

Olfactory Stimulation in Premature Neonates: The Relevance of Early Experience

Misha Croes, Wei Chen, Loe Feijs

Department of Industrial Design

Eindhoven University of Technology

Den Dolech 2, 5612 AZ Eindhoven, the Netherlands

E-mail: {m.j.g.croes, w.chen, l.m.g.feijs}@tue.nl

Sidarto Bambang Oetomo

Neonatal Intensive Care Unit

Maxima Medical Center

De Run 4600, 5500 MB Veldhoven, the Netherlands

E-mail: s.bambangoeotomo@mmc.nl

Abstract – While in the womb, a fetus experiences olfactory stimulation by means of the surrounding amniotic fluid. This prepares the fetus’s olfactory system to its postnatal life. If a child is born prematurely, it is deprived of this preparation because it is hospitalized in an incubator in the Neonatal Intensive Care Unit. This sudden transformation from the womb to an overly stimulating hospital environment imposes increased stress to the vulnerable neonates. This paper discusses various studies that show the importance of early olfactory stimulation, an approach to improving olfactory stimulation and protection, and suggests examples of implementing these improvements in future research and design.

Keywords –NICU; early experience; odors; stress; olfaction.

I. INTRODUCTION

Of the total amount of childbirths about 11% (USA) is born premature [1]. Recent advancements in neonatal care have ensured that these prematurely born infants have an ever rising survivability rate [2]. Despite these advancements, prematurely born infants are prone to develop long term problems due to exposure to stressful environmental stimuli (light, noise, smells, etc.) [3].

Most of these prematurely born infants will, immediately after childbirth, be placed in an incubator at hospital’s Neonatal Intensive Care Unit (NICU). Over the years extensive research about the impact of premature childbirth has shown that these children, and their parents, go through quite a stressful period [4][5]. Because of the premature exposure to a postnatal environment, external stimuli are perceived as extra stressful and painful by prematurely born babies compared to their full term counterparts [6].

In order to support during their stay in the NICU various innovations have been devised. Among these innovations are for instance a sound system for the NICU [7], the Babybloom incubator [8], the sound awareness system SoundEar [9], the Smart Jacket [10], and the remote cuddling FamilyArizing system [11] are all developed with the intention to improve the NICU experience for parents and their children.

We concluded, however, that none of these interventions consider the olfactory development and environmental impact on prematurely born infants.

Through this paper, we provide not only a review of relevant literature, but we also draw attention to the importance of early exposure to odors in prematurely born infants. We want to highlight the importance of both protecting neonates from stressful environmental odors as well as providing them with comforting parental odors in the NICU. Finally, we formulate various challenges future research might face.

II. OLFACTORY DEVELOPMENT

During fetal growth the first nasal tissue can be observed during week 7 or 8 of pregnancy [12]. The swallowing reflex is detectible from week 12 onwards and around 18 weeks gestational age nonnutritive sucking begins. Around the same time (week 17) the fetus is capable of tasting. Smelling however only starts in around gestational week 24 [13]. Coordinated sucking and swallowing are perceivable from gestational week 35 to 40 [13], the end of the final trimester. This means that the sense of smell is fully functional in prematurely born neonates in the NICU (24> weeks of gestational age).

In humans, the receptors for the olfactory system are located high in the nasal chambers in the epithelium in the nasopharynx or nasal cavity. These receptors are not only stimulated during inhalation (orthonasal route), but also when infants suck or when children and adults swallow (retro-nasal route) [13].

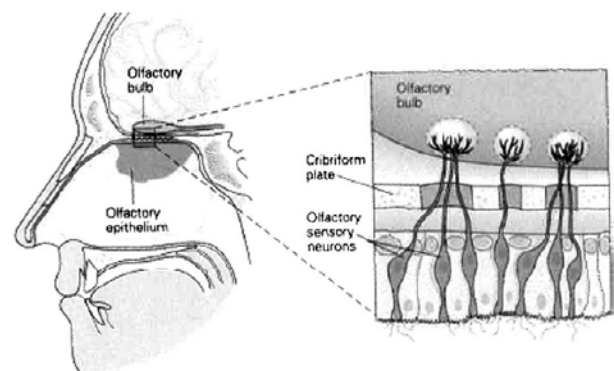


Figure 1. Nasal cavity [12].

From the nasal cavity olfactory neurons go through the cribriform plate to the olfactory bulb. Positioned directly underneath the prefrontal cortex, the olfactory bulb

transmits its signals to the olfactory cortex, which is located in the brain’s limbic system [12]. The pathways that go through the thalamus back to the orbitofrontal cortex are thought to be responsible for the perception and discrimination of odors [12]. Furthermore, olfactory information is communicated from the amygdala to the hypothalamus and to the hippocampus. These are thought to mediate the emotional and motivational elements of odor and many of the physiologic and behavior effects of scents [12].

III. STRENGTH OF MATERNAL ODOURS

Already in the womb neonates are fully capable of detecting and discriminating odors/flavors through their olfactory system starting at 24 weeks gestational age [13]. During the third trimester the child’s olfactory system is preparing for the future world it will live in by tasting parts of its mother’s diet through the amniotic fluid [14]. Extremely prematurely born neonates are deprived of this experience and are instead presented with new unfamiliar environmental odors inside the NICU. Various researches have shown, however, that prematurely born infants prefer maternal odors over these new environmental odors.

In their study, Schaal et al. [15] showed, for instance, that prematurely born infants are capable of distinguishing their mother’s body and breast milk odor from other mother’s odor samples. A test by Russel et al. [16] showed that mothers show similar capabilities of recognizing their own baby. Furthermore research concludes that babies show positive head turning and appetitive mouthing if presented with flavors which were part of their mother’s diet during pregnancy [17][18]. This shows that during pregnancy the fetus already tastes and smells their mother’s diet, providing them an initial preference immediately after birth [19]. Similar tests show that babies calm down faster after smelling maternal breast milk [20].

Furthermore it has been shown show that neonates have less apnea without bradycardia and less apnea with severe bradycardia if presented with a pleasant odor [21]. In addition it is demonstrated that neonates cry less during separation from their parents if presented with amniotic fluid odor [14].

Concerning non-maternal odors in the use of pain relief, Goubet et al. [22] introduced vanillin to premature neonates. They have shown that infants showed less crying if presented with this familiar odor. Some aromas seem to distract infants from slightly painful stimuli. However, they are not distracting enough for more painful procedures [23].

During our literature study, we were surprised to find no literature concerning design or procedural interventions for communicating paternal odors to prematurely born infants. Although the effects in literature are quite promising, as far as we know, nobody has tried to specifically develop systems or products that provide the possibility of communicating paternal odors to the child. Nowadays, the

only practice that enables odor communication in the NICU is the use of odor cloths. Worn by mothers, these pieces of fabric are left next to the child in the incubator to provide a more comfortable incubator experience. However, these cloths need to be washed often and don’t provide any indication if they still contain maternal odors or not.

Due to the observation of this gap in research and development within the NICU, we identify a new research niche. In this paper, we present our vision of how to approach the development and implementation of paternal odor communication in the NICU.

IV. APPROACH

Traditionally the means of relieving stress and pain in neonatal patients was to provide them with anesthetics and/or sedatives. In recent years, research has shown that there are other means of providing pain and stress relief in prematurely born neonates. In this section, we would like to take the opportunity to propose an overview of the overall approach in neonatal environmental stress relief.

The main approach in the NICU, in order to reduce environmental stress relief, is the reduction of environmental stimuli. We like to refer to this as “phase 1” in the overall process. In order to achieve this we observed redesigns of the NICU architecture (e.g., single patient rooms), its apparatuses (e.g., incubator), providing the neonate with protection (e.g., goggles for neonate) and educating both medical practitioners and parents (e.g., the NIDCAP program).

The main goal of these interventions is to ensure that stressful environmental stimuli are reduced to, what we like to call, the “no-stress-line” (see Figure 2). This no-stress-line depicts the pivot point where all stressful environmental stimuli no longer have a stressful effect on the neonate.

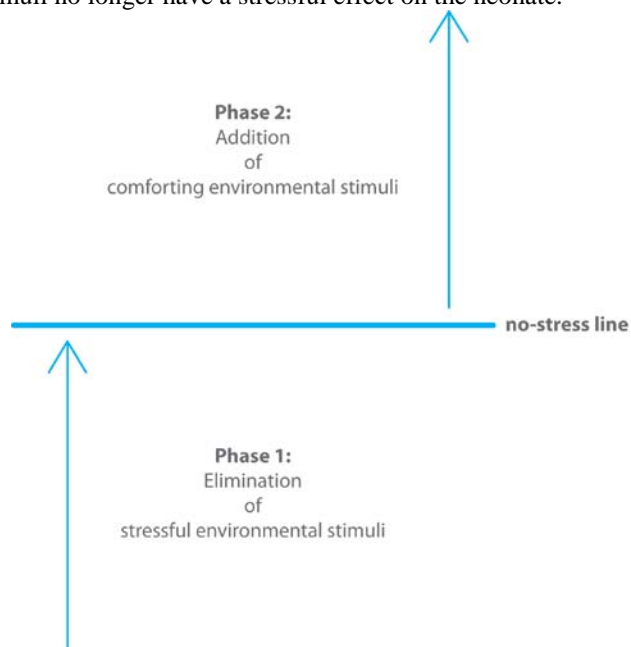


Figure 2. Approach diagram.

From the no-stress-line onward we come to what we like to call “phase 2”. This area depicts environmental stimuli that provide the neonate with comforting environmental stimuli. Although the child might not experience stress, the addition of comforting environmental stimuli in phase 2 ensures a rise in the quality of the NICU experience for neonates.

Overall, we see in presented studies that such interventions have a favorable influence on neonates in the NICU.

For instance, the sound system developed by Panagiotidis and Lahav [7] is specifically designed for the NICU to communicate maternal sounds inside the incubator. Resulting tests with the system have shown that the presentation of maternal heartbeat and voice produce short term improvements on the physiological stability of preterm babies [24]. Furthermore, Doheny et al. [25] showed a reduced frequency in apnea and bradycardia in premature neonates through the presentation of the same maternal sounds in the NICU.

Concerning the implementation of comforting stimuli into the NICU, we like to place phase 1 chronologically prior to phase 2. If stressful environmental stimuli are not removed, there is no need for implementing comforting stimuli in phase 2. This is because, usually, the comforting stimuli have to be presented in such quantities that they themselves become stressful environmental stimuli.

In the following sections of this paper, we present how we envision the implementation of the here mentioned approach on the early olfactory experience of neonates.

V. CLINICAL IMPLICATIONS

We are convinced that a number of measures could be taken to improve the early olfactory experience of premature infants. The first step would have to be to identify stressful environmental olfactory stimulants in the vicinity of premature neonates. Although no conclusive study has been found, detergent and adhesive remover are proposed as unpleasant odors to premature neonates [26]. In order to provide a more concrete answer on which environmental odors are stressful for neonates, we believe more dedicated research is needed.

First, research should determine which of the odors in the vicinity of neonates are classified as stressful for the neonate. Secondly it should be investigated how frequent a neonate is, in general, exposed to these odors. The logical next step would be to eliminate the exposure of these stressful odors to the child. This can be done by means of providing the child with protection to the odors or looking for ways to remove or replace odorous chemicals.

In phase 2, the child should be presented with comforting environmental (paternal) odors, odors that have shown their favorable influence on premature neonates.

Here, we like to propose various suggestions about what we believe are viable implementations in order to improve

early olfactory experience for prematurely born infants in the NICU.

VI. PHASE 1

First, we would like to highlight opportunities that are expected to provide less frequent experience of stress.

A. Identification of Stressful Odours

Before the protection of prematurely born infants to stressful environmental odors can start, the odors should first be identified. A survey of 99 neonatal units in France resulted in nine groups of products with a total of 76 distinct commercial preparations [27].

Overall, depending on their respiratory support, preterm neonates were on average exposed 1320-1800 times to chemical unpleasant odors during their first month of life of neonatal care [27].

Bartocci et al. [26] described a method of measuring the impact of odors on prematurely born neonates by means of near-infrared spectroscopy. In their study, they describe that the presentation of a pleasant odor (vanillin) ensures an increase in blood flow in the orbitofrontal cortex, while the presentation of a unpleasant odor (detergent and adhesive remover) ensures a decrease of blood flow in the orbitofrontal cortex [26].

B. Removal of/protection against stressful odours

The moment when odors are classified as stressful to premature neonates, it is time to consider means of removing them or providing protection against them.

First of all, it should be considered if odorous materials and chemicals could be replaced with less obtrusive alternatives.

Another means to reduce the exposure of stressful environmental odors to neonates could be changing staff behavior. For instance, it has been shown that by means of using ethanol-based hand disinfection, medical practitioners can ensure a high variable concentration of ethanol vapors in incubators [28]. Although one might search for non-ethanol based disinfectant, it is also plausible to ensure that medical practitioners ensure a longer evaporation time between the application of disinfectant and manipulations in the incubators [28].

By reconsidering behaviors of both parents and medical practitioners, the exposure to stressful odors might be diminished as well.

VII. PHASE 2

Sequential to Phase 1, it is important to proceed into Phase 2; during this phase comfortable stimuli are made available to the child in the NICU.

A. Support Kangaroo Care

Kangaroo Care (KC) is a well implemented method in the NICU [29][30]. During KC, the neonate is placed onto one of the parent’s naked chest in a supine position. During

KC the parent's body provides the child with warmth, protection and familiar odors. Especially when the child is on the mother's chest, the child is able to smell familiar odors from the mother's chest and nipples.

This early presentation of familiar odors is expected to be an important factor in the child-parent bonding [31].

B. Introduce maternal odors in the NICU

Earlier in this article, we showed the importance of maternal odor presentation to prematurely born infants in the incubator. Until the current time however no specifically designed apparatus could be found that is capable of providing maternal odors to prematurely born infants. We believe it would be highly beneficial to develop such a scent dispenser for the NICU in order to provide neonates with maternal odors.

C. Early food experience

In their 2011 article Lipchock et al. [13] describe the importance of early exposure to food related odors and tastes for the quality of food learning in neonates. As a fetus the child would be exposed to elements of the maternal diet through swallowing the amniotic fluid. As a premature neonate, this experience is mostly lost.

It has been established that the cultural appreciation of food starts well before consuming solid foods [13]. This corresponds with research performed by Marlier et al. [19], who show that a fetus already learns to appreciate tastes of their amniotic fluid in the womb as a preparation for foods outside the womb. Since prematurely born infants are usually tube fed, the taste of their food (usually maternal breast milk) is taken away from them.

Besides learning, a child might have of early food experiences, smelling and tasting food in itself also provides pleasure [12].

VIII. CHALLENGES IN ODOR RESEARCH IN THE NICU

During our process of thinking about and working on odor designs for the NICU, we came across various obstacles that we believe should be taken into account for future designs and development.

A. Odor library

First of all, there is the point where one odor is not the same for everybody. Since the olfactory bulb is closely positioned to the prefrontal cortex it is known that memories and odors are strongly connected [32].

As adults, we already have an extended "library of odors" at our disposal. We already have an immense amount of experiences with various odors. This helps us to interpret new odors better and ensures that odors are already linked to certain experiences. For prematurely born babies, this library is virtually empty.

Research both by Schleidt and Genzel [33] and Delaunay-El Allam et al. [34], for instance, showed that newly born babies are able to learn new scents and couple

them to the positive experience of being close to their mother. This means that there might also be a risk of connecting new odors to negative experiences. This risk that should be taken seriously.

B. Human body odours

The second major obstacle that researchers are likely to face while developing new odor communication designs for the NICU is the fact that you likely have to work with human odors. Human odors are as unique as a person's fingerprint and are, therefore, close to impossible to replicate artificially [35]. Furthermore, people go through cycles during which the content of their odors [36] and their perception of odors changes [32]. For instance, the menstrual cycle of a woman determines the odor strength and type of a woman [37]. This together with our diets [38] ensures that our personal odor varies over time. This all makes it quite difficult pinpoint which variables impact the experience of people if presented with human body odors.

C. Anxiety odours

Finally, there is the point where even maternal odors could ensure stress in neonates. Various researches show that human sweat is capable of communicating anxiety among humans [39][40][41][42]. Because the NICU is quite a stressful environment for parents as well, researchers run the risk of capturing and communicating anxiety related odors from the parents to the child. Unfortunately, no research could be found that further supports this hypothesis specifically in the NICU.

IX. CONCLUSION AND FUTURE WORK

While in the womb, a fetus experiences a specific olfactory and gustatory stimulation. However, if prematurely born, infants are deprived of this experience and are exposed to a highly stimulating environment of, among others, lights, sounds and odors. Therefore, the long hospitalization of prematurely born infants in the NICU is likely to have adverse effects on the long term development of these neonates. An extensive bundle of research suggests that the presentation of maternal/paternal odors to prematurely born infants has a positive effect on both the stress reduction as well as comforting of babies in the NICU. However, both in literature and in practice, hardly any interventions can be found which implement these insights on olfactory stimulation. We believe that as a first step for implementation, emphasis should be put on the removal of stressful odors (Phase 1) and sequentially implementation of comforting odors (Phase 2) in the NICU. The implementation of these comforting will probably encounter various obstacles. Since the child has a virtually empty "odor library", researchers run the risk of teaching babies new scents and coupling them to negative experiences. Furthermore, since we are talking mainly about human body odors, there is still a large portion of research need on the capturing and preservation of these odors. We

believe that it is possible to design and develop systems that will overcome these obstacles and provide better care to neonates and their parents in the NICU.

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XI. REFERENCES

- [1] R. Goldenberg and D. Rouse, “Prevention of premature birth,” *New England Journal of Medicine*, 1998.
- [2] D. Wilson-Costello, “Is there evidence that long-term outcomes have improved with intensive care?,” *Seminars in fetal & neonatal medicine*, vol. 12, no. 5, pp. 344-354, Oct. 2007.
- [3] S. Blackburn, “Environmental impact of the NICU on developmental outcomes,” *Journal of Pediatric Nursing*, vol. 13, no. 5, pp. 279–289, Oct. 1998.
- [4] Y. M. Ahn and N. H. Kim, “Parental Perception of Neonates, Parental Stress and Education for NICU Parents,” *Asian Nursing Research*, vol. 1, no. 3, pp. 199–210, 2007.
- [5] E. Cignacco et al., “The efficacy of non-pharmacological interventions in the management of procedural pain in preterm and term neonates. A systematic literature review,” *European journal of pain (London, England)*, vol. 11, no. 2, pp. 139-152, Feb. 2007.
- [6] R. E. Grunau, L. Holsti, and J. W. B. Peters, “Long-term consequences of pain in human neonates,” *Seminars in fetal & neonatal medicine*, vol. 11, no. 4, pp. 268-275, Aug. 2006.
- [7] J. Panagiotidis and A. Lahav, “Simulation of prenatal maternal sounds in NICU incubators: a pilot safety and feasibility study,” *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, vol. 23 Suppl 3, pp. 106-109, Oct. 2010.
- [8] www.babybloomhealthcare.com, 14-09-2012
- [9] <http://soundear.com/>, 14-09-2012
- [10] S. Bouwstra, W. Chen, L. Feijs, and SB, “Smart jacket design for neonatal monitoring with wearable sensors,” *2009 Body Sensor*, 2009.
- [11] M. Croes, S. Bambang Oetomo, L. Feijs, Eds., “Designing remote connectedness between parents and their premature newly born – a design proposal”, *Neonatal Monitoring Technologies: Design for Integrated Solutions*. Eindhoven: IGI Global. 2012. 1-536. Web. 14 Sep. 2012. doi:10.4018/978-1-4666-0975-4
- [12] J. V. Browne, “Chemosensory Development in the Fetus and Newborn,” *Newborn and Infant Nursing Reviews*, vol. 8, no. 4, pp. 180-186, Dec. 2008.
- [13] S. V. Lipchock, D. R. Reed, and J. a Mennella, “The gustatory and olfactory systems during infancy: implications for development of feeding behaviors in the high-risk neonate,” *Clinics in perinatology*, vol. 38, no. 4, pp. 627-641, Dec. 2011.
- [14] H. Varendi, K. Christensson, R. H. Porter, and J. Winberg, “Soothing effect of amniotic fluid smell in newborn infants,” *Early human development*, vol. 51, no. 1, pp. 47-55, Apr. 1998.
- [15] B. Schaal, R. Soussignan, and L. Marlier, “Olfactory cognition at the start of life: The perinatal shaping of selective odor responsiveness,” *Processing*, pp. 421-440, 2002.
- [16] M. Russell, T. Mendelson, and H. Peeke, “Mother’s identification of their infant’s odors,” *Ethology and Sociobiology*, vol. 4, no. 1, pp. 29-31, 1983.
- [17] R. Schaal, B., Marlier, L., Soussignan, “Human Foetuses Learn Odours from their Pregnant Mother’s Diet,” *Chemical Senses*, vol. 25, no. 6, pp. 729-737, Dec. 2000.
- [18] J. A. Mennella, C. P. Jagnow, and G. K. Beauchamp, “Prenatal and postnatal flavor learning by human infants,” *Pediatrics*, vol. 107, no. 6, p. e88, 2001.
- [19] L. Marlier, B. Schaal, and R. Soussignan, “Neonatal responsiveness to the odor of amniotic and lacteal fluids: a test of perinatal chemosensory continuity,” *Child development*, vol. 69, no. 3, pp. 611-623, Jun. 1998.
- [20] S. Nishitani et al., “The calming effect of a maternal breast milk odor on the human newborn infant,” *Neuroscience research*, vol. 63, no. 1, pp. 66-71, Jan. 2009.
- [21] L. Marlier, C. Gaugler, and J. Messer, “Olfactory stimulation prevents apnea in premature newborns,” *Pediatrics*, 2005.
- [22] N. Goubet, C. Rattaz, V. Pierrat, A. Bullinger, and P. Lequien, “Olfactory experience mediates response to pain in preterm newborns,” *Developmental psychobiology*, vol. 42, no. 2, pp. 171-180, Mar. 2003.
- [23] B. Golianu, E. Krane, J. Seybold, C. Almgren, and K. J. S. Anand, “Non-pharmacological techniques for pain management in neonates,” *Seminars in perinatology*, vol. 31, no. 5, pp. 318-322, Oct. 2007.
- [24] L. Doheny, S. Hurwitz, R. Insoft, S. Ringer, and A. Lahav, “Exposure to biological maternal sounds improves cardiorespiratory regulation in extremely preterm infants,” *The journal of maternal-fetal & neonatal medicine the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, no. November 2011, pp. 1-4, Feb. 2012.
- [25] L. Doheny, J. A. Morey, S. A. Ringer, and A. Lahav, “Reduced frequency of apnea and bradycardia episodes caused by exposure to biological maternal sounds,” *Pediatrics international official journal of the Japan Pediatric Society*, vol. 54, no. 2, pp. e1-3, Apr. 2012.
- [26] M. Bartocci, J. A. N. Winberg, G. Papendieck, T. Mustica, G. Serra, and H. Lagercrantz, “Cerebral Hemodynamic Response to Unpleasant Odors in the Preterm Newborn Measured by Near-Infrared Spectroscopy,” vol. 50, no. 3, pp. 324-330, 2001.
- [27] P. Kuhn, D. Astruc, J. Messer, and L. Marlier, “Exploring the olfactory environment of premature newborns French survey of health care and cleaning products used in neonatal units,” no. January 2008, pp. 334-339, 2011.
- [28] C. Paccaud, D. Vernez, M. Berode, and N. Charri, “Hand-disinfectant alcoholic vapors in incubators,” vol. 4, pp. 15-19, 2011.
- [29] N. Charpak et al., “Kangaroo Mother Care: 25 years after,” *Acta paediatrica (Oslo, Norway 1992)*, vol. 94, no. 5, pp. 514-522, May 2005.
- [30] [S. Ferber and I. Makhoul, “The effect of skin-to-skin contact (kangaroo care) shortly after birth on the neurobehavioral responses of the term newborn: a randomized, controlled trial,” *Pediatrics*, 2004.
- [31] R. H. Porter and J. Winberg, “Unique salience of maternal breast odors for newborn infants,” *Neuroscience and biobehavioral reviews*, vol. 23, no. 3, pp. 439-449, Jan. 1999.
- [32] R. S. Herz and T. Engen, “Odor memory: Review and analysis,” *Psychonomic Bulletin & Review*, vol. 3, no. 3, pp. 300-313, Sep. 1996.
- [33] M. Schleidt and C. Genzel, “The significance of mother’s perfume for infants in the first weeks of their life,” *Ethology and Sociobiology*, vol. 11, no. 3, pp. 145-154, May 1990.

- [34] M. Delaunay-El Allam, L. Marlier, and B. Schaal, "Learning at the breast: preference formation for an artificial scent and its attraction against the odor of maternal milk.," *Infant behavior & development*, vol. 29, no. 3, pp. 308-321, Jul. 2006.
- [35] D. J. Penn et al., "Individual and gender fingerprints in human body odour.," *Journal of the Royal Society, Interface / the Royal Society*, vol. 4, no. 13, pp. 331-340, Apr. 2007.
- [36] C. J. Wysocki and G. Preti, "Facts, fallacies, fears, and frustrations with human pheromones.," *The anatomical record. Part A, Discoveries in molecular, cellular, and evolutionary biology*, vol. 281, no. 1, pp. 1201-1211, Nov. 2004.
- [37] A. Rikowski and K. Grammer, "Human body odour, symmetry and attractiveness.," *Proceedings. Biological sciences / The Royal Society*, vol. 266, no. 1422, pp. 869-874, May 1999.
- [38] J. N. Lundström and M. J. Olsson, "Functional neuronal processing of human body odors.," *Vitamins and hormones*, vol. 83, no. 10, pp. 1-23, Jan. 2010.
- [39] K. Haegler et al., "No fear no risk! Human risk behavior is affected by chemosensory anxiety signals.," *Neuropsychologia*, vol. 48, no. 13, pp. 3901-3908, Nov. 2010.
- [40] A. Prehn-Kristensen et al., "Induction of empathy by the smell of anxiety.," *PloS one*, vol. 4, no. 6, p. e5987, Jan. 2009.
- [41] D. Rubin, Y. Botanov, G. Hajcak, and L. R. Mujica-Parodi, "Second-hand stress: inhalation of stress sweat enhances neural response to neutral faces.," *Social cognitive and affective neuroscience*, Jan. 2011.
- [42] W. Zhou, P. Hou, Y. Zhou, and D. Chen, "Reduced recruitment of orbitofrontal cortex to human social chemosensory cues in social anxiety.," *NeuroImage*, vol. 55, no. 3, pp. 1401-1406, Apr. 2011.