Gentle as a mother’s touch: C-tactile touch promotes autonomic regulation in preterm infants

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ABSTRACT

Preterm infants are challenged to adapt to an extraterine milieu, while their interoceptive system and autonomic regulation capacity is still immature. Caressing parental touch is known to foster parasympathetic regulation in infants by stimulating C-tactile (CT) afferents and in preterm infants, slow stroking stimulation also leads to a heart rate decrease. The particular impact of maternal stroking has not yet been investigated and factors influencing the maturation of the CT system in preterm infants remain unclear. We therefore analysed 53 standardized events in which preterm infants (24 to 36 weeks gestational age at birth) were stroked by their mothers. Video analysis revealed that mothers use CT optimal velocities to stroke their preterm child. Analysis of pulse oximetric data showed no effect of stroking on infantile blood oxygenation, but a significant decrease of the heart rate. Compared to term-born children, this decrease was delayed by about two minutes. Furthermore, our data suggested that more immature preterm infants benefited less from stroking than more mature ones. We conclude that maternal stroking touch targets CT afferents in preterm infants and that the preterm CT system is not yet mature.

1. Introduction

Each year, approximately 15 million infants are born prematurely, i.e., at a gestational age < 37 weeks, accounting for 11% of annual global births [1]. While late (< 37 weeks) and moderate (< 34 weeks) preterm infants constitute the largest part of affected live births and show high survival rates [1,2], viability increases in very (< 32 weeks) and extremely (< 28 weeks) preterm born children, as well [3]. Despite advances in neonatal intensive care and increasing survival rates in developed countries [4,5], prematurity remains an important risk factor for infant death, severe morbidity and disability as well as developmental impairment throughout childhood [6–8]. These risks are in part related to a compromised autonomic regulatory capacity [9,10]. Preterm infants are born at a developmental stage characterised by an imbalance within the autonomic nervous system [11]. Particularly, the impaired ability of the parasympathetic nervous system to apply its vagal brake leads to higher heart rates and reduced heart rate variability (HRV) as an expression of immature regulatory patterns [12,13]. The result is unstable cardiac output and consequently unstable cerebral blood flow, which further endangers the developing brain through intracranial haemorrhage or hypoxia [14]. This autonomic dysfunction even persists beyond term age, especially in children with prematurity associated morbidities [15–17].

The deficits in autonomic regulation are indicative of an impaired capacity for interoception in the preterm child. Interoception describes the continuous monitoring of the sensory representation of the body’s physiological state, e.g., whether one feels cold, hungry, hurt or aroused [18,19]. Such monitoring enables the individual to maintain a stable internal milieu and thus perform allostasis by regulating their behaviour and autonomous processes in response to perceived deviations and anticipated needs. This is possible because the brain has the capacity to predict physiological states based on experience. These predictions are continuously modelled in agranular cortices such as the anterior cingulate cortex and the anterior insula [20,21]. They are further shaped by incoming interoceptive signals represented in the granular cortex of the dorsal posterior insula [18,19], leading to a prediction error when
The anticipated sensations are not matched [20,21]. In addition to the insula and the anterior cingulate cortex, the allostatic-interoceptive system comprises other areas of the salience network (SN), as well as the default mode network (DMN), and connecting hubs, such as the superior temporal sulcus [22].

The third trimester of pregnancy represents a crucial time window for the allostatic-interoceptive system, as there is an ongoing neuronal migration, synaptogenesis, and myelination of the developing nervous system [23]. While the insular cortex already shows term equivalent connectivity at 31 weeks gestational age [24], default mode network connections are not observable in foetuses younger than 35 weeks gestational age [25] and the salience network demonstrates immature network topologies at time of birth [26]. Furthermore, the autonomous system itself undergoes a relevant maturation process with the number of myelinated vagus nerve fibres increasing linearly from 24 weeks gestational age [27].

A possible tool engaging those neural pathways is the stimulation of C-tactile (CT) afferents. This subset of non-myelinated C-fibre fibres plays a crucial role in the sensation of interpersonal touch experiences and is hypothesized to transmit the affective value of human cares [28–29]. CT afferents are stimulated by slow stroking of the skin [30,31] and react vigorously to a gentle, slowly moving, skin temperature between 1 – 10 cm/s, with a maximum at 3 cm/s [32–34].

While conveying seemingly exteroceptive sensations from the skin surface, CTs utilise a pathway that is suited to target interoceptive processing and hence promote allostasis [35]. Non-myelinated C-fibres transmit information about the physiological condition of body tissues and synapse in lamina I of the spinal chord’s dorsal root to further project to brainstem and thalamus [18]. Based on their common neuroanatomical properties, Morrison argues that CT-afferents evolutionarily diverged from thermoreceptive C-fibres and that this specialization promoted social thermoregulation and social bonds [36]. The cortical projection of CTs and other afferent C-fibres is located in the posterior Insula, i.e. the primary interoceptive cortex [37]. The subsequent central integration of CT afferent information involves further regions of the allostatic-interoceptive network, specifically the dorsal anterior cingulate cortex and superior temporal sulcus [38], which underlies the potential role of CT-afferents in (social) allostasis [39]. Touch is hypothesized to facilitate allostatic active inference especially in infant care [40]. This is further supported by the observation that the anterior insular cortex is both a central structure of the allostatic interoceptive network and a key hub in the processing of, notably, tactile prediction errors [41].

Interpersonal touch in general has several physiological and psychosocial benefits in early human development. In term born infants, it attenuates noxious evoked brain responses [42] and carries epigenetic potential as maternal stroking reverses the DNA methylation seen in infants of postnatal depressed mothers [43]. With regard to social development, touch provides a potential pathway to promote the acquisition of self-regulatory and social skills [44,45]. As an example, when a social stress situation is accompanied by maternal touch, 6-month-old infants demonstrate reduced physiological stress responses, including better parasympathetic control [46]. It has been shown that parents utilize affectional touch, such as embracing, hugging and stroking, when interacting with their children across cultures [47]. In doing so, they intuitively use velocities suitable for activating CT afferents [48,49], and their infants demonstrate a typical parasympathetic reaction, i.e. a decrease in heart rate in response [50]). Regarding cortical processing, soft brush stroking elicits typical activation in the posterior insular cortex of the neonatal brain already in the first month of life [51]. Based on these observations, it can be supposed that CT targeted touch performs allostatic functions early in development and thus also in preterm infants.

However, research evidence is sparse, especially in how mothers interact tactiley with their preterm child. Nonetheless, studies suggest a beneficial effect of social touch in general such as a positive relation between duration of holding and quality of mother-infant-interaction in preterm born children [52]. Touch-based interventions are already established in the care of preterm infants and positively affect development. For example, parental skin-to-skin contact in the form of Kangaroo care reduces preterm infants’ morbidity and mortality [53]. Moreover, it improves the cardiac autonomic functioning in infancy and throughout childhood resulting in more attenuated stress responses at 10 years of age [54]. Other tactile interventions, such as massage therapy reduce the length of hospital stay by improving weight gain [55]. Manzotti et al. [56] showed that stroking touch, that is specifically suited to target CTs, fosters autonomic functioning by decreasing heart rate and increasing blood oxygen saturation in preterm infants. This study, however, did not allow investigation of infantile maturation status and it did not allow to study the characteristics of intuitive, maternal touch. This is interesting as premature birth and hospitalisation pose particular challenges to the mother-infant relationship, such as building emotional closeness despite physical separation and evolving a parental role [57].

In the present study, we examined the effect of maternal stroking touch on preterm infants’ autonomic nervous system. We hypothesized that mothers would use CT optimal velocities to stroke their children. Concordant with the findings of Manzotti et al. [56], we further hypothesized that maternal stroking would promote parasympathetic tone, reflected by a decrease in heart rate (HR), and improve tissue oxygenation, as measured by peripheral oxygen saturation (SpO2). Lastly, we explored the effect of maternal stroking touch at the individual level and the influence of infantile maturity on the change in HR and SpO2.

2. Methods

The study protocol was approved by the Ethic Committee of Dresden University Hospital (registration number EK 283072016) and followed the Declaration of Helsinki Ethical principles for Medical research involving human subjects. Written and informed consent was obtained.

2.1. Sample

From January 2020 to October 2020, forty-two preterm born infants were recruited at the Department of Neonatology and Paediatric Intensive Care at Dresden University Hospital with the inclusion criteria of gestational age < 37 weeks at birth and clinically stable condition. Criteria for an infant’s exclusion were current need for intensive care measures, congenital malformations of the nervous system, brain damage due to asphyxia or hypoglycaemia, and congenital metabolic diseases. Further exclusion criteria in parents were acute severe mental disease and insufficient knowledge of German language.

Of the forty-two eligible infants, thirty-six parents were willing to participate, while six declined participation. Two infants had to be excluded during trial, as they were too agitated before the time of the investigation. Due to technical problems, one infant’s pulse data could not be collected and video recording failed for one more, which left thirty-two mother-infant-dyads with full data. In a follow-up investigation two to fifteen days later (\( M = 7.90 \pm 3.52 \) days), twenty-three mother-infant dyads were examined again. In the meantime, mothers received further instructions on preterm infant care. Once more, pulse data collection failed for two infants, which left twenty-one mother-infant-dyads with full data in the follow-up investigation.

The 32 mothers were aged 25–42 years (\( M = 32.06 \pm 4.06 \) years) and for 17, their preterm born infant was the first child. Twenty-eight of the participants reported that they were either married or shared a common household with their partner.

Infants (18 female, 14 male) were born with a gestational age of 24–36 weeks (\( M = 29.41 \pm 3.50 \) weeks) and a mean birth weight of 1090.00 ± 417.34 g. At the time of the first investigation infants were 7 to 84 days postnatal (\( M = 39.44 \pm 26.18 \)) (see Table 1 for all descriptive data and Supplementary Fig. S1). Timing of the investigation differed.
among participating infants depending on the extent of prematurity and severity of medical conditions. Appropriate onset was determined by paediatricians and supervising nurses.

Guided by the findings of Schlatterer et al. [16], we recorded pre- and postnatal complications from the medical charts. The latter were subsumed into five categories: respiratory complications (in 87.50% of the children), infectious diseases (43.75%), cardiovascular complications (28.13%), complications of the gastrointestinal system (21.88%), and neurological complications (18.75%). Supplementary Table S1 displays a full list of diagnoses recorded in each category. By adding up the number of above categories affecting each infant, a comorbidity score was calculated, ranging from 0 to 5.

2.2. Procedure

After informed consent, mothers were asked to answer the Brief-PHQ-D (Brief Patient Health Questionnaire - PHQ, German version; [58]) to screen for mental illness and a questionnaire for sociodemographic data. Medical chart review was performed and data on potential covariates, namely gestational age at birth and at the time of investigation, was collected (compare Table 1).

In order to minimize extra stressors for the infants by our investigation, the study protocol was embedded in structured care trainings offered to parents of preterm born children at Dresden University Hospital. These trainings include voluntary theoretical education on handling preterm born infants and practical training sessions, in which mothers take over the independent care of their children and bathe them themselves for the first time. After bathing, mothers placed their un-pressured infants in prone position to reduce external stressors and promote regulatory capacity.

Before starting the stroking procedure, supervising nurses were instructed to gather 60 s of baseline data of the resting infant. In the meantime, mothers warmed their hands and, furthermore, rubbed a small quantity of rapeseed oil into their hands, as is common practice in the hospital’s care training procedure to minimize the potential for irritation. Thereafter, stroking was performed by the mothers, who were asked to stroke their infant for at least 60 s. However, they were allowed to continue for as long as the stroking seemed pleasurable to the infant and themselves. After the stroking, the video monitoring and pulse oximetry were stopped, the infant got dressed again and routine care was continued (Fig. 1).

Potential effects on the autonomic nervous system were operationalized by the dependent variables infant’s HR and SpO2. Therefore, a non-adhesive monitoring sensor was attached to the infant’s foot and pulse oximetry data was collected continuously via Nellcor™ Portable SpO2 Patient Monitoring System, PM10N (CE 0123). The device offered a sampling frequency of 1 Hz using dynamic averaging [60].

To allow analysis of stroking velocity, a tape measure was placed at the edge of the changing mat for reference purpose and the investigation area. Therefore, changing mat and infant were in full view. Depending on the mother’s movements and posture, their hands and forearms were visible most of the time. Occasionally, they leaned over their infants, which brought their face, or back of the head into view. Videos were recorded with a Panasonic HC-V727 and a resolution of twenty-five frames per second.

Setting and procedure were the same for the follow-up investigation. Between investigations the structured care training continued which involved nurses encouraging the mothers in daily routine to use slow stroking velocities, presumably suiting to activate C-tactile fibres, in tactile interaction.

| Demographic data                | Mothers                                                                 |
|--------------------------------|------------------------------------------------------------------------|
| Age at birth                   | 32.06 ± 4.06                                                            |
| Median number of children      | 1 (1 – 2)                                                               |
| Prenatal complications         |                                                                        |
| Multiple gestations            | 6 (18.75%)                                                              |
| Pre-eclampsia                  | 5 (15.63%)                                                              |
| Pregnancy induced hypertension | 9 (28.13%)                                                              |
| Foetal or intraternal growth restriction (FGR/JUGR) | 9 (28.13%) |
| Premature rupture of membranes | 4 (12.50%)                                                              |
| Chorioamnionitis               | 3 (9.38%)                                                               |
| Infants                        |                                                                        |
| Demographic and clinical data  |                                                                        |
| Sex                           |                                                                        |
| Male                          | 14 (43.75%)                                                             |
| Female                        | 18 (56.25%)                                                             |
| Gestational age at birth (weeks) | 29.41 ± 3.50                                                       |
| Birth weight (g)               | 1090.00 ± 417.34                                                        |
| Comorbidities                  |                                                                        |
| Respiratory complications      | 28 (87.50%)                                                             |
| Infectious diseases            | 14 (43.75%)                                                             |
| Cardiovascular complications   | 9 (28.13%)                                                              |
| Complications of the gastrointestinal system | 7 (21.88%) |
| Neurological complications     | 6 (18.75%)                                                              |
| Comorbidity score (average no. of categories affected per infant) | 2.00 ± 1.63 |
| First investigation n=32       |                                                                        |
| Postnatal age (days)           | 39.44 ± 26.18                                                           |
| Postmenstrual age (weeks)      | 35.00 ± 1.61                                                            |
| Weight (g)                     | 1766.66 ± 278.58                                                         |
| Follow-up investigation n=21   |                                                                        |
| Time difference to first investigation (days) | 7.90 ± 3.52 |
| Postnatal age (days)           | 55.10 ± 25.20                                                            |
| Postmenstrual age (weeks)      | 36.24 ± 1.64                                                            |
| Weight (g)                     | 2023.76 ± 349.93                                                         |
2.3. Statistical analysis

For all statistical analysis, SPSS (Version 28) was used.

2.3.1. Stroking velocity

To analyse stroking velocities we used Tracker Video Analysis and Modelling Tool [61] with a step size of ten frames. A calibration stick with the respective length, and coordinate axes were positioned along the tape measure on the changing mat. For each stroke, the movement of the mother’s hand along the infant’s back and, where applicable, extremities was tracked. Depending on visibility and contact area, a defined region of a single finger (fingernail, proximal or distal interphalangeal joint, metacarpophalangeal joint) or dorsum of the hand was selected for each stroke. This region was marked manually on a continuous basis with the respective step size and velocity of the movement was computed automatically. For further analysis, a mean stroking velocity for each investigation (mean duration 265.17 s ± 114.01) was calculated. Upon reviewer advice, we inspected the dynamics of stroking velocity over time to rule out potential tiring effects. The individual velocity profiles are presented in Supplementary Fig. S4.

In order to examine, whether mothers use CT optimal velocities, we tested if their mean stroking velocity differed significantly from 3cm/s, the known optimal stimulus velocity for C-tactile afferents [33]. Normal distribution for mean velocities observed in each investigation was assured using the Kolmogorov-Smirnov test (first investigation: \( D(32) = 0.15, p = 0.077 \), follow-up investigation: \( D(21) = 0.14, p = 0.200 \)). As

Fig. 1. Visualisation and timeline of the study. Infants were placed in prone position on a changing mat and baseline data was gathered. Thereafter, mothers stroked their children for as long as it seemed pleasurable to the infant and themselves. Video was recorded to analyse stroking velocity.

Fig. 3. Heart rate development during stroking touch. Data are presented as mean HR in beats-per-minute (bpm) and 95%-CI for each 10s-interval. The horizontal line represents the mean baseline HR (M = 170.36 bpm) as a reference. Since maternal stroking duration differed, the observed number of cases declines over time. Markers lighten gradually according to the number of cases included in each interval. Statistical analysis was limited to the first 280s of stroking touch (n_{min} = 21) as indicated by the vertical dashed line. There is a significant time effect on HR during stroking. The horizontal grey line indicates significant deviation from baseline level as revealed by post hoc tests.
we aimed to provide evidence for the null hypothesis ("Mother’s mean stroking velocity does not significantly differ from 3 cm/s"), we chose Bayesian one sample inference. Bayes factor was calculated under a default diffuse prior for the first investigation and for the second investigation, separately. We further performed Bayesian testing to ensure that stroking velocities did not differ between assessment times, as infant data from both sessions were used together for the following analysis.

### 2.3.2. Autonomic response

To analyse autonomic response parameters, firstly, mean heart rate and mean peripheral oxygen saturation was determined for baseline and stroking condition in each investigation. Mean baseline values were calculated for the 60 s preceding the stroking. In six of fifty-three investigations, the required duration was not met (M = 57.72 s ± 7.39; Min. 22 s) and data was hence averaged for the shorter period. For the stroking condition, mean heart rate and oxygen saturation were calculated for the whole length (M = 265.17 s ± 114.06, see Fig. 3).

In the next step, we analysed whether maternal stroking affects the infant’s autonomic response. Pearson correlation first revealed that of the potential covariates only birth weight (r = 0.51, p = 0.003) and postnatal age (r = 0.43, p = 0.015) related to mean heart rate, but not gestational age at birth, time of investigation and number of comorbidities. Hence, birth weight and postnatal age were included in further modelling (for a full correlation matrix, please see Supplementary Fig. S2) of repeated-measures generalized linear mixed models with the target of mean heart rate and the fixed effect of condition (baseline vs. stroking). We included each child as a subject and repeated investigations as repeated measurement. Satterthwaite approximation and robust covariance were used to control for unbalanced data. To enhance the overall model fit for none, each one, and both covariates. Competing models were deemed implausible based on $\Delta AIC = AIC_{\text{min}} - AIC$ and their respective relative likelihood (P) falling below .125 (compare [62]). This revealed a minimized AIC of 800 for inclusion of postnatal age compared to 826 ($\Delta AIC = -26, P < 0.001$) for no covariate included, 810 ($\Delta AIC = -10, P = 0.006$) for birthweight, and 807 ($\Delta AIC = -7, P = 0.030$) for both covariates. Hence, the model including postnatal age was chosen.

In an explorative approach, we further reviewed the time course of the mean infantile heart rate. For each child, we combined the HR by averaging the 60 s of baseline and each following 10 s interval of the stroking condition. Since maternal stroking duration differed, the observed number of cases declined over time. In order to maintain a stable base for statistical analysis, we included the first 280 s of stroking ($n_{\text{min}} = 21$) into the analysis. This decision based on visual inspection of the confidence intervals (see Fig. 3). We analysed the data using a repeated-measures generalized linear mixed model with the target of aggregated HR and the fixed effect of time. Again, Satterthwaite approximation and robust covariance were used.

Thereafter, we repeated the modelling targeting peripheral oxygen saturation and the fixed effect of condition (baseline vs. stroking). Regarding potential covariates, none of the considered parameters related significantly ($\alpha = 0.05$) to oxygen saturation at baseline (see Supplementary Fig. S1). In line with our analysis of the effects on mean heart rate, we tested whether the random factors postnatal age and birth weight minimize the AIC and found the lowest AIC of 463 when postnatal age was included (compared to no covariate: $AIC = 513 (\Delta AIC = -50, P < 0.001)$; birth weight: $478 (\Delta AIC = -15, P < 0.001)$; both covariates: $465 (\Delta AIC = -2, P = 0.368)$). Hence, models including postnatal age alone as well as both covariates were deemed plausible.

### 2.3.3. Individual level

Thirdly, we investigated the individual time course of the infantile

| Scoring | Gestational age at birth | Birth weight | Postnatal age | Comorbidity |
|---------|--------------------------|--------------|---------------|-------------|
| 0       | < 28 weeks               | < 1000g      | < 15 days     | 0           |
| 1       | Extremely preterm        | Extremely low birth weight |               | 1           |
| 2       | 28 to < 32 weeks         | < 1500g Very low birth weight | 15 to < 33 days | 2 to 3     |
| 3       | Very preterm             | Moderate     | 33 to < 64 days | 4 to 5     |
| 4       | 32 to < 34 weeks         | Late preterm | ≥ 64 days     |             |

Maturation Index = Scoring for (Gestational age at birth + Birth weight + Postnatal age) - Scoring for (Comorbidity)

HR and SpO2 during stroking to explore how many and which children showed a significant autonomic response. Again the combined HR, averaged over the 60 s of baseline and each following 10 s interval of the stroking condition, was used. We then tested for each child separately, whether the HR bins significantly decreased over time using linear regression with time as independent variable and heart rate bins as dependent variable. The same procedure was followed for SpO2. To further investigate differences in the infants’ maturing process and its subsequent influence on parasympathetic response to stroking touch, we computed a maturation index, which comprised the variables gestational age at birth, birth weight, postnatal age and the comorbidity score. The classification procedure is outlined in Table 2. Theoretically, the index ranged from 0 to 11 points. For further inferential statistics, we dichotomised the index based on the median of our sample ($Mdn = 4, Min = 2, Max = 8$). Hence, infants scoring less than 5 points were considered less mature. In order to examine, whether infant maturity assessed by our index had an impact on the change in heart rate (i.e. HR decrease, no change, HR increase) or change in SpO2 (i.e. SpO2 increase, no change, SpO2 decrease), we performed Fisher-Freeman-Halton Exact test.

### 3. Results

#### 3.1. Stroking velocity

Out of the 32 mothers, 31 chose velocities within the CT optimal range of 1–10 cm/s. Only one mother stroked marginally slower with a mean velocity of 0.84 cm/s in the first and 0.91 cm/s in the follow-up investigation (Fig. 2). In the first investigation, we observed a mean stroking velocity of 3.25 ± 1.87 cm/s and Bayes testing revealed moderate evidence for our Null Hypothesis, namely mothers’ mean stroking velocity not differing from 3 cm/s ($BF = 5.53$). Among the 21 mother-infant-dyads investigated again 2 to 15 days later, mean maternal stroking velocity was 2.69 ± 1.31 cm/s. Bayes testing again revealed moderate evidence ($BF = 3.44$) for our Null Hypothesis. Further, there is anecdotal evidence that maternal stroking velocity is stable between investigations ($BF = 2.52$).

#### 3.2. Autonomic response

Infants showed a significantly decreased mean heart rate during stroking compared to baseline ($F(1,39) = 5.7, P = 0.022, Semi-partial $R^2 = 0.13$; see Table 3). Fig. 3 shows that the heart rate fluctuated around baseline level initially. Thereafter, a steady decrease was observable. Hence, there was a significant main-effect of time intervals on heart rate.
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During stroking ($F(29,256) = 60.5, p < 0.001$, Semi-partial $R^2 = 0.87$). Post-hoc tests showed that the difference to baseline heart rate is significantly lower from 140 s onwards (see Fig. 3). We controlled for multiple comparisons using the Benjamini-Hochberg-Procedure.

In terms of peripheral oxygen saturation, there was no significant effect of mothers’ stroking touch, regardless of the model chosen ($F_{\text{postnatal age}[1,104]} = 0.4, p = 0.516; F_{\text{both covariates}[1,104]} = 0.4, p = 0.557$; see Table 3).

### 3.3. Individual level

In 35.8% of the total investigated cases, a significant decrease in heart rate was observed. However, heart rate did not significantly change in 52.8% and even significantly increased in 11.3% of investigations. Fig. 4 displays that among the infants who showed a decrease or no relevant change in heart rate, the different degrees of maturity are fairly distributed. However, children displaying an increase in heart rate in reaction to stroking touch are rather less mature. This observation remains anecdotal, as inferential testing did not reveal a significant association between dichotomised maturity and the change in heart rate ($p = 0.387$, Cramer’s $V = 0.207$).

Regarding SpO2, a significant increase was observed in 28.3% of investigated cases. There was no change in 50.9% and a SpO2 decrease in 20.8% of investigations (Supplementary Fig. S3). Fisher-Freeman-
Halton Exact test revealed no significant association between dichotomised maturity and change in SpO2 (p = 0.579, Cramer’s V = 0.159).

### 4. Discussion

In summary, mothers of preterm born children used velocities suitable for activating C-tactile afferents when stroking their offspring. In response, their preterm infants showed increased parasympathetic tone reflected in an average decrease in heart rate. However, the decrease appears stable only after 140s, indicating an immaturity of the CT projection pathway. Our data on the relation between infant maturity and changes in heart rate is also suggestive of a not yet fully developed CT system in preterm infants. Results are discussed in detail in the following paragraph.

Our observation that mothers utilize CT optimal stroking velocities, is consistent with findings in mothers and their term born children [65, 48]. After premature birth, however, the mother-infant relationship is shaped by separation. Due to hospitalisation and medical treatment, mothers of preterm infants experience limited and altered opportunities of physical contact with their child, which is critical for building emotional closeness [57]. Still, they target the CT system with appropriate stroking velocities emphasizing a strong behavioural pattern of maternal affective touch. These results are nevertheless limited, as this study was performed in a hospital with an established family-centred approach to infant care including additional voluntary parental education. The protocol was implemented in a hospital-based training programme and, therefore, does not fully represent natural stroking conditions. Further, the study was conducted after an average of 39 postnatal days hence not depicting entirely inexperienced mothers.

In line with Manzotti et al. [56], we observed a heart rate decrease in response to stroking touch in preterm infants. This effect appears to be quiet stable as, contrary to the experimenters of the aforementioned study, the mothers in our sample used a broader spectrum of CT-suited velocities. We were further able to replicate this beneficial effect of CT touch in a sample of preterm infants with a lower mean gestational age at birth (M=29.41 weeks vs M=33.4 weeks) who, on the other hand, were exposed to more typical and atypical postnatal experiences, including medical interventions, due to a longer hospital stay. By investigating a younger and more heterogeneous group of preterm infants, and choosing mothers themselves to deliver CT touch, we achieve higher external validity. Our findings are still subject to methodological limitations as we did not interrupt maternal stroking and thus face variations in the duration of tactile interaction. Although we observed a decrease in heart rate compared to baseline, the lack of a tactile control condition also limits our results. However, Manzotti et al. [56] have already shown that changes in heart rate were only found in response to stroking and not static touch, which makes our approach admissible in the context of these results. Taken together, the data show that CT-targeted stimulation in preterm infants enhances the parasympathetic tone, possibly by fostering interoception and allostatics.

Our explorative time pattern analysis of heart rate during stroking touch exceeds previous analyses and provides new thought-provoking impulses. In experimental conditions, CT touch is commonly delivered for a short period of time (e.g. 10 to 30 s) inducing immediate physiological responses. For instance, Fairhurst et al. [50] detected a heart rate decrease in 9-month-old infants during ten seconds of CT optimal touch. In comparison, we report a delayed heart rate response to CT touch in preterm infants reaching a stable deviation from baseline only after 140 s of stroking. This observation is consistent with data presented by Manzotti et al. [56] showing the maximum change in heart rate after 180 s of dynamic touch.

There are two possible explanations for the delayed autonomic effect of CT touch in preterm infants. On the one hand, it can be hypothesized that CT-afferents and their higher order projection neurons to the insular cortex are still poorly developed after preterm birth. The sense of touch is among the earliest sensory modalities to develop with somatosensory neurons arising from the neural crest and undergoing transcription factor-dependent specification within the first trimester of pregnancy [66]. Already early on, small diameter fibres, such as C fibres, proliferate in genetically ordered temporal and spatial association with lamina I neurons of the dorsal root ganglion, forming connections to second order neurons of an afferent interoceptive pathway [18]. Nevertheless, recent animal data show that embryonic somatosensory neurons in mice pass a transcriptionally unspecialized stage co-expressing genes that are mutually exclusive in postnatal neurons which is indicative of ongoing maturation [67]. Although it is unclear yet, how this finding translates into human development, it seems at least possible that maturation of CTs is not completed in the third semester of pregnancy.

On the other hand, the delayed autonomic reaction might be caused by immature connectivity of the cortical networks in which CT-afferents feed. As described, there is relevant anatomical overlap of the central processing of CT touch and the allostatic-interoceptive network. However, connectivity of core networks (e.g. DMN and SN) and hubs is still evolving during the third trimester of pregnancy and post term birth [23]. Arzt et al. [68] further propose that the development of the central nervous system’s predictive nature requires postpartum experience and therefore a neonate’s sensory, social and interoceptive sensations are dominated by prediction errors shaping the neural circuits. These developmental processes are likely vulnerable to the stress of premature birth and the impact of a defiant extra-uterine milieu associated with subsequent hospitalisation. Due to hospitalisation, the opportunity for tactile mother-infant interaction is limited and altered in its character. Hence, the acquired predictive models may not match the natural interaction and maternal CT-touch may initially result in a prediction error. The delayed autonomic response to maternal stroking touch could therefore represent the organism’s effort to adapt its model to a social stimulus that feeds into its regulatory system by recruiting a network that is itself still immaturely connected. This is supported by our data on maturational differences, as a maladaptive increase in HR is rather seen in more immature children.

In contrast to Manzotti et al. [56], we did not observe a relevant change in blood oxygenation in response to CT-touch. On the one hand, this can be explained by a ceiling effect, as the mean SpO2 during baseline period is already in an optimal range (M=96.36% ± 2.5 SD). On the other hand, the increase in oxygenation due to increased parasympathetic tone possibly succeeds the changes in HR and may therefore not be represented in our data. This interpretation is again in line with Manzotti et al. [56], as the maximum change in SpO2 is seen during post touch period in this study.

Taken together, our study showed that maternal stroking promotes parasympathetic tone in preterm infants. On an individual level, this beneficial effect is observed three times more often than a possible adverse effect in the form of an increase in heart rate. Our findings suggest that such intervention does not pose a risk of increasing HR in more mature preterm infants, but may also benefit more immature infants when closely monitored. Furthermore, our data indicate that the typical response cascade to CT-stimulation is not fully developed in preterm infants. Further studies may shed light on the developmental window of regulatory responses to CT-touch by including children of a younger gestational age earlier post birth and establishing a longitudinal design including a tactile control condition that does not primarily target the CT-pathway.

Our findings highlight the positive impact of physical closeness and touch in the care of preterm infants. CT-touch-based interventions have the potential to complement already well-established practices such as Kangaroo Care, especially in cases where Kangaroo Care is not feasible. The natural and intuitive use of CT optimal stimulation in maternal tactile interaction makes such interventions highly feasible in clinical care. Our study has provided preliminary indications in this regard. However, due to the lack of a control condition and the artificial setting, further studies are needed for a clear recommendation.
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Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability
Participants of this study did not agree for raw data to be shared. Due to the sensitive nature of data acquired in this research, data is only available upon reasonable request.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2022.113991.

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