PREMATURITY AND THE PHYSIOLOGY OF BONDING

A scientific perspective on love

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de rector magnificus prof.dr.ir. F.P.T. Baaijens, voor een commissie aangewezen door het College voor Promoties, in het openbaar te verdedigen op woensdag 24 januari 2018 om 16:00 uur

door

Deedee Roselie Kommers

geboren te Eindhoven

Dit proefschrift is goedgekeurd door de promotoren en de samenstelling van de promotiecommissie is als volgt:

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Het onderzoek dat in dit proefschrift wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.

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Worldwide, one in every ten babies is born prematurely. Later in life, the majority suffers from minor morbidities, such as academic underachievement, behavioral problems, and deficits in higher-order neurocognitive functions. As stated in **Chapter 1**, these outcomes can be improved by enhancing parent-infant bonding. The goal of this project was therefore to enhance parent-infant bonding in our NICU by providing insight into the physiology of bonding.

As described in **Chapter 2**, bonding is the process of co-regulation: when an organism assists another organism in the regulation of the internal environment. In other words, assistance in maintaining homeostasis. In order to support each other, organisms need to be able to read the other's internal state, which is enabled by the expression of physical parameters, or cues. In a NICU, maximal cue-exchanging, i.e. maximal co-regulation occurs during periods of skin-to-skin contact, also referred to as Kangaroo care. Several important cues or cue-modulators have been reported. Three of them are oxytocin, heart rate variability, and behaviors. Therefore, we executed studies to measure these three elements during Kangaroo care and compare the results to baseline.

We first performed a study to investigate the feasibility of measuring oxytocin unobtrusively in preterm infants. This study is presented in **Chapter 3.** The saliva of preterm infants was collected prior to and during 30 Kangaroo care sessions using cotton swabs. The saliva was then pooled to acquire vials with sufficient volumes to measure oxytocin using a radio-immuno assay. The obtrusiveness of the collections was measured with a Likert scale. The obtained saliva was sufficient to fill six vials; three containing saliva collected at baseline and three containing saliva collected during Kangaroo care. Oxytocin was detectable in all six vials. Based on the Likert-scores, we concluded that oxytocin was measured unobtrusively in the pooled saliva of preterm infants both before and during Kangaroo care and it could thus be investigated as a biomarker in subsequent studies.

We therefore performed a second study, measuring oxytocin in preterm infant twins during Kangaroo care and comparing results to baseline. In addition, we measured the infants' state

of comfort prior to and during the saliva collections, as well as the intensity of the parent-infant interaction before and during Kangaroo care using previously developed Likert-scales. Results are presented in **Chapter 4**. During Kangaroo care, oxytocin was significantly lower compared to baseline (mean 1.39 pg/ml (SD 0.58 pg/ml) versus 2.40 pg/ml (SD 1.64 pg/ml), p = 0.03). Furthermore, discomfort at baseline and parent-infant interaction intensity together significantly influenced OT responses (p = 0.006). For that reason, we attributed the remarkable response of the oxytocin system to a stressful baseline environment in combination with differences between preterm infant and adult physiology.

This was supported by our findings on heart rate variability presented in **Chapter 5.** Instead of increasing, which is the heart rate variability response to improved regulation seen in adults, heart rate variability immediately decreased due to parental co-regulation during Kangaroo care. Eight features of heart rate variability were used to visually and statistically compare pre-Kangaroo care, during-Kangaroo care and post-Kangaroo care periods. Two of these features were newly developed for preterm infants specifically, in order to capture heart rate variability caused by instability of the cardiorespiratory system due to immaturity of regulatory mechanisms. These features showed that the decrease in heart rate variability was caused by a decrease in regulatory instability during Kangaroo care. Heart rate variability appeared a useful parameter to assess (co-) regulation in preterm infants.

In **Chapter 6**, regulation in preterm infants was studied using behavioral observations. A qualitative study in which nurses in training observed mother-infant Kangaroo care sessions showed that infants appeared calm and asleep for most of the time. None of the infants cried. During interviews, mothers confirmed that their infants were more comfortable while kangarooing compared to when in the incubator. In addition, kangarooing increased the maternal experience of bonding. In the final part of our project, we therefore strived to simulate or support the effect of Kangaroo care. However, first we discussed the consequences of suboptimal perinatal bonding, because these are less frequently addressed in literature than the consequences of other threatening unnatural stimuli.

We reviewed the literature to describe the physiological impact of suboptimal postnatal bonding, as can be seen in **chapter 7**. That chapter integrates information from animal and clinical studies on the adverse hormonal, epigenetic and neuronal consequences

of suboptimal bonding, and emphasizes that many clinicians do not attribute sufficient importance to these consequences despite the fact that they can be reversed by interventions aimed at enhancing bonding.

In addition, we examined the effect of suboptimal antenatal bonding on infant crying behavior and demonstrated that mothers with lower antenatal bonding scores were more likely to report their infant to cry excessively at the age of six weeks. These results are presented in **Chapter 8.** In total, 894 women were included of whom 47 reported their infant to cry excessively (5.3%). Antenatal bonding scores were significantly related to the reporting of crying behavior, even after adjustment for relevant variables ($p = 0.02$). Several limitations need to be taken into account when interpreting these results based on maternal reports of bonding and crying behaviors. However, the findings support enhancement of both pre- and postnatal bonding to improve perinatal outcomes.

We therefore assigned students from the Eindhoven University of Technology to develop devices aimed at enhancing bonding and performed a literature survey to generate an overview of already existing strategies and technologies to enhance bonding, which is presented in **chapter 9**. Consecutively, we chose two suitable devices, a breathing mattress called the BabyBe and a smart incubator blanket called Hugsy, to assess whether they could simulate or support the effect of Kangaroo care in clinical studies. Those studies are discussed in **Chapter 10** and **Chapter 11**.

An observational within-subject study design was performed to compare BabyBe- and KC periods in 20 preterm infants. Similar to in our previous study, heart rate variability decreased during KC and after KC due to improved regulatory stability. In addition, the simulated chest motions and heartbeat sounds during BabyBe activity also tended to reduce both heart rate variability and regulatory instability, but these effects were not significant.

A successive observational within-subject study design was performed to analyze two other methods of simulating or supporting the effect of Kangaroo care in preterm infants. In one group of 20 preterm infants, Hugsy was used to expose infants to parental scent and heartbeat sounds prior to and after Kangaroo care, and during transfers. Another group of 20 preterm infants was exposed to breathing motions and heartbeat sounds prior to and after Kangaroo

care sessions using the BabyBe. Days on which either one of the interventions was used to provide parental stimuli to preterm infants were compared to control days with regard to heart rate variability and comfort scores. COMFORTneo scores decreased significantly on days with parental stimuli, reflecting increased comfort. Furthermore, even though speculative, infants appeared to recover faster from the transfer back to the incubator as measured with heart rate variability. Overall, albeit short of statistically significant evidence, chapter 10 and 11 suggest that technological applications could be valuable for enhancing bonding in the future.

This conclusion and other findings were contemplated in the general discussion that is presented in **Chapter 12**. In summary, bonding is the process of co-regulation and aspects thereof can be measured in preterm infants during Kangaroo care, since the latter changes regulation significantly. This provides opportunities for enhancing bonding in NICUs. While technology might be valuable for this purpose in the future, increasing the duration of Kangaroo care itself appears most efficient. In our NICU, the average duration of Kangaroo care increased significantly over the course of this research project ($p < 0.001$).

ABOUT THE AUTHOR

Deedee Kommers was born in Eindhoven on December 7th, 1987. After finishing secondary school at the Lorentz Casimir Lyceum in Eindhoven in 2005, her fascination with the embryology, anatomy and physiology of the human body and mind drove her to study one year of Cognitive Artificial Intelligence and six years of Medicine at the Utrecht University. During these years, Deedee lived in Utrecht but continued to play hockey in the southern part of the Netherlands with the semi-professional first women's team of Were Di in Tilburg. After completing the elective part of the medical curriculum with courses focusing on neuroscience and psychobiology, she chose to do her final internship in one of the pediatric departments of the Wilhelmina Children's Hospital. The period of childhood has always been of particular interest to Deedee, due to its major impact on body and mind. When the Eindhoven University of Technology (TU/e) gave her the chance to study physiological processes in the earliest stages of life, namely in infants born prematurely, Deedee therefore did not hesitate to grab this opportunity and she moved back to Eindhoven in 2013. During this project, Deedee won the 2016 Dutch Neonatal Chiesi Fellow Award, was invited as a keynote speaker to the Gravens conference, and won the 2017 Maxima Medical Centre Scientific Evening Award. The results of the project are presented in this dissertation, titled 'Prematurity and the Physiology of Bonding'. Currently, Deedee is still studying prematurity as a postdoctoral researcher at TU/e, while also working as an independent consultant for projects aimed at enhancing health care from a bonding perspective.