in fact, PT's difficulties may even increase while growing up [14]. The extent of deficits a PT-born child

may endure in life is associated with the complex interaction between multiple biological and environmental constraints following PT birth that occurs during a critical period of brain development and thus leads to atypical development [2, 3]. Studies examining environmental and biological factors as predictors of language skills in this group of children have been conducted [15, 16]. Stipdonk et al. concluded, in their very recent review, that language difficulties in the PT population are a consequence of an atypical brain connectivity between several brain regions, such as the cerebellum, corpus callosum, and arcuate fasciculi [17]. Nonetheless, it is essential to note that not all children born PT function lower than their peers born at term. In this paper, atypical language development and evidence of neuroplasticity during early development will be discussed in more detail.

## 2. Normal Language Development

**2.1. Auditory System.** Prior to the development of language comprehension and speech production, the auditory system has to develop. Already very early in gestation, the fetus's auditory system is formed. Between the 23rd and 25th weeks of pregnancy, important structures of the auditory system such as the cochlea are already in place. After 26 weeks of gestation, hair cells in the cochlea become fine-tuned for specific frequency bands, converting acoustic signals into electrical stimuli and forwarding them through the auditory nerve to the auditory cortex in the brain. Therefore, between the 26th and 30th weeks, the fetus is able to detect and react to sound stimuli [18]. This fine-tuning process takes place in the uterus where both internal (e.g., respiration, heart rhythm, and digestion) and external sounds (e.g., voices and music) can be perceived. Both types of sounds stimulate the auditory system by means of bone conduction, meaning that sounds are conducted to the inner ear through the skull. The observed frequencies are distributed tonotopically as on the basilar membrane in the cochlea, making the uterus the ideal place for auditory maturation as it acts as a low-pass filter, protecting newly developed hair cells from potentially harmful high-pitch tones. At the same time, high-frequency areas on the membrane will develop and the fetus can perceive human speech sounds (e.g., intonation, pitch, and intensity). Perceiving these high frequencies (+2 kHz) will enable later language processing. After the 30th week of gestation, the auditory system is mature enough to detect complex sounds and distinguish different phonemes in speech [18, 19].

**2.2. Early Language Processing.** Because hearing is functional during the last trimester of gestation, it is of interest to know whether and how these immature cortical circuits process speech. In utero, information about prosody and rhythm of the mother's speech is led to the fetus' inner ear by means of bone conduction through which they have the opportunity to learn about properties of their native language. Perceiving this speech signal is sufficient enough to shape an infant's phoneme perception prior to birth [20]. In addition, a clear difference was reported in the response to familiar versus unfamiliar language offers, showing that even before birth,

the brain is being tuned to its language environment [21]. Furthermore, after only a few hours of postnatal exposure, neonates respond specifically to speech [22] and are able to discriminate between different prosodic patterns [23]. Brain networks sensitive to phonemes and voices are present at the very onset of cortical organization allowing the brain to already discriminate between small differences in speech syllables. This cortical activation during discrimination is not solely limited to primary auditory areas but also involves more inferior frontal regions [24]. Using noninvasive neuroimaging studies, speech-processing right after birth can be assessed. Stronger responses in the left temporal areas can be found when sentences are heard in the mother language whereas they are weaker when these same stimuli are played backwards, therefore erasing prosodic specificities of the mother tongue [25]. In 3-month-old infants, dominance in the left temporal areas for both forward and backward speech, with more activation in the left angular gyrus for forward speech, was found [26]. Minagawa-kawai et al. [27] also described a clear left lateralized cerebral basis for speech processing in 4-month-olds. Hence, it can be concluded that even early in infancy, there is a neural precursor of functional organization in the brain.

**2.3. Later Language Processing.** Language acquisition after birth is made possible through the interaction between structural characteristics of the mother language and language offerings in the environment (child-directed speech). The overall process can be seen as a set of language skills that continuously grows. An infant learns to interact with the environment by producing sounds, actions, and behaviors. Different phases can be distinguished such as the prelingual phase (from birth to 12 months of age) when an infant starts vocalizing and babbling. Second is the early-lingual phase (from 1 to 2.6 years of age), during which a child shows signs of word comprehension and starts producing isolated words and short, telegraphic sentences. Next, in the differentiation phase (from 2.6 to 5 years of age), grammar starts to develop and sentences become more complete. Finally, during the completion phase (starting from 5 years of age), bases acquired in the preceding phases are further elaborated, for example, by developing reading and writing skills through education [28] (Figure 1).

## 3. Differences in Language Development between Full-Term and Preterm Born Infants

**3.1. Prelingual Phase.** In the first year of life, development of receptive language is crucial. During this period, the infant will learn to understand the mother language and how to respond accordingly. A prerequisite for this development are language offerings in the infant's environment (e.g., IDS (infant-directed speech)) and a correct-functioning hearing organ. In order to understand and produce speech, the infant needs to listen to a caregiver. Prelingual skills such as vocalizations, eye movements/gazes, gestures, and shared attention with a parent or caregiver are an important part of that process. During the first months of life, an infant establishes

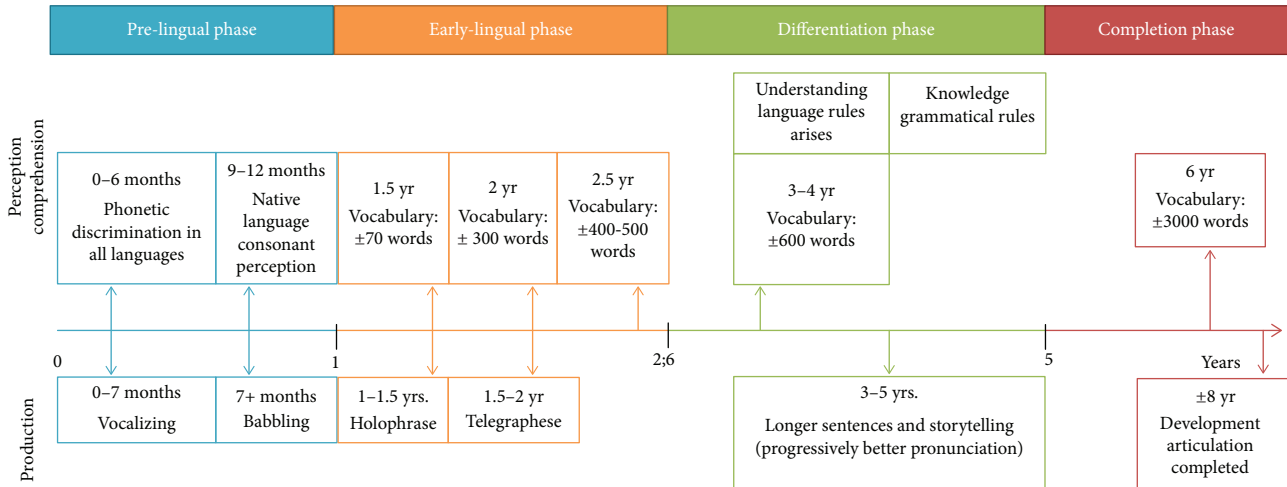


FIGURE 1: This figure shows the four language developing phases and the changes that occur in speech perception/comprehension and production in typically developing children during their first years of life.

an infant-caregiver relationship by using eye contact, smiling, producing sounds, etc. [12]. Thus, speech perception is not solely an auditory process and the ability to detect auditory-visual matches in speech is already present at a young age [29]. Indeed, newborns prefer, for example, to look at the mother's face over a stranger's one when listening to the mother's voice [30]. Around the age of 6 months, infants can pay attention to the visual characteristics of speech, and as of 8 months they are able to observe auditory and visual characteristics of speech at the same time [31]. This skill is important during phonological development. Hence, infants benefit from a rich auditory and visual environment early in development [32]. However, for infants born PT who reside in the NICU, full-time parental presence and speech offerings in the environment are not always the case. Dysfunctions in early social communication with the parents, due to long periods of separation in the NICU, can have negative consequences on the communication between the infant and the caregiver [33]. The influence of PT birth on specific social experiences will be discussed later on in this review.

By listening to speech, an infant becomes more sensitive to characteristics of their native language, while during the second half of the first year of life, those of other languages disappear [34]. In typical development, children begin to enhance their native language discrimination abilities through the ages of 6 to 12 months, when the brain tunes itself to native phonemes and decreases the ability to discriminate between nonnative phonemes [35]. Jansson-Verkasalo et al. [34] studied these discrimination abilities in PT-born infants, focusing on the discrimination of two Finnish native phonemes and one native versus a nonnative phoneme in 6-month-old VPT born infants and full terms. No significant difference was found between the VPT and full-term groups at 6 months of corrected age when discriminating between the native and nonnative phonemes. However, between 6 and 12 months of age, the full-term group's response to nonnative stimuli decreased in relation to their response to the native phoneme.

This typical decrease in nonnative vowel discrimination was not found in the VPT-born group as they continued to respond to the nonnative vowel. Additional research performed by Peña et al. [36] reported that neural maturation and not duration of exposure per se was a relevant factor for phoneme discrimination. Only at 9 months of age, PT-born infants performed at the same level as full-term controls (4 months of age). This finding is supported by later research concluding that the shaping of phonological representations by the environment is constrained by brain maturation factors [37]. At a later stage, a child develops phonological awareness to distinguish between phonemes and syllables and build different phonemic representations. More specifically, the awareness that individual sounds are the building blocks of words, e.g., "cro - co - dile," allow a child to divide words into syllables, recognize and use rhymes, form phonemes into syllables and words, and identify the beginning and ending sounds of a word. Phonological awareness is an important prerequisite as it is the building block for future reading skills and vocabulary size [38]. Even without distinct brain damage, vocabulary and grammar difficulties were found throughout the first years of life in PT-born children and may even persist up to the school years as language competencies continue to be affected by weaker phonological awareness skills [39].

**3.2. Early-Lingual and Differentiation Phase.** After the first year of life, when the foundation of language comprehension has been laid, the infant will start to experiment more with spoken language. Expressive language involves learning to pronounce speech sounds and engage in communication. The expressive aspect of language can be subdivided into different skills, (1) lexicon/semantics: vocabulary, learning the meaning of words and (2) morphosyntax: grammatical development. A child learns to understand changes of word forms in different syntactic contexts and learns how to form correct sentences. A child will develop his or her vocabulary around the second year of life. On average, a child has

acquired about 200-400 words at this age. Possessing an early lexicon has a highly predictive value for later language skills. In PT children, a linear relationship was found between gestational age at birth and later language outcomes. The lower one's gestational age at birth, the smaller the vocabulary size and quality of word use [40]. When comparing PT children, without any major cerebral damages, with their full-term peers, differences in linguistic development can be assessed [41]. Stolt et al. [42] examined the difference between the lexicon size of PT-born children in comparison to full-term peers at 2 years of age, but no significant difference was found. Contradictory results however were found, when PT and full-term born children were divided into three age groups (18-24 months old, 24-30 months old, and 30-36 months old). Both the PT and full terms showed an expansion of their expressive lexicon with increasing age. However, the lexicon of PT-born children was significantly smaller than those of their full-term peers [43]. Later, around 12-18 months of age, grammatical knowledge starts to develop. An experiment performed by Kunnari et al. [44] showed early delays in grammatical development in PT-born children by studying spontaneous speech samples at the age of 2. Results showed no difference in vocabulary size between the groups, but the maximum sentence length was significantly shorter in PT. Secondly, Stolt et al. [45] showed that VPT children, at the age of 2, had weaker grammatical skills than a full-term control group. However, when considering their lexicon size, less significant differences were found between both groups [42]. So, even though a delay in grammatical development was found in the VPT group, when taking lexicon size into consideration, it still develops in a similar manner as the full terms.

**3.3. Completion Phase.** As the child grows older, he or she will master the language better and start forming longer sentences. The meaning of words becomes better understood, and they can be formulated more accurately. This development is stimulated by education and acquiring reading skills. Reading requires good cognitive and intellectual development and is an essential skill for later academic purposes. Several prerequisites have to be established in order to learn how to read, i.e., phonological awareness, speech perception, and verbal skills. Each of these abilities contributes to the acquisition of two processes that are essential for becoming literate: firstly, decoding (single word reading) in which words are extracted from the mental lexicon, and secondly, word comprehension (semantics). In a meta-analysis performed by Kovachy et al. [46], fourteen studies assessing reading abilities in PT-born children between the ages of 6 and 13 years showed significantly lower scores for both decoding and reading comprehension. Similar results were found when studying long-term effects of prematurity on reading skills [47]. Significant correlations were found between lexical production and reading comprehension and between phonological awareness and reading comprehension in the PT group. Thus, comprehension, lexicon, and grammar can be negatively affected by PT birth, which may lead to an atypical development in reading and writing.

## 4. In Children Born Preterm, Is the Language Deficit Specific or Linked to a Global Cognitive Delay?

Language development is not solely dependent on language processes but also depends on basic cognitive processes (e.g., memory, processing speed, and attention) [48]. As abovementioned, PT birth and the complex interaction it entails between biological and environmental constraints may alter the pattern of brain development across brain regions, leading to atypical trajectories that may result in a global deficit of neuropsychological functions. In PT birth, language disorders are more often described as a result of such a general cognitive deficit [49, 50]. Indeed, it was found that PT children show high levels of comorbidity between cognitive functions and language. This might be accounted for by their similar functional dependence and demands [51]. Ortiz-mantilla et al. [52] indicated that language disabilities in very PT children can be explained primarily by general cognitive deficits which originate from global disturbances in brain development rather than damages to specific regions. In a study performed by Wolke et al., a detailed assessment of cognitive and language functions was described in a large sample of extremely PT children and term controls at the age of 6. It was shown that extremely PT survivors performed significantly lower on language assessment compared to term peers but also scored lower on measures of general cognitive functions. When controlling for general cognitive performance, the authors did not observe specific language difficulties in this population [50]. A tight relationship was found between phonological working memory and grammar in VPT children [53]. Also, dysregulation of attention, a system closely associated with language, influences social interactions and a child's opportunities for language learning may decrease [54]. In order to decipher whether language difficulties may be linked to overall cognitive delay or specific difficulties, studies should use cognitive abilities as a control variable and also address specific aspects of linguistic development and processes. Moreover, identifying deficits in general cognitive processes may help in the early detection of children at risk for impaired language development [55, 56].

## 5. Why Might There Be a Difference in Development?

**5.1. Neuroanatomical Factors.** Several recent studies have shown that cerebral abnormalities associated with PT birth may be a substantial determinant of cognitive and language development. Therefore, identifying predictors of development disorders through neuroimaging studies should help improve our knowledge.

**5.1.1. Atypical Functional Brain Organization.** Variations in cognitive, language, and speech development are likely to be the result of underlying abnormalities in the brain associated with functional organization outcomes. During normal development, language organization is extensive and bilateral in the infant's brain. Later, with increasing age, it becomes more lateralized in the left hemisphere. In healthy



3-month-old infants, mature cortical areas are active when processing language. By this time, speech perception is already left-lateralized with activity in the superior temporal gyrus and the angular gyrus [26]. In PT newborns, shortly after birth, on the other hand, an asymmetry in the areas surrounding the perisylvian fissure is found, suggesting that specific anatomical organization favors functional lateralization even before language exposure [57]; this includes a larger depth of the right-sided superior temporal sulcus and a left shift of the planum temporale. Advanced structural maturation of the left-sided frontotemporal dorsal pathway of language was shown in 1-4-month-old infants indicating an early presence of circuitry underlying phonetic processing [58]. Mürner-Lavanchy et al. [59] examined language organization in PT-born children compared to controls using neuropsychological assessment and an fMRI language task. At early school age, PT subjects showed an atypical bilateral language organization in the frontal-temporal regions, whereas at 11-12 years of age they revealed left-sided language organization resembling that of the full-term group. These findings might reflect a delay of neural language lateralization in children born PT. Furthermore, Zhang et al. [60] studied 24 VPT-born children in comparison to matched controls at 7 years of age. In the VPT group, a greater regional vulnerability in the superior temporal sulcus and cingulate regions, with an abnormal asymmetry in the right hemisphere, was found. Similar results were reported in a study comparing 16-year-old VPT-born children with matched controls using the Peabody Picture Vocabulary Test and resting-state fMRI. In the VPT group, a positive correlation was found between more left lateralization and better language scores, with more activity in the left angular gyrus and inferior parietal lobe. On the other hand, a negative correlation was found between right hemisphere lateralization and language scores. Thus, less activation in these right hemispheric regions would lead to better language scores. It was hypothesized that early interventions strengthening the altered network can be advantageous for PT [61]. However, future research is needed to monitor how these interventions lead to changes in connectivity over time. Overall, these results show a delayed and atypical neural specialization for language systems in PT born compared to full-term-born children.

**5.1.2. Structural Abnormalities.** Approximately 50-70% of VPT born infants are affected by diffuse white matter abnormalities such as loss of white matter volume, corpus callosum thinning, and delayed myelination [62]. The presence and severity of these cerebral injuries increase the risk of later neurocognitive impairment in PT children. In a recent study, it was reported that the mean score on language tests at the age of 4 and 6 years significantly declined as severity of white matter abnormalities increased [62].

The corpus callosum plays a crucial role in the exchange of interhemispheric information. Thus, a deviation may be associated with weaker cognitive performances. A study, in which the relation between the corpus callosum regions and preverbal skills was assessed in 14-15-year-old born VPT using structural MRI and neuropsychological tests, found a

negative effect of VPT birth on the development of the corpus callosum. More specifically, a decreased volume in the corpus callosum posterior areas was positively associated with lower verbal IQ and reduced verbal fluency scores. Overall, this study demonstrates the involvement of the corpus callosum in speech and language processes and describes an interhemispheric asymmetry [63]. Additional research in the same domain showed an altered brain structure in VPT adolescents which accounted for lower spelling and reading scores in this population [64]. A subsequent MRI study demonstrated the importance of the interhemispheric frontal and temporal connections to predict language impairment. Results showed that the combination of anatomical measures of the interhemispheric connectivity between the corpus callosum and the anterior commissure explained 57% of the variance in linguistic abilities [65]. Finally, Reidy et al. [66] demonstrated that white matter alterations occurring during the neonatal period were predictive of abnormal language performances in VPT-born children at the age of 7.

**5.2. Postnatal Environmental Factors.** Considering brain development is mostly shaped by early sensory experiences, exposure to language in the infant's environment is of utmost importance [67]. Since PT-born infants are exposed earlier to the environment outside of the uterus, one can wonder what the impact of this early exposure to the auditory environment has on the developing brain.

**5.2.1. Effect of Exposure to Auditory Stimuli in the NICU.** When born prematurely, infants spend the first weeks or even months of their life in the NICU. During this critical period for development, they are deprived of the sounds they would otherwise be hearing in utero. As discussed earlier, the intrauterine environment allows the fetus to perceive low-frequency sounds in an attenuated fashion, ensuring the development of the auditory system [68]. However, when born PT, infants are prematurely led into a more invasive environment which can have profound effects on the auditory brain maturation and subsequent speech and language acquisition [18]. Although PT infants residing in the NICU are deprived of maternal sounds, they are not deprived of all auditory stimulation. Unlike in utero, the auditory stimulation available to the infant depends on the NICU environment they are residing in. Firstly, the NICU environment may be too loud for the infant to reside in. While being placed in an open room, they are exposed to unpredictable multiple high-frequency sounds (electronic/machines) and voices (e.g., parents, nurses, and doctors) which may prevent them from being exposed to meaningful and infant-directed language inputs. In addition, excessive exposure to loud ambient noises can negatively affect the infant's physiological stability (e.g., affect the cardiovascular and respiratory systems), which in turn may cause a risk for neurodevelopment [69]. Secondly, the environment can be too quiet when the infant is placed in an incubator that does not allow them to perceive language stimuli [70].

A study by Caskey et al. [71] showed that a larger range of language exposure in PT babies can have a positive effect on later language development in the first weeks after birth.



They hypothesized that PT-born babies residing in the NICU would have higher cognitive and language scores if they were exposed more to adult talk. In this study, a positive correlation was found between the number of words heard during the first weeks of life and the language and cognitive scores of the Bayley Scales for infant development III at 7 and 18 months of corrected age. Similar results were found by Montirosso et al. [72] when comparing very PT-born infants residing in 19 different NICUs to FT controls. Infants residing in a high-quality developmental care unit (better infant pain management, improved control of external stimuli, and more parental involvement) showed better receptive language skills than those residing in low-quality developmental care. Hence, these studies support the view that exposure to adult talk in the NICU is associated with better language and cognitive and communicative development at an older age [71]. It can be concluded that early adequate exposure to language and sensory stimulation is of great importance.

**5.2.2. Dysfunctional Caregiver-Infant Relationship.** For infants residing in the NICU, full-time parental presence is not the case. Dysfunctions in early social communication, due to long periods of separation in the NICU, can have negative consequences on an infant's behavior and emotional and physiological well-being. Moreover, an important aspect affecting language development in PT born children is the quality of the infant-caregiver relationship. Multiple studies show that when a child and their caregiver participate in quality interactions, language development will improve. Increased psychological stress experienced by mothers of PT infants has been linked to differences in the mother-infant interactions in this population [73, 74]. On the Care Index, a measurement index that assesses mother-infant interactions, mothers of PT infants who are affected by maternal depression and anxiety have been found to be more controlling or unresponsive when interacting with their child, compared to mothers of FT infants [73, 74]. On the other hand, maternal anxiety may lead to more intrusive behavior, in which mothers provide less sensitive and a more controlling style of parenting. Zerkowicz et al. [75] studied whether anxiety affects maternal interaction and leads to less optimal communication into the preschool years. During their stay in the NICU, mothers were tested using the self-report State-Trait Anxiety Questionnaire, which is commonly used to indicate caregiver distress. Later, in a 24-month follow-up period, free play between the mother and child was observed. Results showed that anxiety during time in the NICU leads to less sensitive and responsive interactions between mother and child. In return, children involved their mothers less during playtime [75]. In light of the importance parent-infant interaction plays in language development, early intervention targeting these disordered dyads in the PT population could be beneficial. When PT-born infants participated in a postdischarge intervention program and attended regular visits to a pediatric hospital, better scores were found on the BSID. Moreover, mothers in the intervention group showed more positive and sensitive interaction behavior towards their child [76].

## 6. Can Preterm Infants Benefit from Early Auditory Exposure?

Although most abovementioned findings suggest a negative impact of PT birth, some studies suggest that PT infants can also benefit from early natural auditory exposure. Already at 29 weeks of gestational age, PT infants possess the ability to process subtle changes in phonemes and voices [24]. Hence, they are able to encode acoustic properties in order to perceive and process speech offerings in their environment. Furthermore, Nishida et al. [77] demonstrated that the duration of extrauterine exposure is correlated with enhanced brain responses. A shorter latency of oxyhemoglobin measures, using near-infrared optical tomography, was found in the PT group in response to verbal stimulation. Plus, despite potential structural differences, functional changes in the PT brain occur for both auditory recognition (differentiate between voice vs. reversed voice) and language decoding [78]. Also, differences in activation for the discrimination of two voices (mother vs. nurse) were found [79]. In addition, several auditory-evoked potential studies showed no differences in central auditory pathway maturation [80–82] or even reported that exposure of PT infants to the extrauterine environment is associated with advances in development compared to full terms [83]. Peña et al. [84] showed that PT infants benefit from early exposure to a visual environment (face-to-face interaction); at the age of 6 months, they performed the same as full terms with the same chronological age displaying that exposure does positively impact the development of gaze following. PT birth does open not only the possibility of a natural increase of positive auditory exposure [72] but also the possibility to intervene earlier to enrich their auditory experience. As it has been shown for the tactile experience, in which massage intervention affects the maturation of brain electrical activity, favoring a process more similar to that observed in utero in term infants [85], early auditory interventions can impact the PT infant's brain development. In fact, despite immature auditory pathways, early auditory interventions may have a positive influence on the PT infant's brain development. For example, PT infants residing in an environment in which they are more exposed to maternal sounds (mother voice) show larger auditory cortices [67]. Moreover, music interventions in the NICU have been shown to promote early language development and induce functional connectivity between the auditory cortex and additional brain areas associated with music processing [86, 87].

An early intervention found to be effective is interaction through maternal speech and singing, showing favorable effects on an infant's physiological state such as heart rate, oxygen saturation levels, and respiration rate [88]. Furthermore, a meta-analysis performed by Filippa et al. [89] evaluating 15 maternal voice interventions in 512 PT infants showed that maternal speech has a supporting role in clinical outcomes such as physiological state, behavior, and neurological development. More specifically, early exposure to the maternal voice through bone conduction can support neurobehavioral outcome and auditory development [90]. Hence, it can be suggested that PT birth may not always

result in negative effects on language development. They may even perform better in specific discrimination tasks in comparison to their full term peers and prematurity can constitute a precious window of opportunities for enriching the PT infants' sensory experience.

## 7. Conclusion

The aim of this paper was to provide a detailed review of the literature on language development in PT-born children and to examine how prematurity can lead to atypical linguistic performances. According to the research discussed, it can be concluded that during the first years of life, crucial for gaining adequate social and adaptive skills, language development can be affected by PT birth. In VPT, altered brain maturation, leading to atypical functional organization and structural changes, was associated with abiding language impairments. In addition, environmental factors such as a long stay in a NICU with underexposure to significant auditory stimuli and nonoptimal infant-caregiver interactions have been associated with weaker language outcomes. Several intervention methods were proven useful in promoting the parent-child relationship, resulting in better interactions which have positive effects on cognitive and language development of children born PT. Moreover, we described some evidence of beneficial effects from early exposure to language, voices, and music in PT children. Further research is needed to assess the influence of this exposure on language development more thoroughly.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

## Authors' Contributions

Manuela Filippa and Cristina Borradori Tolsa contributed equally to this work as last authors.

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## Research Article

# Alterations of the Brain Microstructure and Corresponding Functional Connectivity in Early-Blind Adolescents

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Although evidence from studies on blind adults indicates that visual deprivation early in life leads to structural and functional disruption and reorganization of the brain, whether young blind people show similar patterns remains unknown. Therefore, this study is aimed at exploring the structural and functional alterations of the brain of early-blind adolescents (EBAs) compared to normal-sighted controls (NSCs) and investigating the effects of residual light perception on brain microstructure and function in EBAs. We obtained magnetic resonance imaging (MRI) data from 23 EBAs (8 with residual light perception (LPs), 15 without light perception (NLPs)) and 21 NSCs (age range 11–19 years old). Whole-brain voxel-based analyses of diffusion tensor imaging metrics and region-of-interest analyses of resting-state functional connectivity (RSFC) were performed to compare patterns of brain microstructure and the corresponding RSFC between the groups. The results showed that structural disruptions of LPs and NLPs were mainly located in the occipital visual pathway. Compared with NLPs, LPs showed increased fractional anisotropy (FA) in the superior frontal gyrus and reduced diffusivity in the caudate nucleus. Moreover, the correlations between FA of the occipital cortices or mean diffusivity of the lingual gyrus and age were consistent with the development trajectory of the brain in NSCs, but inconsistent or even opposite in EBAs. Additionally, we found functional, but not structural, reorganization in NLPs compared with NSCs, suggesting that functional neuroplasticity occurs earlier than structural neuroplasticity in EBAs. Altogether, these findings provided new insights into the mechanisms underlying the neural reorganization of the brain in adolescents with early visual deprivation.

## 1. Introduction

It is well established that early-blind adults, i.e., those individuals who lose sight at birth or within a short period after birth, show alterations in the neural structure and function due to the absence of visual inputs. Structurally, the morphological changes of the grey matter (GM) in early-blind adults have been studied extensively and include decreased GM volume in the primary visual area [1–5]; increased GM volume in the occipital, frontal, and entorhinal cortices [4] and the globus pallidus [6]; and increased cortical thickness of the early visual areas [2, 7, 8]. In addition to GM alterations,

white matter (WM) alterations were also identified based on the diffusion tensor imaging (DTI) datasets of early-blind adults. In detail, microstructural alterations were mainly found in the optic radiation and the lateral geniculate nucleus with decreased WM volume [2, 9, 10] or density [9, 11]. Other microstructural disruptions due to early visual deprivation were also found in the inferior longitudinal fasciculus [12] and the occipital/temporal/parietal thalamocortical projections [4, 13]. In addition, Leporé et al. [3], using tensor-based morphometry, reported interesting hypertrophy in the prefrontal and parietal WM and in a section of the splenium of the corpus callosum in early-blind adults.

Interestingly, some studies [11, 14] also identified increased fractional anisotropy in the corticospinal tract in early-blind adults by tract-based quantitative analysis, suggesting structural neuroplasticity. To some extent, such morphological changes reflect deprivation-induced processes, both neurodegenerative and neurodevelopmental, following the loss of visual input and/or altered visual experience [3, 5].

In addition to structural alterations, functional changes were also identified in early-blind adults in many studies. Task-based research using functional magnetic resonance imaging (fMRI) demonstrated that the occipital cortex could process nonvisual information, such as tactile [15, 16] and auditory input [16–20], and some complex cognitive- and verbal-related input [17, 21–23]. These results collectively suggested that the visual cortex of blind individuals exhibits cross-modal reorganization properties. Moreover, activity in the primary, secondary, and tertiary visual cortices of blind adults was increased, spatially and in amplitude, after sensory substitution training, even in short-term (10 min) [24]. Using resting-state fMRI (rs-fMRI), both decreased functional connectivity [7, 22, 25–28] and increased functional connectivity of the occipital cortex [25, 29, 30] were identified in early-blind adults compared with sighted controls, providing extra evidence of functional neuroplasticity in early-blind adults.

However, these results about structural and functional disruptions and neuroplasticity were derived from early-blind adults. Recently, we investigated resting-state interhemispheric functional connectivity in early-blind adolescents (EBAs) and found significantly lower voxel-mirrored homotopic connectivity (VMHC) in the primary visual cortex, visual association cortex, and somatosensory association cortex [31]. Although the study focused on EBAs, it is still unclear if this group would show structural and functional alteration patterns similar to those of early-blind adults. Moreover, most of the previous studies on early blindness included subjects with residual light perception, thus failing to exclude possible effects of residual light perception on the structure and function of the blind brain. Therefore, we aimed to (1) investigate whether and how the brain's structure and function are altered in EBAs and (2) investigate the effects of residual light perception on brain structure and function. Given the evidence just discussed, we hypothesized that structural and functional alterations in EBAs would mostly be identified in the brain regions associated with vision. To verify this hypothesis, we recruited a cohort of 23 EBAs (8 with residual light perception (LPs), 15 without light perception (NLPs)) and 21 NSCs (age range: 11–19 years old) to explore the structural and functional brain changes in EBAs using the whole-brain voxel-based analysis (VBA) and the resting-state functional connectivity (RSFC).

## 2. Materials and Methods

**2.1. Subjects.** Twenty-three EBAs with onset age < 1 year were enrolled from the Guangzhou City Blind School. Among them, 8 EBAs with residual light perception were included in the LP group (6 males and 2 females) and 15 EBAs without light perception were included in the NLP group (8 males and 7 females). Twenty-one age- and sex-matched normal-

sighted volunteers were recruited as the NSC group (10 males and 11 females). The demographics of the three groups are summarized in Table 1. All subjects met the following inclusion criteria: (1) right-handed and (2) age ranging from 11 to 19 years. The exclusion criteria were (1) any history of psychiatric or neurologic diseases, (2) symptomatic or atypical neuralgia, and (3) identifiable MRI abnormalities, such as demyelination, vascular malformations, or tumors. All individuals and their guardians signed a written informed consent form prior to the MRI examinations. All research procedures were approved by the Ethics Committee of the First Affiliated Hospital of Jinan University.

**2.2. Data Acquisition.** A 3.0T MRI scanner (Discovery MR750 System; General Electric, Milwaukee, WI, USA) with an 8-channel head coil was used. The subjects were scanned in the supine position and were placed head first into the scanner. The position of the head was fixed using several foam cushions. For each subject, the DTI and rs-fMRI data were acquired. For DTI, we acquired 75 diffusion-weighted images ( $b = 1000 \text{ s/mm}^2$ ) and 5 nondiffusion-weighted images ( $b = 0 \text{ s/mm}^2$ ) using a spin-echo echo-planar imaging sequence with the following parameters: number of excitations = 1, repetition time (TR) = 6000 ms, echo time (TE) = 68 ms, acquisition matrix =  $128 \times 128$ , and voxel size =  $2 \text{ mm} \times 2 \text{ mm} \times 3 \text{ mm}$ . The array spatial sensitivity encoding technique was used with an acceleration factor of 2 to reduce acquisition time and anamorphosis. The rs-fMRI data were acquired using an echo-planar imaging pulse sequence, sensitive to blood-oxygen-level-dependent contrast (TR = 2000 ms, TE = 35 ms, flip angle =  $90^\circ$ , matrix size =  $64 \times 64$ , field of view =  $256 \times 256 \text{ mm}^2$ , slice thickness = 3 mm, gap = 0.6 mm, 240 time points, sequence length = 8 min, and 41 slices in the axial plane). During rs-fMRI, subjects were instructed to stay awake, not to move, to think of nothing in particular, to relax, and to keep their eyes closed.

**2.3. VBA and Statistics Analysis.** We performed DTI preprocessing using the FMRIB Software Library (FSL5.0; <http://www.fmrib.ox.ac.uk/fsl>), including eddy-current and motion correction, brain mask creation for the DTI data, exclusion of voxels outside the braincase, and diffusion tensor reconstruction with the “DTIFIT” toolbox [10]. All diffusion-related parameters including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated. Following this, individual FA maps were analyzed using the statistical parametric mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). The FA maps were normalized to the standard Montreal Neurological Institute (MNI) template and smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel to reduce the effects of misregistration in spatial normalization [32]. Two-sample *t*-tests were conducted to assess intergroup differences in FA between the groups with age and sex as covariates. In order to account for multiple comparisons, the AlphaSim method was used with a voxel-level threshold of

TABLE 1: Clinical characteristics of early-blind adolescents and normal-sighted controls.

No.	Age (years)	Gender	Age of onset (months)	Causes of blindness
LP01	11.8	M	2	ROP
LP02	14.7	M	2	Cataract
LP03	14.4	M	0	CG; EA
LP04	11.0	M	0	CRL
LP05	12.3	M	3	ROP
LP06	12.5	F	8	ROP
LP07	13.8	M	0	CRL
LP08	15.0	F	0	CRL
NLP01	14.3	M	3	ROP
NLP02	16.3	M	2	ROP
NLP03	17.2	M	8	OT
NLP04	11.0	M	0	ROP
NLP05	13.8	F	1	ROP; EA
NLP06	17.9	F	5	Cataract; EA
NLP07	12.3	F	3	ROP
NLP08	17.1	F	0	ROP; OA
NLP09	17.8	M	0	ROP
NLP10	14.5	F	1	ROP
NLP11	14.8	M	4	ROP
NLP12	14.9	M	0	CRL
NLP13	11.1	F	3	ET; EE
NLP14	13.2	M	0	CRL
NLP15	13.7	F	0	ROP
NSC01	12.5	F	—	—
NSC02	12.0	M	—	—
NSC03	14.0	M	—	—
NSC04	17.2	M	—	—
NSC05	13.6	M	—	—
NSC06	12.5	M	—	—
NSC07	13.3	M	—	—
NSC08	18.3	F	—	—
NSC09	12.1	M	—	—
NSC10	18.2	F	—	—
NSC11	15.5	M	—	—
NSC12	16.5	M	—	—
NSC13	13.9	M	—	—
NSC14	18.7	F	—	—
NSC15	17.6	F	—	—
NSC16	17.0	F	—	—
NSC17	15.4	F	—	—
NSC18	15.0	F	—	—
NSC19	11.0	F	—	—
NSC20	15.0	F	—	—
NSC21	13.0	F	—	—

Abbreviations: LP: early-blind adolescents with light perception; NLP: early-blind adolescents without light perception; NSC: normal-sighted controls; M: male; F: female; ROP: retinopathy of prematurity; OT: oxygen toxicity; EA: eyeball atrophy; CRL: congenital retinal lesions; CG, congenital glaucoma; OA: optic atrophy; ET: eyeball tumor; and EE: eyeball extraction.

TABLE 2: Demographic characteristics of the recruited subjects.

	LP	NLP	NSC	ANOVA statistics	<i>p</i> value
Gender (M/F)	6/2	8/7	10/11	$F = 0.857$	0.432
Age (years)	$13.2 \pm 1.5$	$14.7 \pm 2.3$	$14.9 \pm 2.3$	$F = 1.782$	0.181

Abbreviations: LP: early-blind adolescents with light perception; NLP: early-blind adolescents without light perception; NSC: normal-sighted controls; ANOVA: analysis of variance; M: male; F: female.

$p < 0.001$  and a cluster-level threshold of  $p < 0.05$ . VBA of the MD, RD, and AD maps was performed similarly.

The clusters showing significant differences in the DTI parameters between the groups were identified according to the standard brain atlas, and the DTI values from these significant clusters of the corresponding tensor parameter maps (FA, MD, RD, and AD) in the subjects were extracted. Subsequently, correlation analysis followed by an independent two-sample  $t$ -test was performed using the Statistical Package for the Social Sciences (SPSS) software (version 23.0; IBM Corporation, NY, USA). For correlations between DTI metric values and age, the Pearson correlation coefficient was computed separately for each group. Two-sample  $t$ -tests were used to detect differences in the DTI values between the groups.

**2.4. Resting-State fMRI Data Preprocessing.** The rs-fMRI data were preprocessed using the toolbox for Data Processing & Analysis for Brain Imaging (DPABI, <http://rfmri.org/dpabi>) [33]. The preprocessing steps were (1) discarding the first 10 time points to avoid transient signal changes that occurred before magnetization reached the steady state and subjects' adaptation to the scanning noise; (2) slice timing correction; (3) head motion realignment; (4) normalization to the standard MNI template in the DPABI package; (5) smoothing with a 6 mm Gaussian kernel; (6) linear regression to remove confounding factors, including six head motion parameters, as well as the ventricle, WM, and global signals; (7) scrubbing with interpolation to remove volumes with head motion spatial shift larger than 1.5 mm and rotation greater than  $1.5^\circ$  in any direction; and (8) band-pass filtering from 0.01 to 0.1 Hz. The resulting images were manually inspected by two experienced researchers for image quality.

**2.5. RSFC and Statistics Analysis.** To investigate the corresponding functional alterations, the clusters showing significant group difference in VBA were selected as the seed ROIs for RSFC analysis. Firstly, the peak coordinates of each significant cluster obtained from VBA were determined and used to create a ROI with a radius of 6 mm. Secondly, the RSFC was examined with a seed-voxel correlation approach, in which the correlations of the mean time-course signal in a seed region with all other voxels in the whole brain were calculated. Before statistical analysis, the correlation coefficients were transformed into  $z$  values using the Fisher  $r$ -to- $z$  transformation to improve the normality. Two-sample  $t$ -tests between the groups were then performed using the DPABI toolbox, with age, sex, and head motion parameters as covariates. The statistical results were corrected for multiple comparisons using the AlphaSim method, with a voxel-

level threshold of  $p < 0.001$  and a cluster-level threshold of  $p < 0.05$ . Finally, the results were projected onto a smoothed International Consortium for Brain Mapping (ICBM152) surface template using the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) [34].

### 3. Results

**3.1. Demographic Characteristics.** Six male and two female subjects were included in the LP group and eight male and seven female subjects in the NLP group; we also recruited 21 age- and sex-matched NSCs. Analysis of variance (ANOVA) followed by two-sample  $t$ -tests and chi-square tests were performed to detect age and sex differences, respectively, between the various groups (Table 2). No significant differences in the demographic characteristics were identified between the three groups (age:  $t = -1.657$ ,  $p = 0.112$  comparing the LP and NLP groups;  $t = -1.883$ ,  $p = 0.071$ , LP vs. NSC;  $t = 0.271$ ,  $p = 0.788$ , NLP vs. NSC; sex:  $p = 0.400$ , LP vs. NLP;  $p = 0.238$ , LP vs. NSC; and  $p = 1.000$ , NLP vs. NSC).

**3.2. VBA Results.** The two-sample  $t$ -test revealed a reduced FA in the left occipital lobe/subgyral, right parahippocampal gyrus, and right superior occipital gyrus in NLPs compared to NSCs. We also found higher MD in the bilateral lingual gyrus, as well as higher RD in the right lingual gyrus and right parahippocampal gyrus in NLPs, compared with NSCs ( $p < 0.001$ , AlphaSim corrected; Table 3 and Figure 1). No significant AD alterations were observed between these two groups. Compared with NSCs, LPs showed significant FA reduction in the bilateral middle occipital gyrus, left lingual gyrus, left cuneus, left parahippocampal gyrus, and right parietal lobe/subgyral ( $p < 0.001$ , AlphaSim corrected; Table 3 and Figure 2). No significant differences in MD, RD, and AD were found when comparing the LP and NSC groups. No elevated FA or reduced diffusivity parameters were found for any of the clusters in NLPs or LPs compared with NSCs, even with a loose threshold ( $p < 0.01$ , AlphaSim corrected). Unfortunately, the comparison of all diffusion tensor maps between the LP and NLP groups showed no results at the voxel level, at AlphaSim-corrected  $p < 0.001$ . However, some voxels in the brain of the LP group exhibited trends (at a voxel-level AlphaSim-corrected  $p < 0.01$ ) towards increased/decreased DTI parameters compared with NLPs, including reduced FA in the right fusiform gyrus, right middle temporal gyrus, and superior occipital gyrus; increased FA in the right superior frontal gyrus; increased MD, RD, and AD in the right fusiform gyrus and middle temporal gyrus; and reduced MD, RD, and AD

TABLE 3: Brain regions with significant changes in diffusion tensor imaging metrics.

Between-group comparison	DTI parameter changes	Localizations of peak voxels	Abbreviations	Cluster size (voxels)	T score	Peak MNI		
						x	y	z
NLP vs. NSC ( $p < 0.001$ , AlphaSim corrected)	FA reduction	Left occipital lobe/subgyral	OG.L	5196	-7.73	-32	-62	-2
		Right parahippocampal	ParaHIP.R	978	-10.06	12	2	-22
		Right superior occipital gyrus	SOG.R	255	-8.34	24	-92	32
	MD elevation	Left lingual	LING.L	3698	5.85	-28	-54	-4
		Right lingual	LING.R	3596	5.84	20	-54	2
	RD elevation	Right lingual	LING.R	4030	6.74	14	-80	0
		Right parahippocampal	ParaHIP.R	7113	7.07	10	4	-18
		Left parahippocampal	ParaHIP.L	319	-6.58	-12	2	-20
		Left middle occipital gyrus	MOG.L	198	-5.98	-26	-100	2
		Left occipital lobe/subgyral	OG.L	224	-5.71	-32	-68	-2
LP vs. NSC ( $p < 0.001$ , AlphaSim corrected)	FA reduction	Left lingual	LING.L	142	-5.11	-4	-74	-4
		Right middle occipital gyrus	MOG.R	62	-5.99	38	-70	0
		Left cuneus	CUN.L	154	-5.98	-8	-84	30
		Right parietal lobe/subgyral	PG.R	120	-6.65	32	-40	24

Abbreviations: LP: early-blind adolescents with residual light perception; NLP: early-blind adolescents without light perception; NSC: normal-sighted controls; FA: fractional anisotropy; MD: mean diffusivity; RD: radial diffusivity; and MNI: Montreal Neurological Institute.

in the bilateral caudate (Table SI and Figure SI in the Supplementary Materials).

**3.3. Correlation Analysis Results.** Correlation analysis showed positive and significant correlations between the MD and RD values of the right lingual gyrus and age in NLPs (MD:  $r = 0.601$ ,  $p = 0.018$ ; RD:  $r = 0.536$ ,  $p = 0.040$ ), but negative and significant correlations in NSCs (MD:  $r = -0.488$ ,  $p = 0.025$ ; RD:  $r = -0.508$ ,  $p = 0.019$ ). In NSCs, the FA values of the left occipital lobe/subgyral ( $r = 0.538$ ,  $p = 0.012$ ) and the right superior occipital gyrus ( $r = 0.560$ ,  $p = 0.008$ ) were positively correlated with age, while the MD values of the left lingual gyrus were negatively correlated with age ( $r = -0.508$ ,  $p = 0.019$ ) (Figure 3).

**3.4. Head Motion Effects.** Head motion time courses were computed by estimating the shift in each direction and the rotations about each axis for each of the 230 consecutive volumes. To assess the head motion confounders, we calculated the mean framewise displacement among the three groups (LP:  $0.35 \pm 0.23$  mm; NLP:  $0.22 \pm 0.17$  mm; and NSC:  $0.26 \pm 0.27$  mm). Moreover, ANOVA was used to identify potential differences in head motion between the 3 groups, but none was found. (ANOVA:  $F = 0.845$ ,  $p = 0.437$ ).

**3.5. RSFC Results.** The whole-brain RSFC of the brain regions with significant microstructural alterations was analyzed and compared between the NLP and NSC groups. The left occipital lobe/subgyral of NLPs showed enhanced RSFC with the left inferior frontal triangular areas, left middle frontal gyrus, and right inferior frontal opercular areas; the right parahippocampal gyrus of NLPs showed enhanced RSFC with the left superior frontal gyrus; the right superior occipital gyrus of NLPs showed enhanced RSFC with the right

supramarginal gyrus/left superior frontal gyrus and decreased RSFC with the left fusiform gyrus ( $p < 0.001$ , AlphaSim corrected; Table 4 and Figure 4). When comparing LPs with NSCs, only the left middle occipital gyrus showed a significantly decreased RSFC in LPs with the right middle occipital gyrus, when setting the bilateral middle occipital gyrus, left parahippocampal gyrus, left lingual gyrus, left cuneus, and right parietal lobe/subgyral as ROI seeds ( $p < 0.001$ , AlphaSim corrected; Table 4).

To investigate the effects of residual light perception on the brain function in blind brains, the differences in the whole-brain RSFC of the brain regions showing microstructural alterations between the LP and NLP groups were analyzed and compared. A trend of RSFC change in LPs relative to NLPs could also be observed and specifically enhanced RSFC between the right fusiform gyrus and the right superior frontal orbital areas/right middle temporal gyrus and between the right superior frontal gyrus and the left inferior temporal gyrus. On the contrary, the RSFC between the right superior frontal gyrus and the right post-central gyrus/superior frontal gyrus was decreased in the LP compared to the NLP group ( $p < 0.01$ , AlphaSim-corrected; Table SII and Figure SII in the Supplementary Materials).

## 4. Discussion

We investigated the alterations of brain microstructure and their corresponding functional connectivity in EBAs with and without light perception using the DTI and rs-fMRI datasets. Compared to NSCs, both EBA groups showed significant brain microstructural disruptions mainly in the posterior visual pathway of the occipital lobe and the extrastriate visual cortex. Moreover, the correlations between bilateral



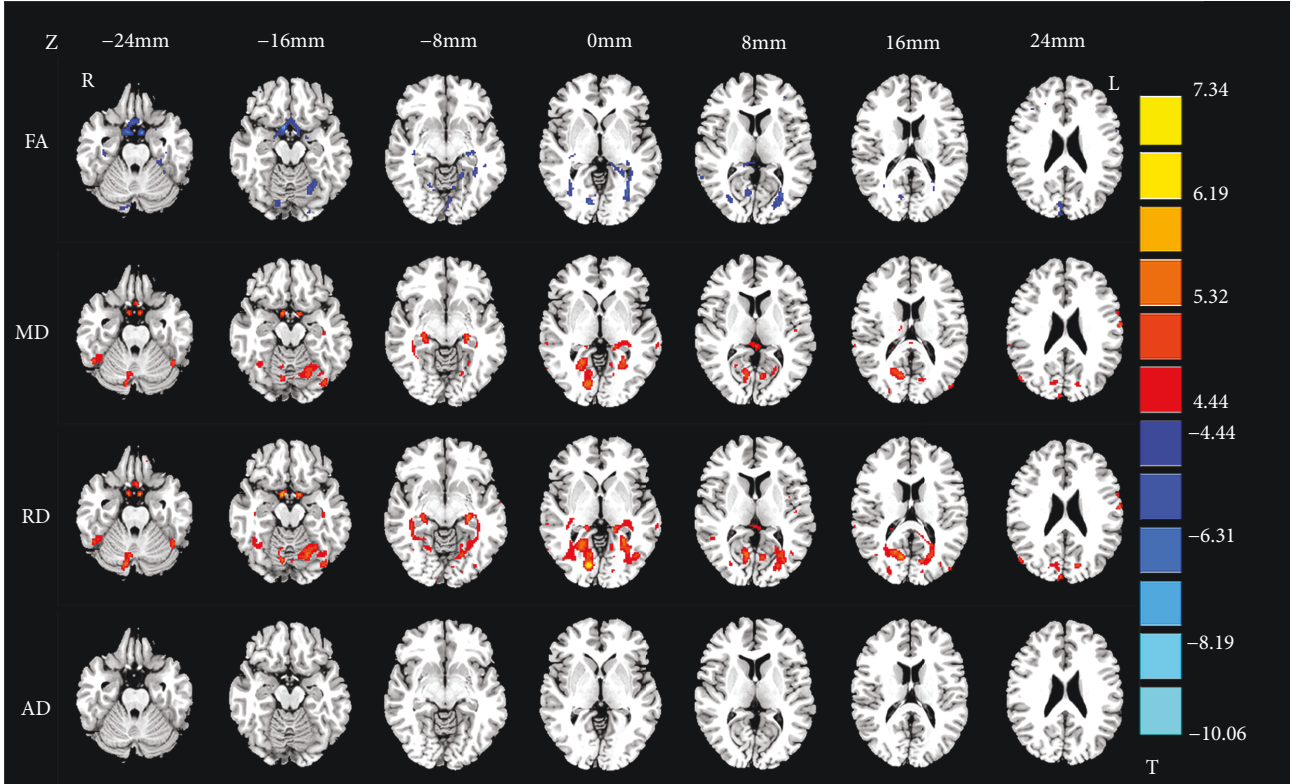


FIGURE 1: Group differences of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in NLPs compared to NSCs ( $p < 0.0001$ , AlphaSim corrected). Blue regions denote lower FA values and red regions denote higher diffusivity values. The numbers at the top indicate the  $z$  value of MNI coordinates.

occipital cortex FA or bilateral lingual gyrus MD and age were consistent with the developmental trajectory of the brain in NSCs, but inconsistent or even opposite in EBAs. Additionally, using brain regions with significant DTI parameter changes in our study as the ROIs, we identified enhanced RSFC in the occipital cortex with the bilateral frontal cortex and the homolateral parietal cortex and reduced intrahemispheric RSFC in the right visual cortex in NLPs, as well as reduced interhemispheric RSFC within the middle occipital cortex in LPs compared with NSCs. Our findings provide additional evidence that early visual deprivation may lead to functional neuroplasticity earlier than structural neuroplasticity in EBAs.

**4.1. Disruptions in the Brain Microstructure of EBAs.** The FA reduction in the bilateral visual pathway of the occipital cortex in both EBA groups, elevated MD of the bilateral lingual gyrus, and elevated RD of the right lingual gyrus in NLPs vs. NSCs were consistent with the findings of previous research on young or middle-aged blind adults [2, 9, 12, 35, 36]. These structural disruptions were also supported by other evidence of reduced anatomical connectivity associated with the visual cortex [12, 37] and decreased GM and WM volume in the occipital cortex of blind individuals [6, 38]. Our study also validated the GM and WM changes in the visual cortex of EBAs at the microstructural level, which can be explained by transneuronal degeneration and/or immaturity due to early visual deprivation [9, 39]. Moreover, we found

diminished FA in the left parahippocampal gyrus of LPs and the right parahippocampal gyrus of NLPs compared to NSCs. The right parahippocampal gyrus is important for learning and visuospatial configuration of objects [40], while the left parahippocampal gyrus is involved in cumulative verbal memory [41]. Considering the asymmetry function of the bilateral parahippocampal gyri during learning, their inconsistent alteration in the two groups may provide evidence of different learning patterns between the LP and NLP groups.

Furthermore, to investigate the effects of residual light perception on brain microstructure, we compared the DTI parameters between LPs and NLPs. The results showed increased FA in the right superior frontal gyrus and reduced diffusivity parameters in the bilateral caudate nucleus in LPs compared with NLPs. Since the superior frontal gyrus is anatomically connected with the cognitive control network and functionally involved in complex cognitive processing [42, 43], the increased FA of the right superior frontal gyrus in LPs vs. NLPs may suggest that residual light perception could play a role in complex cognitive function or reduce the damage to cognitive function induced in EBAs by the lack of visual information. As the caudate nucleus is known to integrate spatial information with motor behavior and is associated with some learning processing [44–46], its decreased diffusivity parameters in LPs vs. NLPs demonstrate that the function of guiding motor performance and learning in the caudate nucleus may be partly mediated by light perception.

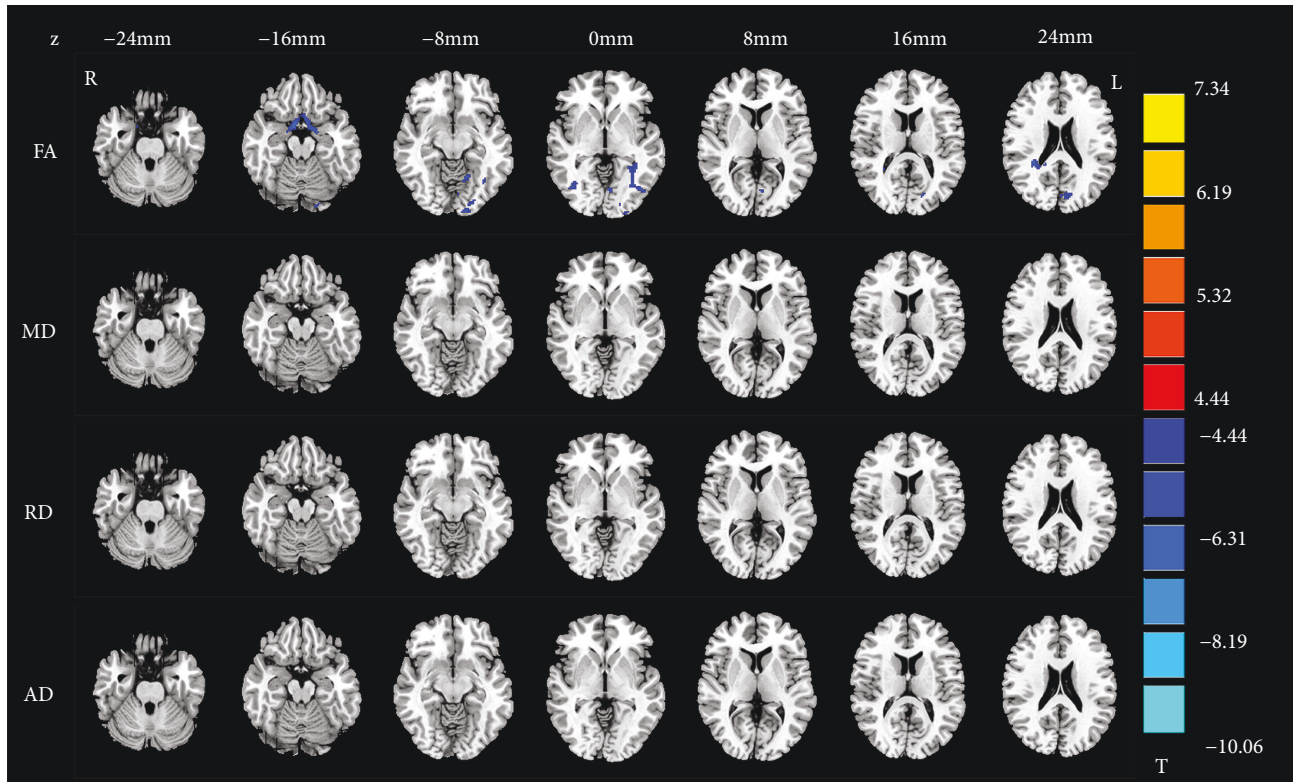


FIGURE 2: Group differences of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in LPs compared to NSCs ( $p < 0.001$ , AlphaSim corrected). Blue and red regions denote lower and higher DTI parameters, respectively. The numbers at the top indicate the  $z$  value of MNI coordinates.

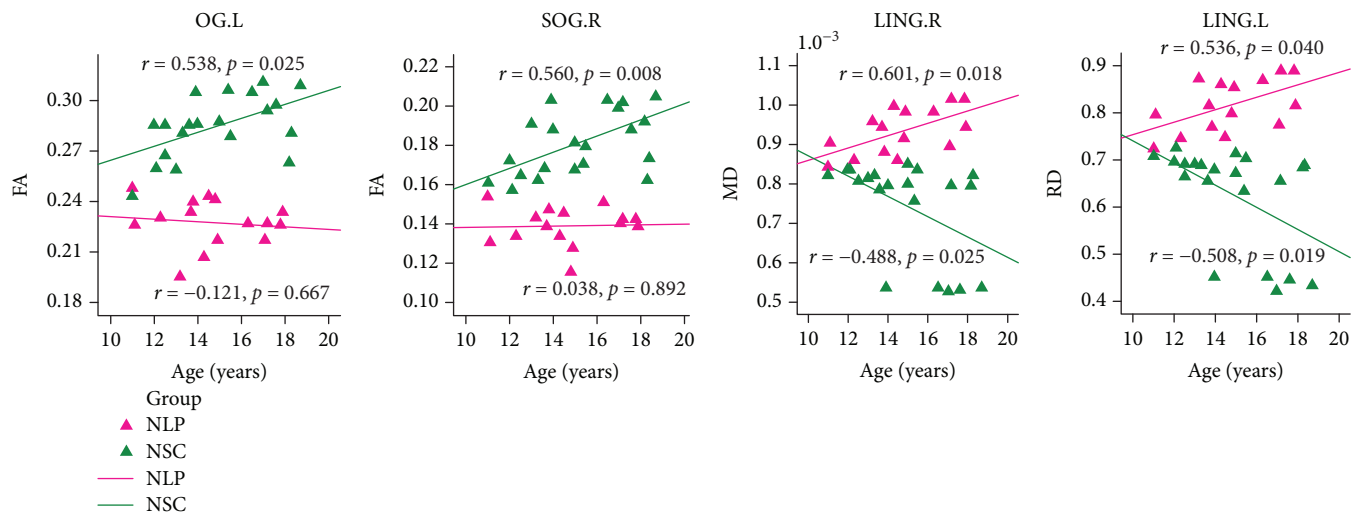


FIGURE 3: Pearson's correlation analyses between age and DTI metrics of OG.L, SOG.R, LING.R, and LING.L, respectively, in the NLP and NSC groups. In the scatter plots, the DTI metrics of each significant region are displayed for each subject in the specific groups, with dots for NLPs shown in violet and NSCs in green. The correlation coefficients and  $p$  values are next to each scatter plot. All abbreviations of brain regions are shown in Table 3.

We also calculated the correlations between age and DTI metrics of the altered brain regions in the three groups. The FA of the bilateral occipital cortex was positively correlated with age in NSCs but not in NLPs, and the MD and RD of the right lingual gyrus were negatively correlated with age

in NSCs, but positively in NLPs. The trends of DTI parameters alteration with age in NSCs were consistent with the developmental trajectory of WM in the young [47–49], while these trends were not observed or were reversed in NLPs. This inconsistency suggests that microstructural disruptions

TABLE 4: Brain regions with significant changes of RSFC between groups.

Between-group comparison	ROI seeds	Brain regions	Abbreviations	Cluster size (voxels)	$T$ score	Peak MNI		
						$x$	$y$	$z$
NLPs vs. NSC	OG.L	Left inferior frontal gyrus, triangular part	IFGtri.L	77	5.12	-39	33	6
		Right inferior frontal gyrus, opercular part	IFGoper.R	115	6.77	57	21	33
	ParaHIP.R	Left middle frontal gyrus	MFG.L	97	5.68	-45	18	18
		Left superior frontal gyrus	SFG.L	67	5.96	67	-24	30
	SOG.R	Left fusiform gyrus	FG.L	188	-5.93	-24	-66	-15
		Right supramarginal gyrus	SMG.R	62	5.16	60	-33	39
LPs vs. NSC	MOG.L	Left superior frontal gyrus	SFG.L	48	4.63	24	-93	6
		Right middle occipital gyrus	MOG.R	47	-5.15	24	-93	6

The results were corrected by the AlphaSim method at a voxel level of  $p < 0.001$ . Abbreviations: RSFC: resting-state functional connectivity; ROI: region of interest; OG.L: left occipital gyrus; ParaHIP.R: right parahippocampal gyrus; SOG.R: right superior occipital gyrus; MOG.L: left middle occipital gyrus; LP: early-blind adolescents with residual light perception; NLP: early-blind adolescents without light perception; NSC: normal-sighted controls; MNI: Montreal Neurological Institute.

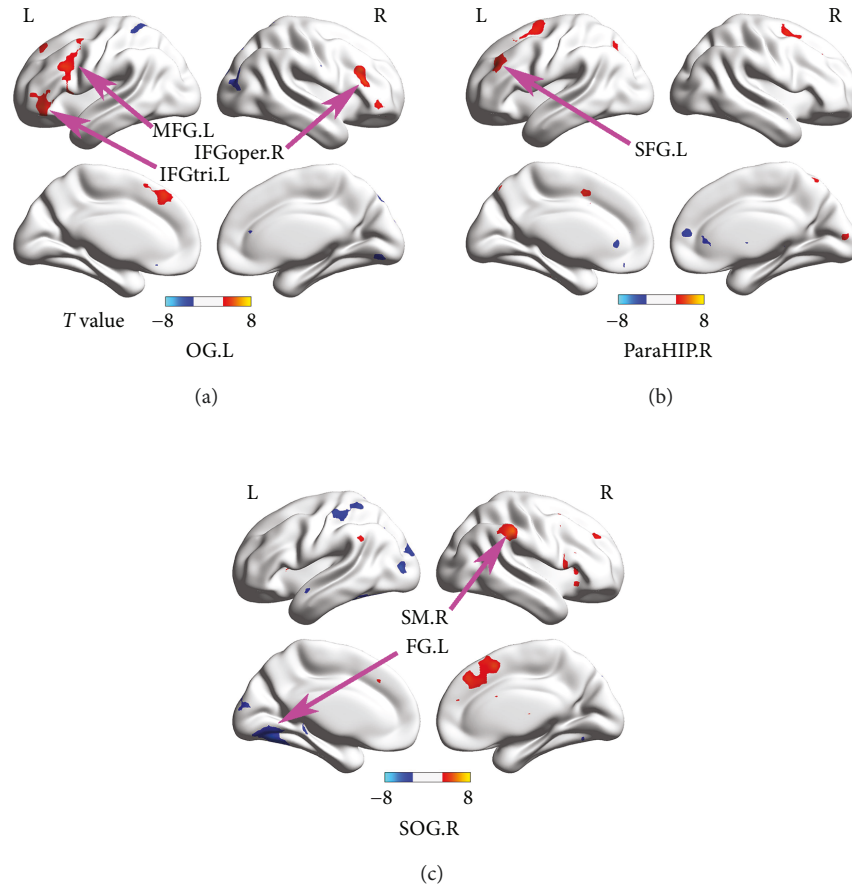


FIGURE 4: Brain regions that showed altered functional connectivity with OG.L (a), ParaHIP.R (b), and SOG.R (c), respectively, in NLPs compared to NSCs. Two-sample  $t$ -tests were performed to explore the between-group differences. The results were corrected by the AlphaSim method at a voxel level of  $p < 0.001$ . All abbreviations of the brain regions are shown in Tables 3 and 4.

caused by early visual deprivation in the corresponding brain regions may progressively accumulate in adolescents. Given the continuous development of WM in adolescence, a

probably more reasonable explanation for the trend shown by the NLPs is the coexistence of blindness-induced damage and normal cerebral development.



**4.2. Alterations in Functional Connectivity.** Changes in brain microstructure preferentially point to abnormalities in brain functional connectivity [50, 51]. Resting-state fMRI can reflect the integrated features of intrinsic functional connectivity in the brains of visually impaired persons [27]. Many previous studies reported changes in RSFC between the occipital cortex and other sensory [7, 25–27, 52], somatosensory [25, 26, 28, 52, 53], and motor cortices [25, 26, 28] in early-blind adults. In the current study, the occipital gyrus in NLPs showed enhanced RSFC with some frontal areas, including the left inferior frontal triangle, left middle frontal gyrus, left superior frontal gyrus, and right inferior frontal opercular areas. Such findings are consistent with those of previous studies [54, 55]. In healthy humans, these frontal regions are classically considered as high-level areas related to language and cognition and involved in verbal fluency [56, 57], single word and motor speech production [58, 59], and error detection and imitation [60, 61]. Beyond these classical functions, they also participate in verbal working memory [62, 63]. In blind individuals, the occipital visual cortex and the frontal language and cognitive areas were activated when performing Braille reading tasks [64, 65]. These findings indicated that these frontal areas might play an important role, related to the language network, in the blind brain. Additionally, compared with sighted controls, early-blind participants had more extensive activity in the occipital visual areas and frontal language areas when performing a vibrotactile memory task [64, 65]. All evidence may explain why the RSFC between the occipital areas and frontal areas was increased in the NLPs. From another perspective, the elevated RSFC between the occipital visual areas and the frontal language regions can provide compelling evidence for the existence of functional neuroplasticity in NLPs.

We also observed reduced interhemispheric RSFC between the bilateral middle occipital gyrus in LPs and between the right superior occipital gyrus and the left fusiform gyrus in NLPs compared with NSCs, extending the findings of many previous studies [22, 25, 31, 66]. According to some published reports, such reduced interhemispheric communication may be interpreted as extensive abnormalities in WM integrity, particularly in the corpus callosum [67, 68]. Many existing studies found WM abnormalities in the splenium of the corpus callosum, thought to play a crucial role in the communication between the two cerebral hemispheres, in early-blind young, middle-aged, or elderly adults [3, 10, 35, 69, 70]. However, no WM structural abnormalities were found in the splenium of the corpus callosum in the present study. One possible reason may be that the posterior part of the corpus callosum continues to develop during adolescence and increases in density [47, 48, 71, 72], likely counteracting the neurodegenerative effects of visual deprivation [73]. Based on prior and present findings, we speculated that the RSFC changes in EBAs might result not only from a combination mechanism of general loss and complementary plasticity [25] but also from an antagonistic mechanism of neural development. Thus, our findings provide new information regarding the functional profiles that emerge in the early life of blind adolescents.

Furthermore, we evaluated the RSFC differences between the LP and NLP groups to investigate the differences in functional connectivity patterns depending on residual light perception. Compared with NLPs, LPs showed enhanced RSFC in the right fusiform with the homolateral middle temporal gyrus and reduced RSFC in the right superior frontal gyrus with the right postcentral gyrus. In sighted subjects, the fusiform and middle temporal gyri have been reported to be involved in the ventral and dorsal visual streams, respectively, and to be robustly activated during object shape/location detection and visual-motor tasks [74, 75]. There is no doubt that light perception is crucial for such processing. Therefore, the residual perception of light in LPs may account for the enhanced RSFC between these regions. Given that the postcentral gyrus is well-known as the primary somatosensory area and is associated with fine touch sense, the decreased RSFC of this area in LPs may suggest that the touch sense of early-blind individuals with residual light perception is not as strong as that of those without light perception.

**4.3. Limitation.** Our findings of the effects of residual light perception on brain microstructure and function in EBAs were derived at a loose level of statistical significance, presumably due to the small sample size. Therefore, these results should be interpreted with caution, and further studies with larger sample size will be needed to provide solid evidence of these phenomena.

## 5. Conclusion

The present study demonstrated significant microstructural and functional alterations in EBAs with and without residual light perception when compared to NSCs. Our findings provide additional evidence that early visual deprivation may lead to functional neuroplasticity earlier than structural neuroplasticity in EBAs. The structural alterations in EBAs contain complex mechanisms including general loss, complementary plasticity, and neural development. Collectively, these results provided new insights into the mechanisms underlying the reorganization of the brain in adolescents with early visual deprivation.

## Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author Dr. Hengguo Li (lhgjinu@263.net) on reasonable request.

## Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Authors' Contributions

ZZ, XL, FH, JZ, and JL acquired and analyzed data. JX, XL, and HL conceived this study and designed the experiments. ZZ wrote the article with the help of JX, LS, and QH. All

authors were involved in data interpretation and critically revising the manuscript.

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## Supplementary Materials

Table SI: brain regions with significant changes in diffusion tensor imaging metrics between LPs and NLPs. Table SII: brain regions with significant changes of RSFC between the LP and NLP groups. Figure SI: group differences of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) using voxel-based analyses in LPs compared to NLPs (AlphaSim corrected with a voxel-level threshold of  $p < 0.01$  and a cluster-level threshold of  $p < 0.05$ ). Blue and red regions denote decreased and increased DTI parameters, respectively. The numbers at the top indicate the  $z$  value of MNI coordinates. Figure SII: brain regions that showed altered functional connectivity with FG.R (A) and SFG.R (B), respectively, in LPs compared to NLPs. Two sample  $t$ -tests were performed to explore the intergroup differences. The results were corrected by the AlphaSim method at a voxel level of  $p < 0.01$ . All abbreviations of the brain regions are shown in Tables SI and SII. (*Supplementary Materials*)

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## Research Article

# Effects on Parental Stress of Early Home-Based CareToy Intervention in Low-Risk Preterm Infants

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Parenting a preterm infant is more challenging than a full-term one. Parent involvement in early intervention programs seems to have positive psychosocial effects on both the child and parent. CareToy is an innovative smart system that provides an intensive individualized home-based family-centred EI in preterm infants between 3 and 9 age-corrected months. A RCT study, preceded by a pilot study, has been recently carried out to evaluate the effects of CareToy intervention on neurodevelopmental outcomes with respect to Standard Care. This study aims at evaluating the effects of CareToy early intervention on parenting stress in preterm infants. Parents (mother and father) of a subgroup of infants enrolled in the RCT filled out a self-report questionnaire on parenting stress (Parenting Stress Index-Short Form (PSI-SF)) before (T0) and after (T1) the CareToy or Standard Care period (4 weeks), according to the allocation of their preterm infant. For twins, an individual questionnaire for each one was filled out. Results obtained from mothers and fathers were separately analysed with nonparametric tests. 44 mothers and 44 fathers of 44 infants (24 CareToy/20 Standard Care) filled out the PSI-SF at T0 and at T1. CareToy intervention was mainly managed by mothers. A significant ( $p < 0.05$ ) reduction in Parental Distress subscale in the CareToy group versus Standard Care was found in the mothers. No differences were found among the fathers. CareToy training seems to be effective in reducing parental distress in mothers, who spent more time on CareToy intervention. These findings confirm the importance of parental involvement in early intervention programs. This trial is registered with Clinical Trial.gov NCT01990183.

## 1. Background

Parental stress can be defined as “a complex process in which adults feel overwhelmed in their role in relation to the responsibilities associated with it” [1]. According to Abidin’s parenting stress theory that represents the theoretical framework of this study, the parental stress is “a multidimensional concept which is cumulative, highly influenced by environment, and a result of parent-child transactions that promote negative feelings in parents” [2]. Abidin’s parenting stress theory [2, 3] includes three levels of stressors: those arising from the parental domain (e.g., sense of competence as a parent and attachment with a child); the child domain

(e.g., adaptability to situations, mood); and the situational, contextual, and social domain (e.g., life events and work environment). These three domains work together to elicit appraisal by parents.

In general, a “physiologic” dose of stress could be motivational, but excessive parental stress may have negative consequences on the child and on the family as a whole [3].

The transition to parenthood is a crucial step whose evolution of both mental and emotional aspects has individual repercussions [4] often more evident in mothers [5] and, as a consequence, alters couple stability [6, 7].

Although stress in its definition is related to the condition of becoming a parent per se, there are some factors which can

increase parental stress. Preterm birth is an event with several significant consequences, which can affect the child, parents, and caregiver-infant dyad [8]. A recent meta-analysis [9] has showed that parents and more specifically mainly mothers of preterm infants experience markedly more parental stress compared to parents of term-born infants. This might be related to possible complications of birth, updating the idea that the preterm birth is a source of stress in itself.

Moreover, normal stress of parenthood increases in relation to the frequent problems of a preterm infant, such as medical complications and physical and emotional isolation between parents and infants [10]. Parents with lower gestational age infants probably reported more life stress in relation to long periods spent in neonatology intensive care units (NICUs), which often puts a strain on marital relations [11]. Moreover, due to the needs of the infant, one parent may choose to decrease working hours or to cease working at all, resulting in lower family income [12].

There is evidence pointing to a high correlation between preterm birth and increased parental stress: preterm birth has a negative effect on the relationship between the mother and infant [13–15]; families of preterm infants have frequently reported higher levels of stress [16, 17] than those of full-term infants [9]. Parenting stress in mothers of preterm infants at one year of age is significantly greater than that found in mothers of full-term infants [18].

Most studies have investigated only maternal stress, and there is less evidence about paternal stress. Previous studies in high-risk groups of parents of chronically ill children or children with behavioural problems have shown that mothers and fathers presented similar levels of stress and anxiety [19]. Studies which measure parenting stress in both parents show a correlation between partners' levels of stress [20]. According to this, parental stress has been demonstrated to be mutually shared among family members and acts as a sort of predictor of general family well-being [21].

Moreover, there are several studies showing a relationship between parenting self-efficacy and parenting stress; this suggests that parent outcomes may be a reliable measure of psychoeducational program effectiveness, at least in the short term [22–24].

In relation to the importance of a parental role in infant care, the literature suggests that their involvement in early intervention (EI) programs seems to have positive psychosocial effects both on child and on parents [25].

It is well known that preterm infants need early intervention to improve their outcome [26]. Due to age and following a standard guideline, active involvement and compliance of the family are crucial for maximizing intervention effects. As stated above, there is a relationship between active participation of parents in the intervention of their child and levels of stress. Therefore, it has been hypothesized that a reduction of parental stress, together with parental psychological health, is important for improving efficacy of interventions focused on child behaviour [27]. These findings suggest and justify the assessment of parenting stress as an outcome measure in the evaluation of an early intervention program [28].

It is therefore crucial to detect, identify, and monitor parental stress in order to understand and characterize

families so as to prevent negative consequences, especially on child development, and maximize the overall benefits of the intervention.

One of the most widely used scales for the assessment of parental stress is the Parenting Stress Index (PSI) [2, 29–35].

PSI, in its original form (Parenting Stress Index Full Length (PSI-FL)), requires considerable time to be elaborated and, given the long battery of tests to be imposed on infants and parents, could result in missing or incomplete information or misunderstanding of questions by parents leading to unreliable answers. For this reason, in 1995, Abidin developed a short form of PSI (PSI-SF), a 36-item tool based on factor analyses of PSI-FL indicating a three-part solution with three dimensions labelled as Difficult Child (DC), Parental Distress (PD), and Parent-Child Dysfunctional Interaction (P-CDI). The validation of the PSI-SF has been based on two samples of Caucasian primarily married mothers of young children (mean age under 4 years). Correlation between total scores on the long and short forms was quite high (0.87) in these samples. In recent years, many authors have adopted the PSI-SF as an outcome measure [36–38] and it has already been used with mothers of preterm infants [39, 40]. The PSI-SF is nowadays a well validated clinical and research tool which assesses stress associated with parenting.

*1.1. Present Study.* On the basis of the previous theoretical framework and background, the assumption of this study is that a playful early intervention aimed at promoting parent-child interaction using a semistructured tool (CareToy) [41–43] in the home environment could have effects not only on infant development but also on parental stress. A RCT study (Clinical Trial.gov NCT01990183) [44], preceded by a pilot study [45], has been recently carried out and has demonstrated positive effects of CareToy intervention on neurodevelopmental outcomes (i.e., improvement of early motor and visual functions) compared to Standard Care. The aim of this study is to investigate the effects of CareToy early intervention carried out on preterm infants, compared to Standard Care, on parental stress.

## 2. Materials and Methods

*2.1. Participants.* This study is a part of the CareToy project. Through a European consortium, the clinical partners responsible for the assessment of enrolled infants were IRCCS Fondazione Stella Maris in Italy and Elsass Institute in Denmark. This study was approved by the local ethics committees of the two institutions. The inclusion criteria were (i) birth between 28 + 0 and 32 + 6 (weeks + days) of gestational age and (ii) 3 ± 9 age-corrected months who had achieved a predefined cut-off score in gross motor ability derived from the Ages and Stages Questionnaire-Third Edition (ASQ-3, a developmental screening tool to be filled in as a self-reported questionnaire).

The exclusion criteria for the CareToy project were (i) birth weight below the 10th percentile; (ii) brain damage (i.e., intraventricular haemorrhage < grade 1, any degree of periventricular leukomalacia, or brain malformation or



severe nonneurological malformations); (iii) any form of seizure; (iv) severe sensory deficits (blindness, deafness); and (v) participation in other experimental rehabilitation studies. Enrolment was carried out in Italy and in Denmark, and parents were selected from families enrolled in the CareToy project.

## 2.2. Intervention

**2.2.1. CareToy Intervention.** CareToy [41–43] is a modular system based on a traditional baby playpen which has been completely sensorized and defined as a biomechatronic gym with sensorized toys. It is delivered at home and is aimed at providing an intensive, highly customized, home-based, family-centred training program, remotely monitored by a clinical centre. Training is composed of specific goal-directed activities, called CareToy scenarios, remotely planned and periodically upgraded by a rehabilitative staff, according to specific infant needs and progress. Training has a high degree of variability and complexity and is multiaxial, promoting different aspects of motor, cognitive, relational, and visual developments during playtime with parents, who are guided in promoting developmental skills of their infant such as head rotation and gaze movement, manipulation skills, and eye-hand coordination. CareToy scenarios can be variably carried out in the supine, prone, or sitting position.

The system is connected to a clinical centre thanks to a telerehabilitation module with customized software to download activities (CareToy scenarios) and send data to the clinical staff so that they can monitor and upgrade scenarios. Every family has a password corresponding to their personalized program. For the first sessions, the training therapists go to the family's house to teach them how to use the system and, above all, how to interact and play with their child. Afterwards, parents continue on their own with the training, continuously remotely guided for each activity (e.g., figures and diagrams about how to prepare the system and how to position the infant are shown) by the software. In this way, parents play a decisive role in the management of training and are free to choose when and how to play with their infant.

If necessary, therapists are available by phone and, in some cases, to visit homes to provide assistance, but in our experience, this seldom happens and mainly in families with twins.

At the end of each day, the CareToy system automatically sends a training report to the rehabilitation staff, who then can monitor and adjust the system for subsequent training in order to progressively promote more complex abilities when the previous ones have been achieved.

In the aforementioned RCT [44], CareToy training was programmed for a mean daily duration of 30–45 minutes for 4 weeks (a total of 28 days).

**2.2.2. Standard Care.** As described in detail by Sgandurra et al. [43, 44], Standard Care consisted of a bimonthly follow-up visits, during which current care advice on the early management of preterm infants and booklets dedicated

to home care of preterm infants were distributed, according to standard recommendations of Italy and Denmark. Parents were trained on how to manage the care of their infants with illustrated material and counselling by the clinical staff (e.g., about how to handle or stimulate play with their preterm infants). In rare cases, sporadic sessions with a physical therapist for special assistance were arranged. In such cases, the number and type of performed activities were recorded on a dedicated diary.

**2.3. Outcome Measures.** According to study design [38], clinical assessment was performed at baseline (T0, in the week before the 4th week of CareToy Intervention/Standard Care) and in the week after the end of CareToy Intervention/Standard Care period (T1, primary endpoint).

The PSI-SF, a screening instrument for the early identification of parent-child systems which are under stress and at a risk of developing dysfunctional parenting behaviour, is the outcome measure used for addressing the aim of this study.

The PSI-SF consists of 36 items, derived directly from the full-length PSI. Answers are obtained using a Likert scale, which ranged from 1 (Strongly Disagree) to 5 (Strongly Agree). The range of total PSI-SF scores varies from 36 to 180. Scores above the 85th percentile (90 raw score) are considered clinically significant, and higher scores indicate severe levels of parenting stress.

The instrument produces a total stress score indicating the overall level of parenting stress with three subscales: Parental Distress (PD) which measures the level of distress due to the role of mother/father and personal factors; Parent-Child Dysfunctional Interaction (P-CDI) which reflects whether and how the child meets parental expectations; and Difficult Child (DC) which measures the behavioural characteristics of the child that makes them either easy or difficult to manage.

In this study, we presented data using the Parenting Stress Index-Short Form related to the changes detected at primary endpoint (T1) with respect to the baseline (T0). The current data refer to a subgroup of parents (both mothers and fathers) of infants enrolled in the CareToy project who accepted to complete the PSI-SF at T0 and T1.

Mothers and fathers were asked to fill out the questionnaire separately. For twins, an individual questionnaire for each infant was completed.

**2.4. Statistical Analysis.** All statistical analyses were carried out by means of the Statistical Package for Social Sciences (SPSS, version 20.0), with  $p$  values  $< 0.05$  considered to be statistically significant. Medians and 95% confidence intervals (CI) of infant, mother, and father characteristics and baseline measures for the total sample and separately for each group (CareToy and Standard Care) were calculated to check for baseline differences. Changes in the total stress and in each subscale (PD, P-DCI, and DC) score were calculated separately for the mother and father at baseline (T0) and after the intervention period (T1) for each group. All analyses at baseline and any delta changes (T1–T0) were analysed by means of a Mann–Whitney  $U$  independent sample test. Chi-square tests were carried out for categorical variables.



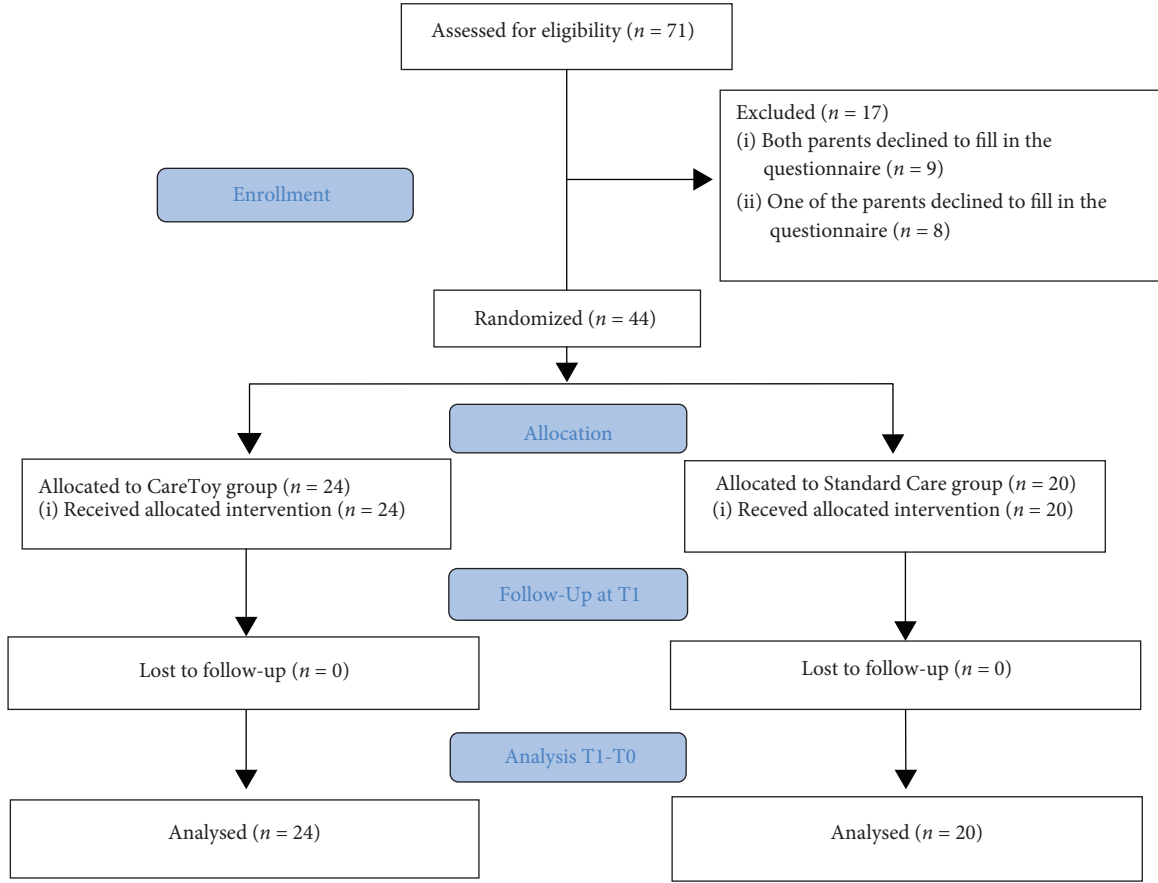


FIGURE 1

Finally, a multiple regression analysis for PD delta changes in mothers allocated to the experimental group was used to verify if these changes were related to the combined effect of the PD baseline values at T0 and the hours of CareToy training (predictors). Unstandardized  $\beta$  coefficients and significances were reported in addition to model effect sizes ( $R^2$ ) and  $p$  values.

### 3. Results

**3.1. Participants.** Out of 71 families, a total number of 44 mothers and 44 fathers of 44 infants enrolled in the CareToy project (24 CareToy/20 Standard Care) filled out a PSI-SF at T0 and T1 (Figure 1). The sample was composed of 44 mothers (mean age  $37.52 \pm 4.48$ ) and 44 fathers (mean age  $40.78 \pm 5.34$ ). The description of samples of parents and infants is presented in Table 1.

#### 3.2. Intervention

**3.2.1. CareToy Training.** CareToy intervention was performed by all infants considering a minimum drop-out criterion of 51% of planned scenarios in order to include their data in the analysis. The total amount of training had a mean value of  $9.55 \pm 3.81$  hours within the whole group of infants. In the 91.67% (22/24) of cases, CareToy training was mainly performed by mothers.

TABLE 1: Description of samples of parents and infants.

Characteristics of the sample	Total	CT group	SC group
Infants	44	24	20
Infant age (months)	$3.85 \pm 0.93$	$3.73 \pm 0.86$	$3.99 \pm 1.02$
Twins	20	12	8
Infant sex (no. of males)	24	15	9
Infant nationality (no. of Italians)	25	13	12
Mother age (years)	$37.52 \pm 4.48$	$37.54 \pm 4.45$	$37.50 \pm 4.77$
Father age (years)	$40.78 \pm 5.34$	$40.31 \pm 4.97$	$41.40 \pm 6.00$
Marital status (no. of married)	30	17	13
Involvement in the training (no. of mothers)		22	

**3.3. Outcome Measure.** At T0, no differences were found in the total stress and in all subscales scores between mothers and between fathers of the two groups (CareToy vs. Standard Care). No differences were also found between fathers and mothers at T0 considering both total sample and the two groups separately. A significant ( $p < 0.05$ ) reduction in the

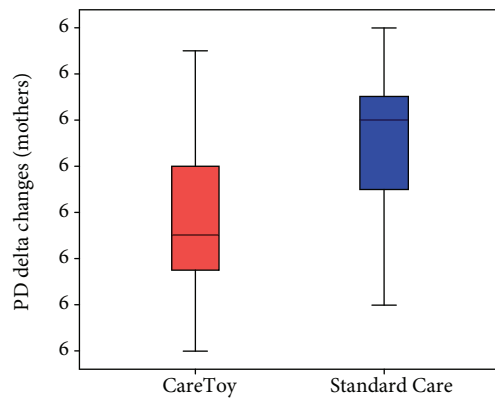


FIGURE 2

Parental Distress subscale in the CareToy group versus Standard Care was found in mothers (Figure 2, Tables 2–4) at T1. No difference was found in the other subscales and in the total stress for mothers. Moreover, no difference for all assessed scores was found between fathers of the two groups.

Multiple regression analysis of PD delta changes in mothers allocated to the CareToy group with the two predictors (PD values at baseline and hours of CareToy training) produced  $R^2 = 0.704$ ,  $F(2, 23) = 27.49$ , and  $p < 0.001$ . PD delta change values were significantly correlated with PD at T0 ( $\beta = -0.504$ ,  $ES = 0.069$ ,  $t = -7.368$ , and  $p < 0.001$ ) and for hours of CareToy training ( $\beta = -0.557$ ,  $ES = 0.164$ ,  $t = -3.391$ , and  $p = 0.003$ ).

#### 4. Discussion

This paper presents the results of one of the first studies in which parents are the main figures directly involved in infant treatment. In fact, CareToy training, even if planned and remotely monitored by the rehabilitation staff, is actually carried out at home by the parents who are free to choose the best moment, both for them and for their infant, to execute the planned CareToy scenarios.

As expected, thanks mainly to the possibility of obtaining maternal leave from work (as described in a previous work [12]), mothers were more involved and active in training than fathers. Even if the availability of the CareToy system at home potentially allows its use during free time (e.g., evening or weekends), only two fathers took advantage of this to use the system. Moreover, these results are in accordance with the literature, in which paternal stress seems to be lower (Tables 2 and 3) [9] and less affected by the intervention [46, 47].

The different degrees of involvement could explain the different results between mothers and fathers. In fact, at baseline, mothers and fathers had similar scores for the various PSI-SF subscales. After 4 weeks, however, changes in the PD subscale were significant only in the group of mother-infant dyads who carried out CareToy training. Therefore, we can suppose that CareToy intervention plays

a role in decreasing the PD subdomain of mothers in the CareToy group.

We might hypothesize that the direct involvement of mothers in carrying out CareToy training enhanced their ability to have stronger positive feelings regarding their role as caregivers. Mothers can perceive that they are promoting the development of their infants under the guidance of a competent driver, i.e., the remote management and control of the rehabilitation staff. The main aspect of CareToy is that the mother, after having completed the instructions of setting up the scenarios, is completely free to play and discover the planned activities with her infant. Furthermore, the mother does not have the burden of thinking how to organize the stimulation activities because the various scenarios automatically propose the goal-directed activities to the mother-infant dyad and automatically change the sequences in relation to the activities performed by the infant.

Another important aspect is that the CareToy telerehabilitation program could be a sort of coaching for the main users, namely, mother-infant dyads. Through the activities experienced during CareToy training, mothers learn how to manage the various positions of her child and how to execute the proposed activities which can then guide her to a better understanding of the goals of the activities. This can, in turn, lead to greater self-confidence, more realistic expectations, and a deeper understanding of her infant's signals and needs.

Moreover, if mothers improve their understanding of the most appropriate stimulation and if infant feedback becomes more positive, a virtuous circle in which stimulation and reward are positively reinforced will be established, as some studies on preterms have already shown [48]. We can hypothesize that, even if CareToy training is directed at infants, involvement of mothers in conducting training represents a sort of behavioural parenting programs. This hypothesis can be supported by the results of this study that are in line with the evidence in meta-analyses on behavioural parenting programs that reduce the parent domain of stress.

The last important aspect could be related to the direct use of a highly technological device, the CareToy system, instead of a standard baby gym, toys, and traditional rehabilitative tools. Involvement in a scientific and highly resonant research project could increase self-confidence and give the perception of taking utmost care of the infant. This last aspect could also explain the increased parental stress values of the control group because they realized they did not have a chance, at that time, to use the CareToy system with their infants. Examining the single change values (Figure 3), we can see that the range of changes for the CareToy group was significant varying from -15 to +4 and the majority of cases had a decrease of about -5, -4, and -3. For the Standard Care group, we can see that the lack of an early intervention program could cause an increase in the level of stress in some cases.

**4.1. Limitations and Future Perspectives.** In this study, as part of the CareToy project, no inclusion and exclusion criteria were set for parents. In order to improve the

TABLE 2: Baseline (T0) and outcome (T1) values of mothers for the total sample and separately for each group (CT and SC).

PSI-SF domains	Mothers (T0)					
	Total median [95% CI]	CT median [95% CI]	SC median [95% CI]	Total median [95% CI]	CT median [95% CI]	SC median [95% CI]
PD	24.00 [23.02-28.00]	23.00 [22.06-29.86]	25.00 [21.69-28.31]	25.00 [22.36-25.82]	24.50 [20.48-26.02]	26 [22.93-27.17]
P-CDI	22.00 [20.54-23.28]	21.00 [18.96-22.04]	22.00 [21.22-25.83]	20.00 [18.60-21.57]	19.00 [16.98-21.36]	21.00 [19.08-23.21]
DC	21.00 [20.41-23.11]	21.00 [19.16-21.84]	22.00 [20.75-25.63]	21.00 [19.67-22.47]	20.00 [17.72-21.69]	23.00 [20.71-24.53]
Total stress	70.00 [65.21-73.14]	65.00 [61.72-72.19]	73.00 [65.38-78.05]	65.00 [61.72-68.77]	64.00 [57.28-66.97]	67.00 [63.68-73.94]

TABLE 3: Baseline (T0) and outcome (T1) values of fathers for the total sample and separately for each group (CT and SC).

PSI-SF domains	Fathers (T0)			Fathers (T1)		
	Total median [95% CI]	Total median [95% CI]	Total median [95% CI]	Total median [95% CI]	CT median [95% CI]	SC median [95% CI]
PD	22.00 [20.33-24.38]	22.00 [20.33-24.38]	22.00 [20.33-24.38]	21.00 [20.33-23.98]	22.50 [19.58-25.50]	21 [19.48-23.95]
P-CDI	20.00 [19.57-22.07]	20.00 [19.57-22.07]	20.00 [19.57-22.07]	18.00 [18.28-21.10]	19.00 [18.11-22.64]	18.00 [17.17-20.64]
DC	21.00 [20.55-23.49]	21.00 [20.55-23.49]	21.00 [20.55-23.49]	20.00 [19.43-22.43]	19.50 [18.05-23.29]	22.00 [19.76-22.71]
Total stress	63.00 [61.14-69.26]	63.00 [61.14-69.26]	63.00 [61.14-69.26]	62.00 [58.73-66.82]	63.50 [56.71-70.45]	61.00 [57.48-66.23]

TABLE 4: Delta changes (T1-T0) with related z-scores and level of significance for mother and father values.

Delta (T1-T0)	Mothers			Fathers		
	PSI-SF domains	CT median [95% CI]	SC median [95% CI]	z (p)*	CT median [95% CI]	SC median [95% CI]
PD		-3 [-4.73/-0.68]	2 [2.12/2.22]	-2.237 (0.025)	1 [-1.42/1.59]	1 [2.55/1.50]
P-CDI		-0.50 [-3.47/0.80]	-2 [-4.06/-0.71]	-0.925 (0.355)	-1 [-2.82/1.15]	-1 [-2.93/0.02]
DC		-1 [-2.06/0.48]	0.00 [-2.10/0.96]	-0.046 (0.963)	-0.50 [-2.51/0.18]	-1 [-2.31/0.31]
Total stress		-3.50 [-8.26/-1.41]	-2.00 [-6.44/0.63]	-0.592 (0.554)	1 [-5.53/1.69]	1 [-6.52/0.52]

\*Mann-Whitney nonparametric test.

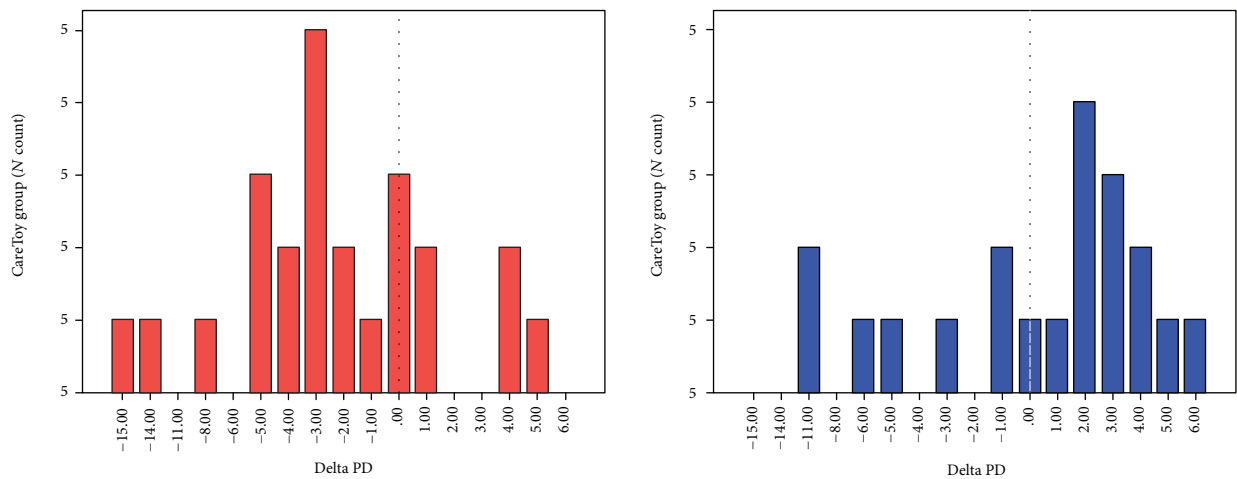


FIGURE 3

quality of future investigations, it would be interesting to adopt some inclusion criteria based on parent cognitive level and record data about the psychopathological history and risk of parents.

## 5. Conclusions

To our knowledge, in the literature, a few articles have evaluated parental stress as an outcome before and after an

intervention. Moreover, available data only deal with interventions directly focused on parents or on both infants and parents (e.g., Mother-Infant Transaction Program (MITP); [28]).

This study represents an important starting point for the comprehension of levels of parental stress in relation to their active participation in an intervention focused on their infant. Enabling parents to perform home training may help reduce their feelings of stress on the one hand and maximize infant outcome on the other, and these aspects could have positive consequences on the entire family.

One future perspective could be to investigate parental stress levels also at follow-up points in order to assess medium- and long-term effects of training.

## Data Availability

All the data used to support the findings of this study are included in the article.

## Disclosure

Giuseppina Sgandurra and Elena Beani are co-first authors.

## Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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## Review Article

# How Early Experience Shapes Human Development: The Case of Psychosocial Deprivation

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Experience plays an essential role in building brain architecture after birth. The question we address in this paper is what happens to brain and behavior when a young child is deprived of key experiences during critical periods of brain development. We focus in particular on the consequences of institutional rearing, with implication for the tens of millions of children around the world who from an early age experience profound psychosocial deprivation. Evidence is clear that deprivation can lead to a host of both short- and long-term consequences, including perturbations in brain structure and function, changes at cellular and molecular levels, and a plethora of psychological and behavioral impairments.

## 1. Introduction

Experience is the engine that drives much of postnatal brain development. Based primarily on research using rodent and nonhuman primates, a great deal is known about how the nature and the timing of experience influences the course of the developing brain. Not surprisingly, the *absence* of key experiences during these critical periods can exert serious and in some cases, lasting effects on multiple domains of development. For example, much has been learned from studies of rodents and nonhuman primates in which sensory loss is induced (e.g., the animal is deprived of light or sound; [1]) or in which animals are selectively reared (e.g., deprived of seeing faces; [2]). Similarly, great insight into how the absence of experience alters brain development has been gained by studying human infants who have experienced sensory loss early in life, such as those born with cataracts or who are born deaf, and who subsequently have their vision or hearing restored at different points in development [3–6].

A far more insidious and widespread form of deprivation involves the millions of children around the world who

experience psychological neglect early in life—for example, children who are neglected by their families (>500,000 in the US alone in 2013; [7]), children left behind by parents who have migrated to another country to look for work (61 million in China in 2014; [8]), or children who are orphaned or abandoned by their parents and then reared in institutions (>140 million abandoned/orphaned children, 8 million living in institutions; [9, 10]).

Here, we discuss how early psychosocial deprivation during critical periods of development shapes neural, biological, and behavioral development during childhood and beyond. Drawing from research on rodents, nonhuman primates, and humans, we consider what is known about the timing of deprivation as well as the timing of recovery from deprivation—specifically, whether critical periods impose constraints on recovery. We begin our critical and selective review of findings related to critical periods by discussing what is known in development, drawing first on the animal literature and then turn our attention to the literature on human infants. We then consider one specific type of experience that is common across rodents and mammals, that is,

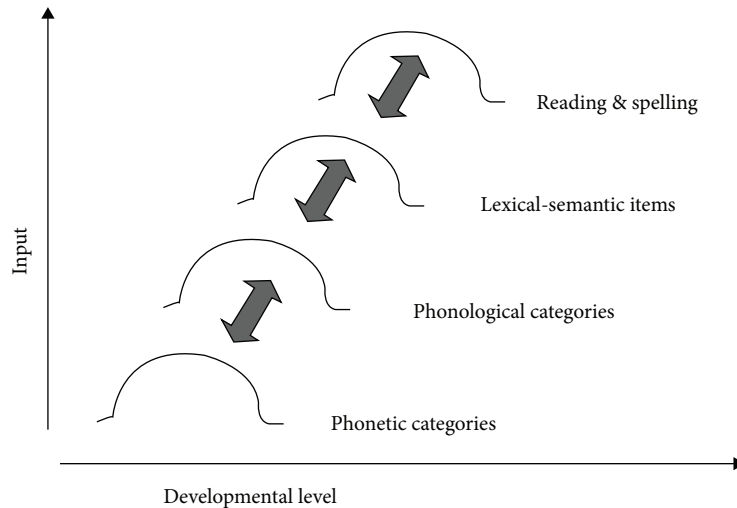


FIGURE 1: Possible multiple sensitive periods for the speech processing system. Figure was reproduced from Werker and Tees [13] (under the Creative Commons Attribution License/public domain).

maternal caregiving. We review what is known about the influence of timing of caregiving on species-typical socioemotional development. We then summarize the findings from the Bucharest Early Intervention Project, the only project of its kind to examine the effects of early intervention in a randomized control trial with children who have been abandoned and are living in institutions. We specifically highlight findings that address the issue of critical periods in human development during which the influence of experience has a significant impact for particular domains. We conclude our review by discussing the implications this knowledge has for the millions of children around the world who experience inadequate caregiving because they have been abandoned, orphaned, or raised in a neglecting family.

## 2. Conceptual Framework: Critical vs. Sensitive Periods

A key issue in modeling the effects of inadequate caregiving on development is to understand the issue of *timing* of exposure to adversity and timing of environmental enhancement—this concept of timing is generally referred to as a sensitive or critical period. Although “sensitive periods” and “critical periods” are often used interchangeably, they differ in fundamental ways. Knudsen [11], for example, has argued that *sensitive period* is a broad term often used to describe the effects experience has on the brain during limited periods in development. If a key experience fails to occur during a sensitive period, it may be difficult, without tremendous effort, to redirect development along a typical trajectory; even then, function in the affected domain (e.g., language) may not fully recover. A human infant forming a secure attachment to a caregiver seems to reflect a sensitive period. *Critical periods*, by contrast, result in irreversible changes in brain function. If a key experience fails to occur during a critical period, behavior is believed to

be permanently affected. Filial imprinting in animals likely represents a critical period.

Of course, both sensitive and critical periods represent time windows during which experience exerts a particularly strong influence on neural circuit formation. Knudsen [11] has argued that whatever plasticity exists *beyond* a sensitive period is constrained by what transpired *during* a sensitive period. In other words, one can reshape existing circuits only to a limited degree. Two additional points are also worth noting. First, there are cascades of sensitive/critical periods during development; thus, there will be multiple, cascading critical periods for different neural circuits and for different complex phenomena such as caregiving and language. Moreover, even *within* a domain there will be different critical periods (for example, within the domain of language, there may be different critical periods for language discrimination, understanding word forms, and for discriminating phonological categories; [12]). An example of this may be the conceptual model presented by Werker and Tees [13]. See Figure 1.

Second, great inroads have recently been made in understanding the molecular cues and brakes that regulate critical periods, including how to lift such brakes [14, 15]. Because the term “critical period” has endured in the popular lexicon, we use that term throughout this paper, although in nearly all instances the phenomena we describe most likely reflect sensitive periods. Figure 2 [16] illustrates the concept of critical periods. The X axis of this figure represents age and development, and the Y axis represents degree of neural plasticity. There are multiple factors presented in this figure. First, as can be seen, there are the contributions early in life of genes that program brain development. Second, as can be seen different domains (sensory, language, cognitive) have different trajectories of increasing and then diminishing plasticity across development, suggesting different times when experience for these different domains will have its most profound impact. Finally, the figure suggests that there

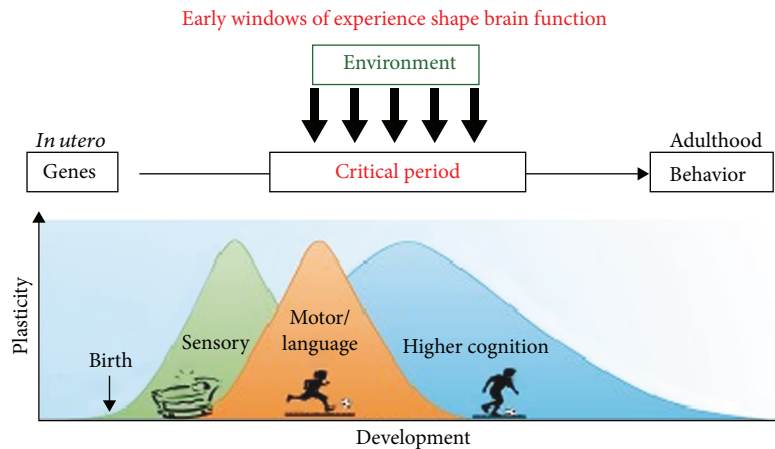


FIGURE 2: Figure illustrating the interaction of experience and maturation during critical periods in development. Figure was reproduced from Hensch and Bilimoria [16] (under the Creative Commons Attribution License/public domain).

are windows of plasticity or critical periods across these different domains of functioning.

### 3. Animal Models of Psychosocial Deprivation and Inadequate Caregiving

A variety of data from rodents and nonhuman primates have addressed issues regarding critical periods in the development of typical and atypical behavior. These studies have manipulated the timing of early experience and the quality of caregiving in the development of neural and physiological systems that support physical growth, stress responsivity, and homeostasis. Although detailed molecular mechanisms involved in each of these aspects are still under study, there is a convergence of this work that emphasizes the importance of early experience and, particularly in the rodent, the presence of critical periods early in postnatal life during which experience plays a singular role.

**3.1. Stress Hyporesponsive Periods in Rodents.** Research with rodents provides a particularly unique opportunity to manipulate many of the variables that are important in early experience, including timing of an event and quality of that event. Some of the first work on this topic was conducted by Levine [17] and Denenberg et al. [18], in which the precise time when particular types of postnatal experience occurred was manipulated (e.g., handling of the rat pup outside the nest) and outcomes of such manipulation on stress physiology were examined. For example, Levine [19] removed rat pups from the nest at different times after birth and examined the rat's subsequent ability to mount a cortisol response in reaction to a stressor. He found that timing of removal from the nest (and handling that occurred when the rat pup was removed) affected cortisol responses. Denenberg [18] found that pups removed from the dam on the 10th day of postnatal life were affected as adults in their ability to learn and to regulate their emotion and state of arousal [20]. Pups handled in the first ten days were also better able to deal with later stressors [21]. This early work suggested that there is a stress hyporesponsive period (i.e., when the system was not

responsive to external stressors). Subsequent work by Plotsky et al. [22] and by Roth and Sullivan [23] has shown that the presence of the rat dam early in life was critical in regulating the stress response of the pup. Anticipating the work that would occur almost 50 years later, Denenberg and Whimbey [24] found that rat pups that were handled at 20 days postnatal life had offspring that were more fearful than control animals (animals from rat dams that were not handled). Indeed, whether the rat dam was the biological mother or foster mother mattered less than the history of handling that the biological mother had as an infant on her infant's behavior. This work presages the epigenetic processes elucidated by Meaney and others, showing the intergenerational effects of early experience on later emotionality in offspring (e.g., [25]).

The work of Roth and Sullivan and that of Sullivan and Gratton [23, 26] are notable here as it expanded and revised the idea of a stress hyporesponsive period in the rat pup. Sullivan charted a sequence of critical periods during which, in the presence of the rat mother, the pup is hyporesponsive to stress. Indeed, if the dam is given a scent (e.g., peppermint) and the pup is fear conditioned (shocked paired with the odor) to that scent, the shock will not elicit a stress/cortisol response. Sullivan and Wilson [27] have detailed the neural structures and hormonal regulators that appear responsible for this lack of stress response. Essentially, in the early postnatal days of life of the rat pup, connections between the amygdala and prefrontal cortex are not established. Once these are established, the rat pup will mount an adult-like stress response even in the presence of its mother. Thus, the effects of early handling and early experience are a function of context (presence or absence of the mother) and appear to target brain structures (amygdala, prefrontal cortex, and hippocampus) that are integrally involved in stress physiology.

The effects of inadequate maternal care on infant development also have been examined. Denenberg et al. [18] studied the effects of having rat dams rotate between litters. His studies suggested the centrality of consistent caregiving for pup survival. In more recent work, Ivy et al. [28] have proposed a model in which they produced



inadequate care in female rats by restricting the nesting materials for the dam with her pups in the cage. These restrictions led to fragmented interactions between the dam and the pups. This abnormal activity was accompanied by inadequate care—anxious-like behaviors—and by increased stress physiology, suggesting that the dams were under chronic stress. In addition, the rat dams did less licking and grooming of their infant pups than control dams. These studies examine the effects of manipulating environmental resources on maternal caregiving and provide evidence on perturbations in infant behavior as a result of problematic and inadequate maternal caregiving.

**3.2. Maternal Caregiving Disruptions in Rodents.** Other research has examined the interactions between the rat dam and her pups to identify the joint influences of each on the physiology of the other. Hofer [29], for example, separated and experimentally manipulated different aspects of the presence of the rat dam on the rat pup, including milk, body warmth, smell, and movements. He and his colleagues showed that each of these aspects of the rat dam “regulated” the physiology of the rat pup, and this in turn regulated the rat dam’s physiology. His work showed that maternal proximity during a critical period of the rat pup’s development operated to downregulate the rat pup’s physiological functioning. His interest and emphasis on lactation anticipated the work that is now central to the hormonal bases of caregiving in the role of oxytocin [30]. Hofer [31] coined the term “hidden regulators” to describe this effect because there were no obvious behavioral referents for these regulators. Hofer’s microlevel detail about the temporal synchrony between the rat dam and her pups served as an important impetus for the studies of face to face interaction in human infant-caregiver pairs [32].

**3.3. Maternal Caregiving Disruptions in Nonhuman Primates.** Animal research on the importance of maternal caregiving has not been limited to rodents. For example, the work on the effects of maternal separation was extended to nonhuman primates by Harlow and Zimmermann more than half a century ago [33]. In a series of studies, infants were separated from their mothers at an early age, and either reared in isolation or with peers. These separated (and in some instances, isolated) animals exhibited symptoms of depression and motor stereotypies. More importantly, when these animals were exposed to younger peers, this experience appeared to reverse many of the negative effects of the early separation [33]. The work of Harlow and Suomi [34] delineated how maternal deprivation and being raised with peers led to animals who were anxious and impulsive as adults and displayed an abnormal stress response [35].

Rosenblum and Pauly [36] examined the effects of inadequate care in Bonnet macaques. They observed infants where the mother had either consistently available resources, lack of resources, or inconsistent/unpredictable conditions. They reported that in the inconsistent conditions infants displayed significantly greater emotionality and alternations in their stress physiology. Sanchez and colleagues [37] also demonstrated that inconsistent and abusive caregiving in

the Rhesus macaques compromised infant behavior and stress physiology. Across these studies, there is strong evidence that inadequate care is associated not only with heightened stress physiology in the infant but also maladaptive behaviors as they mature.

O’Connor and Cameron as well as Sabatini et al. [38, 39] assessed the effects of maternal deprivation in Rhesus macaque infants by removing the mother from the infant’s social group at different infant ages. This led to dramatic social abnormalities and aberrant behaviors in the infant monkeys depending upon whether the mother was removed at 3 months, one month, or one week after birth. The earlier the removal, the more disturbed the behaviors in the monkey. Many abnormalities in these maternally deprived monkeys persisted into adulthood, and they were associated with reductions in dendritic branching in the prefrontal cortex and in gene expression in the amygdala.

The notion of critical periods may be traced to the work of ethologists such as Konrad Lorenz who described imprinting in birds. Lorenz noted that baby ducklings would follow the individual who moved within their line of sight right after they were hatched. If there was no one there, they would not imprint. If a bird was only present after a certain period of time, then the ducklings would not imprint. A moving stimulus was most effective in initiating imprinting during the “critical period” [40].

Hubel and Wiesel’s studies on the visual system reinforced the idea that experiences during a critical period impacts typical development. Hubel and Wiesel were interested in the effects of early experience on the typical development of visual function. They completed experiments first on cats, and then on monkeys, in which they either deprived a single eye or both eyes of visual experience and examined the changes that occurred in the occipital cortex, the area of the brain involved in early visual processing. They found that depriving one eye of typical visual experience led to aberrant vision, and in fact the second eye actually “took over” regions of the occipital cortex normally activated by the other eye. In addition, there appeared to be a sensitive period during which experience had a significant role in the development of typical visual processing. After that sensitive period, it was more difficult for brain organization supporting typical visual processing to occur [1].

Hubel and Wiesel’s work stands as the preeminent work on the effects of early experience and sensitive periods. There have been a number of other researchers who have examined the idea of sensitive periods in the visual and other domains in human infants. Before describing that work, it is important to have a clear definition of just what a sensitive period means. Eric Knudsen, a neurobiologist at Stanford who studies the effects of early experience, writes:

*“Experience exerts a profound influence on the brain and, therefore, on behavior. When the effect of experience on the brain is particularly strong during a limited period in development, this period is referred to as a sensitive period. Such periods allow experience to instruct neural circuits to process or represent information in a way that is adaptive for the individual. When experience provides information that is essential for normal development and alters*

*performance permanently, such sensitive periods are referred to as critical periods.” [41]*

Knudsen differentiates between a sensitive and critical period. A sensitive period is one during which experience exerts its effect during a limited time. However, when experience is essential and alters performance permanently, then such a period is called a critical one. He provides a possible mechanism by which this may occur in the brain, in which experience “instructs” neural circuits to process information. That is, somehow, experience wires brain circuitry in a way that is adaptive for the individual.

#### 4. Summary

The picture that emerges from research with rodents and nonhuman primates on maternal deprivation is compelling: unless deprivation ends early, by reuniting the animal with its biological mother or by cross fostering the animal with another, adequate mother, there are long-term consequences of early maternal deprivation. Deprived offspring exhibit symptoms of what in the human would be considered anxiety or depression. They show cognitive deficits (e.g., poorer spatial memory, reduced interest in novelty), and more importantly, they show a variety of attachment-related problems, including indiscriminate social behavior. Similar findings are found among animals reared with mothers who provide inadequate care.

#### 5. Caregiving Quality in Human Psychological Development

Human infants are born requiring the care and support of adult caregivers for survival. An essential role of parenting in the earliest years of life is providing regulation that assists the developing immature infant. Through reading and responding to infant behavioral cues, caregivers provide essential input necessary for the proper elaboration of essential domains of development, such as stress response systems, attentional systems, and attachment.

**5.1. The Stress Response System.** There is considerable development and plasticity across the first few years of life in the developing stress response systems—the hypothalamic-pituitary-adrenocortical system and the autonomic nervous system. As in studies with rodents, inadequate caregiving such as severe psychosocial neglect has been shown to disrupt concurrent and later functioning of both of these systems [41–43]. However, caregiver relationships characterized by responsive caregiving seem to buffer the young infant’s cortisol responses and enhance recovery during stressful situations [44, 45]. Further, experiments assessing interventions to restore adequate caregiving and enhance parenting in the early years have demonstrated restoration of healthier diurnal cortisol regulation, cortisol responses to stress, and autonomic nervous system responses to stress [41, 46].

**5.2. Attachment.** Human infants have a propensity to form selective attachments to their caregivers by 7 to 9 postnatal

months under typical circumstances. Only in extreme conditions of neglect or deprivation do human infants fail to form such attachments [47–49]. Early patterns of interaction between infants and parents are predictive of subsequent qualitative differences of attachment between them, and characteristics of parents assessed prenatally have been shown to predict individual differences in the quality of attachment between infants and parents more than one year later [50, 51]. Interventions designed to enhance caregiving quality have been shown experimentally to enhance security of attachment in high-risk groups [52–54].

Though infants contribute to coregulated patterns of interaction during the first year of life, the direction of effects in early infancy is largely parent to infant. Beginning soon after birth, caregivers adapt their behaviors by responding to newborn states of alertness, leading to synchronous interactions [55]. Through rhythmic crossmodal matching of infant behaviors, emotional states, and biological rhythms, parents shape infants’ relational responses [56–58]. This biobehavioral synchrony between infants and parents provides experiences for infants that lead to healthy development of stress response systems, regulated attention, and secure attachments [56, 59]. Adverse environments that fail to provide these experiences lead to disruptions in these domains.

#### 6. The Psychological and Biological Toll of Early Psychological Deprivation

Having established that access to species-typical (adequate) caregiving during critical periods of development plays an important role in subsequent psychological and neurobiological development, we now turn our attention to a more precise examination of the role of critical periods in human infants deprived of adequate caregiving in the first months and years of life. We begin this section with a brief overview of what is known about an increasingly studied model of human deprivation—the effects of institutional rearing on development. We then turn our attention to whether the negative sequelae of early institutional rearing can be reversed by removing children from institutions and providing them with adequate caregiving. A particular theme highlighted is timing—whether recovery from institutional rearing is influenced more by the duration of institutional care or by the age of placement into adequate caregiving environments. We conclude this section by highlighting some of the major unresolved issues and then close out the paper with a discussion of the scientific and policy implications of such work on psychological deprivation.

#### 7. The Effects of Institutional Rearing on Development

Since the turn of the 20th century, there has been interest in the effects of institutional rearing on young children’s behavior. After World War II, Bowlby wrote a report for the World Health Organization in which he described the conditions of orphaned and abandoned children living in institutions and cautioned about the negative effects of psychosocial deprivation on the cognitive and socioemotional

development of the young child [60]. In the United States, Goldfarb demonstrated the negative effects of institutionalization on children's behavior with emphasis on externalizing behavior and aggression [61, 62]. Spitz also described a syndrome referred to as hospitalism that was the result of infants being left in pediatric units without appropriate social stimulation [63].

Over the years, there have been numerous studies of infants and young children growing up in institutional settings (e.g., [64, 65]). Though none of these involved randomized controlled trials, many involved comparisons among children with regard to the age in which they were adopted out of the institution, with a particular focus on cognitive and social behavior. In general, the findings suggest that the older a child is at time of adoption (and usually the longer a child has lived in an institution) the lower the child's IQ and poorer the child is with regard to adaptive behavior. Tizard and colleagues, for example, assessed children being raised in residential nurseries in the UK, comparing them to children living with their biological families [66, 67]. Children adopted at a young age had IQ scores that were lower than similarly aged children raised with their biological families, but by age 8 those adopted before age 4.5 were doing better (and on par with children raised in biological families) compared to children adopted later in childhood. Bolstering these early findings are a meta-analysis of IQ among institutionally reared children; here, van IJzendoorn et al. [68] reported that the length of time living in an institution was the best predictor of lower IQ. This finding is somewhat qualified by the context of care in institutions. For example, children adopted from institutions in China appear to fare better than those adopted from Eastern Europe [69]. Country effects likely reflect the level of deprivation children experience in various settings.

Two studies that followed children adopted out of institutions in Romania after the communist Ceausescu era found that recovery of IQ was significantly related to age of adoption. In one study by Ames and Carter [70], those children adopted after 4 months of age displayed lower IQ scores compared to those adopted before 4 months of age; likewise, in the English and Romania Adoptees (ERA) study, children adopted into homes in the UK before six months of age were indistinguishable on IQ compared to controls whereas those adopted after 6 months had IQs that were significantly lower [71].

**7.1. Social-Emotional Disturbances.** Of all the domains studied in previously institutionalized children, the one in which children show the greatest deficits is social and emotional behavior. Goldfarb and colleagues in the late 1940s and 50s described an abnormal psychiatric profile among children and adolescents living in institutions. He described a constellation of behaviors called "over-friendliness" in which children were unable to form deep emotional ties with an adoptive parent [61]. Hodges and Tizard in their studies also found that while IQ scores may have normalized among children with a history of institutionalization, most continued to have seriously disturbed attachments [72]. Here too, some children exhibited persistence of "overly friendly"

behavior, whereas others exhibited extremes of social unresponsiveness and emotional inhibition. Similar problems in attachment have been noted in infants raised in Greek [73] and Ukrainian institutions [47], although there, the younger a child was at age of adoption the more likely the child was to have a secure attachment. In the samples studied by Ames and Carter [70] and Rutter et al. (e.g., [74]), there was increased risk for disorganized attachments among young children with a history of institutional rearing.

**7.2. Psychiatric Disturbances.** Children with a history of institutional rearing also have demonstrated significant psychiatric problems. These have ranged from autistic-like social abnormalities [75] to aggressive behaviors and callous unemotional traits [76, 77] to hyperactivity [78] to poor executive control [79–83] and perhaps most characteristic of children with a history of institutional care, inattention/overactivity [67]. Particularly intriguing was Rutter et al.'s [74] observation that nearly 10% of the previously institutionalized sample at age 4 demonstrated socially aberrant behavior they referred to as "quasi-autism." Although at 4 years, the clinical picture of children so designated was indistinguishable from classic autism, by age 6 years their clinical picture had changed sufficiently that they were designated "quasi" autistic rather than displaying autism proper. By age 11 years, 75% of the children from age 6 continued to manifest quasi-autism, remarkable stability given that autism proper is not due to so-called "maternal deprivation" (cf. [84]). Similar autistic social behaviors have been reported in a small number of children in the Bucharest Early Intervention Project (BEIP; see [85]).

**7.3. Neural Consequences.** Over the past 20 years, there have been a number of studies using different neuroimaging and biological techniques designed to examine the effects of early institutional care on brain and biological development. In terms of effects on the brain, these studies suggest that basic brain structure and function are affected by the experience of early institutionalization. For example, reductions in both gray and white matter volume have been reported [86–88] as have reductions in EEG power [89–91]. Tottenham et al. [92] have reported an enlarged amygdala volume, although this finding has not been replicated by others (cf. [87, 88, 93]). Finally, Gee et al. [94] have examined the functional connectivity between the amygdala and prefrontal cortex in children with a history of institutionalization. They report precocious connectivity in postinstitutionalized children and suggest that this "mature" pattern is a function of adversity and the lack of caregiver buffering early in life.

**7.4. Biological Effects.** In terms of molecular effects, the most striking finding is that children with a history of institutional rearing show reduced telomere length (TL) early in life [95]; more importantly, over the course of the first decade of life such children show a far more dramatic decline in TL than children without a history of institutional care [77]. Accelerated cellular aging may have important implications for subsequent health outcomes.



## 8. Recovery from Early Institutional Rearing

The pernicious effects of institutional rearing on brain development and behavior suggest that deprivation early in life is particularly harmful. This evidence may also inform neuroscience about the presence of critical periods in human development. Studies of young children with a history of institutionalization, in general, cannot address these issues directly since it is not possible to randomize children to contexts of deprivation or family care. Among the most rigorous studies documenting the effects of early institutionalization are the ERA study and the BEIP. The ERA study is a natural experiment following 165 adopted children who had experienced early deprivation in Romanian institutions for varying amounts of time ranging from a few months to 42 months of age and a comparison group of 52 nondeprived adopted Romanian children. Advantaged and motivated adoptive parents provided a dramatic caregiving contrast to the institutional rearing conditions from which ERA study children were adopted. All children were assessed comprehensively at 4, 6, 11, 15, and 22 years of age on measures of cognitive, social, emotional, behavioral, and health outcomes. Investigators documented significant gains in children following adoption (suggesting that the critical periods had remained open, a possible by-product of deprivation), but they identified four deprivation-specific patterns that persisted through all follow-up assessments in some children: severe cognitive impairment, inattention/overactivity, disinhibited attachment (i.e., indiscriminate behavior), and autistic-like social behaviors (i.e., quasi-autism). Associated with these patterns were serious behavioral, emotional, and peer relationship problems extending into adulthood [96]. They also reported that virtually all of the children displaying these deprivation-specific patterns were adopted after the age of 6 months, suggesting that restoring adequate caregiving by 6 months of age led to nearly complete recovery. The children in that study were not adopted at random, so the degree to which these results generalize to nonadopted groups of children who experienced severe early deprivation is unclear.

The BEIP has examined the issue of critical periods in brain and behavioral development in an even more precise fashion. After excluding children with identifiable genetic or neurological syndromes or signs of fetal alcohol exposure, 136 children between six and 31 months of age were recruited from all six institutions for young children in Bucharest. It was assumed that these 136 children would be representative of those placed into Romanian institutions for young children more generally. Following a comprehensive assessment, these 136 children were randomized to care as usual (continued institutional care) or to special foster care that was created, supported, financed, and managed by a BEIP clinical team [97]. Foster care had only recently become legal in Romania and was not widely available at the time the study began. Children were assessed at 30, 42, and 54 months. At that point, the trial was concluded, and the BEIP foster care network was transferred to local governmental authorities. Additional assessments were conducted for all three groups at 8 and 12 years, and another follow-up is

underway at age 16 years. (For discussion of the ethical issues the BEIP investigators faced, see [98, 99].)

The design of BEIP allowed examination of the effects of early deprivation on young children with a history of institutionalization, but more importantly for this review, the data are able to address questions about critical periods in exposure to adversity and their effects on brain development and psychological functioning. The 68 children randomized to be taken out of the institutions and placed into foster care ranged in age from 6 to 30 months. Critical periods could be identified by examining their brain and behavioral development at the follow-up assessments as a function of their age of placement into foster families. Findings from BEIP indicate that children placed at or below 24 months of age had higher IQ scores at 54 months of age [100], more mature patterns of brain electrical activity at age 8 [90], more secure attachments to their adult caregivers at 42 months of age [101], less indiscriminate behavior through 8 years [102], and healthier stress responsivity in both sympathetic and cortisol reactivity at 12 years [41]. Not surprisingly, critical periods for recovery varied by domain. For example, for receptive and expressive language, the cut off was placement by 15 months of age [103], whereas for physical growth and stereotypies it was 12 months of age [81, 104].

In addition, some domains of functioning showed intervention effects but no evidence of a critical period. These domains included psychiatric symptoms and disorders [76, 105] and peer social competence [106, 107]. Finally, there were domains of functioning that were mostly unaffected by the intervention (including ADHD; [76, 105]; and most executive functions; [79, 80, 108]) and even a few domains that seemingly were unaffected by exposure to early adversity (face and emotion processing; [79, 96, 109–111]). The lack of critical periods for some domains is not surprising given the complexity and heterogeneity of the domains of functioning being assessed (e.g., psychopathology). We would expect that the more complex the domain of functioning the less likely any one critical period would be identified. Critical periods are reflected in behaviors, but they operate at the level of circuitry [11]. Within broad constructs of clinical interest, such as language, IQ, and attachment, there are multiple critical periods for the different processes underlying language abilities. Table 1 presents a summary of the findings on critical periods by domain in the BEIP.

The data from the BEIP and the ERA studies provide some of the best evidence for critical periods in brain and behavioral development in the human child. There are continued questions to be raised with regard to exactly how broadly or narrowly shaped these critical periods are and more generally what the timing and dose of exposure is for a particular critical period. However, they clearly identify the importance of family care in the life of the young child. The institutional context documents what is *not* happening in the child-caregiver relationship that affects brain, cognitive, and social development. And the rodent and nonhuman primate data point to the effects of general lack of stimulation and interaction as having a primary influence in these critical period effects.



TABLE 1: Timing of placement effects: Domains assessed in the Bucharest Early Intervention Project and the age before which the intervention had its greatest impact, suggesting a sensitive period for that domain.

Domain assessed	Sensitive period “closes”
Stereotypes	12 months
Expressive language	15 months
Receptive language	15 months
Reading	24 months
Security of attachment	24 months
Organization of attachment	24 months
IQ at 54 months	24 months
ERN during flanker 8 years	20 months
Alpha and theta 8 years	24 months
Teacher-rated social skills 8 years	20 months
Cortisol response 12 years	24 months
RSA response 12 years	18 months
Competence 12 years	20 months

## 9. Implications and Lessons Learned

Although it is well known that exposure to adverse early experience can derail development (see [112] for a review), the *lack* of experience can be particularly insidious, as the brain awaits instructions to guide its assembly that it fails to receive. As a result, neural circuitry is seriously compromised, which in turn results in delays and impairments in behavior. In the case of institutional care, particularly when children are abandoned in the first months of life and remain in institutional care for more than a few years, the effects are particularly extreme. The evidence we reviewed indicates that recovery from the deleterious effects of institutional care are largely mediated by timing—that is, the age at which a child is removed from an institution and placed into a family. This is also illustrated by the results of the ERA, where children placed into families before six months of age are identical to their nonadoptive siblings, whereas those adopted after six months are at increased risk for persistent trajectories of impaired cognition, disinhibited social behavior, inattention/overactivity, and autistic features.

On the other hand, the results from BEIP are more nuanced. Clear timing effects were apparent at younger ages—those placed into families before 2 years of age fared better than those placed after 2 years of age—but in several domains these timing effects disappeared by the time children were 8 to 12 years old. For example, children randomized to foster care before the age of 24 months had significantly higher IQs at 4.5 years than those randomized after 24 months. However, no timing effects were evident at age 8 and 12 years [107]. Note, however, that we cannot rule out the possibility that the children placed after 24 months started to catch up, whereas the development of those placed before 24 months remained constant. More importantly, however, intervention effects were maintained—at 12 years full scale IQ scores among the children in foster care are still higher than the children who received care as usual, and EEG

power remains higher in children placed in foster care than those assigned to the care as usual group.

One possible explanation is compensatory processes in brain development that allow some recovery of function through alternative pathways/neural circuits despite early disturbances in brain architecture. An example is Knudsen’s [113] work on visual/auditory mapping in owls, which demonstrated that alterations in input led to new compensatory circuitry. This argues for a sensitive period interpretation of the findings—that is, prolonged and continuous effort (i.e., living in a high-quality foster care family for many years) may overwrite the effects of early deprivation—but only in some domains. Another possibility is that early deprivation temporally extended the sensitive period, making it possible that later placed children continued to accrue benefits compared to the children who experienced care as usual. Better understanding of the development of specific circuits and their sensitivity to environmental input in humans will help clarify these findings.

Millions of orphaned, abandoned, and maltreated children around the world require care outside of their families. Some experience profound neglect while living with their families. Others have parents who seek employment far away and have placed them in less than ideal care settings. The ravages of disease (e.g., HIV AIDS, Ebola, and Zika) and war continue to plague many countries, leading to orphans and sometimes child-headed households. These situations force societies to determine how best to care for orphaned, abandoned, and maltreated children. Evidence we reviewed indicates that the forms of care arranged for such children will play a critical role in their subsequent health and development.

Finally, studies of children experiencing profound neglect have proved particularly informative in elucidating the role of experience, more generally, during critical periods of brain development. This, in turn, has led to new insights into the nature, timing, and duration of the key experiences young children must have to launch them on a pathway of healthy development; they also speak to the importance of intervening early in the lives of children experiencing early neglect (and likely, adversity more generally). We would do well to heed these lessons, as the success of our societies rests on the healthy development of its children, and steps can and should be taken to ensure all children have the opportunity to live up to their developmental potential.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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## Research Article

# fMRI Evidence of Magnitude Manipulation during Numerical Order Processing in Congenitally Deaf Signers

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Congenital deafness is often compensated by early sign language use leading to typical language development with corresponding neural underpinnings. However, deaf individuals are frequently reported to have poorer numerical abilities than hearing individuals and it is not known whether the underlying neuronal networks differ between groups. In the present study, adult deaf signers and hearing nonsigners performed a digit and letter order tasks, during functional magnetic resonance imaging. We found the neuronal networks recruited in the two tasks to be generally similar across groups, with significant activation in the dorsal visual stream for the letter order task, suggesting letter identification and position encoding. For the digit order task, no significant activation was found for either of the two groups. Region of interest analyses on parietal numerical processing regions revealed different patterns of activation across groups. Importantly, deaf signers showed significant activation in the right horizontal portion of the intraparietal sulcus for the digit order task, suggesting engagement of magnitude manipulation during numerical order processing in this group.

## 1. Introduction

Numerical processing abilities are closely associated with mathematical success [1], and ordinal relationships have been suggested to be important for efficient number processing [2]. In general, the literature suggests that deaf individuals often have poorer mathematical abilities than their hearing peers [3, 4]. However, in a recent study, we have shown that when groups are carefully matched on age, education, and nonverbal intelligence, arithmetic abilities are similar between groups [5]. It is not known whether the same neural networks underpin numerical order processing in deaf signers and hearing nonsigners. In the present study, we investigated this. For deaf children born into deaf families, sign language is the natural form of communication [6]. Signed languages are complete natural languages that have their own vocabulary and grammar, and developmental milestones are reached in the same order for signed and spoken languages [6–8]. Deaf people also use manual systems for representing numerals and letters of the alphabet [9]. Despite

the often reported discrepancy in mathematical skills between deaf and hearing individuals, there is less evidence of differences in the fundamental numerical skills of subitizing [10], magnitude processing [10], and number comparisons [3]. Indeed, deaf children have been shown to perform better than hearing children on spatial tasks [11] and nonsymbolic subtraction tasks [12]. Their problems seem to be more specifically related to numerical processing that requires more abstract manipulation involving linguistic representations. This has been shown to apply in particular to relational statements (e.g., less than, more than, and twice as many as) [13, 14], arithmetic problems that require reading [15], fractions [16], and multiplication [5, 17]. It has been suggested that the establishment of verbal number representations in deaf individuals might be altered or delayed, due to weaker associations between concepts and a high reliance on item-specific, compared to relational processing [18, 19]. Only one previous imaging study to our knowledge has investigated the neural correlates of numerical processing in deaf signers [20]. Results showed that learning the numerals

of a new sign language activates the numerical processing networks established for hearing individuals. However, we are not aware of any previous studies investigating numerosity judgment or numerical order processing in deaf signers. Findings from brain imaging suggest that numerosity judgment in hearing individuals engages bilateral parietal regions. Activation of the posterior superior parietal cortex occurs during number comparison [21], approximation [22], and counting [23]. However, this region has been shown to be activated during a range of visuospatial tasks including mental rotation, spatial working memory, and attention orienting [24, 25]. Thus, it is not reserved for numerical processing. Numerical processing also activates the left angular gyrus when verbal coding and processing are required. Thus, a greater activation of this region has been found for exact, compared to approximate, calculation [22], for small, compared to larger, digits [26], for multiplication compared to addition [27] and subtraction [28], and for addition compared to subtraction [29]. The bilateral horizontal portion of the intraparietal sulcus is thought to be the locus of magnitude manipulation and thus the mental number line [30, 31]. Activation in this region has been reported for subtraction compared to multiplication [32, 33], for approximate compared to exact calculation [22], and for number words compared to other words [34]. It has also been suggested that the function of this region is specific to magnitude manipulation [33]. In the present study, we investigated numerical order processing in deaf signers and hearing nonsigners, well-matched on age, education, and nonverbal intelligence, by presenting a digit order task during functional magnetic resonance imaging (fMRI). In order to determine whether activation patterns were specific to digit ordering, rather than ordering in general, we also administered a letter order task based on the same stimulus material, which consisted of sets of three printed digit/letter pairs. Activation relating simply to visual stimulation engendered by the stimuli was subtracted using a visual control task also based on the same stimulus material. Four hypotheses were tested: (1) At a whole brain level, there will be general similarities between groups for both the digit and the letter order task. (2) For the digit order task, there will be bilateral activation in regions of interest including the superior parietal lobule (SPL) and the horizontal portion of the intraparietal sulcus (hIPS), as well as in the left angular gyrus (IAG) for both groups. (3) Activation for the digit order task will be greater than that for the letter order task in hIPS, reflecting the magnitude manipulation specificity of this region, generalizing it to deaf signers. (4) Hearing nonsigners will show greater activation in the IAG compared to deaf signers for both digit order and letter order, reflecting differential engagement of linguistic representations.

## 2. Methods

**2.1. Participants.** The study included 16 deaf adults ( $M = 28.1$  years,  $SD = 3.44$ , range 21–32; eleven women) and 17 native Swedish-speaking hearing adults ( $M = 28.6$  years,  $SD = 4.85$ , range 22–37, twelve women, one of whom was excluded; see Data Analysis, leaving 16 hearing nonsigners).

The participants were all right handed and reported at least 12 years of formal schooling (equivalent to high school degree). Five participants in each group had a university degree or equivalent level of education. Intelligence was screened using Raven's standard progressive matrices. This resulted in no statistically significant differences between groups in age ( $t(30) = 0.166$ ,  $p = 0.869$ ), nonverbal IQ ( $t(30) = 1.512$ ,  $p = 0.141$ ), or educational level (high school vs. university degree;  $\chi^2(32) = 0.00$ ,  $p = 1.00$ ; Table 1). Participants had normal, or corrected-to-normal, vision and reported no neurological or psychiatric illnesses. They also complied with the following exclusion criteria: pregnancy, claustrophobia, medications (except for contraceptives), and non-MRI compatible metal implants.

Fifteen of the deaf participants were deaf from birth and one from the age of six months. All reported using Swedish Sign Language (SSL) daily as their primary language. Six were exposed to SSL from birth and the others before the age of two.

The prevalence of congenital deafness is around 1 in a thousand live births, and only 5% of congenitally deaf children are born into signing families. Thus, deaf early signers constitute a very small population. Further, many deaf signers are opting for cochlear implantation which is a counter indication for fMRI. The group of deaf participants in the present study is similar in size to, or larger than, those in many other studies (cf. 11 deaf participants in Emmorey et al.'s study [35]; 7 deaf participants in MacSweeney et al.'s study [36]). It is also unusually homogenous in terms of education, a factor that is often not reported. It would have been preferable to have a larger group, but this was not possible due to demographic constraints.

All participants gave written informed consent and were compensated for time and travel expenses. Approval was obtained from the regional ethical review board in Linköping, Sweden (Dnr 190/05).

**2.2. Stimuli and Tasks.** Stimuli were identical across tasks and the control condition. They consisted of sets of three-digit/letter pairs, e.g., V2 X5 U7. The pairs included the digits 0–9 and the letters B, D, E, G, H, K, L, M, O, P, Q, T, U, V, X, and Z, as well as the characters Å and Ö that are listed at the end of the Swedish alphabet. There were 20 unique sets of pairs. Each pair was also reversed within each set, e.g., 2V 5X 7U, giving 40 unique stimuli. It is important to note that the digit/letter order within pairs was never mixed within stimuli. Further, congruent (the same correct response for both tasks) and noncongruent (different correct responses for the two tasks) trials were balanced. Participants completed six different tasks, of which three are investigated in the present study. Those three tasks were digit order ("are the presented digits in an ascending numerical order?"), letter order ("are the presented letters in an alphabetical order?"), and visual control task ("are there two dots over any of the presented letters?"). Correct responses were 50% "yes" and 50% "no," distributed orthogonally across conditions. Results from the three remaining tasks (multiplication, subtraction, and phonological similarity) are reported in two articles (Andin et al. [37]; under revision) with the digit order

TABLE 1: Participant characteristics.

	<i>M</i>	Age SD	Range	Sex Female/male	Education University*	<i>M</i>	Raven SD	Range
Deaf signers	28.1	3.44	21–32	11/5	5	52.3	5.13	44–60
Hearing nonsigners	28.5	4.78	22–37	12/5	5	54.7	4.04	45–59

\*Number of participants with university degree or equivalent education.

task serving as a baseline for the arithmetic tasks and the letter order task as a baseline for the phonological task. In neither of these articles are the ordering tasks considered in their own right.

**2.3. Procedure.** All participants took part in a behavioural testing session at least one month prior to the fMRI session for task familiarization and to ensure compliance during scanning. Before entering the scanner, participants practiced the tasks again and were instructed to respond as accurately and as quickly as possible during the presentation of each trial, by pressing one of two buttons using their right thumb and index finger. A professional accredited sign language interpreter provided deaf participants with a verbatim translation of test instructions and remained on hand to relay questions and answers. When participants were installed in the scanner, instructions were repeated again, orally for hearing individuals and as text on the screen for the deaf participants.

In the scanner, participants viewed the screen through an angled mirror on top of the head coil. Stimuli were presented using the Presentation software (Presentation version 10.2, Neurobehavioral Systems Inc., Albany, CA) and back projected onto a screen positioned at the feet of the participant. Each trial started with a 1000 ms period during which a cue displayed on the screen indicated which task was to be performed next. The cues were “1 2 3” for digit order, “a b c” for letter order, and “..” for the control task. After the cue, the stimulus was displayed for 4000 ms while the participant responded. Task presentation was blocked, and there were five trials per block. Thus, each block lasted for 25,000 ms. Between blocks, there was a 5000 ms break and a  $\pi$  symbol was presented. Participants were instructed to move as little as possible. In total, there were 4 runs with 12 blocks in each. Of the 12 blocks, six blocks (two per condition) were considered in the present analysis.

**2.4. Data Acquisition.** Functional gradient-echo EPI images (repetition time (TR) = 2500 ms, echo time (TE) = 40 ms, field of view (FOV) = 220 × 220 mm, flip angle = 90 deg, in-plane resolution of 3.5 × 3.5 mm, slice thickness of 4.5 mm, slice gap of 0.5 mm, with enough axial slices to cover the whole brain) were acquired on a 1.5 T GE Instruments scanner (General Electric Company, Fairfield, CT, USA) equipped with a standard eight-element head coil, at the Karolinska Institute. The initial ten-second fixation period without task presentation was discarded to allow for T1-equilibrium processes. Anatomical images were collected using a fast spoiled gradient echo sequence, at the end of the scanning session (voxel size 0.8 × 0.8 × 1.5 mm, TR = 24 ms, TE = 6 ms).

**2.5. Data Analysis.** Data quality was checked using TSDiffAna (Freiburg Brain Imaging). As a result, the first run was discarded for three deaf participants and one hearing participant who moved more than 3 mm in at least one direction. Remaining data was preprocessed and analysed using statistical parametric mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) running under MatLab r2010a (MathWorks Inc., Natick, MA, USA). Preprocessing included realignment, coregistration, normalization to the MNI152 template, and spatial smoothing using a 10 mm FWHM Gaussian kernel, following standard SPM8 procedures.

Blocks with more than two incorrect answers were discarded from the analysis (two-letter order blocks and one-digit order block were removed from the hearing group, and two-letter order blocks were removed from the deaf group), because the response pattern in some cases suggested nonadherence to the task. Data from one hearing participant were removed due to artefacts probably caused by metallic hair dye. Thus, data from 16 participants in each group were included in the functional analysis. Analysis was conducted by fitting a general linear model (GLM) with regressors representing each of the two experimental conditions of interest here (digit order and letter order) and the visual control, as well as the six motion parameters derived from the realignment procedure. At the first-level analysis, contrast images consisting of digit order versus visual control and letter order versus visual control were defined individually for each participant. To investigate hypothesis 1 that there will be general similarities between groups for both the digit and the letter order task at the whole brain level, the contrast images from the first level analysis were brought into second-level analyses where sample *t*-tests for the two groups separately and one for the two groups together were performed. The presence of any group differences was tested for using two independent sample *t*-tests, one for letter order and one for digit order. The significance was determined using family-wise error (FWE) correction for multiple comparisons at  $p < 0.05$  for the voxel level for peak values for the whole brain. Images were prepared using SPM8 and MRIcron software (ver. 6/2013, McCausland Center for Brain Imaging, Columbia, USA).

Hypotheses 2–4 were investigated using separate region of interest analyses (ROI) for the left angular gyrus (LAG), left and right superior parietal lobules (ISPL and rSPL), and left and right horizontal portions of the intraparietal sulcus (lHIPS and rHIPS; using the toolbox MarsBar, release 0.44). The ROIs were defined in accordance with the probabilistic cytoarchitectonic maps from an SPM anatomy toolbox (version 1.8). To investigate hypothesis 2 that for the digit order



task there will be activation in all five ROIs for both groups, group level contrasts were obtained to determine significant activation within the five ROIs. Further, to investigate the final two hypotheses that activation for the digit order task will be greater than that for the letter order task in HIPS (hypothesis 3) and that hearing nonsigners will show greater activation in the IAG compared to deaf signers for both digit order and letter order (hypothesis 4), individual contrast values from the HIPS and IAG of the ROI analysis were extracted for further statistical analyses. These analyses were carried out as a  $2 \times 2 \times 2$  (task [digit order, letter order]  $\times$  hemisphere [right, left]  $\times$  group [deaf signers, hearing nonsigners]) analysis of variance in HIPS (hypothesis 3) and as an independent  $t$ -test in the IAG (hypothesis 4). The analyses of contrast values from the ROI analyses as well as the in-scanner response time and accuracy data analyses were performed using SPSS statistics 22 (IBM, SPSS Statistics, version 22, IBM Corporation, New York, USA). The design of the analyses of variance for response time and accuracy was  $2 \times 2$  (task [digit order, letter order]  $\times$  group [deaf signers, hearing nonsigners]). As for the imaging data, blocks with more than two incorrect answers were removed from the behavioural analysis.

### 3. Results

**3.1. Behavioural Data.** Behavioural data are shown in Table 2. Response time data revealed the main effect of task ( $F(1, 30) = 308.4, p < 0.001$ , partial  $\eta^2 = 0.911$ ). This showed that the digit order task ( $M = 1608$  ms,  $SD = 1847$ ) was performed faster than the letter order task ( $M = 2344$  ms,  $SD = 234$ ). There was no main effect of the group ( $F(1, 30) = 0.004, p = 0.952$ , partial  $\eta^2 = 0.000$ ) (deaf signers:  $M = 1979$  ms,  $SD = 240$ ; hearing nonsigners:  $M = 1973$  ms,  $SD = 304$ ), and there was no group  $\times$  task interaction ( $F(1, 30) = 0.006, p = 0.937$ , partial  $\eta^2 = 0$ ).

As with the response time data, accuracy data revealed a main effect of task ( $F(1, 30) = 22.4, p < 0.001$ , partial  $\eta^2 = 0.428$ ). This showed that performance on digit order was more accurate ( $M = 97.2\%$ ,  $SD = 3.56$ ) than that on letter order ( $M = 91.4\%$ ,  $SD = 3.14$ ). Again, there was no main effect of the group ( $F(1, 30) = 0.988, p = 0.328$ , partial  $\eta^2 = 0.032$ ) (deaf signers:  $M = 93.8\%$ ,  $SD = 4.13$ ; hearing nonsigners:  $M = 94.9\%$ ,  $SD = 1.78$ ) and no group  $\times$  task interaction ( $F(1, 30) = 1.49, p = 0.231$ , partial  $\eta^2 = 0.047$ ).

#### 3.2. Imaging Data

**3.2.1. Whole Brain Analyses.** The results of the whole brain analysis to test hypothesis 1 are shown in Table 3. Neither group showed any significant activation for the digit order contrast. For the letter order contrast, the deaf group showed significant activation in the right occipital gyrus (however, only at the cluster level, not at the peak level) and the hearing group showed significant activation in the frontal, parietal, and occipital regions. Although the activation for the hearing group was more widespread than that for the deaf group, independent  $t$ -tests showed no significant group effects for either contrast.

Because the groups show similar activation for both tasks, combining them might give additional information otherwise obscured by the low number of subjects. Therefore, the activation patterns for the two tasks were further investigated by collapsing across groups (cf. Mayer et al. [38]). The general activation pattern for both groups combined revealed a peak activation for digit order in the right cerebellum and activation in the bilateral frontal, parietal, and occipital regions for letter order (Figure 1). These regions included left lateralized activation in the superior parietal lobule, supplementary motor area, and precentral gyrus; right lateralized activation in the superior occipital gyrus; and activation in the bilateral middle occipital gyrus, superior frontal gyrus, and inferior parietal sulcus (Table 3).

**3.2.2. Region of Interest Analyses.** To investigate our region-specific hypotheses, we analysed the variations in brain activity associated with the digit and letter order tasks in the two groups within the bilateral superior parietal lobule (SPL) and horizontal portion of the intraparietal sulcus (HIPS) as well as the left angular gyrus (IAG). In line with the second hypothesis, the digit order task significantly activated the rHIPS for deaf signers ( $t = 1.76, p = 0.05$ ). However, this task did not significantly activate this region for the hearing nonsigners or any of the other regions of interest for either group. Letter order, on the other hand, showed significant activation for both groups in the rSPL (deaf signers:  $t = 2.08, p = 0.028$ ; hearing nonsigners:  $t = 4.97, p < 0.001$ ), lHIPS (deaf signers:  $t = 2.56, p = 0.011$ ; hearing nonsigners:  $t = 5.15, p < 0.001$ ), and rHIPS (deaf signers:  $t = 3.50, p = 0.001$ ; hearing nonsigners:  $t = 5.34, p < 0.001$ ) as well as in the lSPL for hearing nonsigners ( $t = 4.57, p < 0.001$ ).

Regarding our third hypothesis, we performed a mixed design  $2 \times 2 \times 2$  ANOVA and found a significant main effect of task ( $F(1, 30) = 8.68, p = 0.006$ , partial  $\eta^2 = 0.224$ ) in HIPS. However, contrary to our prediction, letter order generated greater activation than digit order in both hemispheres (left  $F(1, 30) = 7.41, p = 0.011$ , partial  $\eta^2 = 0.198$ ; right  $F(1, 30) = 10.9, p = 0.003$ , partial  $\eta^2 = 0.266$ ). There was also a significant main effect in the hemisphere ( $F(1, 30) = 9.30, p = 0.005$ , partial  $\eta^2 = 0.237$ ) with greater activation in the right hemisphere. There was no significant main effect of the group ( $F(1, 30) = 0.79, p = 0.79$ , partial  $\eta^2 = 0.002$ ).

Finally, we did not find support for our fourth hypothesis of a significant difference between groups on the digit order task within the IAG ( $t(30) = 0.159, p = 0.875$ ).

### 4. Discussion

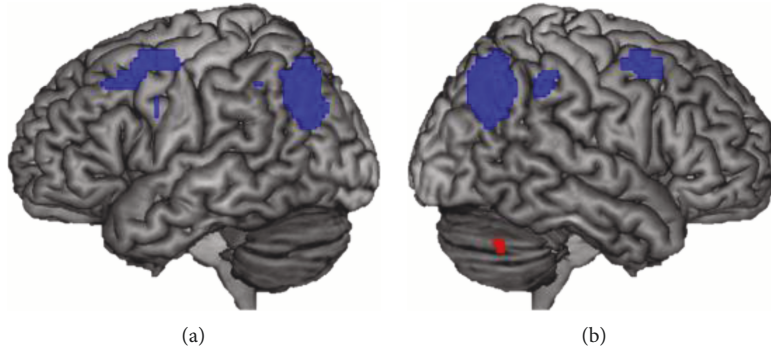
The main purpose of the present study was to investigate neuronal networks for order processing in deaf and hearing individuals. We predicted general similarities across groups for both the digit and letter order tasks with some language modality-specific activation. Specifically, we hypothesized (1) general similar activation across groups at whole brain level, (2) significant activation for the digit order task in regions of interest in the parietal cortex across groups, (3) significantly greater activation for digit order compared to letter order in HIPS, reflecting magnitude specificity, and (4)

TABLE 2: Behavioural in-scanner data.

	Response time (ms)				Accuracy (% correct)			
	Deaf signers		Hearing nonsigners		Deaf signers		Hearing nonsigners	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Digit order	1612	192	1603	314	96.0	6.87	98.6	1.86
Letter order	2345	327	2342	336	91.6	5.13	91.2	3.63

TABLE 3: Whole brain analysis. Activation foci for each contrast versus visual control for the two groups separately and combined. All peaks with significant activation are listed ( $p_{\text{fwe}} < 0.05$ ).

Group	Task	Cluster level		Peak level		MNI coordinates			Brain region of the peak
		Size	$p_{\text{fwe}}$	$T$	$p_{\text{fwe}}$	$x$	$y$	$z$	
Deaf signers	Letter order	89	0.016	5.19	0.342	23	-72	44	r. superior occipital gyrus
		42	<0.001	9.10	0.004	16	-72	54	r. superior parietal lobule
				8.01	0.016	30	-72	39	r. middle occipital gyrus
Hearing nonsigners	Letter order	18	<0.001	8.90	0.005	30	9	59	r. middle frontal gyrus
		14	<0.001	8.89	0.005	-12	-75	49	l. precuneus
				7.30	0.043	-26	-68	54	l. superior parietal lobule
		6	0.001	8.37	0.010	-30	-79	34	l. middle occipital gyrus
		4	0.003	7.81	0.022	-54	-5	44	l. postcentral gyrus
Both groups combined	Digit order	5	0.006	6.01	0.010	23	-61	-36	r. cerebellum
		137	<0.001	8.06	<0.001	23	-72	44	r. superior occipital gyrus
				7.87	<0.001	34	-68	34	r. middle occipital gyrus
		99	<0.001	7.65	<0.001	-26	-72	29	l. middle occipital gyrus
				7.20	0.001	-23	-68	49	l. superior parietal lobule
Both groups combined	Letter order	31	<0.001	7.40	<0.001	27	6	54	r. superior frontal gyrus
		77	<0.001	7.14	0.001	-5	2	59	l. SMA
				6.93	0.001	-16	2	59	l. superior frontal gyrus
				6.69	0.002	-5	16	44	l. SMA
		18	<0.001	6.28	0.006	44	-40	44	r. inferior parietal sulcus
		2	0.015	5.58	0.030	-44	2	29	l. precentral gyrus
		1	0.023	5.39	0.045	-44	-47	44	l. inferior parietal sulcus

FIGURE 1: Activation pattern for digit order (red) and letter order (blue) in (a) left and (b) right hemispheres for both groups combined. Images are thresholded at a FWE-corrected  $p$  values of  $<0.05$ .

significant group differences in the IAG for the digit order task, reflecting differential engagement of linguistic representations across groups. The results showed that there were general similarities across groups in relation to both task and regions but that none of our hypotheses was fully supported.

Overall and in line with the previous studies [39], we found little neural activation in the deaf group due to substantial individual variability.

We predicted that the digit order task would activate bilateral parietal regions including the superior parietal

cortex and the horizontal portion of the intraparietal sulcus in both groups. However, in the whole brain analysis, there was no evidence for either group of a general activation in bilateral parietal regions that has previously been attested for numerical ordering tasks. In fact, the digit order task versus visual control only elicited significant activation in the right cerebellum, when collapsed over groups. A meta-analysis conducted by Arsalidou and Taylor [40] of neuroimaging studies investigating numerical and arithmetic processing tasks showed that the cerebellum is generally activated for both number and calculation tasks. Arsalidou and Taylor [40] suggested that the role of the cerebellum was coordination of visual motor sequencing, which in the present study might be related to the visual inspection of the digit/letter string.

In the analysis performed on the five regions of interest based on our hypotheses, the only region to be significantly activated for the digit order task was the rHIPS for deaf signers. For hearing nonsigners, no significant activation was found. Hence, for the hearing group, we found no support for the notion of magnitude manipulation specificity of the horizontal portion of the intraparietal sulcus. Several studies [41] found that the mere presentation of single numbers compared to single letters generated activation in the intraparietal sulcus bilaterally, indicating automatic numerosity processing. The tasks in the present study (both experimental tasks and control task) were based on the same stimulus material to keep visual stimulation under control. Thus, any automatic number processing elicited simply by seeing numbers, even when they were not necessary for task solution, would have been removed by subtraction in the digit order versus visual control contrast. However, although there was no main effect of the group in the analysis of variances performed on the HIPS regions, deaf signers showed a significant activation of the rHIPS that was not found for the hearing group. This is in line with preliminary data from our lab, where we have found stronger activation for deaf signers compared to hearing nonsigners in the rHIPS in response to arithmetic tasks (using the same stimulus material as in the present study; [42]). Taken together, this indicates qualitatively different processes for deaf compared to hearing individuals relating to number processing. Notably, behavioural results did not differ significantly between groups despite activation of different brain regions. This suggests that deaf signers can make use of different brain regions compared to hearing nonsigners to reach the same goal.

In both the whole brain analysis and the ROI analyses, we found significant activation across groups for the letter order task within the visual processing system which not only included occipital regions but also extended into the parietal and frontal regions of the dorsal stream. This is in line with recent work showing more activation for letters than numbers in the left inferior and superior parietal gyri as well as a preferential role of the parietal cortex for letter identity and letter position encoding [43], indicating a prominent role for the dorsal processing stream in letter identification and position encoding [43, 44]. The greater engagement of the visual processing system for the letter order task compared to the digit order task probably reflects both the specificity

of the visual system for letter processing and the greater demands of determining relative order of three items in a larger set. A recent study showed the sensitivity of earlier and later regions of the visual processing system to letter orientation and how this sensitivity develops from childhood to adulthood [45]. Further, while the set of Arabic digits used in the present study had ten items, the set of letters had 18 items (B, D, E, G, H, K, L, M, O, P, Q, T, U, V, X, Z, Å, and Ö) which in turn are part of the 29-item Swedish alphabet. Thus, the two experimental tasks used in the present study elicit two different kinds of ordering, one which requires numerical order processing within a small well-defined closed set and one that requires alphabetical order processing within a larger closed set, arbitrarily defined.

Interestingly, in the ROI analyses, the ISPL was significantly activated in hearing nonsigners, corroborating findings from previous studies suggesting the ISPL to have a central role in letter positioning [43, 44]. Deaf signers performed similarly to the hearing nonsigners on the letter order task but did not show any significant activation in the ISPL. Hence, for deaf signers, we found no evidence that ISPL engagement is necessary for letter ordering. However, we cannot exclude the possibility that the lack of ISPL engagement on this task underlies difficulties on higher level language tasks for this group. Lack of significant activation in this area has previously been found in a letter substitution task for individuals with dyslexia [44]. Although not investigated here, it is possible that the poorer reading ability generally found in deaf individuals [46] may stem from an inability to engage the ISPL in early letter processing.

Finally, we predicted that differential engagement of linguistic representations by deaf signers and hearing nonsigners during the digit order task would be reflected in differences in the activation of the IAG. Surprisingly, there was no significant activation in the IAG for either group and no significant differences in activation of this region related to either task or group. This region has been shown to be involved in verbal number processing, such as multiplication and simple subtraction [25, 33, 37]. The IAG has also been shown to play an important role in orthographic-to-phonological conversion [47], and so we had expected both our experimental tasks to engage this region. One explanation of our results is that both tasks are solved using nonlinguistic ordering manipulations rather than verbal processing.

## 5. Conclusion

The main finding of the present study is that there are similarities in the recruitment of neuronal networks during order processing in deaf signers and hearing nonsigners. The digit order task showed relatively little activation across groups possibly relating to the simplicity of the task. However, recruitment of the rHIPS in deaf signers only for this task suggests that compared to hearing nonsigners this group makes use of qualitatively different processes, such as magnitude manipulation for number order processing. Extensive activation of the dorsal stream relating to the letter order task indicates a prominent role for letter identification and position encoding. This finding prompts further investigation of

the effects of deafness and sign language use on the neural networks underpinning core arithmetic processes.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

There are no conflicts of interest to report.

## Acknowledgments

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## Research Article

# The Effects of Maternal Mirroring on the Development of Infant Social Expressiveness: The Case of Infant Cleft Lip

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Parent-infant social interactions start early in development, with infants showing active communicative expressions by just two months. A key question is how this social capacity develops. Maternal mirroring of infant expressions is considered an important, intuitive, parenting response, but evidence is sparse in the first two months concerning the conditions under which mirroring occurs and its developmental sequelae, including in clinical samples where the infant's social expressiveness may be affected. We investigated these questions by comparing the development of mother-infant interactions between a sample where the infant had cleft lip and a normal, unaffected, comparison sample. We videotaped dyads in their homes five times from one to ten weeks and used a microanalytic coding scheme for maternal and infant behaviours, including infant social expressions, and maternal mirroring and marking responses. We also recorded maternal gaze to the infant, using eye-tracking glasses. Although infants with cleft lip did show communicative behaviours, the rate of their development was slower than in comparison infants. This group difference was mediated by a lower rate of mirroring of infant expressions by mothers of infants with cleft lip; this effect was, in turn, partly accounted for by reduced gaze to the infant's mouth, although the clarity of infant social expressions (indexed by cleft severity) and maternal self-blame regarding the cleft were also influential. Results indicate the robustness of parent-infant interactions but also their sensitivity to specific variations in interactants' appearance and behaviour. Parental mirroring appears critical in infant social development, likely supported by the mirror neuron system and underlying clinical and, possibly, cultural differences in infant behaviour. These findings suggest new avenues for clinical intervention.

## 1. Introduction

Parent-infant social interactions are foundational for later child psychological functioning [1]. These interactions start shortly after birth and develop rapidly. By two to three months, infants deploy a range of communicative expressions during face-to-face encounters, including smiles, and tongue protrusions and wide mouth openings termed “prespeech”

[2, 3]. Prospective studies through the postpartum weeks have demonstrated the “functional architecture” of these interactions, whereby infant social expressions are accompanied by specific, highly organised, parental behaviours [4, 5]. Thus, parents gaze almost exclusively to their infant's face [6] and respond selectively to infant social vs. non-social cues by mirroring them and positively marking their occurrence with salient signals (e.g., eyebrow flashes) [2, 4, 7–10]. Such

parental responses appear both intuitive and functionally important [5, 11], likely recruiting brain networks differentiating infant facial signals from other social cues [12]. Thus, the few studies focussed on the first two months indicate that parental mirroring and positive marking, and especially the former, increase the expression of infant social communication over this same period [2, 4, 7, 10] and predict later neural processing of faces [13].

Two important challenges arise from previous research: the first is to clarify the functional significance of early parental interactive behaviour by investigating it in different interactive contexts; the second is to determine the nature of infant stimuli eliciting parenting responses, that is, whether the latter depend on highly specific infant cues or are relatively robust and elicited by a broad range of infant facial expressions and configurations.

These issues are difficult to address with normal community samples, given their limited variability; however, they may be usefully elucidated in clinical conditions in which social interactions are perturbed [14]. For example, the “cute” infant facial configuration [15] may be required for intuitive parenting responses, and if infant facial stimuli are distorted by a relatively minor facial structural abnormality, such as cleft lip, alterations occur in adult gaze patterns [6, 16] and in neural responses associated with feelings of reward [12]. Whether this abnormal infant facial configuration affects key parental interactive responses like mirroring, and what mechanisms are involved, is unknown. Further, to the extent that infant cleft lip *does* influence important parental behaviours, the question arises whether this may, in turn, alter the development of infant social expressiveness. Although research shows that, by two to three months, normal levels of infant social engagement with the parent are reduced in the context of cleft lip [17–19], it is not known how these difficulties develop over the preceding weeks, or what the role might be of parental responsiveness. Given that, in this population, early interaction difficulties predict cognitive impairments in infancy and childhood [19–21], understanding how such difficulties evolve is not only of scientific interest but also of substantial clinical importance, as it could inform preventive interventions.

We addressed these issues in a prospective study of the development of infant social expressiveness and the role of parental responsiveness over the first ten postpartum weeks, comparing the development of parent-infant interactions in a normal population with those where the infant had cleft lip. We conducted systematic, naturalistic videotaped observations of interactions in the home and coded key infant social behaviours and parental mirroring, positive marking, and gaze.

Consistent with previous studies, we hypothesized that, compared to unaffected comparison infants, those with cleft lip (CLP) would not show the usual increase in social expressiveness over the first two months [4]. We also hypothesized that this relative failure to increase social expressiveness in infants with cleft lip would be predicted by reduced maternal responsiveness - particularly mirroring - to infant social cues in the CLP group.

A number of mechanisms may cause reduced maternal mirroring of infants with cleft lip. Three possible mechanisms are as follows.

- (a) **Reduced Infant Attraction Effects on Maternal Gaze.** Reduced mirroring may occur because the cleft interferes with the normal parental attraction to infant cues [12, 22]. We investigated this by using eye-tracking glasses to record maternal gaze to the infant’s mouth during interactions to determine whether any impact of the cleft on mirroring of social expressions could be accounted for by a reduction in gaze.
- (b) **Opacity of Infant Cues.** Independently of any impact on maternal gaze, the physical alteration caused by the cleft may reduce mirroring responses by interfering with the clarity of infant social cues. Thus, despite evidence showing naïve observers’ ratings of infant emotional expression in the context of craniofacial anomaly to be highly accurate [23], it has been suggested that parents of infants with clefts experience difficulty in interpreting infant behaviour during interactions [17]. We investigated this possibility, using cleft severity as a proxy for the degree of interference caused to infant facial signals.
- (c) **Maternal Mental State.** Mothers have raised risk for depression in the context of infant perinatal health problems [24]. Depressive disorder can affect both maternal mirroring of infant expressions during social interactions [25, 26] and discrimination of infant emotional expressions and neural responses to infant faces [27–29]. We assessed maternal depressive symptoms to determine whether they mediated any reduction in maternal mirroring of social expressions in infants with cleft lip. Other aspects of maternal mental state might also be relevant; in particular, mothers of affected infants can experience considerable preoccupation concerning their infant’s condition, with self-blame being prominent [30]. Cognitive difficulties of preoccupation, or negative rumination, concerning the mother’s own role may be especially disruptive to the processing of infant cues [31]. Accordingly, we also recorded mothers’ responses to the cleft itself, including feelings of self-blame. We conducted secondary analyses to see if these cognitions related to maternal mirroring in the index group.

## 2. Methods

**2.1. Procedure.** We recruited 10 infants with cleft lip, with or without cleft palate (CLP group), and 20, unaffected comparison infants. We video-recorded three minutes of mother-infant interaction at 1, 3, 5, 7, and 9 weeks, while mothers wore a mobile eye-tracker system to record their gaze. Mothers provided written informed consent. The study was approved by the NHS Research Ethics Committee (No. 11/SC/0242) and the University of Reading Ethics



FIGURE 1: Infant prespeech mouth gestures: comparison group - (a) tongue protrusion and (b) mouth opening; CLP group - (c) tongue protrusion and (d) mouth opening.

Committee (No. 11/45). It was conducted in accordance with the Declaration of Helsinki.

**2.2. Measures.** Infant social expressions and maternal responses were scored on a one-second time basis, using a reliable coding scheme.

**2.2.1. Infant Behaviour.** Social facial expressions – e.g., smiles and prespeech (tongue protrusions, active wide-open shaping of mouth) (Figure 1 shows examples for both groups). These expressions have a clear structure, distinct from other, nonsocial, typically vegetative, mouth movements (e.g., low-level, continuous movements, like sucking or chewing) [3, 32].

### 2.2.2. Maternal Behaviour

(1) *Mirroring.* Mirroring is either exact matches or else matching of the principal features of infant social behaviour with minor modification.

(2) *Positive Marking.* Positive marking is responses highlighting or “marking” infant social behaviour with smiles and “attention-attracting” cues, without mirroring.

(3) *Maternal Gaze to the Infant’s Mouth.* Using the eye-tracking data, dynamic (i.e., tracking the infant’s movement) areas of interest (AOI) were drawn over the infant’s mouth to record the duration of maternal gaze.

**2.2.3. Maternal Reports (9 Weeks).** Mothers completed the Edinburgh Postnatal Depression Scale (EPDS, [33]) to assess depressive symptoms.

Mothers in the CLP group completed the Parental Appraisal of Cleft Questionnaire [30], and the self-blame factor was used.

## 3. Results

**3.1. Sample.** Maternal groups were demographically similar. Depressive symptoms were low, with both groups’ mean scores being in the non-clinical range. Although infant groups differed on some measures (e.g., gestation) (Table 1), none was related to any study outcome, and they were therefore not included in further analyses (see Supplementary Materials (available here)). (One CLP group infant with later diagnosed visual impairment was excluded.)

**3.2. Effect of Cleft Lip on Infant Social Behaviour.** Infant social expressiveness increased significantly over the first two months, regardless of group ( $X^2(1) = 508.338$ ,  $p < .001$ ; ERPM (estimated rate per minute) M(SE): 1st month = 1.67 (0.19); 2nd month = 6.31 (0.67)). The extent of increase differed, however, between CLP and comparison infants, as shown by a significant interaction between group and infant age ( $X^2(1) = 23.029$ ,  $p < .001$ ). The increase in social behaviours over time in the comparison group (from M(SE) 1st m



TABLE 1: Sample characteristics.

		CLP N = 9	Comparison N = 20	p
Infants	Gestation-weeks (M(sd))	38.97(2.41)	40.79(1.60)	0.024
	Birth weight-gm. (M(sd))	2980.79(436.54)	3731.94(608.07)	0.003
	Infant gender (% male)	11.11	60.00	0.020
	Birth order (% first born)	66.67	35.00	n.s
	Infant feeding (%)	Breast	75.00	0.004
		Formula	5.00	
		Mixed	20.00	
	Cleft type (%)	Lip	33.33	
		Lip and palate	66.67	
Mothers	Maternal age (M(sd))	32.65(5.38)	33.70(2.76)	n.s
	Maternal education (% graduate)	33.33	60.00	n.s
	Maternal ethnicity (% white)	100.00	90.00	n.s
	Depression symptoms (EPDS) (M(sd))	5.71 (4.54)	4.11 (3.43)	n.s

onth = 1.33(0.17) to 2nd month = 6.75(0.79), a five-fold increase) was significantly greater ( $p < .001$ ) than in the CLP group (M(SE) 1st month = 2.11(0.39); 2nd month = 5.89 (1.04), a 2.7-fold increase) (Figure 2(a)).

**3.3. Maternal Responsiveness.** Mirroring showed the same pattern as infant social behaviour. Thus, there was a main effect of infant age, with mirroring increasing from the first to the second month ( $X^2(1) = 53.123$ ,  $p < .001$ ; ERPM M(SE): 1st month = 0.18(0.04); 2nd month = 0.65(0.13)), and there was also a significant interaction between group and infant age ( $X^2(1) = 22.116$ ,  $p < .001$ ). In this case, only in the comparison group did mirroring increase significantly over time (M(SE) comparison - 1st month = 0.12(0.03); 2nd month = 0.98(0.20) ( $p < .001$ ); CLP - 1st month = 0.27(0.10); 2nd month = 0.43(0.15)), with the increase being significantly greater in the comparison than in the CLP group (8.33-fold vs. 1.58-fold, respectively) ( $p < .001$ ) (Figure 2(a)).

Importantly, these effects of infant age and group on maternal mirroring remained significant when controlling for the rate of infant social behaviours.

For positive marking, only a main effect of infant age emerged ( $X^2(1) = 110.332$ ,  $p < .001$ ; ERPM M(SE): 1st month = 0.09(0.02); 2nd month = 0.74(0.12)), with the rate increasing from the first to the second month, regardless of group. This effect remained significant when controlling for the rate of infant social behaviours.

**3.4. The Mediating Role of Maternal Mirroring.** We then examined our key question of whether the reduced increase over time in infant social expressiveness in the CLP group compared to the control group was mediated by maternal mirroring. This was confirmed ( $b = 0.262$ ,  $SE = 0.128$ , 95% CI = 0.011–0.513,  $p = .041$ ) with the effect of cleft lip on infant social behaviour becoming non-significant with the inclusion of maternal mirroring in the model (see Figure 3(a)). The direct/total effect ratio (using absolute values [34]) showed that 66.06% of the effect of cleft lip on

infant social behaviour was accounted for by its effect on maternal mirroring.

**3.5. Influences on Mirroring.** We next investigated possible influences on mirroring, starting with maternal gaze. There were main effects on gaze of both infant age ( $X^2(1) = 4.410$ ,  $p = .036$ ; estimated percentage M(SE): 1st month = 9.57 (2.97); 2nd month = 18.27(3.17)) and group ( $X^2(1) = 4.830$ ,  $p = .028$ ; M(SE): comparison = 18.89(2.45); CLP = 8.95 (3.83)). Thus, the duration of maternal gaze to the infant's mouth increased overall from the first to the second month, but it was consistently lower in CLP than in comparison group mothers (Figure 2(b)). Accordingly, we ran a second mediation model to test whether reduced gaze to the infant's mouth in CLP group mothers constituted an indirect path through which cleft lip influenced maternal mirroring. There was some evidence for this, with a significant indirect effect being found ( $b = 0.167$ ,  $SE = 0.084$ , 95% CI = 0.001–0.332,  $p = .049$ ). Nevertheless, the age-dependent effect of cleft lip on maternal mirroring still remained significant (see Figure 3(b)), and the direct/total effect ratio showed that the mediating effect of maternal gaze accounted for only 19.34% of the effect of cleft lip on maternal mirroring.

We then examined the influence of cleft severity on maternal mirroring, subdividing the index group in secondary analyses as follows: high severity (cleft lip and palate) vs. low severity (cleft lip only) vs. none - i.e., the comparison group. There was a significant interaction between severity and infant age on the rate of maternal mirroring ( $X^2(2) = 26.622$ ,  $p < .001$ ; ERPM M(SE): high severity cleft - 1st month = 0.33(0.14); 2nd month = 0.36(0.15); low severity cleft - 1st month = 0.16(0.10); 2nd month = 0.62(0.34); comparison - 1st month = 0.12(0.03); 2nd month = 0.98(0.20)). Neither subgroup of mothers of infants with clefts showed the extent of mirroring seen in comparison group mothers in the second month. Nevertheless, the overall lower rate of change in mirroring over time in mothers of infants with a cleft

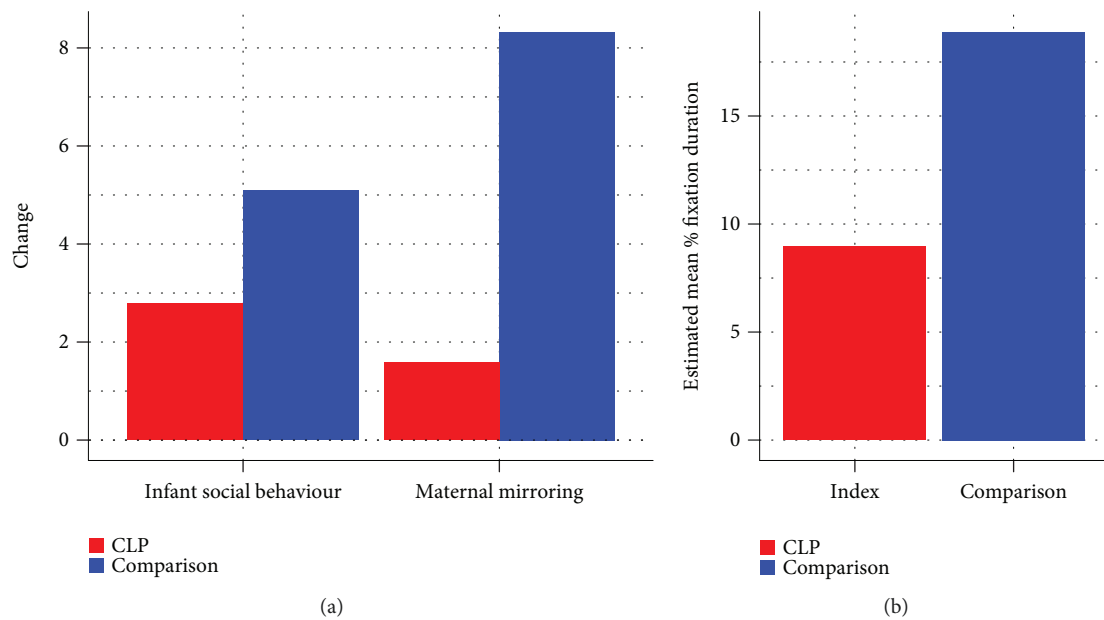


FIGURE 2: Group effects on (a) change in infant and maternal behaviour showing by how many times the rate per minute increased from the 1st to the 2nd month (e.g., for infant social behaviour, the increase over time was 2.7-fold in the CLP group vs. 5.08-fold in the comparison group) and (b) percentage of maternal gaze time to the infant's mouth.

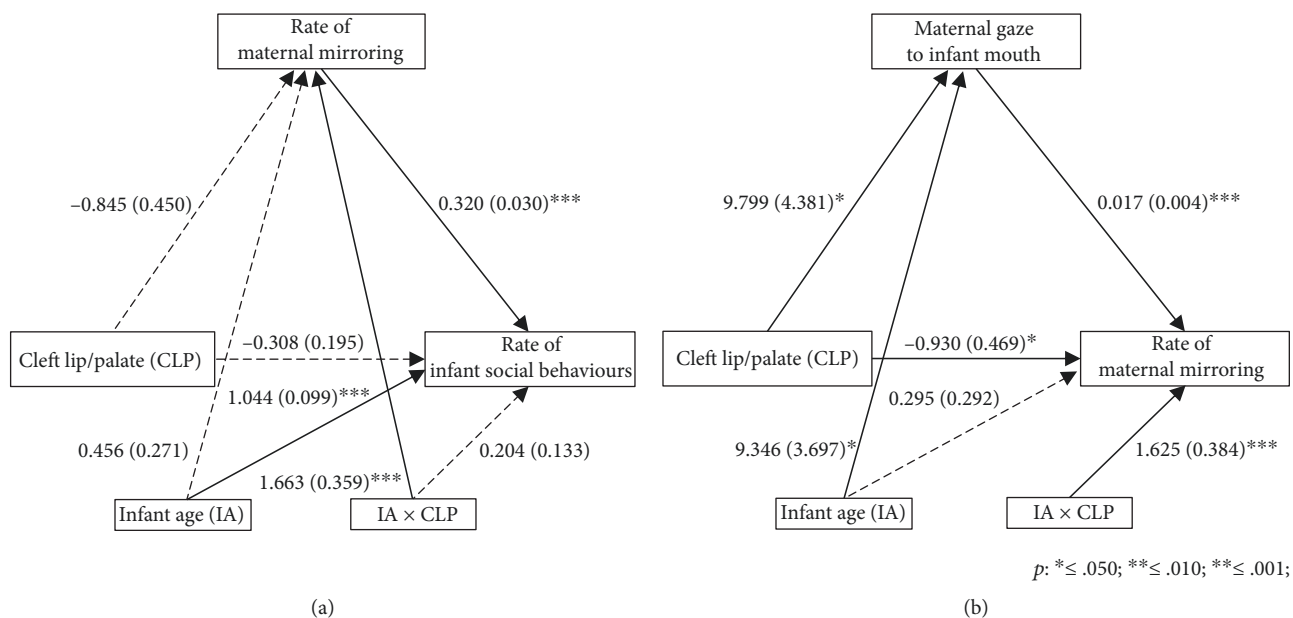


FIGURE 3: Mediation models, with unstandardised coefficients and their standard errors, showing (a) the indirect effect of the presence of a cleft lip on infant social behaviours, through maternal mirroring, and (b) the indirect effect of the presence of a cleft lip on maternal mirroring, through maternal gaze to the infant's mouth.

appeared to be confined to the high severity subgroup, where the change was non-significant ( $p = 0.814$ ), as opposed to the low severity group ( $p = 0.011$ ). These effects remained significant when controlling for the rate of infant social behaviours.

A high severity of the infant's cleft may have reduced the rate of maternal mirroring in the second month because it caused mothers to gaze away from the infant's mouth. We

therefore reran the model used to investigate the mediating role of maternal gaze on mirroring, using the three-group cleft severity variable (i.e., high, low, and none). Given limited subgroup sizes, findings warrant caution. Nonetheless, a significant ( $b = -0.191$ ,  $SE = 0.096$ , 95%  $CI = -0.380 - (-0.002)$ ,  $p = .048$ ) mediational role of gaze was identified for the subgroup of infants with high severity clefts, with no such effect found in the low severity subgroup. Having said

this, the direct/total effect ratio showed that the mediating effect of maternal gaze accounted for only 21.87% of the effect of the high severity of the cleft on maternal mirroring.

Finally, we investigated the role of maternal mental state. There was no group difference in depression scores, precluding examination of their mediational role in explaining the effect of infant cleft lip on maternal mirroring. However, in an exploratory analysis including only the CLP group, self-blame scores emerged as significantly negatively associated with the rate of maternal mirroring ( $X^2(2) = 26.622, p < .001$ ).

#### 4. Discussion

In this novel study, capitalizing on an “experiment in nature” [23, 35] to interrogate social developmental mechanisms, we found that infants with cleft lip did not show the normal rate of increase in social behaviours over the first two months of life. This was not because the cleft prevented the performance of social expressions, since these behaviours were identified reliably and they showed an increase with age. Rather, the effect of cleft lip on infant social development was accounted for by the fact that mothers of affected infants did not mirror social expressions back to their infants to the same extent as mothers of unaffected infants. We found reduced gaze to the infant’s mouth to be important in reducing mirroring in CLP group mothers, as was the severity of the cleft and maternal feelings of self blame; small sample size precluded investigation of the combined effects of these three factors.

Two key questions arise from our findings. The first concerns the mechanisms whereby maternal mirroring affects the development of infant social expressiveness. It has been suggested that mirroring is effective by virtue of its being frequent and highly contingent [36, 37]. This characterization of mirroring was not supported by our study, where, consistent with other research (e.g., [7]), it was neither frequent nor highly contingent (even in the comparison group, mirroring, although occurring highly selectively, followed only a small proportion (16%) of infant social cues [4]). Explanations for the positive effects of mirroring are therefore required that do not rely on either frequency or contingency. One hypothesis is that infants have a strong propensity to capitalise on others’ mirroring [4], a propensity rooted in the preparedness of the infant brain to identify commonalities between own and others’ motor patterns. In the present case, we suggest that the innate ability to generate certain active motor gestures, such as mouth openings and tongue protrusions, is complemented by a readiness to apprehend equivalence when these same gestures are observed in others ([38], p. 13). Accordingly, when the caregiver mirrors these gestures shortly following their production by the infant, the resulting instantiation of action-perception connections that are nascently present will strengthen the neural circuits involved, thereby increasing the probability of the behaviour occurring. This proposal is in line with theoretical accounts suggesting a strong canalization during development of brain circuits and related learning processes to sustain the link between infant motor facial gestures and perception of others’ facial expressions [39, 40]. It is also supported by

behavioural evidence, including from neonates, for the enactment and detection of imitation of others’ facial gestures [41, 42], and by neurophysiological studies showing that being imitated activates areas of the STS region and inferior frontal gyrus [43], areas forming part of the *mirror neuron system* (MNS), the neural mechanism involved in self-other matching [44–46]. This mechanism has been documented early in development (e.g., [16, 47–49]), including in social contexts (e.g., [13, 50, 51]), with Rayson and colleagues finding, for example, that maternal mirroring of infant social expressions at two months predicts later infant neural processing of others’ facial expressions of emotion [13].

A further possible mechanism involves the reward processing system. Thus, human and macaque studies have shown that being mirrored leads to greater reward-related responses, including self-reported liking, preferential gaze, and ventral striatal activity [52–54]. Accordingly, maternal mirroring is likely to reinforce infant communicative gestures through eliciting such reward-related activity, leading to their increase. The question of *why* being mirrored elicits reward-related activity remains open. One possibility is that it simply reduces prediction errors for encoding another’s action [55]. But it is also possible that the reward system is mobilised selectively, privileging a specific subset of actions, such as pre-speech gestures, that have evolved to serve communicative functions [32]. Together, these data indicate a neurofunctional architecture, whereby action-perception mechanisms in infants are sensitive and prepared to detect specific social configurations in the environment and are reinforced through behaviourally responsive, and rewarding, matching.

The second key question our findings concern is the *influences* on parental mirroring. Since the infant facial configuration of cleft lip disrupts the normal neural activation associated with feelings of attraction and motivation to interact [12], we examined parental gaze to the infant. We found that mothers did gaze less to their infant’s mouth in the context of cleft lip and that this contributed to the reduction in these mothers’ mirroring responses. Nevertheless, even for infants whose cleft was severe, the effect of the cleft on mirroring accounted for by reduced maternal gaze was small. This might indicate, consistent with Field and Vega-Lahr [17], that, aside from any effects on parents’ overall intuitive attraction response, specific disturbances to infant facial gestures disrupt the tendency to mirror. One possibility is that fundamental biological motion dynamics [56], or kinematics, that afford perception of intentionality [57] are harder to discern in facial gestures executed in the context of cleft lip [58]. Notably, this intentional dimension of observed behaviour is key in determining imitation, even by infants [59, 60]. Another possibility, less bound up with the dynamics than with the *physical* structure of facial gestures, is that the normal signal:noise ratio of infant social expressions is reduced in cleft lip (for example, in mouth-opening gestures, the extent of change from the baseline, closed, position to its apex will be smaller in infants with a cleft than in unaffected infants).

Both suggestions might fruitfully be investigated in experimental studies of social action-perception, where critical features of infant communicative gestures are manipulated.

Finally, our study indicates the role of maternal factors in determining mirroring responses, an association already demonstrated in the context of depression [25, 26]. In the current study, consistent with previous research [18, 19], maternal depressive symptoms were not, in fact, associated with infant cleft lip. Nevertheless, mothers' beliefs about their infant's cleft, and specifically feelings of self-blame, adversely affected their interactions and reduced mirroring, suggesting that further examination of the role of maternal cognitions in infant face processing is warranted.

#### 4.1. Wider Significance

**4.1.1. The Robustness vs. Fragility of the Parenting System and Its Influence.** While we identified difficulties in the interactions of parent-infant dyads where the infant has cleft lip, it is notable that the basic structure of engagements, its "functional architecture" [4], was preserved, with key maternal responses still occurring to infant social expressions and predicting their development. The findings concerning the intactness of maternal responsiveness are consistent with experimental evidence for adults' ability to discriminate different infant emotional expressions despite facial anomalies [14, 23], and they point to the robustness of the intuitive parenting system, even under challenging conditions.

With regard to the influence of parental responses, it was notable that we found that relatively small variations in levels of mirroring had significant effects on infant social development.

While our own results are situated within the context of a clinical difficulty, the principle that modest variability in parental facial responsiveness significantly influences the development of infant social expressiveness likely has wider relevance, including the understanding of cultural variations (e.g., [61, 62]). In particular, parents' propensity to mirror certain infant behaviours, and ignore others, is likely to represent a fundamental mechanism for establishing a shared currency of communication and meaning that can then be developed and elaborated in culturally specific ways. The identification of commonalities and variations across and between cultures in the infant's linguistic environment, and their impact on auditory processing and vocal production, has received considerable research attention [63, 64]. Similar endeavour in relation to cross-cultural variation in adult-infant *facial* communication stands to add significantly to our understanding of the fundamental nature of the functional architecture of early communication.

**4.1.2. Clinical Implications.** Our findings suggest that specific mechanisms may reduce maternal responsiveness in the context of cleft lip, including possible difficulties in recognising infant social cues, and maternal preoccupation about the infant's condition. Accordingly, interventions might usefully be directed at both these sources of difficulty. Thus, it may be helpful to support parents' awareness of their infant's communicative bids, possibly through video feedback. It may also be helpful to direct interventions at parental negative cognitions, such as self-blame, that may disturb attention to infant cues and interfere with processing their social behaviours.

#### 4.2. Strengths and Limitations

**4.2.1. Strengths.** There are almost no data on the development of social expressiveness through the early weeks, and none, to our knowledge, in clinical contexts, where sample recruitment and retention present significant challenges. Our study is therefore notable in providing evidence in this limited field, particularly since the study of clinical variations can help identify developmental processes that may remain obscure in normal populations. A further study strength is the use of a theoretically based microanalytic coding scheme to elucidate mechanisms underlying parent-infant interactions more precisely than is possible with more global measures.

**4.2.2. Limitations.** Our clinical sample, although comparable to others including cleft lip (e.g., [58]), was small, precluding examination of the combined effects of different processes affecting maternal mirroring. These processes need further empirical examination.

### 5. Conclusions

Despite the infant facial anomaly of cleft lip, core components of the parent-infant interaction system - infant social expressions and maternal responsiveness - are retained, indicating the system's robustness. Nevertheless, interactions in the context of infant cleft lip differed from those in a normal sample, indicating that the parent-infant system is also sensitive to variation.

Maternal mirroring of infant expressions was reduced in the context of cleft lip and accounted for the slower development of affected infants' social expressiveness. The findings are consistent with evidence from neuroscience concerning the "mirror neuron system" and support theories concerning its role in early infant social development. They indicate important avenues for clinical interventions.

#### Data Availability

The data used to support the findings of this study are available from the last author upon request.

#### Disclosure

Laura Bozicevic and Leonardo De Pascalis' current address is the Institute of Psychology Health and Society, University of Liverpool, UK, and Kyla Vaillancourt's current address is the Institute of Psychiatry, King's College London, UK.

#### Conflicts of Interest

The authors have no conflicts of interest.

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## Supplementary Materials

The supplementary material contains details of Procedure, Measures, and Data Analysis Plan. (*Supplementary Materials*)

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