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Effects of social and sensory deprivation in newborns: A lesson from the Covid-19 experience

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ABSTRACT

Background: Infancy is a complex period of human life, in which environmental experiences have a fundamental role for neurodevelopment. Although conditions of social and sensory deprivation are uncommon in high income countries, the Covid-19 pandemic abruptly modified this condition, by depriving people of their social stimuli of daily life.

Aim: To understand the impact of this deprivation on infants' behaviour, we investigated the short-term effects of isolation and use of individual protective systems by mothers during the first two weeks of life.

Methods: The study included 11 mother-infant dyads with mothers tested positive to SARS-CoV-2 at the time of delivery (Covid group) and 11 dyads with a SARS-CoV-2 negative mother as controls. Neurobehavioral, visual, and sensory processing assessments were performed from birth to 3 months of age.

Results: Findings showed the effect of deprivation on some neurobehavioral abilities of infants in the Covid group; in addition, differences in sensory maturation trends were observed, although they tended to gradually decrease until disappearance at 3 months of age.

Conclusion: These findings suggest the significant effects of early sensory and social deprivation during the first two weeks of life, but also provide several insights on the ability of the brain to restore its aptitudes by deleting or reducing the effects of early deprivation before the critical periods' closure.

1. Introduction

Infancy is a complex period of human life, characterized by a dramatic increase in sensory-motor abilities. The experience and its accompanying developmental processes allow the infant to increasingly improve the use of motor behaviours, manual activities, and vocalizations in an adaptive and efficient way [1]. Indeed, the newborn is an active organism, who can use motor behaviours and process sensory stimuli, already at birth, for his adaptive needs and for interacting with their environment [2].

In this context, vision has a key-role for the evolution of neurodevelopment, not only because it permits the exploration, adaptation and learning of the infant, but also because it allows to create a relationship with caregivers through eye-contact, to develop preverbal communication, and to structure cognitive, motor, affective, and social intentionality, and reciprocity [3]. The newborn is already capable to perceive and process information of face and gaze and these early abilities highlight the innate tendency to social interaction, that is gradually enriched through experience after birth [4]. Recently, Krieber-Tomantschger and collaborators [5] have suggested that in early infancy, between 4 and 16 weeks of post term age, it is possible to observe several developmental changes of visual attention; such changes show the presence of a hierarchy of visual functions from exogenously controlled simple alertness to emerging endogenous sustained attention.

These developmental changes in infant's sensory processing and behaviour are the most visible effects of the interaction between biology and environment: during infancy, brain plasticity is strongly dependent on experience or environmental influence. Environmental stimuli substantially affect the psychophysical maturation of the infant, thus making the first months of life a particularly delicate period for maturation of the individual [6].

Several studies have showed the existence of temporal windows in

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the first years of postnatal life, called critical periods, during which neural circuits show greater sensitivity for acquiring instructive and adaptive signals from the external environment [7]. During these critical periods of high developmental plasticity, sensory, motor, and social experiences are strong determinants of learning and have the crucial role of guiding the final maturation of neural circuits and behaviour [8]. Of note, the mother can be considered one of the most important sources of sensory experience (visual, auditory, tactile, vestibular, olfactive, etc. …) for the infant, thus regulating physical growth and promoting neural maturation of brain structures involved in cognitive functions [9].

Studies on rodents and monkeys have shown that early separation from maternal social-sensory stimulations may shape behavioural and neurochemical phenotype of offspring in adulthood, producing a substantial amount of stress, with long-term behavioural consequences [10].

Although conditions of social and sensory deprivation are uncommon in high income countries, the Covid-19 pandemic has forced all people into isolation and deprived them of their social stimuli of daily life. About adulthood, several studies highlighted the negative effect of isolation during pandemic emergency. Sun and colleagues [11] estimated the prevalence of depression and anxiety in isolated or quarantined populations at 12 and 10.8 %, respectively. Moreover, according to these authors, higher education level, being healthcare workers, being infected, longer duration of segregation and higher perceived stress level were identified as risk factors for depression and anxiety. These findings are in line with results of Fumagalli et al. [12], that highlighted as the most traumatic elements about experiences of COVID-19 positive mothers who gave birth during the pandemic were the sudden family separation, self-isolation, the partner not allowed to be present at birth and the use of masks and gloves in the physical interaction with the newborn. Similarly, about childhood, Byrne et al. [13] underlined as the parent-reports about developmental outcomes of a birth cohort of babies born into lockdown during the COVID-19 pandemic indicated some potential deficits in early life social communication.

In fact, some authors suggested as the social deprivation due to pandemic during sensitive time windows of heightened plasticity, such as neonatal life, could have catastrophic effects, with possible long-term consequences in children. Shuffrey et al. [14] have suggested that birth during the pandemic, but not in utero exposure to maternal SARS-CoV-2 infection, was associated with differences in neurodevelopment at six months of life. In addition, maternal postnatal anxiety during the Covid-19 emergency has been indirectly linked to the infants' regulatory capacity at 3 months of life [15].

In order to understand the impact of the pandemic-related neonatal deprivation on the development of infants' behaviour, we carried out a prospective and longitudinal study investigating the short-term effects of the isolation and of the use of individual protective systems during the first two weeks of life by mothers tested positive to SARS-CoV-2 at the time of delivery. We hypothesized that these infants would show temporary differences in self-regulation and early sensory processing abilities compared to controls born from SARS-CoV-2-negative mothers.

Our findings could be used as a paradigmatic model to verify the effects of early sensory and social deprivation in the human being during the first two weeks of life; also, our data could improve our knowledge about the ability of the brain to restore its aptitudes, by counteracting or reducing the effects of early deprivation before the closure of the critical periods.

2. Methods

2.1. Study design

Between March 2021 and November 2022, mothers were recruited from the Maternity Department of IRCCS San Gerardo dei Tintori in Monza (Italy) to participate in a longitudinal study examining associations among early experiences and child development. Since the difficult period due to the pandemic, recruitment was performed by convenient sampling. The study aimed to recruit and follow 30 mother-infant dyads, from birth to 3 months of age of the infants. Although 30 mothers were enrolled in the study, only 22 completed the follow-up. Drop out of the dyads from the study was caused by the worsening of respiratory symptoms in some SARS-CoV-2 mothers ($n = 2$), family organization-related challenges in performing the structured assessment at the pre-planned time-points ($n = 4$), and fear of viral contamination in SARS-CoV-2 negative mothers ($n = 2$).

2.2. Participants

Participants for this study included 11 mothers tested positive for SARS-CoV-2 infection at the time of delivery (Covid Group), and 11 mothers negative to SARS-CoV-2 infection at the time of delivery and during the following three months (Control Group). All participating infants were negative to SARS-CoV-2 infection and all recruited mothers were either asymptomatic or with very few symptoms of the infection.

Inclusion criteria were: (i) Apgar Index of the infant at $5' > 7$; (ii) Gestational Age at the time of delivery ≥37 weeks; (iii) fluently spoken Italian language in the mother. Exclusion criteria were: (i) presence or suspicion of sensory, genetic, or neurologic disorders in the infant; (ii) small or extremely small growth for gestational age of the infant; (iii) pre-existing severe maternal medical conditions or pregnancy complications; (iv) neonatal poor condition at birth or neonates who required any form of resuscitation; (v) worsening of symptoms of SARS-CoV-2 infection in the mother. All procedures involving human subjects in this study were approved by the local Research Ethics Committee (3140/2020 Ethics Committee Brianza). The study was conducted according to the guidelines of the Declaration of Helsinki. A written informed consent was obtained from all the mothers.

2.3. Procedure

Main clinical data about newborns at birth (gestational age, weight at birth, gender) were collected by reviewing of the pertinent medical records at the time of recruitment (T0). All infants were evaluated between the 14th and the 22nd day of life (T1) and, subsequently, between the 45th and the 55th day of life (T2). Finally, an evaluation by parent-report questionnaire was performed when infants were 3 months of age, or within 10 days after the completion of the third month of age (T3). Time points are illustrated in Fig. 1. Mothers were swabbed for SARS-CoV-2 infection on the day before or on the same day of delivery, whereas infants were swabbed within the first 24 h after birth. Subsequently, for the Covid Group, the swab was performed in both mothers and children every 8 days. During the first two-three days after childbirth, infants and mothers were kept in isolation in the Covid-ward of the Maternity Department. Afterward, Covid Group-infants continued the isolation at home with their mothers, without any direct contact with other people until the end of the quarantine period (range 10–22 days of isolation). For this reason, T1 assessment was carried out no >5 days after the first negative swab for SARS-CoV-2 infection in mothers and, thus, not >5 days after the end of the quarantine period. During at home-isolation, Covid Group-mothers were instructed to always wear FFP2 masks and hand gloves and to frequent use hand disinfectant during daily care of the newborn. These individual protective systems were used by the mothers during skin-to-skin contact with their infants for the main daily routines (e.g., breastfeeding and bathing).

2.4. Outcome measures

2.4.1. Neonatal Behavioural Assessment Scale (NBAS)

The NBAS is a valid and reliable standardized instrument for the evaluation of neurobehavior in newborns [16–18]. It comprised 28 behavioural items, 18 elicited (including neonatal reflexes), and 7 supplementary items. In our study, the NBAS was performed by an NBAS-

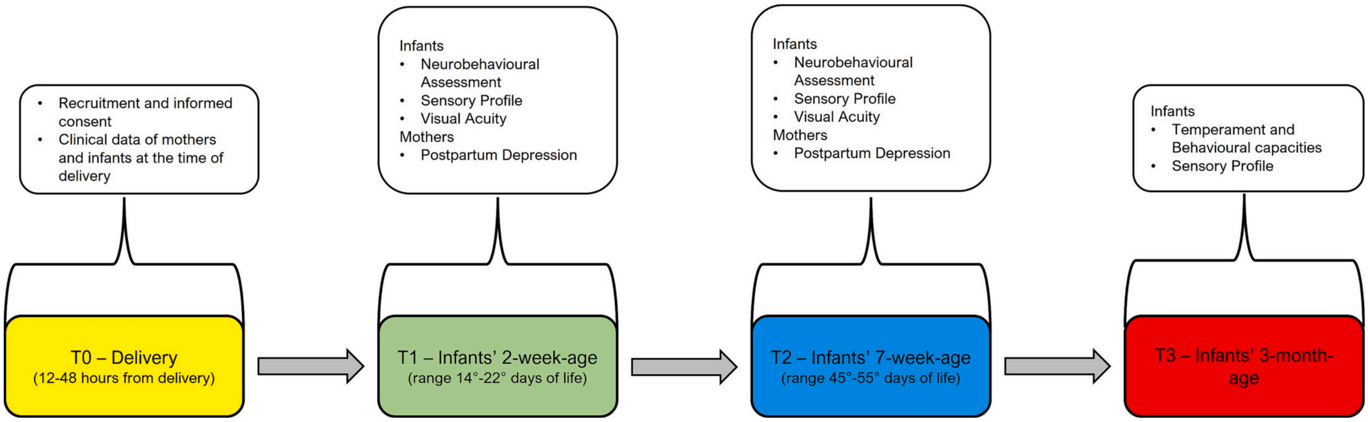

Fig. 1. Schematic overview of the perinatal and postnatal assessments included in the study design.

trained examiner with expertise in assessing the infant's behavioural capacities and neurological status (neurodevelopmental therapist). The examination takes approximately 20 min to be administered: some items require that the infants is asleep or half-sleep, while other items require the infant to be awake and alert. Most of the items are scored on a 9-point scale, with a higher score indicating better performance. Individual items can be grouped together, and their average score calculated, to create six predefined behavioural clusters including orientation to stimuli, habituation to stimuli, motricity, regulation of behavioural states, range of behavioural states, and autonomic stability. Moreover, the examiner registers the number of smiles during the examination and the number of atypical neonatal reflexes. In our study, NBAS assessments were conducted at T1 and T2 e the results obtained from the examinations were considered as main outcome measure.

2.4.2. Lea Grating Test (LeaGT)

The LeaGT is used by an expert examiner to measure binocular visual acuity in newborns [19]. The test uses some paddles to present gratings with parallel lines of decreasing width. According to the preferential looking principle, the measurement is based on observing the child's eye movements when the grating paddles are presented to the child. For the examination, a paddle with striped pattern is presented in front of the infant simultaneously with a paddle with grey surface of the same size and luminance. Infants were held on their mothers' laps or on an infant seat at a distance of 28 cm from the test. The grating detection thresholds were defined as the spatial frequency of the finest grating that resulted in two positive responses. The frequency of gratings is defined as cycles per centimetre on the surface of the paddles (from 0.25 to 8.0 cycles per centimetre) and then converted in cycles per degree (cpd). In our study, assessments with LeaGT were conducted at T1 and T2.

2.4.3. Sensory Profile-2 (SP-2)

The SP-2 is a norm-referenced collection of five parent- and teacher-report questionnaires that assess sensory processing in children (birth to 14 years, 11 months), in relation to everyday sensory events [20]. For this study the age-appropriate version was used, that is the Infant Sensory Profile 2 (from birth to 6 months), in its Italian validated version [21]. It is composed of a total of 36 items that assess general, auditory, visual, tactile, and vestibular processing abilities. Items are rated on a 5-point Likert scale from 5 (Almost Always) to 1 (Almost Never). High scores indicate that the parent observed the sensory behaviour frequently, whereas low scores indicate the behaviour was observed rarely. After completion of the questionnaire, it is possible to have a total score and four general sensory styles or quadrants: sensory seeking (how likely an infant is to pursue sensory input), registration (how likely an infant is to miss sensory input), sensitivity (how likely an infant is to notice sensory input) and avoiding (how likely an infant is to withdraw from sensory input). In our study, SP-2 was administered at T1, T2 and T3.

2.4.4. Infant Behaviour Questionnaire – Revised Short Form (IBQ-R-S)

The IBQ-R-S is the short form of the Infant Behaviour Questionnaire – Revised, that is a parent-report questionnaire for infants' ages 3 to 12 months [22–24], of which reliability and validity have been supported for samples from different cultures, included Italian culture [25]. In the IBQ-R-S, mothers respond to 91 questions about their children's typical behaviour on a 7-point Likert-type scale (1 = never, 4 = about half the time, and 7 = always). The IBQ-R-S yields 14 scales (Activity Level, Distress to Limitations, Fear, Duration of Orienting, Smiling and Laughter, High Intensity Pleasure, Soothability, Falling Reactivity/Rate of Recovery from Distress, Cuddliness, Perceptual Sensitivity, Sadness, Approach, and Vocal Reactivity). In our study, IBQ-R-S was administered at T3.

2.4.5. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a ten-item self-administered scale investigating the presence of depressive symptoms in woman who has just given birth, during the previous 7 days. Each item has four possible answers, scoring from 0 (absence of the symptom) to 3 (symptom very intense and present for most of the time). Therefore, the EPDS total score ranges from 0 to 30. Clinically, a score >9 is considered the cut-off for the risk of postpartum depression. For this study, it was used the Italian validated version [26] at T1 and T2.

2.5. Statistical analysis

For the statistical analysis, the mean values and standard deviation of clinical scores at different outcome measures was determined by using IBM® SPSS® Statistics software (IBM SPSS Statistics Version 28.0. Armonk, NY: IBM Corp). After evaluating the normal distribution of the dataset by using a Shapiro- Wilk's test and performing preliminary analysis for verifying the comparability of the two groups at birth (T0), we decided to use a parametric approach. At first, we performed *t*-tests for two independent sample to determine whether significant differences in different parameters at T1, T2 and T3 between the two groups occurred. Subsequently, we used paired sample t-tests to analyse differences in each group across the different time-points (NBAS: T1 vs T2; LeaGT: T1 vs T2; SP-2: T1 vs T2, T2 vs T3 and T1 vs T3). The statistical level of significance was set by the *p*-value ($p \leq .05$).

3. Results

Twenty-two infants (10 males and 12 females), born between 2021 and 2022, participated in this study. Main data about the clinical parameters of mothers and characteristics of delivery in the two groups are reported in Table 1, while main data about infants of the two groups at

Table 1
Sociodemographic and clinical data about mothers.

	Covid group	Control group	p-Value
Maternal age (mean, sd)	35.5 (5.4)	32.4 (5.1)	.184
Education (Under-graduate degree or more)	3	7	.99
Employed (yes)	11	9	.24
Living children (yes)	3	4	.44
Mode of birth (vaginal)	9	11	.24
Blood loss (mean, sd)	463 (358) ml	254 (129) ml	.84

birth were reported in Table 2. Preliminary standard statistical tests (*t*-test and chi-squared test) were employed to check the comparability of the two groups both in terms of perinatal conditions of infants (gestational age, weight, and gender) and regarding socio-demographic and clinical data of the mothers. No significant differences were found between the two groups (see Tables 1 and 2). All mothers of the Covid Group confirmed the use of a FFP2 mask for the most of time during isolation, and always when they were at a distance <1 m from their infant. They always used gloves and/or hand disinfectant for the manipulation of their infant or of objects used by their infant (feeding-bottle, clothes, baby diaper, etc.…). Moreover, all mothers of the Covid-Group confirmed the tendency to reduced cuddling for the fear of contamination.

3.1. NBAS

Results about NBAS in the two groups were reported in Table 3. Independent *t*-test between groups at T1 showed significant differences, with lower scores in the Covid Group, in autonomic stability ($p = .023$) and in the number of smiles ($p = .023$). Moreover, a higher number of abnormal reflexes in children of Covid Group was observed ($p < .001$). No differences were found in the other scores, although Covid Group also showed lower scores with a tendency to statistical significance in orientation to stimuli ($p = .066$) and in motricity ($p = .078$).

At T2, independent *t*-test confirmed significant differences between the two groups in orientation to stimuli ($p = .005$) and autonomic stability ($p = .021$), with lower scores in infants of Covid Group. A slight statistically significant difference persisted in abnormal reflexes ($p = .044$), although with an evident tendency to normalization of the infants of Covid Group in comparison to scores at T1. In addition, lower scores in the range of behavioural of states, with a tendency to statistical significance, was found in the Control Group compared to the Covid Group ($p = .054$).

As regards the Covid Group, paired sample *t*-test showed statistical differences between T1 and T2 in orientation to stimuli ($p = .026$), motricity ($p = .022$) and number of smiles ($p = .016$), although a global increase of the most of scores were evident and compatible with a typical maturation.

Finally, regarding the Control Group, paired sample t-test showed only a significant difference between T1 and T2 in orientation to stimuli ($p = .016$), although also in this group a global increase of neurological condition (in particular autonomic stability, number of abnormal reflexes and number of smiles) confirmed a typical neurologic maturation of newborns.

Table 2
Clinical data about infants.

	Covid group	Control group	p-Value
Gender (M, F)	5;6	5;6	1.000
Gestational Age (mean, sd)	39.7 (0.8) wks	39.4 (1.6) wks	.513
Gestational Age (range of weeks)	39–41	37–42	
Birth weight (mean, sd)	3476 (495.6) gr	3316 (516.1) gr	.468
Birth weight (range of gr)	2870–4700	2640–4230	
Weight at T1 (mean, sd)	3635.4 (468.3)	3498.1 (568.4)	.543
Weight at T2 (mean, sd)	5018.6 (654.0)	4559.1 (743.8)	.139

3.2. LeaGT

Visual acuity was evaluated only in 16 infants (7 Covid Group vs 9 Control Group) at T1 and only in 17 infants (7 Covid Group and 10 Control Group) at T2, for lack of sufficient collaboration. Independent *t*-test showed no statistical differences between the two groups at both time-points, while paired sample t-test showed a substantial difference between T1 and T2 in the Control Group ($p < .001$) and only a tendency to statistically significant difference between T1 and T2 in the Covid Group ($p = .052$), thus suggesting a slower maturation trend in infants of Covid Group (see Fig. 2).

3.3. SP-2

Data about SP-2 scores were graphically represented in Fig. 3.

Mean sensory processing scores of infants of the two groups were compared at T1, T2 and T3. Although total scores at SP-2 tended to cluster around the normative mean for infants in both groups, a tendency to a significant difference between the two groups was found at T1 ($p = .058$), with the score of Covid Group being lower than that of the controls. This means that infants of Covid Group were reported to engage in low levels of sensory behaviours in comparison with infants of Control Group at T1, but not at T2 and T3. Regarding the scores in the four sensory quadrants, we identified a significant difference in the Registration Quadrant at T1 ($p = .023$), thus confirming the tendency of infants of Covid Group to likely miss sensory input from the environment. No difference was recognized at T2 and T3.

Also, we did not identify differences between T1 and T2 and T2 and T3 in Covid Group-infants by means of paired sample *t*-tests, whereas there was a substantial difference between T1 and T3 ($p = .003$). In turn, Control Group-infants did not show any difference at any paired time-point comparison.

3.4. IBQ-R-S

Temperament and behavioural abilities of infants at 3 months of age (T3) were compared using the independent *t*-test. No differences were found between the two study groups in the Total Score as well as in the several behavioural domains (see Table 4).

3.5. EPDS

Levels of post-partum depression were compared at T1 and T2 through independent t-test. No differences were found between the two groups at either T1 (Mean Covid Group 6.6, SD 3.7; Mean Control Group 4.4, SD 3.4; *p*-value: 0.168) or T2 (Mean Covid Group 3.5, SD 2.7; Mean Control Group 3.4, SD 2.6; p-value: 0.937). At T1, there were only two mothers, both belonging to the Covid Group, who obtained a score higher than the clinically meaningful cut-off (i.e., 9), whereas no mothers of either study groups obtained a pathological score at T2.

4. Discussion

To the best of our knowledge, this is the first longitudinal and prospective study that documents the possible short-term consequences of COVID-19 pandemic-related isolation during the first two weeks of life on infants' behaviour. The study highlights that a brief social and sensory deprivation in infants during the first weeks of life, due to positivity to SARS-CoV-2 infection of mothers at the time of delivery, influences early adaptive abilities of neonates, although these differences seem to no longer be present at 3 months of age.

In this study, it was used the Covid-19 pandemic to create a kind of

Table 3
Description of NBAS clusters scale components and their scores in neonates of the two groups at T1 and T2. The asterisks indicate significant difference (* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.005$).

NBAS Cluster	Individual Item in Cluster	T1		p-Value	T2		p-Value
		Covid group Mean (SD)	Control group Mean (SD)		Covid group Mean (SD)	Control group Mean (SD)	
Orientation Infant's ability to attend to animate and inanimate visual and auditory stimuli.		5.05 (1.0)	6.02 (1.3)	.066	6.03 (.6)	6.9 (0.6)	.005**
	Orientation response to:						
	Inanimate Visual (ball)	5.09 (1.3)	6.3 (1.9)	.090	5.09 (1.0)	6.8 (1.2)	.002***
	Inanimate Auditory (rattle)	4.8 (1.5)	5.4 (1.5)	.339	6.09 (1.5)	7.09 (1.2)	.104
	Inanimate Visual-Auditory (rattle visual/sound)	5.3 (1.7)	6.3 (1.5)	.131	6.3 (.9)	6.9 (1.1)	.162
	Animate Visual (examiner face)	5.8 (1.9)	6.0 (1.7)	.816	6.6 (.8)	7.4 (1.0)	.081
	Animate Auditory (examiner voice)	4.5 (1.4)	5.6 (1.5)	.090	5.8 (1.4)	6.8 (0.7)	.050*
	Animate Visual-Auditory (examiner face-voice)	5.5 (1.0)	6.6 (1.6)	.071	6.4 (.9)	7.8 (0.6)	<.001***
	Alertness	4.3 (1.3)	5.6 (2.2)	.091	5.9 (1.9)	5.6 (1.1)	.695
Habituation Infant's ability to respond to and inhibit discrete stimuli while asleep.		6.02 (0.8)	5.6 (0.6)	.224	5.5 (.6)	5.6 (0.8)	.771
	Response decrement to:						
	Light (to face)	5.9 (1.2)	5.2 (1.2)	.169	5.5 (1.1)	5.2 (1.2)	.466
	Rattle	6.2 (1.2)	5.6 (0.8)	.110	5.9 (.9)	5.9 (1.0)	1.00
	Bell	6.3 (1.5)	5.6 (1.2)	.142	5.6 (1.5)	5.6 (1.4)	1.00
	Pinprick	5.7 (1.6)	6.0 (0.6)	.608	5.1 (1.1)	5.8 (1.4)	.197
Motricity Motor performance and the quality of movement and tone.		5.09 (0.6)	5.6 (0.6)	.078	5.8 (.5)	5.8 (0.2)	.829
	General Tone	5.6 (0.5)	5.7 (0.5)	.666	5.8 (.4)	5.5 (0.5)	.186
	Motor Maturity	5.7 (1.5)	6.4 (1.4)	.258	7.1 (1.3)	6.7 (0.8)	.458
	Pull-to-sit	4.2 (0.7)	4.3 (1.0)	.813	5.3 (.9)	5.3 (0.6)	1.00
	Defensive Movements	5.2 (1.2)	7.0 (0.8)	.008 **	6.5 (1.1)	6.8 (0.4)	.459
	General activity level	4.8 (0.5)	4.5 (0.9)	.572	4.3 (.8)	4.9 (0.3)	.049*
Regulation of State		4.9 (0.9)	5.6 (1.4)	.183	5.1 (.8)	5.1 (1.3)	1.00
Infant's ability to regulate his or her state in the face in increasing levels of stimulation.	Cuddliness	5.9 (0.9)	7.0 (1.3)	.039 *	5.7 (.9)	6.1 (0.9)	.367
	Consolability with intervention	4.3 (2.3)	4.6 (2.6)	.734	5.5 (1.5)	4.5 (2.3)	.241
	Self-Quieting Activity	5.4 (1.7)	5.4 (2.0)	.912	5.7 (1.3)	5.3 (1.5)	.462
	Hand-to-Mouth Facility	4.0 (1.6)	5.4 (2.0)	.077	3.6 (2.4)	4.7 (2.1)	.268
Autonomic stability		6.6 (0.8)	7.3 (0.5)	.23 *	6.7 (.9)	7.5 (0.5)	.021*
Signs of stress related to homeostatic adjustments of the central nervous system.	Tremors	6.8 (2.2)	8.0 (1.8)	.186	6.9 (2.1)	9.0 (0.00)	.004***
	Startles	7.4 (0.7)	8.4 (1.0)	.026 *	7.4 (1.0)	8.0 (1.2)	.264
	Lability of Skin Colour	5.4 (1.0)	5.4 (0.9)	1.00	5.7 (.9)	5.5 (0.7)	.602
Range of State Infant arousal and state lability		4.06 (0.6)	3.6 (0.7)	.132	4.4 (.6)	3.9 (0.4)	.054
	Peak of Excitement (overall motor activity and crying)	2.5 (0.8)	2.6 (0.8)	.796	3.8 (.7)	2.9 (1.3)	.062
	Rapidity of Build-up (timing and number of stimuli introduced before infant becomes agitated)	4.2 (1.2)	3.2 (1.7)	.129	3.9 (1.0)	3.2 (0.9)	.108
	Irritability	5.2 (0.9)	5.4 (0.9)	.488	5.6 (1.2)	5.4 (1.0)	.709
	Lability of States (number of state changes during the exam)	4.4 (0.9)	3.3 (1.7)	.074	4.4 (1.3)	4.3 (1.2)	.865
Number of abnormal reflexes	During the exam	3.4 (1.2)	1.2 (1.2)	<.001***	2.4 (1.8)	0.9 (1.3)	.044*
Number of smiles	During the exam	0.9 (0.7)	2.3 (1.6)	.023*	2.9 (2.3)	3.6 (1.9)	.430

natural experiment addressing the role of early stimulation on different aspects of early human development. The main result of the present study was the differences in developmental trajectories between infants of Covid Group, after environmental deprivation, and infants of Control Group: in particular, immediately after the isolation period, neonates of Covid Group showed not only substantially lower abilities in autonomic stability and number of smiles, but also more signs of neurological immaturity and increased stress, in comparison with control neonates. Subsequently, at about 7–8 weeks of age, infants of Covid Group showed also important differences in ability of orientation to stimuli.

Also, some effect of early reduction of environmental stimulation was evident in behaviour related to sensory processing evaluated with parent-report questionnaire SP-2. As a matter of fact, mothers of the Covid Group reported low levels of behaviours in response to sensory stimuli in comparison with data reported by the mothers of Control Group, although this difference tended to gradually decrease until it completely disappeared at 3 months of age. Consequently, also temperament and regulatory capacities of the two groups at 3 months of age were similar.

These behavioural differences in consequence of a reduction of early stimulation during sensitive periods of development are in line with data of several authors, that suggest that early skin-to-skin contact contribute to the infants' regulation abilities in terms of socio-affective abilities, motor system balance and sleep organization during the transition from the womb to the extrauterine environment [27,28]. Brett and colleagues [29] suggested that the early mother–child relationship also appears to be highly influential for a myriad of developmental outcomes indicating the widespread neurobiological impact of early caregiving. Also, our data suggest that infants precociously exposed to an environmental impoverishment may have a different trend of maturation, although this

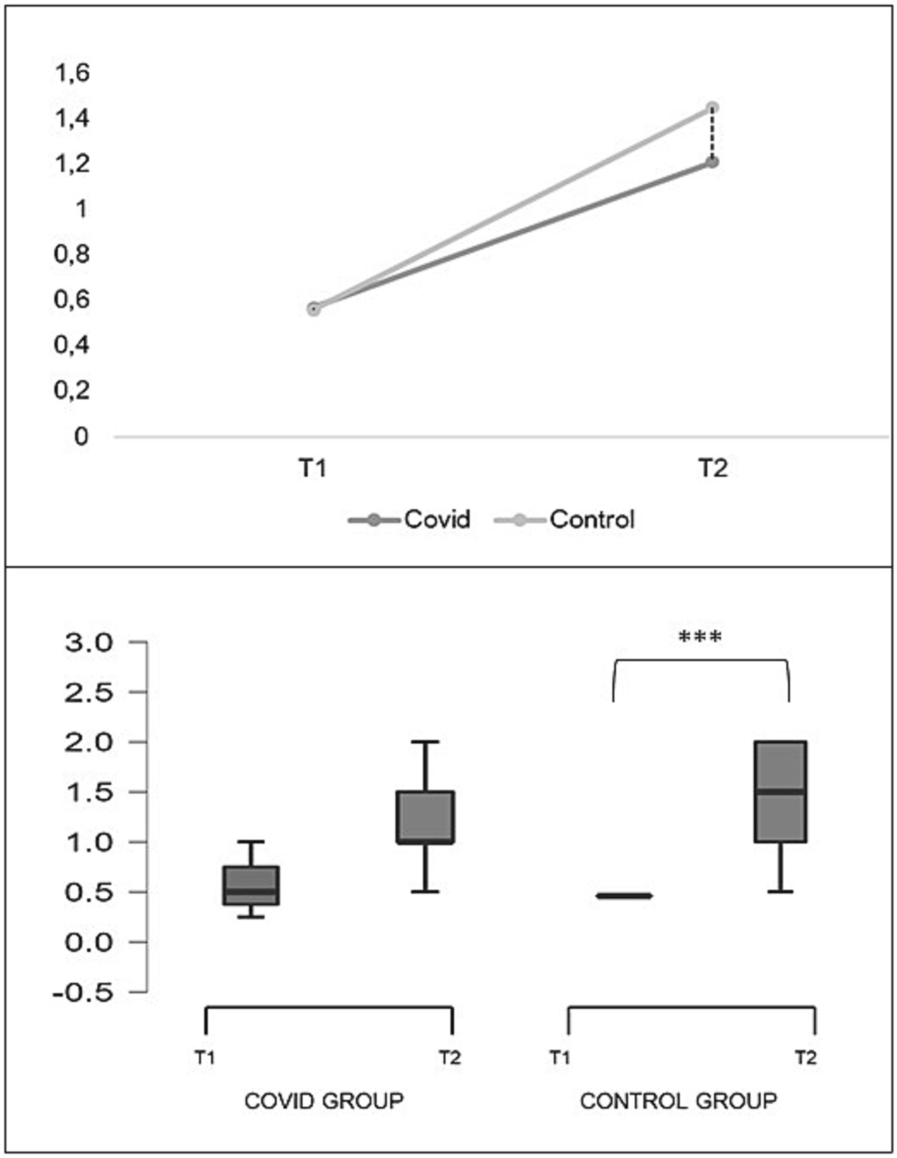

Fig. 2. Graphic representation of visual acuity development (expressed in cycles per degree) in the Control and Covid Groups at T1 and T2.

effect is transient if the environmental sensory and social stimulation is re-established before the closure of critical periods. In fact, the possibility to restore these dysfunctions could probably be linked to the timing of deprivation. Moreover, in our study, the skin-to-skin contact between the mother and her infant was allowed, even if the opportunities to interact were reduced and altered for the continuous use of individual protective systems by the mother and for the absence of other people during the first two weeks of life of the infants. All mothers of the Covid Group referred the tendency not to touch or cuddle their infants for the fear of contamination. This is in line also with results of Fumagalli and colleagues [12] that highlighted as the limited physical contact with the newborn was one of the most traumatic aspects of childbearing experience of COVID-19 positive mothers who gave birth in the months of health emergency.

Another important result regards the fact that social-sensory deprivation seems to have an influence also on visual system maturation. Immediately after the period of deprivation, neonates of both study groups showed the same visual acuity; however, afterward, visual acuity continued to develop faster in the Control subjects than in the subjects of the Covid group. These findings suggest that an early deprivation might affect the developmental trajectories of the sensory systems, particularly of the visual system, which were considered as paradigmatic of brain maturation in this study. This is in line with results obtained in animal model by Narducci et al. [30]. These authors have demonstrated that a reduction of early sensory-motor stimulation in rearing environment of rat pups leaded to a marked delay of functional properties of visual system development, including visual acuity and the latency of visual cortical responses to the sensory input.

Indeed, development of sensory systems is a crucial aspect for several aspects of brain maturation, and early sensory experiences are essential to develop the capacity to synthesize information from different sensory modalities [31]. It has been widely demonstrated that a sensory deprivation, also in only one sensory modality, may also have cascading effects on pathways serving the non-deprived senses and on development of multisensory processes that are a fundamental in learning and adaptation to the environment [32]. In particular, the development of vision within a putative sensitive period in human development appears necessary for the maturation of the neural circuitry enabling the mutual enhancement of congruent cross-modal stimulation later in life [33]. As a matter of fact, in children, early sensory experiences permit the early activation of multisensory processes, although their maturation continues for a long period during the late infancy and during the school age

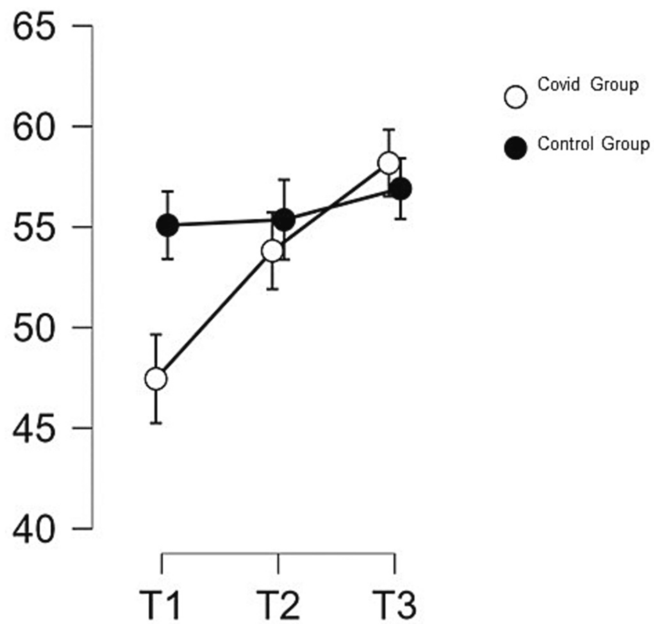

Fig. 3. Graphic representation of sensory processing abilities (Total Score of SP-2) in the Control and Covid Groups at T1, T2 and T3.

Table 4
Descriptive statistics of the IBQ-R-S scales at T3 between the two groups.

	Covid Group (*n* = 11)	Control Group (n = 11)	p-Value
	Mean (SD)	Mean (SD)	
Total score	4.08 (0.6)	4.4 (0.5)	.232
Activity level	2.82 (0.7)	3.2 (0.9)	.265
Distress to limitations	3.6 (0.8)	3.7 (0.9)	.786
Fear	3.5 (1.3)	4.1 (1.2)	.232
Duration of orienting	4.7 (0.8)	4.7 (1.2)	.936
Smiling and laughter	4.5 (0.9)	4.6 (0.9)	.741
High pleasure	4.5 (0.9)	4.7 (0.8)	.678
Low pleasure	4.7 (0.6)	4.5 (0.9)	.628
Soothability	4.6 (0.8)	4.9 (0.4)	.194
Falling reactivity	4.4 (0.9)	4.5 (0.6)	.925
Cuddliness	5.1 (1.4)	4.7 (0.8)	.379
Perceptual Sensitivity	4.1 (1.0)	4.1 (1.1)	.943
Sadness	4.0 (1.2)	4.6 (0.9)	0.225
Approach	4.3 (1.4)	4.5 (1.5)	0.749
Vocal Reactivity	4.6 (0.7)	4.2 (1.0)	0.367

[34–37].

Thus, the negative effects of reduction of early sensory and social stimulation on our subjects suggest the essential role of environment on early brain maturation processes. Because of the primary role that sensory functions play during infancy for cognitive and social-communication development, this study supports the importance of applying "early" intervention programs in children at risk of environmental impoverishment or at risk of developmental disorders.

Therefore, it might be interesting to explore eventually long-term effects of these period of isolation in our sample, since that also Byrne and collaborators [38] recently reported that children born during the pandemic had not differences in most developmental or behavioural domains of standardized tests compared with their pre-pandemic counterparts, except in the communication developmental domain.

About this, in addition to studies based on protocols of reduced or altered sensory experience in animal models, relevant progress in understanding the influence of environmental experience on development is coming from the use of Environmental Enrichment protocols; these protocols provide an enhanced range of opportunities for sensory, motor, cognitive and social stimulation to promote brain maturation on animal model [7]. Consequently, some authors have recently tried to translate the protocols of Environmental Enrichment in human models and have demonstrated the positive effect of early multisensory stimulation on neurodevelopment of infants at risk of developmental disorders [39–42].

5. Limitations

The authors recognize three main limitations of this study. The first refers to the study design, based on the challenges to better measure the quantity of deprivation and to control other biases. The second is the limited sample size, making our results preliminary. The third concerns the relatively short follow-up of the participants' self-regulation and sensory processing capacities. If, on one hand, we are inclined to consider very carefully the sensory differences between the Covid and the Control Group subjects, on the other hand, we feel that our results are very promising and may provide several insights in prospectively investigating the effects of environmental deprivation and enrichment in infants. Thus, we believe that the limitations of our study are outweighed by its originality. It would be worthwhile to conduct a larger study, using more specific and objective measures; however, several relevant ethical and procedural limitations are to be anticipated. Obviously, the difficulties in this study design and execution were mainly related to ethical problems, which also make the study difficult to replicate. Meanwhile, a possible future step could be to study the possible long-term effects of early deprivation on the study participants, in order to define the neurodevelopmental trajectories of the two groups.

6. Conclusion

Our study provides several insights on the influence of environment on brain maturation and neurodevelopment. The small size of our sample and the relatively brief follow-up warrant cautious interpretation of the results. Of note, the recruitment of infant-mother dyads has been extremely challenged by the Covid-19 health emergency. Nevertheless, our results and that of other studies on effects of early social and sensory deprivation on neurobehavioral abilities may suggest the importance of programs of early intervention through the collaboration between midwifes, paediatric nurses, psychologists, and developmental therapists for children at risk of neurodevelopmental disorders or of environmental impoverishment (situation of poverty threshold, long hospitalization, etc.…).

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Declaration of competing interest

The authors declare no conflict of interest.

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