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**PSYCHOBIOLOGICAL FOUNDATIONS OF EARLY SENSORY-MOTOR DEVELOPMENT AND IMPLICATIONS
FOR NEONATAL CARE**

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I. Introduction

In mammals, somatosensation and chemosensation are the first sensory systems by which the developing organism becomes acquainted with its environment (Segond, 2008). Somatosensory perception includes tactile, thermal and pain perception through cutaneous receptors, as well as postural and movement information through muscle and tendon receptors. Chemosensory perception includes the olfactory, gustatory and trigeminal systems, involved in nutrition, social interactions, and emotional reactivity and regulation. In humans, these two systems emerge *in utero* and prepare the foetus for neonatal life. Because of this developmental heterochrony, they are the foundation of cognitive and affective development (Humphrey, 1970; Lecanuet & Schaal, 1996; Schaal, 2000; Schaal, Hummel, & Soussignan, 2004). Although the importance of these ontogenetically and phylogenetically earlier systems for individual development has been acknowledged for a long time, they are the least studied in the human neonate, compared with later modalities such as audition (Fitzgerald & Andrews, 1994; Streri, Hevia, Izard, & Coubart, 2013). Clinicians dealing with premature and other fragile newborns have initiated a regain of interest for these perceptions by suggesting therapeutic interventions in these modalities, but their efforts are impeded by the lack of fundamental knowledge that could drive their hypotheses and frame their observations. In this chapter, we propose a framework to study neonatal psychobiological development focusing on tactile and chemical senses. We want to emphasize how these senses are crucial modalities to understand very early development, and how they can bring rational arguments and testable hypotheses to the growing field of sensory therapies and developmental care in preterm and term neonates. We hope that these modalities will attract more attention from both researchers and clinicians in the future.

II. Prenatal development of somatosensory and chemosensory perceptions

a. Somatosensation

The somatosensory system underlies the perception of a wide range of stimuli. It can be subdivided into four functionally distinct subsystems: tactile perception, proprioception, nociception and thermoception. Each has a specific set of peripheral receptors — in the skin, muscles and joints — and neural pathways (for a complete review see: Abaira & Ginty, 2013). The receptors can be distinguished according to the type of stimulus to which they respond, and according to their anatomical situation (exteroceptors or interoceptors). The tactile subsystem is sensitive to the size, shape and texture of objects and their movement on the skin. Four types of tactile cutaneous receptors, distributed throughout the body, were identified. The Merkel discs and the Meissner corpuscles are receptors involved in discriminative touch. They have small and well-defined cutaneous receptive fields and are located in the superficial layers of the skin (dermal-epidermal

junction). The Ruffini receptors and the Pacini corpuscles, located in the deeper layers of the skin (dermis) and the subcutaneous tissue, have wide and blurry receptive fields and are involved in non-discriminative touch. Proprioception refers to the perception of one's body position and movements, and depends on mechanoreceptors in muscles and joints. Neuromuscular spindles are sensitive to muscle length, articular receptors are sensitive to the position of the joints, and golgi tendon organs are sensitive to muscle tension. Both tactile and proprioceptive information are conveyed to the brain via the lemniscus pathway. Nociception refers to pain perception, and thermoception to the perception of temperature. Both are supported by highly arborized free nerve endings, transmitting information to the brain by slow unmyelinated (C) and fast myelinated (A δ) fibres through the spinothalamic pathway.

The foetus develops somatosensory sensitivity through the activation of receptors in his skin, muscle and tendon, by uterine contractions, movements of the mother, and his own motor activity (Granier-Deferre & Schaal, 2005). The study of reactions to tactile stimulation in aborted fetuses allowed the description of the cephalocaudal expansion of tactile receptors (Hooker, 1938; T. Humphrey, 1964; 1970). As soon as 7-8 weeks of gestational age (wGA), rooting motor responses are elicited by light touch on the upper lip (Humphrey, 1964). From 11 wGA, tactile receptors are present on facial and palmar-plantar areas, to be finally present on the whole body at 20 wGA. Thus, peripheral anatomical structures of the somatosensory system are present in their final form at the 5th month of gestation. Electrophysiological works in preterm neonates showed that afferent somatosensory pathways to the primary cortex are functional before 25 wGA (Granier-Deferre & Schaal, 2005). The differentiation of specific neuronal responses to innocuous tactile vs. painful stimuli in the somatosensory cortex appears around 35 wGA (Fabrizi et al., 2011), however Bartocci, Bergqvist, Lagercrantz and Anand (2006), showed a central integration of both tactile and painful information in the premature neonate's brain as early as 28 wGA.

b. Olfaction

In adults, odour processing involves the primary olfactory cortex (including the piriform and entorhinal cortices, the olfactory tubercle and the amygdala) and the secondary olfactory cortex (including the orbitofrontal gyrus, hippocampus, thalamus, insula and cingulate gyrus) (Gottfried, Deichmann, Winston, & Dolan, 2002). Aromatic compounds are detected by the main olfactory receptors as well as vomeronasal olfactory receptors (Schaal, 1988), the latter also detecting steroids, glucocorticoids, and peptides involved in immune chemotaxis (Rodriguez, 2013). However, the distinction is not that clear, as main olfactory receptors were observed in vomeronasal receptor cells (Lévai et al. 2006), while olfactory receptors typically present in the vomeronasal olfactory epithelium were found in the main olfactory epithelium of humans (Rodriguez, Greer, Mok, & Mombaerts, 2000).

Neuroreceptors in the vomeronasal epithelium are noticeable from 6 wGA, with the vomeronasal nerve and accessory bulb growing from 6 to 19 wGA (Schaal, 1988). Humphrey (1970) suggested an involution of this system afterwards, although developed vomeronasal organ are still observed later in neonates and even in adults (Schaal, 1988). Although species-specific pheromone responsiveness has been shown in mammals, it remains putative in human neonates (Schaal et al., 2004). Primary olfactory neuroreceptors have been observed in the olfactory epithelium, their axons forming the olfactory nerve fibres and entering the brain as early as 9 wGA. Glomerular structures and mitral cell layers of the primary olfactory bulb are noticeable at 11 wGA, and an activity marking protein can be observed in the olfactory epithelium at 28 wGA (Sarnat & Yu, 2015). Circulation of amniotic fluid in the nasal cavities is induced by foetal swallowing and breathing movements, bringing chemical stimuli on nasal chemoreceptors as soon as nasal plugs dissolve, around 16 wGA (Schaal et al., 2004; Som & Naidich, 2013). Therefore, we assume that fetuses process odours after the 4th month of gestation. The olfactory system is highly plastic, bulb volume and cortical activation varying with experience (Mazal, Haehner, & Hummel, 2016; Plailly, Delon-Martin, & Royet, 2012). High plasticity has been described for the ontogeny of odour hedonic reactivity (Soussignan, Delaunay-El Allam, & Schaal,

2013). Odour preferences during infancy are indeed dependent on foetal and neonatal experiences with the aromatic profile of amniotic fluid and breast milk, both influenced by the mother's diet (Delaunay-El Allam, Marlier, & Schaal, 2006; Delaunay-El Allam, Soussignan, Patris, Marlier, & Schaal, 2010; Mennella, Jagnow, & Beauchamp, 2001; Schaal, 2000).

c. Taste

There are two main types of taste receptors, located in taste buds mostly on the tongue papillae, palate, throat, epiglottis and oesophagus (Tizzano, Cristofolletti, & Sbarbati, 2011). G-protein coupled receptors are stimulated by organic molecules that elicit sweet, bitter and savoury tastes, receptors involving ion channels are stimulated by ions that convey salty and sour tastes (Chandrashekar, Hoon, Ryba, & Zuker, 2006). Anatomical differentiation of the fungiform, circumvallate and foliate papillae are observed from 12 wGA (Witt & Reutter, 1997), but this peripheral differentiation may not lead to different perceptions prenatally (Rao, Shankar, & Sharma, 1997).

Some works reported neonatal aversion for sourness and bitterness (Desor, Maller, & Andrews, 1975; Mennella, 2014) and a neutral reactivity to saltiness, although electrophysiological studies show high reactivity to ammonium chloride in taste cells of animal fetuses (Rao et al., 1997). The reaction of saltiness and bitterness also seems plastic and modulated by prenatal exposure, whereas sweetness appreciation appears earlier and less plastic (Mennella, 2014; Schwartz, Chabanet, & Lange, 2012). The attraction for sweet taste is in fact considered by many authors as predetermined and common to all mammals, shaped by natural selection because a preference for highly energetic foods would be adaptive (Liem & Mennella, 2002; Lipchok, Reed, & Mennella, 2011; Spence, 2012). Mammalian fetuses display more frequent swallowing after saccharine injection in the amniotic fluid (El-Haddad, Ismail, Guerra, Day, & Ross, 2002), and facial responsiveness to sweet taste appears similar in healthy primates and neonates from diverse countries, as well as in anencephalic neonates (Mennella, 2014; Steiner, 1979; A. Ueno, Ueno, & Tomonaga, 2004). These findings support the view of sweetness as an unconditionally attractive stimulus for human fetuses and newborns.

d. Trigeminal perception and somato-chemosensory overlap

The trigeminal system detects various types of chemesthetic stimuli through ion channels receiving chemical molecules and mechanoreceptors, contributing to burning, cool, tingling, irritant sensations. Chemesthetic sensations rely on nervous fibres endings that project to different cerebral areas responsible for different sensations (Trotier & Ishii, 2013). Brain areas processing somatosensory and taste information partially overlap, painful and thermic trigeminal sensations involve the somatosensory, cingular and insular cortices in particular (Faurion, 2006). Tactile trigeminal sensations are transmitted to the somatosensory cortex, allowing, for example, discrimination of the stimulated nostril (Hummel, Iannilli, Frasnelli, Boyle, & Gerber, 2009).

The branches of the trigeminal nerve that innervate nasal, oral and perioral areas are differentiated from 6 wGA and responsive to tactile stimulation at 8 wGA (Schaal, 1988), suggesting very early trigeminal perception, although direct evidence has not been reported. Many food stimuli have combined effects on gustatory, trigeminal and olfactory systems (Gilmore & Green, 1993; Green & Schullery, 2003) and cross-sensory flavour learning presumably starts before birth through the multisensory stimulation of the oronasal cavity while inhaling and swallowing amniotic fluid (Spence, 2012).

III. Transnatal discontinuity in the Neonatal Intensive Care Unit

Birth induces changes in the sensory environment, with both continuity and discontinuity depending on the stimulus. There is preservation of some familiar sensory stimuli such as odours and tastes from the mother's diet, maybe the mother's body odour, that were experienced in the amniotic

fluid and will be re-experienced after birth, notably in breast milk. Other stimuli will be new, such as the father's body odour, formula milk, and most somatosensory stimuli.

In utero, tactile stimulations are present, but temperature is constant and there are no painful stimuli. After birth, stimuli vary in texture, pressure, temperature. Some may even be aversive; others should be pleasant. Passive tactile stimulation, not initiated by the neonate but received by her, constitutes the major part of tactile stimulation received at that age (Als, 1986). It includes caressing, patting, rocking, and all acts of care. These changes are normal and welcome at term, when the organism's brain is structurally and functionally able to process these new stimuli, but the impact of such changes and of the inappropriate sensory environment of the neonatal intensive care unit (NICU) on prematurely born neonates has been a cause for concern among clinicians for years. During their hospital stay, preterm neonates are exposed to constant, non-human tactile stimulation. In fact, in premature neonates the risk of transnatal multisensory discontinuity is amplified, with a higher gap between the ecology of the womb and the NICU that combines sensory deprivations, over-stimulations, noxious, uncomfortable or otherwise inappropriate stimulations, such as disruption of motor coordination during enteral feeding (Bingham, 2009). Maladapted sensory inputs can affect the development of brain structure and function, as well as the infant's behaviour (Als et al., 2004). Several studies focusing on blood draws, frequent in Neonatology, provided evidence that repeated painful experiences have short and long-term deleterious effects in multiple systems (Buskila et al., 2003; Grunau, Holsti, & Peters, 2006; Hermann, Hohmeister, Demirakça, Zohsel, & Flor, 2006; Lidow, 2002; Mitchell & Boss, 2002; Slater et al., 2010). Children born prematurely also frequently develop atypical sensory profiles, especially in the tactile modality (Crozier et al., 2016) and have an increased risk of neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorders (ADHD) (Lindstrom et al., 2011), Autism Spectrum Disorder (ASD) (Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013) as well as educational and social impairments (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; S. Johnson & Marlow, 2011; Larroque, Delobel, Arnaud, & Marchand, 2008). Atypical tactile information processing is commonly reported in these neurodevelopmental disorders, involving impairments in filtering or habituating to tactile input (Cascio, 2010; Puts et al., 2014).

During foetal life, chemosensory, gustatory and olfactory inputs co-occur, particularly after maternal ingestion of flavoured foods. Aromas and tastes pass through the placenta and are present in the amniotic fluid that is inhaled and swallowed by the foetus (Badalian, Chao, Fox, & Timor-Tritsch, 1993). Furthermore, multisensory inputs may be associated with changes in the mother's activity or stress level, impacting foetal environment, resulting in associative learning (Smotherman, 1982). Given the antenatal transmission of neuroendocrine biomarkers of stress and sickness and its impact on foetal behaviour (Weinstock, 2005; Salisbury, Yanni, Lagasse, & Lester, 2004), associative learning may operate regularly between maternal and foetal states. Taste preferences evolve as a function of early experiences as well, influencing food consumption and habits during infancy and childhood (Schwartz, Chabanet, Laval, Issanchou, & Nicklaus, 2013; Yuan et al., 2016). A "taste acceptance windows" for sour and bitter taste in formula milks has been reported from gestation to the first half-year (Mennella, Lukasewycz, Castor, & Beauchamp, 2011), suggesting a sensitive period for long-term structural and functional plasticity to environmental exposure (Liem & Mennella, 2002; Schaal & Durand, 2012). However, duration and repetition of exposure is critical for taste and odour preferences (Delaunay-El Allam et al., 2006; Maier, Chabanet, Schaal, Leathwood, & Issanchou, 2007). Feeding issues are related to modulations in sensitivity and perceived attractiveness of flavours (Mennella, 2014; Mennella, Bobowski, & Reed, 2016; Nehring, Kostka, Kries, & Rehfuss, 2015), although the effect of perinatal exposure on taste acceptance during childhood remains controversial, particularly for sweet taste. Sweet taste is often considered a universally and unconditionally attractive stimulus already prenatally. After birth, this preference should be further reinforced by the gratifying association with satiety and physical closeness with the mother (Barkat, Poncelet, Landis, Rouby, & Bensafi, 2008; Blass & Ciaramitaro, 1994). In premature neonates however, there is no temporal relation between sweet taste (for example oral instillation of sucrose or breast milk in very small amounts), and satiety that comes from enteral feeding, or social touch when the parents visit and if they have the possibility to hold their child. On the contrary, since intra-oral infusion of a sweet solution decreases neonatal

reactivity to moderate acute pain (Stevens, Yamada, Ohlsson, Haliburton & Shorkey, 2016), oral instillation of glucose is commonly used before or during painful procedures. This repeated sweet-painful association could induce aversive conditioning to sweet tasting foods in prematurely born infants, if the appetitive response to sweetness were less hard-wired, reflex-like than previously thought.

IV. Orienting responses: markers of neonatal sensory-motor development

Immediately after birth, neonates interact with their environment through stimuli perception and emission. They are endowed with a sensory-motor skillset that is functional before delivery but continues to develop during infancy, through increasingly complex multisensory influences and motor activity. Although most authors agree that these early skills form the basis of later sensory-motor and cognitive development, studies in perinatal psychobiology are still rare and tend to focus on unimodal perception (often audition and oral language processing) or very specific behavioural patterns (*e.g.*, facial expressions of pain). Hence, early sensory-motor development still remains poorly characterized, particularly inter-sensory or sensory-motor integration. In the absence of experimental validation, the commonly accepted assumption of sensory-motor integration as being the foundation of cognitive development remains an intuition. Such validation is necessary to develop more hypothesis-driven research and therapeutic interventions in neonates.

A relevant approach to studying sensory-motor abilities in very young subjects is to focus on orienting responses. An orienting response directs the subject's attention towards salient stimuli in the environment (Barry, 2009), even in a passive context (*i.e.*, when stimulation is not initiated by the foetus or neonate but seized by him to perceive his environment). Orienting responses involve behavioural components such as movement, for example in neonates when a tactile stimulus (*e.g.*, puff of air, caress) is presented on the forearm (Humphrey, Humphrey, & Muir, 1994), as well as vegetative components such as changes in heart beat (Fearon, Hains, Muir, & Kisilevsky, 2002) or electrodermal activity (Hellerud & Storm, 2002). Orienting responses were initially observed in term neonates during perioral stimulation: when stimulated on one cheek or side of the mouth, newborns turn their head towards the stimulated side (Moreau, Helfgott, Weinstein, & Milner, 1978). This behaviour was named rooting, and interpreted originally as an adaptive reflex facilitating feeding. Another behaviour initially described as an adaptive reflex, but also fits the definition of an orienting response, is sucking. It is the observable response to the oral introduction of the neonate's finger (Hooker, 1952) or pacifier, as well as oral infusion of sweet tasting solutions (Mennella, 2014) and of course the mother's breast. The intensity and frequency patterns of sucking are modulated by attentional, motivational and mnemonic factors (DeCasper & Fifer, 2004). Orienting responses in neonates are also observed towards odorants, such as artificial scents or food odorants to which newborns were exposed repeatedly during foetal life, lactation or simply while sleeping in their crib (Delaunay-El Allam et al., 2006; Goubet, Strasbaugh, & Chesney, 2007; Marlier, Schaal, & Soussignan, 1998), suggesting that familiar odorants are actively sought. On the contrary, irritating stimuli that excite the trigeminal system make newborns turn away from the odorant (Rieser, Yonas, & Wikner, 1976). In addition to head orienting, respiratory responses allow neonates to control olfactory inputs as a function of hedonic valence: neonates' breathing increases when they are exposed to odorants considered as pleasant by adults and decreases when they are presented with odorants considered as disgusting (Doucet, Soussignan, Sagot, & Schaal, 2009; Loos et al., 2014; Soussignan, Schaal, Marlier, & Jiang, 1997).

Very early orienting responses to passive tactile stimulation were observed through habituation paradigms (Rankin et al., 2009; Snyder & Keil, 2008). Habituation is the decrease of some aspect of the orienting response across repeated stimuli. It is considered the simplest form of learning, and thought to allow the organism to preserve its resources when a stimulus is frequent but innocuous (Thompson & Spencer, 1966). This mechanism is therefore adaptive, especially for neonates who have limited energetic resources. The gestational age at which human foetuses first display behavioural orienting responses to a vibrotactile stimulus applied on the mother's abdomen ranges from 22 to 30 weeks

(Leader, Baillie, Martin, & Vermeulen, 1982). Foetuses aged 28 to 37 weeks display habituation to such repeated vibrotactile stimuli (Madison et al., 1986). Both vegetative and behavioural components of orienting responses can also be observed in premature neonates. Neonates born at 33 wGA and tested at 5 weeks of life (term-equivalent) are capable of behavioural habituation to a repeated tactile stimulus (2.5 s long filament stroke) on their lower abdomen (Rose, Schmidt, & Bridger, 1976). Differences in responses to tactile stimulation between preterm and full-term neonates were reported by Rose et al. (1976) and confirmed by Field et al. (1979). They observed that the repetition of tactile stimuli resulted in a decrement of cardiac and behavioural orienting responses in full-term neonates, while preterm only showed a decrease of behavioural responses. More recently, Fearon et al. (2002) found an increasing correlation between cardiac acceleration and body movements induced by repeated tactile stimuli (4 s long forearm stroke) between 30 and 40 wGA. Premature neonates as young as 29 wGA also display differentiated responses to odorants that vary as a function of trigeminal component or hedonic valence. Odorants generally unpleasant for adults trigger more segmental motor extension, grimacing and respiratory frequency decrease, while odorants pleasant for adults induce smiles or mouthing responses and respiratory frequency increase (Marlier, Gaugler, Astruc, & Messer, 2007). At 31 wGA, a progressive facial response decrease to repeated presentation of an odorant, followed by recovery of facial responsiveness to a different odorant, suggest that premature neonate memorize and habituate to the odours encountered in their postnatal environment. This is supported by studies of cortical activation showing habituation (repetition-suppression of the neurovascular response) to both pleasant and unpleasant odorants at 34 wGA (Bartocci et al., 2001; 2000).

After birth, interactions between a richer, more complex sensory environment and cognitive development influence behavioural orienting response towards various types of new stimuli. Blass et al. (1994) revealed that appetitive sucking and head turning, spontaneously induced by a sweet solution, can be observed in response to gentle tactile stroke of the forehead in neonates, up to 48 hours after several associations between tactile and taste stimulations were presented. In this situation, a conditioned expectation is created, and the infant will cry if three tactile stimuli are presented without the gratifying sweet solution. Associative conditioning reinforces rooting and mouthing responses towards odorants when they are experienced in association with a highly rewarding event: breastfeeding. The more neonates are exposed to a chamomile prophylactic balm during breastfeeding, the more head-turning and mouthing is elicited by chamomile scent, reaching levels identical to maternal breast milk odour (Delaunay-El Allam et al., 2006). Appetence to the learned odour is retained several years later (Delaunay-El Allam et al., 2010; Haller, Rummel, & Henneberg, 1999). There is also evidence that prenatal exposure to aromatic compounds, through maternal consumption of sweet foods and beverages, leads to preferential orienting in neonates (Schaal, Marlier, & Soussignan, 2000). Even after weaning, infants accept new food more easily if it is flavoured with compounds experienced during the last trimester of gestation or during breastfeeding (Mennella, Jagnow, & Beauchamp, 2001). This may facilitate acceptance, but entails a risk of excessive selectivity during toddlerhood when early exposure lacks variety. Therefore, long before term, associative conditioning influences multiple aspects of sensory-motor development.

We currently know very little about associative conditioning in premature neonates, but the ability being present in foetuses, it is very likely that similar associations, both positive and negative, are also present among these infants. Mechanical ventilation and feeding tubes cause pain and discomfort associated with feeding. Sucking-swallowing-breathing coordination is immature, causing apnoeic episodes when milk passes through the trachea, leading to long lasting traumatic stress to swallowing (Kerzner et al., 2015). Tactile, motor and chemosensory (taste, smell and texture) deprivation leads to long-term atypical sensory processing and preferences (Crozier et al., 2016; Wickremasinghe et al., 2013). Finally, the gradual maturation of physiological and motor systems may produce various patterns of responses to sensory stimulations at different ages among different neonatal populations. The diversity of orienting responses need to be documented, recognized and utilized by clinicians to propose hypothesis-driven improvements in care procedures, and experimentally validated sensory therapy, to preterm neonates.

V. Tactile and chemosensory therapeutic interventions in Neonatology

During their stay in the NICU, preterm neonates are exposed to stimuli that are inadequate (deprivation, overstimulation or dystimulation) and often invasive, uncomfortable or painful, occurring at the most critical time of growth of the nervous system (Rabinowicz et al., 1996). Animal studies show that perinatal sensory deprivation and motor restriction delays the development of neuronal networks of the sensory-motor cortex and the cerebellum, impacting both neuronal proliferation and motor outputs (Pascual, Fernández, Ruiz, & Kuljis, 1993). On the contrary, sensory and motor enrichment improves neural development (Scafidi, Fagel, Ment, & Vaccarino, 2009). Similar effects are found in human newborns (Als et al., 2004; Anand & Scalzo, 2000). Besides, in preterm neonates, inappropriate stimuli concur with disruption of chronobiological cycles, maternal separation and non-social handling, possibly exacerbating their effects. Because newborns are unable to withdraw from these stimuli, it has been proposed that part of the negative outcomes of premature birth may be attributed to stressful early sensory experience (Als et al., 2004).

In 1986, Als et al. proposed an innovative, personalized approach of the management of preterm neonates based on her synactive theory of development: the Neonatal Individualized Developmental Care and Assessment Program, or NIDCAP. This approach established the status of the baby as the principal contributor to his own development, through approach and avoidance systems interacting with each other and with the environment. According to this theory, any inadequate (in quantity or quality) or disorganized stimulation will cause a withdrawal reaction from the neonate. It is therefore necessary to propose a sensory stimulus only when the corresponding sensory system is capable of processing it (Feldman, 2002), and to allow the neonate to play with his approach and avoidance systems without saturating them. In theory, behavioural responses are used to adjust the level and quality of stimulations to the state of each neonate; in practice this aspect is often overlooked. Either clinical protocols fail to mention the recommendation to modulate stimulation levels as a function of the child's development and reactions, or the recommendation is inconsistently applied (Aita & Goulet, 2003). More generally, efforts are still needed in many NICUs for a reliable application of developmental care programs by all the people involved.

Despite the sometimes difficult implementation of the NIDCAP, it seems possible to improve some aspects of the preterm infant's development by modifying his sensory environment in specific ways. For example, touch is considered an essential component of the NIDCAP, and multiple "therapeutic touch" interventions have been proposed, such as massage for soothing and pain management (Diego, Field, & Hernandez-Reif, 2009), and oral and peri-oral stimulations to promote sucking (Fucile, McFarland, Gisel, & Lau, 2012). Other frequent interventions in Neonatology involve chemical senses, such as oral instillation of breast milk or sucrose solution for pain management during invasive procedures (Elserafy, Alsaedi, Louwrens, Bin Sadiq, & Mersal, 2009; Lago et al., 2014; Simonse, Mulder, & van Beek, 2012), or using carbonated solutions on gauze for oral dampening and hygiene. Adverse consequences of these practices remain undetermined. For example, carbonated solutions eliciting swallowing in adults (Morishita, Mori, Yamagami, & Mizutani, 2014), may have similar but undesirable effects in neonates.

a. Oral feeding improvement

Sensory-motor deprivation and invasive stimulation associated with respiratory and feeding assistance interact with other risk factors of prematurity, often leading to poor coordination between sucking, swallowing and breathing, and to the development of dysphagia (Costanzo, Badet, Clouzeau, & Senez, 2013; Senez et al., 1996). To counteract these effects, various protocols of oro-facial stimulations are used to promote such coordination and facilitate the transition from enteral to oral feeding. Pacifiers are frequently used to elicit non-nutritive sucking (NNS) and promote sucking abilities. Soft pacifiers are associated with more rhythmic and ample sucking movements in preterm

neonates, as compared with stiffer pacifiers, suggesting that flexible pacifiers favour the generation of effective sucking patterns (Zimmerman & Barlow, 2008). Highly organized burst patterns of NNS, with regular inter-burst pauses, are positively linked with subsequent nutritive sucking efficiency (Bingham, Ashikaga, & Abbasi, 2010; 2012; Foster, Psaila, & Patterson, 2016; McCain, 2003). NNS pattern characterization was therefore proposed as a marker of neurodevelopment, but unfortunately such measures are not yet systematic in the NICU.

Protocols combining tactile peri-oral and oral stimulations with NNS are also frequently used to support sucking-swallowing-breathing coordination in premature neonates (Fucile et al., 2012). Inducing a movement imitating NNS burst patterns, through mechanical stimulation, appears more effective than simply offering a pacifier after peri-oral tactile stimulations. The specialization and stabilization of neural networks generating oral rhythmic patterns may be facilitated by the association of trigeminal sensory inputs with such movements. Kinesthetic oral stimulations, inducing rhythmic pressure on a pacifier, promote the progressive organization of rhythmic NNS patterns in preterm neonates aged 34 wGA with ineffective sucking and feeding difficulties. Applied during enteral feeding 3-4 times per day for 10 days, this intervention facilitates the acquisition of oro-motor temporal patterns and the achievement of autonomous oral feeding (Barlow, Finan, Lee, & Chu, 2008). EEG measurements in the somatosensory cortex of neonates at 32 wGA also showed that oral trigeminal and rhythmic kinesthetic interventions are associated with higher and more lateralized neural activity during and after stimulation, compared with simple pacifier use (Barlow et al., 2014a).

This approach may also be beneficial for neonates with respiratory distress syndrome, a condition of prematurity often associated with long term feeding difficulties when preventive interventions are not proposed (Barlow et al., 2014b). However, the subtle limit between neuroprotective stimulation and overstimulation is still debated, and stimulation parameters such as velocity and frequency may have different effects in different conditions, for example between infants with chronic lung disease, respiratory distress syndrome or born from a diabetic mother (Barlow et al., 2014b).

Finally, bimodal stimulations coupling milk odour diffusion with NNS improve the motivation to suck and the maturation of rhythmic and ample NNS patterns (Bingham, Abassi, & Sivieri, 2003; Bingham, Churchill, & Ashikaga, 2007). Besides, when NNS is induced during enteral feeding, sucking responses appear more durable (Rochat, Goubet, & Shah, 1997). Further research is needed to verify whether milk odour diffusion associated with NNS during enteral feeding would be even more effective. More generally, research should aim at testing the effects of multimodal preventive interventions on sucking-swallowing-breathing coordination, oral feeding efficiency and timing of autonomous feeding achievement.

b. Pain management

Another important challenge in Neonatology is analgesia. All hospitalized newborns, especially preterm neonates, are exposed to multiple painful stimulations every day (Barker & Rutter, 1995; Carbajal, 2008; Simons et al., 2003). Repeated perinatal experience with iatrogenic pain leads to changes in nociceptive thresholds (Lidow, 2002; Mitchell & Boss, 2002; Page, 2004) and preterm infants are, at term equivalent age, more sensitive to pain (Slater et al., 2010). This increased sensitivity to somatic pain is still found among adolescents who were born preterm (Buskila et al., 2003; Hermann et al., 2006; Hohmeister, Demirakça, Zohsel, Flor, & Hermann, 2009; Hohmeister et al., 2010). Invasive procedures associated with routine care also contribute to permanent alterations in stress response systems (Grunau et al., 2006) and other sensory systems (Berardi et al., 2000). In addition to sensitization to pain and structural and physiological changes in the central nervous system and autonomic substrate, early and repeated procedural pain leads to physiological instability, dietary problems and sleep disorders (Mitchell & Boss, 2002). These observations of short and long-term consequences yield support to the parental demand to better alleviate their newborn's pain.

Initial efforts in neonatal pain management consisted in pharmacological analgesics, either local or systemic, but these proved unsatisfactory for repeated acute pain because lacking effectiveness,

presenting dangerous side-effects (sedation, respiratory depression) and being potentially toxic in the long term (Anand, 2001; Jain, Rutter, & Ratnayaka, 2001; Carbajal et al., 2005; Sellam, Cignacco, & Engberg, 2010). Because pain is still part of necessary medical care, non-pharmaceutical alternatives are increasingly sought after in Neonatology. Among them, oral administration of sucrose has received the most attention, based on the observation that it decreases facial and vocal expressions of pain. It is now universally recommended in procedural pain management for neonates (Carbajal, Gall, & Annequin, 2004; Pillai Riddell et al., 2015). Sweet taste is considered as having analgesic properties in neonates, mediated by central endogenous release of opiates (Blass, 1994). Nevertheless, recent works have casted doubt on the analgesic properties of oral sweet taste. First, it attenuates neither pain-specific brain activity nor the spinal nociceptive withdrawal reflex in infants (Slater et al., 2010). Second, the development of hyperalgesic responses was reported after repeated painful procedures associated with sweet taste during the neonatal period (Taddio, Shah, Atenafu, & Katz, 2009). Such observations are incompatible with the longstanding vision of sweetness as a hard wired, reflex-eliciting, appetitive and calming stimulus. This controversy led some researchers to propose that sweet taste may simply act as a behavioural distraction or compensation, alike non-nutritive sucking (Wilkinson, Savulescu, & Slater, 2012). As a result, the question begins to be raised of immediate and long-term adverse effects of the cumulative use of sweet solutions during painful procedures in premature neonates (Harrison, Beggs, & Stevens, 2012; Holsti, Whitfield, Grunau, & Oberlander, 2005b). A recent follow up of premature newborns born at 33-34 wGA did not show any difference between repetitive use of oral sucrose vs. placebo during painful procedures on neurobehavioral status of the premature newborns at 40wGA (Banga, Datta, Rehan, & Bhakhri, 2016), questioning the relevance of oral sucrose for pain management.

Familiar odorants and tastes constitute another area of research for chronic stress and pain management in neonates. The mother's milk is frequently mentioned, but any odorant experienced in a calm context also reduces pain responses in premature and term born neonates (Goubet et al., 2007; Rattaz & Goubet, 2005). It may be the reassuring effect of familiarity or the learned association with physical comfort, that make infants anticipate a positive outcome when later stimulated with the target odours and be more distracted by them when a painful procedure intervenes. However, repetitive exposure to the mother's milk odour during painful procedures, especially if the baby already encounters breastfeeding difficulties, may lead to further negative expectations and rejection of breast milk odour. Feeding premature neonates at the mother's breast is always highly difficult, particularly during the crucial period of transitioning from enteral to oral feeding. Therefore, the proposal of mother's milk or mother's milk odour should be proscribed during painful procedures before autonomous oral feeding is achieved. Later though, if breastfeeding is well engaged, it may be use for occasional pain relief, notably during vaccination.

Non-pharmacological alternatives for analgesia also stem from the tactile components of developmental care. The most frequently reported is the Skin-to-Skin method, also called Kangaroo-Mother Care (KMC), which involves placing the premature infant on his parent's torso, without any clothing between them. Several studies have shown that, besides the beneficial effects of this method on physiological regulation and growth, skin-to-skin positioning before and during a painful care procedure decreases behavioural and physiological acute pain reactivity in preterm infants (Castral, Warnock, Leite, Haas, & Scochi, 2008; Freire, Garcia, & Lamy, 2008; Johnston et al., 2008; Ludington-Hoe, Hosseini, & Torowicz, 2005). Even very preterm neonates can benefit from this method, as their endogenous regulation mechanisms appear stimulated by skin-to-skin maternal contact, that decrease their pain reactivity (Johnston et al., 2008). More generally, gentle human touch seems to reduce the behavioural and physiological response to acute pain in premature infants ranging from 27 to 37 wGA (Herrington & Chiodo, 2014). The authors report that when using gentle human touch, neonates did not show the usual decreased respiration rate, elevated heart rate, or increased cry during the painful procedure. Attenuation of brain activation to a punctate stimulus was also observed using therapeutic touch (Honda et al., 2013). Massage therapy may also act either as a soothing stimulus or a distractor: the use of moderate pressure massage therapy in preterm infants aged 22 to 35 wGA led to lower

increase in heart rate during the painful procedure, that may be interpreted as attenuated pain (Diego et al., 2009).

Despite these encouraging reports, it is worth noting that therapeutic touch may also have adverse effects (Johnston et al., 2013). KMC was found safe in ventilated prematurely born children under 30 wGA (van Zanten, Havenaar, Stigt, Ligthart, & Walther, 2007), but some authors report that preterm infants aged 28 wGA and younger have periods of oxygen desaturation when touched, or are unable to maintain their body temperature in KMC (Bauer, Pyper, Sperling, Uhrig, & Versmold, 1998; Scafidi, Field, & Schanberg, 1993). Although most neonates stay physiologically stable during and after massage, some experience physiological instability involving hypoxic episodes immediately after the session (Barnard, Brazelton, & Berry, 1990), suggesting that an over-stimulation point was reached that disturbs the physiological homeostasis of the newborn (Feldman, 2002), without the caregiver noticing. This underscores the need for further research to identify the most appropriate type and amount of touch for preterm infants depending on gestational age, health condition and pain level (Harrison, 2001).

Most studies on therapeutic touch for neonates acknowledge the necessity of appropriate sensory-motor stimulation during the early life of preterm neonates, and its critical role in physical and psychological development, well-being and the attachment bond (Ardiel & Rankin, 2010; Barnard et al., 1990; Harrison, 2001; Reite, 1990; Segond, 2008). Premature birth propels immature and sometimes sick newborns in a highly technical environment where they receive very little comforting or contingent stimulation, since most of the tactile stimulation they experience is associated with procedural touch. It may seem surprising to point to the lack of non-procedural touch in preterm neonates and to use, at the same time, developmental care such as KMC or massage as pain management. Even though they seem effective for analgesia, we should be particularly vigilant that they are used in priority as developmental care and not only associated with painful events. Systematic association between therapeutic touch and pain may lead to aversive conditioning to touch, and long term deficits in passive tactile processing.

Being aware that neonatal pain should be managed, as far as possible, using non-pharmacological methods, we wish to call attention to the need to carry out more fundamental research on sensory-motor processing in neonates and on long-term effects of sensory therapies in and outside a painful context. Such studies would help to propose safer and more effective individual sensory therapeutic protocols. New pain management solutions should be distinct from developmental care and without risk of causing aversion to comforting, developmentally precious stimuli such as human social touch, milk odour or sweet taste. Achieving this goal will also require that processing ability and response to therapy are individually and continuously monitored. Defining markers of adequate vs. inadequate stimulation level and quality is therefore crucial. Such markers may be physiological, cerebral, or behavioural by taking advantage of the orienting responses, and should be absolutely innocuous.

VI. Current directions in research and neonatal care

Since early investigations of passive tactile perception and habituation in preterm neonates in the 1970s (Field & et al, 1979; Rose et al., 1976), such studies have been extremely rare, as recently pointed out a review of neonatal cognition studies (Streri et al., 2013). Yet, passive tactile stimuli constitute the major part of stimulation a preterm newborn receives (Als, 1986) and experimental attention should be given to the way they perceive and use these inputs. We know very little about the influence of early tactile experiences on human development. Moreover, the neonatal environment has evolved since the 1970s, as well as the management of premature infants.

Current efforts are aimed at characterizing tactile perception abilities in preterm neonates and understanding the interaction between such perception and exposure to pain or other stressors. We recently showed that preterm neonates at 35 corrected wGA display manual orienting responses to a vibrotactile stimulus on the upper limb, which decreases across repetition, showing evidence of habituation (Dumont et al., 2017). Dishabituation was observed when the stimulated area or the inter-stimulus interval changed, indicating that preterm neonates discriminate both spatial and temporal

characteristics of a tactile stimulation sequence. These very early tactile and temporal processing abilities are being investigated further, using brain activity measures in addition to behavioural analysis (Dumont et al., 2017). Indeed, Barnard and Bee (1983) proposed that preterm newborns difficulties to organize and synchronize their physiological and behavioural responses could be exacerbated by the temporally unpredictable quality of the stimulation received in the NICU, as opposed to the predominantly rhythmic, predictable sensory environment *in utero*. Since then, authors have argued in favour of a link between rhythm perception, sensory predictability and development (Provasi, Anderson, & Barbu-Roth, 2014), but this long-standing proposition remains to be experimentally tested.

Interestingly, the behavioural habituation described in Dumont et al. (2017) was delayed in subjects born at a younger gestational age, smaller birth weight and having experienced more painful care procedures. Because these factors are strongly correlated, we do not know whether this delay is due to slower learning at younger ages, or to a detrimental effect of painful experiences of tactile processing abilities, or both.

Pain is currently one of the most active research topic in Neonatology. Considerable efforts have been made to promote the use of non-pharmacological alternatives, however we still lack long-term evaluations of their effects on the neurophysiological and behavioural development of preterm infants. Sensory stimulation repeatedly associated with pain, or a stressful context, may entail long term adverse consequences possibly outweighing the benefits of pain management. The question of immediate and long term adverse effects of the cumulative use of sweet solutions during painful procedures in premature newborns has been raised (Holsti, Grunau, Oberlander, & Whitfield, 2005a; Schaal, Goubet, & Delaunay-El Allam, 2011). However, to date such effects remain scarcely documented. We are currently investigating the impact of associating procedural pain with sucking and oral sweetness on the development of feeding skills during the critical transition from enteral to oral feeding. We propose that this association may induce an aversion to sweet taste, perhaps even to sucking, and interfere with normal development of the neural substrates of sucking. This would result in sucking-swallowing impairment affecting the infant's access to autonomous oral feeding and length of stay in the NICU. Similar issues are posed by the trend towards breastfeeding during painful procedure (Uga et al. 2008), that should be evaluated before any claim for spreading the method can be made.

Further research is needed to clarify the interactions between sensory interventions for analgesia, pain and the long term perception of innocuous stimuli used as interventions. In particular, we want to highlight the importance to vary non-pharmacological pain management solutions during the hospital stay of a premature neonate, to limit as much as possible aversive conditioning to initially attractive sensory stimuli.

A promising alternative to sweet-sucking for analgesia is the use of vibration on the site of the procedure (Baba, McGrath, & Liu, 2010). The Gate Control Theory of pain proposed by Melzack & Wall (1965) implies that a tactile input takes priority over pain in neural pathways to the central nervous system, therefore preventing pain perception when presented simultaneously. Vibration has been studied and utilized to supplant pain in various fields like orthopaedics and dentistry. In Neonatology it is still uncommon, although it would offer the advantage of being a non-social, developmentally irrelevant stimulus. This is important because if there is aversive conditioning to sensory interventions, social or food-related stimuli must be avoided. First studies of vibration for analgesia during heel lance report good effectiveness (Baba et al. 2010; Mc Ginnis et al. 2016) but pain responses were assessed with the concomitant use of sucrose and pacifier. Further studies are therefore needed to evaluate the specific effect of vibration.

Finally, the question of oral feeding improvement, although receiving less public attention, is a critical one for premature newborns development and hospital discharge. Positive multimodal intervention respects postural placement with neck and back flexion, brings several sources of stimulation together and involves engaging in social interactions during feeding. The purpose is to promote comfort and relaxation, and to trigger appetitive mouthing movements before stimulating with NNS. Appetitive responses are associated with salivation, that in turn triggers swallowing and

enhances the benefits of NNS. It is particularly recommended before and during enteral feeding, not only to make the newborns practice sucking and to prepare them progressively to the motor activity of oral feeding, but also to help them identify feeding events during the day (Lau, 2015; 2016; Pfister et al., 2008). Lau insists on the importance to respect several stages of development in sucking and swallowing mechanisms when stimulating, and in soliciting regular and progressive practice, as it favours rhythmicity and amplitude gain as well as sucking-swallowing-breathing coordination (Lau, 2015; 2016). We are currently running a protocol promoting step by step solicitations. First, sucking should be elicited by gentle oral tactile stimulations with a pacifier, then encouraged by multimodal stimulations combining peri-oral and oral tactile stimulations, milk taste and odour. In parallel, swallowing must be solicited by proposing small amounts of milk to start, progressively increasing the quantity to allow safe practice of sucking-swallowing coordination. The aim is to provide a smoother and safer transition from enteral to autonomous oral feeding. Parental involvement during that transition must be encouraged for the premature neonate to learn that oral feeding is consistently linked with social interactions, a relationship essential to physical and emotional development in subsequent years.

VII. Conclusion

The challenge of neonatal care is to overcome the untimely transnatal discontinuity caused by premature birth. To do so, therapeutic interventions are proposed in the NICU that involve sensory-motor stimulations. Despite the early development of somatosensory and chemosensory systems, we still lack fundamental understanding of their uni- and cross-modal functioning, as well as their long-term implications in motor, emotional, cognitive and social development. With such knowledge, practitioners could propose informed, innovative and adapted therapeutic interventions. We propose to take advantage of the sensory-motor skill set of preterm infants, such as orienting responses, to study perception in these early developing modalities, to characterize brain and behavioural activities evoked by developmental care and pain management interventions, and to design fact-based preventive and therapeutic sensory stimulations for neonatal care that keep respect a balance between short-term benefits and long-term consequences. Finally, we want to emphasize the importance of parental involvement, not only in therapeutic sensory interventions, but also outside of these interventions. It is crucial to preserve a time dedicated to positive, social interactions that do not overlap with unpleasant or painful procedures.

VIII. References

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