The Human Mammary Odour Factor: Variability and Regularities in Sources and Functions

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Abstract. In the course of evolution, human mothers have been, and still are, under strong selective pressure to induce their newborns' colostrum ingestion promptly after birth. As a concentrate of nutrients, passive immunity, antioxidants, growth factors and symbiotic microbiota, colostrum functions as the evolved antidote to ubiquitous pathogens and threats of neonatal exhaustion. Under such constraints, any means to speed up colostrum/milk intake can only have been beneficial to neonatal viability and adaptive life onset along evolutionary time. The areolar-nipple areas of human lactating females emit lacteal substrates conveying chemostimuli that are attractive and release mouthing and sucking in infants. Current information about areolar glands of Montgomery is summarized here, in terms of variability/regularity in number and distribution, of behavioural activity of their secretion, and of the adaptive value of their occurrence. It is concluded that a majority of lactating women investigated so far bear from 1 to >40 glands/areola, among which some emit a visible secretion. Reciprocally, a majority of neonate infants react to the odour of these secretions. The number of areolar glands correlates with infants' behaviour at the breast, indicating that areolar phenotypic variability has potential fitness consequences on the infant and the mother. Ideas for future studies are outlined to advance our understanding of how human areolar phenotypic variability relates to life history characteristics.

1 Constraints on Mammary Odour Signalling

Various adverse situations can affect breastfeeding initiation in human newborns, highlighting the delicacy of the mechanisms underlying its achievement (e.g. Winberg 2005). For instance, the initiation of nutritive sucking may be delayed from hours to days after birth by local representations and related prescriptions on how neonate infants should be raised. Such delays that impede the transfer of colostrum have been, and still are, far from uncommon in both traditional and highly medicalized societies. For example, in rural India a 1996 study indicates that not only did mothers postpone initiation of breastfeeding (only 0.3% of them allowed sucking within the first postpartum hour), but additionally they replaced the colostrum with artificial prelacteal

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formulas (e.g. Banapurmath et al. 1996; see also Abuidhail 2014). Such delays in putting infants at the breast and avoidance of feeding them colostrum have been recorded on all continents and across time up to now, even in medically advanced societies (e.g. Reissland and Burghart 1988; Barkow and Hallett 1989; Odent 2010; Candau and Schaal 2015).

Besides traditional and medical beliefs, other causes can interfere with optimal breastfeeding initiation, such as maternal inexperience. For example, 49, 22 and 17% of normal term-born newborns in a 2003 Californian sample behaved suboptimally toward the breast on the day of birth and on days 3 and 7, respectively, despite adept advice and assistance being conveyed. These disadvantageous outcomes were strongly associated with primiparity (Dewey et al. 2003). A related French study reached similar conclusions (Michel et al. 2007). Follow-up studies of home births in rural Ghana link such early delays in breastfeeding initiation to subsequent infant morbidity and mortality. In such poorly medicalized conditions, a 1-day postponement in the initiation of breastfeeding explained 16% of neonatal death before day 28; moreover, a delay of only 1 h post-birth to engage breastfeeding explained 22% of neonatal mortality (Edmond et al. 2006). Causal links between early (<24 h) versus late timing of breastfeeding initiation and infant health outcome are multiple and non-exclusive, including (among other nutritive and sensory effects): increased protective exposure to colostral bioactive compounds (immunoglobulins, antioxidants); mother-to-infant transfer of non-pathogenic microbiota; colostrum-induced decrease of intestinal permeability to pathogens; stimulation of mucosal lymphoid tissue through maternal-infant contact. In addition, colostral ingestion lowers exposure risk to pathogens conveyed in prelacteal feeds (e.g. Uruakpa et al. 2002; Debes et al. 2013).

In addition to the denial of early access to the breast imposed by many cultural contexts, inexperienced newborns face intrinsic difficulty to first orient and orally seize a nipple, thus increasing potential threats to viability. Nonhuman and human (historical societies and modern hunter-gatherers) primates have been shown to globally lose 27% of their offspring during the first year of life, a remainder of 47% failing to survive to puberty (Volk and Atkinson 2013). Such early mortality is causally complex and multifaceted (e.g. Lawn et al. 2005; Kinney et al. 2010), with prevailing infectious causes (e.g. 36% in Lawn et al. 2005; see also Edmond et al. 2007). Some authors (Volk and Atkinson 2013) have linked part of this high mortality rate of human infants to the neonates' problematic engagement of suckling. Covariations in the regional scheduling of breastfeeding initiation and records of neonatal mortality corroborate this view (e.g. Debes et al. 2013). Further, the daily risk of infantile mortality is very high in the first postnatal week, with an even higher peak within the 48 h following birth (Lawn et al. 2005). Thus, human mothers are under an extremely strong selective pressure to induce their newborns to promptly suck their breasts and to transfer colostrum to them as soon as possible after birth. Although modest in quantitative terms, colostrum is indeed qualitatively peculiar as a concentrate of nutrients, passive immunity, antioxidants, growth factors and symbiotic microbiota functioning together as the evolved antidote to omnipresent pathogens and threats of neonatal exhaustion (e.g. Hale and Hartmann 2007).

2 Mammary Signalling and the Neonate's Receptive Range

In such highly constrained conditions over evolutionary time, any means that speed up localisation and oral acceptance of the nipple (or *papilla mammae* or *mamilla*) by the newly born infant can only have been beneficial to viability and adaptive life onset. In that line, the most obvious adaptive way certainly is the direct guidance and assistance mothers or other helpers offer the infant when presented to the breast for the first few times. However, aforementioned evidence (Dewey et al. 2003; Michel et al. 2007) indicates that maternal handling of the infant is often suboptimal in initial breastfeeds, especially in inexperienced first-time mothers. The ultimate decision to positively orient, orally grasp the nipple, and express the full latching response is therefore inherent to infants themselves. Multiple observations of the 'breast-crawl' document indeed that human newborns can autonomously reach the breast when they are given time and optimal environmental conditions (e.g. Widström et al. 1987, 1990, 2011; Righard and Alade 1990; Christensson et al. 1992; Varendi et al. 1994; Klaus 1998; Cantril et al. 2014; Girish et al. 2013). To accomplish this early performance, infants rely on a range of motor abilities directed by their senses including somesthesis, with tactile and thermal components, chemosensation, with olfaction and taste, and perhaps even vision (as the human areola-papilla is pigmented contrastedly by dermal melanocytes). These multiple guidance cues are natural features of the breast that have been shown to separately affect neonatal head orientation and oro-motor responses.

Briefly, newborn infants display bilateral rooting movements on their track to the breast and, when reaching it with their chin, they express oral gapes that generally end in seizing a nipple (e.g. Prechtl 1958; Widström et al. 1990). These head sweeping movements expose their perioral tactile receptors to the textural contrasts between the skin of the breast and the softer tissue of the areola, and then between the areolar epidermis and the firmer erectile tissue of the nipple. Such tactile discrepancies may facilitate the infant's directional progression toward the nipple and the labial grasping of it. Otherwise, the metabolic activity of the lactating breast induces a thermal contrast between its epidermal surface and the rest of the chest (Burd et al. 1977). Due to the vasoactivity of Haller's subareolar vascular plexus before nursing episodes, additional thermal contrasts exist between the areola and the rest of the breast, and between the areola and the nipple. These local thermal contrasts were established long ago by thermographic studies (Vuorenkoski et al. 1969; Kimura and Matsuoka 2007) and recently confirmed by surface thermometry (breast versus areola temperature difference: 0.56 °C; Zanardo and Straface 2015; Zanardo et al. 2017). If they are detectable to neonates (which has never been empirically attested) these tactile and thermal differences could operate as proximal cues to finalize their localisation of the areola. Another, more distally conspicuous cue of the areolae for awake infants is their visual contrast with surrounding skin due to their strong pigmentation (e.g. Stolnicu 2018).

Such areolar physical cues are complemented or synergized by chemical cues. Postparturient lactating women may release from there a specific body odour, areolar skin glands being activated by their physiological stage-specific endocrine balance. For example, at that time sebaceous glands excrete then higher amounts of sebum (Burton et al. 1973). Apocrine glands may also produce a lactation stage-specific odour mixture that appears to be detected and differentiated by neonates (Cernoch and Porter 1985; Porter et al. 1992). But an especially attractive odour is given off by the lactating breast. For example, breastfed infants (aged 15 days) prefer the breast odour of an unfamiliar lactating mother over her axillary odour (Porter et al. 1992) and bottle-fed infants tend to prefer the breast odour of an unfamiliar nursing mother to the odour of the formula to which they were conditioned since birth (Porter et al. 1991). Further, when the natural odour of the breast is masked by coating nipples with extraneous odorants (Schaal 1988) or eliminated by washing the nipple-areolar regions (Varendi et al. 1994), the neonates' orientation and searching responses are inhibited or disorganized. Otherwise, when the natural odour is merely blocked by applying a scentless transparent plastic film on the breast, nursing infants display significantly reduced rooting, sucking and mouthing responses, and begin crying sooner (Doucet et al. 2007; see below).

In sum, the areolar-nipple zones of human lactating females convey a range of natural stimuli of diverse nature that may play, among other functions, the roles of guidance beacons and motivational cues which end in efficient oral seizing and initiation of nutritive sucking. These breast cues conveyed by different sensory channels probably operate conjointly. For example, the heightened surface temperature of the areolar discs may regulate the evaporation of odorous substrates from areolar skin glands or remnants of milk, and may therefore maximize and synchronize mammary odour signals in time with the infants' demand for suckling. The mother's reception of distal signals emitted by the crying infant do indeed result in increased temperature of the breast (Vuorenkoski et al. 1969), bringing time-adjusted thermal amplification of areolar odour impressions.

3 Sources of Mammary Odours: The Areola as a Scent Organ

Briefly summarized (for reviews, cf. Schaal and Porter 1991; Schaal et al. 2008; Schaal 2010; Koyama et al. 2013; Schaal and Al Aïn 2014), the human areolar region harbours multiple glandular sources giving off secretions that potentially contribute to the local odour mixture. These are composed of elementary skin glands of all types, which are present in the areolar and papillary dermis. Minute eccrine sweat glands and sebaceous glands are distributed in the areolae (Montagna and MacPherson 1974), while nipples are endowed with simple, hairless sebaceous and apocrine glands, which ducts open distally and in the ostia of the lactiferous ducts (Perkins and Miller 1926; Montagna and Yun 1972; Montagna and MacPherson 1974; Vorherr 1974; Koyama et al. 2013). Increased excretion of sebum has been reported during lactation (Burton et al. 1973), which may contribute to the lactation-specific breast odour to which infants are responsive.

But, more remarkably, the areolar surface is speckled with small bumps, in the form of 1–2 mm-wise structures contrasting with the surrounding areolar skin in elevation and/or pigmentation. Although first described by the Paduan anatomist Morgagni (1719), these structures were later recognized by (and named after) the obstetrician Montgomery (1837) as typical of the gestational and lactational areola. These Montgomery's glands become then notably enlarged as small areolar protuberances and sometimes emit a visible milky secretion. The functional entity of the gland of Montgomery is formed by sebaceous glands associated with isolated mammary acini (Montagna and Yun 1972; Smith et al. 1982). The partial lactational nature of the gland was confirmed by the fact that milk-specific lactose is a constituent of Montgomerian secretion (Naeslund 1957). Further, Montgomerian secretion conveys some odorous volatile compounds also evidenced in colostrum and milk (Schaal et al. 2008).

Finally, the most profuse sources of potentially odorous constituents are obviously colostrum and milk, which are ejected from the milk ducts opening at the top of the nipple. This mainstream lacteal secretion carries multiple volatile compounds in free and conjugated form (e.g. Loos et al. 2017). Collectively, these compounds are efficient in eliciting positive head orientation, mouthing and sucking motions in newborn infants (Soussignan et al. 1997; Mizuno and Ueda 2004; Marlier and Schaal 2005). The nature of these responses is detailed below.

To sum up, the human areolar-nipple structure combines multiple sources of free and conjugated odorous constituents carried in milk, sebum, and apocrine and eccrine sweat. Sebum, as well as the fat fraction of milk, may play the role of fatty fixatives that slow down the evaporative timing of volatiles (e.g. Regnier and Goodwin, 1977). Further, enzymes or bacteria conveyed in milk (e.g. Cabrera-Rubio et al. 2012), as well as salivary enzymes left on the areola by the suckling infant, may promptly alter non-volatile or conjugated substrates into odour-active volatiles, giving off additional odour cues in a way that synchronizes with nursing. Finally, the vasoactive susceptibility of the subareolar vascular plexus may work as a thermal diffusion device which operation is mediated by the mother's emotional responses to seeing, hearing or smelling the infant (e.g. Vuorenkoski et al. 1969). Such co-localized elementary sources of odorous substrates and emission mechanisms are typical of the mammalian design of a chemo-communicative structure (e.g. Adams 1980; Albone 1984; Wyatt 2014), a feat that was well recognized by early German anatomists who ascribed the human breast the function of a *Duftorgan*, a scent gland (Schiefferdecker 1922; Schaffer 1937).

4 Inter-individual Variability of Areolar Odour Sources

Despite its recognized potential for semiochemical mediation, the areolar region of lactating females has attracted little systematic investigation along these lines. The first to describe it in more detail reported the morphological changes of the areola during pregnancy and came out with an endowment range of 12–20 glands (although it is not clear whether these counts are per areola or per individual; Montgomery 1837). So far, three modern studies have investigated the number and distribution of areolar glands in periparturient lactating human females.

In the first of these studies, 64 post-parturient women were intensively trained to identify and locate their areolar glands on both breasts, which they did with high reliability (Schaal et al. 2006). Every pigmented skin elevation (excluding moles) was termed 'areolar gland' (AG) without further histological enquiry (previous histological studies had indeed attested that such visible areolar protuberances, despite variability in size and pigmentation, did combine sebaceous units and lactiferous acini). All but one women in that sample bore AG (average AG number/areola: 8.9, standard deviation

(SD): 5.6; range/areola: 0–38 AG) with 83% of them having 1–15 AG per areola. In a second report on 121 new mothers (Doucet et al. 2012), digital pictures were taken from both breasts for subsequent numeration and distributional analyses of AG. In this case, the mean number of AG per breast was 10.39 (S.D.: 9.04; range: 0–48.5). The majority of these mothers (96.7%) were endowed with AG, 80.2% bearing 1–20 AG/areola (4 of them were AG-less). Finally, a third study (Seidel et al. in preparation) using the same photographic method reported the quasi-general prevalence of AG (98.5%) in a sample of 67 mothers (average number: 8.6 AG/areola, SD: 5.8; range: 0–25 AG/areola; 89.6% bearing 1–15 AG/areola). In all these studies, the AG number was unrelated with breast side, areolar surface, mother's parity and newborns sex. Further, the AG count appeared intra-individually stable between postpartum days 1 and 3.

In some mothers, a fraction of these AG was seen to emit very small amounts of a latescent secretion. In study 1 (Schaal et al. 2006), 12 out of 64 mothers had at least one secretory AG. In study 2 (Doucet et al. 2012), 34 out of 121 women had one or both breasts endowed with at least one AG emitting a noticeable secretion. This latter subgroup of 34 mothers did not differ from the rest of the sample in terms of parity and infant sex, and their secretory AG count was unaffected by breast side, postpartum timing (within 84 h post-birth) or the 24 h cycle. The rate of women bearing secretory AG might be considered low (24.8%) in view of the massive evidence of AG in the samples of studies 1 and 2. However, although visible secretions confirm the functional activity of the AG, unnoticeable oozing from more or all AG cannot be excluded. Thus, an obvious areolar fluid emission may not be necessary for the AG to influence infant responsiveness. In fact, mothers bearing secretory AG did not differ from mothers who do not bear such secretory AG on several maternal (i.e. breastfeeding frequency, latency to lactation onset) and infant variables (i.e. infant breastfeeding score) (Doucet et al. 2012).

The numeric polymorphism of AG number may be balanced by their distribution on the areolae. While AG appear to be randomly spread at first sight (Fig. 1), a closer distributional analysis on the women's samples of study 1 and 2 (Schaal et al. 2006; Doucet et al. 2012) highlights average higher density of AG on the lateral areolar quadrants, and the AG that are obviously secretory are more numerous on the upper lateral quarter (Fig. 2). The uneven distribution of AG on the areolar disc, whether secretory or not, corresponds to the typical positioning of the nursing infant's nose on the areolae. Thus, AG are in the best spatial arrangement to direct related secretions under the nursling's nose.

However, the other areolar quadrants also harbour AG, suggesting that the putative communicative role is inclusive of other functions of AG related to the optimization of sucking and nipple integrity. The hypothesis of the communicative prevalence of AG would be strengthened if their secretory output would be higher at the time of initial breastfeeds or later, right before each suckling episode, their release being potentially stimulated by antecedent infant signals. So far, only suggestive results were obtained on the latter issue, as more women tended to exhibit secretory AG on postpartum days 1–3 than on days 15 or 30 (Schaal et al. 2006).

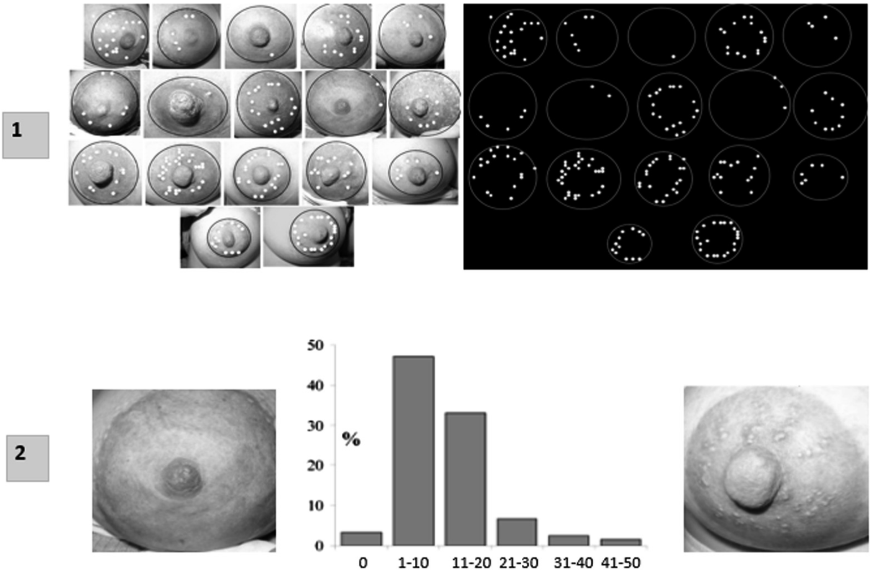


Fig. 1. **1** The variability of the areolar phenotype in a sample of human lactating breasts. Note the inter-individual variation in areolar diameter, number of areolar glands (AG) and their spatial distribution, highlighted in the black panel. Due to various scales, this illustration should be taken only as visually indicative. **2** Frequency (%) distribution of mean counts of AG per areola between birth and postpartum day 3 (sample size: 121 women). Inserts: pictures of extreme AG endowment in the present sample (left: 0 AG; right: >31 AG). After data from Doucet et al. (2007)

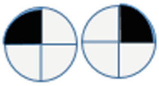
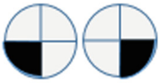
Areolar Quadrant				
AG Secretory AG	2.89* (2.62) 3.74* (4.96)	2.96* (3.22) 1.83 (2.96)	2.23 (2.34) 2.33 (4.04)	2.29 (2.75) 1.48 (3.38)

Fig. 2. Distribution of areolar glands (AG) and of secretory AG on the areolar surface divided into 4 quadrants (upper and lower external, upper and lower internal). Mean numbers and standard deviations (SD); *$p < 0.05$. After data from Doucet et al. (2012)

5 Areolar Secretions and Their Effects on Newborns

The possible effects of mammary, including areolar, secretions have been investigated in a variety of different ways. First, a series of pioneering studies, starting with Macfarlane (1975), have drawn the big picture: providing evidence that infants detect and react to their mother's breast odour but without assessing how various sources of the lactating breast form the whole odour mixture given off. Collectively, these studies showed that a gauze pad carried in contact with the breast for several hours conveys enough ‘signal value’ to alter the attentional and directional responsiveness of newborn infants (Russell 1976; Schaal et al. 1980; Schaal 1986; Makin and Porter 1989; Varendi and Porter 2001).

A second series of studies attempted to separate the perceptual effects of mainstream milk within the whole breast odour mixture. Brain responses recorded through EEG or NIRS confirmed that neonates, born either term or preterm, can detect the odour of human milk or colostrum and discriminate it from orange juice (Yasumatsu et al. 1994), vanilla (Bartocci et al. 2000), or formula milk odours (Aoyama et al. 2010). But behavioural investigations further demonstrated that infants tested on postpartum days 0–14 clearly react to the odour of human milk alone by either arousal modulation, attraction, orientation or appetence displayed orally (Mizuno and Ueda 2004; Marlier and Schaal 2005; Nishitani et al. 2009). Human milk odour is behaviourally effective in neonates never exposed to it before the test, either because they were exclusively fed with a bovine milk-based formula (Marlier and Schaal 2005) or because they were born preterm (Bingham et al. 2003, 2007; Raimbault et al. 2007). Thus, mainstream milk as a separate source of odorous substrates might explain the global attraction-appetence responses of neonates to the lactating breast odour.

In an attempt to further dissociate the components of this intricate mammary odour cocktail, one study assessed the responses of neonates to the mother’s breast after the different putative odour sources were selectively blocked (Doucet et al. 2007). To do so, morphologically, and hence semiochemically differentiable breast areas were overlaid with a scentless plastic film (Fig. 3). Diverse apertures made in this plastic cover were designed to separate the areolar contribution to the total breast odour from the contributions of either the nipple or fresh mainstream milk. Unrestrained 3-day-old newborns were then held close to the fully covered, fully uncovered or selectively uncovered, breast (Fig. 3). As opposed to the fully covered breast which was assumed to be odourless, the whole odour of the uncovered breast affected significantly the infants’ arousal state (increased eye opening) and feeding-preparatory oral responses (mouthing, licking and sucking) (Fig. 3). However, when comparing the odour of the olfactorily intact (uncovered) breast with the “fractionated” breast odours exposing the infants only to the areola versus only to the nipple versus only to milk odours, the infants’ differential responses did not reach significance (although their response to the areola-only odour appeared similar to that elicited by the whole breast odour; Fig. 3).

Thus, the present experiment failed to reveal whether a mammary subregion contributed more than another to the whole odour cocktail of the lactating breast. Either areola, nipple and milk odours convey quasi-equivalent perceptual qualities due to shared constituents [even though distinct milks (areolar versus mainstream) are involved, similar odorous constituents may be present in all considered breast subdivisions; cf. Schaal et al. 2008] or from cross-contamination (the sucking infant spreading and mixing the different milks on the entire areolar-nipple area), or did these odour “fractions” bear equivalent reward value despite being perceptually dissimilar (as shown in Delaunay-El Allam et al. 2006). Anyway, more “radically” isolated exocrine components of breast secretions and finer grained analyses are needed to further assess the source of the attractive-appetitive odour factor in the mammary odour melange.

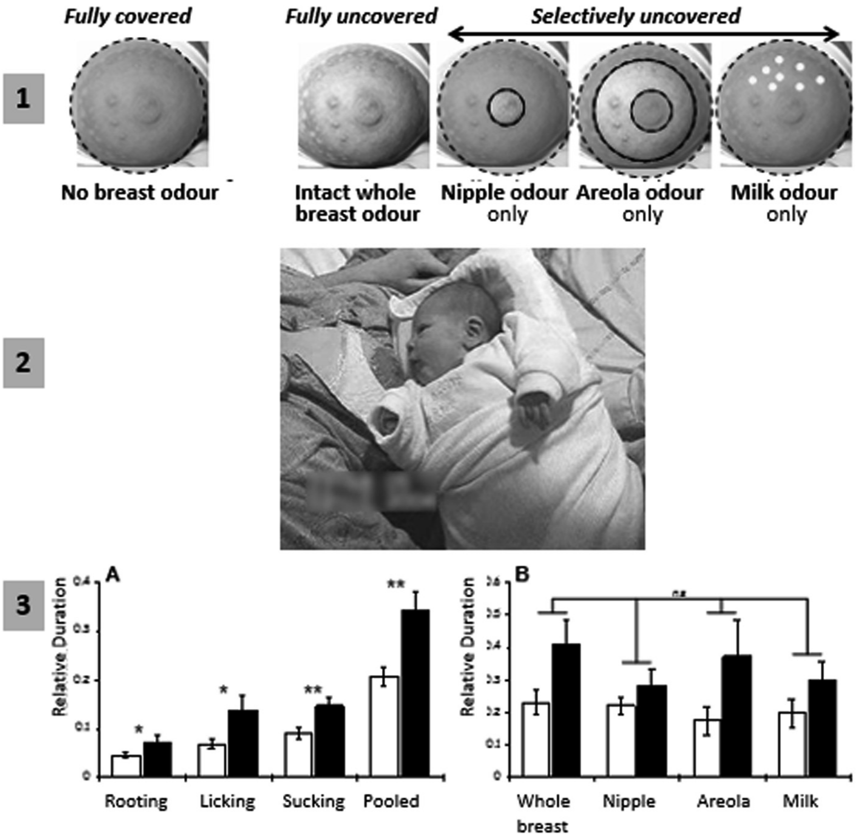


Fig. 3. Design and results of the experiment aiming to behaviourally “fractionate” the potentially discernible odour sources of the breast. **1** The distinct conditions of breast covering with a scentless plastic film and the corresponding odour assumed to be delivered to the neonate. **2** The testing situation which consisted of holding awake newborns in their habitual nursing posture in close proximity, but without contact with their mother’s breast. **3A** Relative duration of infants’ cephalic (i.e. rooting) and oral (i.e. licking, vacuum sucking) responses, and pooled responses, when facing the non-odorous (fully covered) breast (white bars) versus the olfactorily intact (fully uncovered) breast (black bars). B. Duration of infants’ pooled head and oral responses when facing the non-odorous (fully covered) breast (all white bars) versus the whole breast odour (fully uncovered), the nipple odour only, the areolar odour only and milk odour only (all black bars). Significance: $*p < 0.05$; $**p < 0.01$; ns: non-significant. After data from Doucet et al. (2007)

Such exocrine compounds fully isolated from the breast were later assayed in exposing 3-day-old neonates to the odour of the latescent secretion taken directly from AG (Doucet et al. 2009). The native AG secretion was presented on a glass stick. AG secretion components, viz. mainstream milk and sebum from forehead skin, were also presented on a glass stick, assuming *provisionally* that areolar milk and sebum are compositionally similar to mainstream milk and frontal sebum. In addition, the above three stimuli (donated by unfamiliar lactating females) were tested for specificity against control stimuli, including water, vanilla, cow milk and cow milk-based formula. Infant reactive measures consisted in mouth–face movements, as well as variations of heart and respiratory parameters.

As a result, pure AG secretion elicited much higher rates of oral–facial responses than all other stimuli, including mainstream milk and forehead sebum (Fig. 4). This oro-facial response release was both immediate during the 10 s AG secretion presentation and lasted for the next 10 s period. In terms of responding infants among the 19 tested, 12 reacted to AG secretion, while only 5 reacted to human milk, and 4 to sebum [4 reacted to water as the blank].

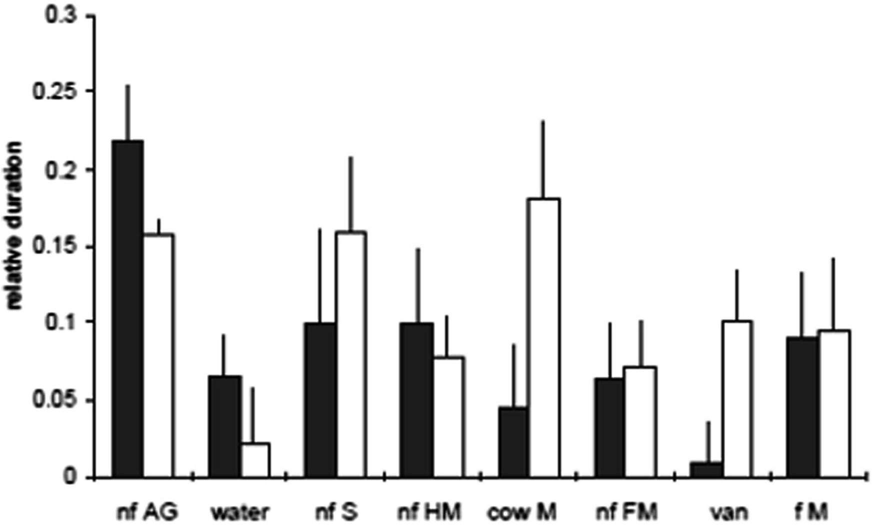


Fig. 4. Mean (± standard error) relative durations of newborns' oro-facial responses during (10 s stimulus period; black bars) and after (10 s post-stimulus period; white bars) presentation of various odour stimuli (AG: secretions of areolar glands; S: sebum; HM: human milk; cow M: cow's milk; FM: formula milk; van: vanillin; M: milk; f: familiar; nf: non-familiar; *n* = 19). Note that the areolar gland secretion (nf AG) elicits significantly more oro-facial responses than all other stimuli during the stimulus presentation period (black bars). After data from Doucet et al. (2009)

The AG secretion was also clearly more behaviourally active than the heterospecific substrates, cow's milk and unfamiliar cow's milk-based formula, and the arbitrary odorant vanilla [5, 3, and 1 responding infants among 19, respectively]. Thus, the behavioural response caused by the AG secretion cannot be interpreted as resulting from the effects of any odorant or of stimulus novelty. Finally, the AG secretion from an unrelated mother released longer oro-facial responses than the familiar milk, either maternal or formula, to which they were exposed at each feed since birth (only 3 responsive infants among 19), suggesting that the intrinsic reinforcing power of unfamiliar AG odour is much stronger than the reinforcing power attached to the familiar milk through repeated alimentary conditioning.

The isolated AG secretion also influenced the responsiveness of the autonomic nervous system. It increased the infants' respiratory rate and inspiratory amplitude more than all other stimuli, including mainstream milk and forehead sebum, the theoretically most resembling components of AG secretion. Otherwise, this effect of AG odour on the respiratory variables was not dependent on the mode of infant feeding (breast or bottle), supporting further the notion that AG odour reactogenic potency does not depend on previous exposure to a lactating breast. Thus, the isolated secretion from the AG conveys volatile compounds the effects of which on neonatal behavioural and autonomous responsiveness are stronger than mainstream milk or frontal sebum.

In sum, this study supports the hypothesis that the human AG secretion carries an odour factor that strongly impinges on human neonates. Specifically, AG odour appears more behaviourally effective than the odours of isolated human milk or sebum. Our premise that the lacteal and sebaceous fractions of AG secretions could be reflected in mainstream milk and frontal sebum may not be accurate, or, to be behaviourally effective, both fractions need to be mingled within the same mixture as is often the case in mammalian chemical signals (Albone 1984; Wyatt 2014). Importantly, in Doucet et al.'s (2009) study, the rate of infants' previous exposure to breast-related stimuli did not affect their response to the odour of AG secretion, suggesting that extensive postnatal exposure is not required for AG odour to become reactogenic. Further investigation is obviously needed to settle these questions, especially in verifying whether AG secretions and mainstream milk convey similar or distinct volatile signals to infants.

6 Adaptive Effects of Areolar Glands on the Infant and the Infant-Mother Dyad

The above ethology-inspired assays highlight that infants detect and react to the effluvium released from the breast by their own mother or by any lactating woman. They bring little insight into how these early emissive and reactive abilities are involved in adaptive processes in the context of real breastfeeds. Other ways of investigating infant responses to mammary odours may complement the aforementioned experimental approaches. They consist in recording reports from particular observers, such as mothers or midwives, who are indeed privileged witnesses of infant behaviour in the hours/days following birth. Not only do they scrutinize infants' condition quasi-continuously, but also, with adequate tutoring, they can evaluate the quality, quantity (intensity), patterning, and timing of infants' actions and interactions in the breastfeeding context. Thus, informed maternal or clinical observations may be a worthy approach to gauge the functional value of olfactory stimuli in infants' life, which is unmanageable in experimental settings. Such "intimate" reports of infant responsiveness to mammary odours have been implemented in two instances.

In the first of these reports, infants' behaviour toward the breast was related to their mothers' endowment in AG (Schaal et al. 2006). Mothers, blind to the hypotheses of the study, rated their nursing infant's behaviour through an *ad hoc* 4-item rating scale applied on days 1–3 after birth. They evaluated the infant's behaviour in terms of (i) duration of bilateral rooting movements, (ii) latching speed, (iii) avidity/intensity of sucking, and (iv) general arousal state while nursing. The outcome variable was the average of a given item's scores for each breast, and then the average over postpartum days 1–3. A global score of maternal perception of infant behaviour aggregated the separate scores of the 4 items. As a result, the mothers' AG count (irrespective of their apparent secretory status) correlated negatively with infants' rooting duration ($r = -0.61$, $n = 17$, $p < 0.05$) and positively with nipple grasping speed ($r = 0.55$, $p < 0.05$). The AG count also correlated positively with the infants' intensity of sucking ($r = 0.40$, $p < 0.05$). Finally, the global score of mother's perception of infant activity at the breast correlated positively with AG number ($r = 0.69$, $p < 0.05$).

The correlations between AG number and the above 4 items of infant behaviour were further examined daily over the first 3 postnatal days. The mean AG number correlated (i) negatively with the mother-reported frequency of rooting activity on days 1 and 2, but no more significantly on day 3 ($r = -0.56$, -0.50 and -0.36; $p < 0.01$, <0.05, and >0.05, respectively); (ii) positively with the speed of nipple grasping on days 2 and 3 ($r = 0.49$ and 0.56, $p < 0.05$); and (iii) positively with sucking intensity on day 1 ($r = 0.64$, $p < 0.01$). Thus, mothers whose areolae are richer in AG appear to report shorter latencies to their infants' nipple seizing and higher sucking activity during the daily breastfeeds, but these correlations appear to be stronger on the two first postnatal days.

A second study sought to check further the above hypothesis in assessing the relationship of AG counts with the neonates' behaviour during their earliest breastfeeds (Seidel et al. in preparation), i.e. when they initiate coping with the novel task of localizing their mother's areola-nipple and acting on it. The newborns' behaviour was assessed by a midwife using the validated Infant Breastfeeding Assessment Tool (IBFAT; Matthews, 1988), itemized along (i) alertness and readiness to feed, (ii) rooting, (iii) fixing (latching) and (iv) sucking pattern (all coded 0–3 on 4-point Likert scales). The aggregated items provided discrete IBFAT scores (range: 0–12) for each of the first 4 breastfeeds that occurred within 24 h from birth, the first one happening in the delivery room (mean time since birth: 53 ± 36 min). Then, a global IBFAT score was defined as the mean of these discrete feed-specific scores. Thus, the present study assessed whether the maternal endowment in AG was influential on the infants' performance during the first four breastfeeding episodes.

In these conditions, mothers having higher (than the median of the group = 8) AG counts reported a higher global IBFAT score as compared to mothers bearing lower AG counts [mean global IBFAT score: 9.9 ± 1.2 versus 8.8 ± 2.3, respectively; $F(1, 63) = 3.96$; $p = 0.05$]. Interestingly, the mothers' AG endowment interacted with their experience of mothering a previous child: a 2-way ANOVA considering parity and AG count yielded a marginally significant effect [$F(1, 63) = 3.36$; $p = 0.07$]. In other words, newborns from primiparous-and-lowly-AG-endowed mothers tended to evince a lower mean global IBFAT score than those of primiparous-and-highly-AG-endowed mothers and of multiparous-and-highly-AG-endowed mothers ($p = 0.03$ and 0.01, respectively). Finally, the mean global IBFAT score of newborns of multiparous-and-highly-AG-endowed mothers was not significantly different from the ones of the newborns from the other above groups. When considering how the AG count relates with infant behaviour at the separate first 4 breastfeeds, it appeared that mothers bearing higher AG number reported higher IBFAT score in their infant than mothers bearing lower AG counts at all 4 breastfeeds, but the difference was significant only on feeds 1 and 4.

These results indicate that a mother's endowment in AG relates somehow with the adaptive sucking responses of infants at the breast. However, multiple other factors qualify this relation. Among these, mothers' parity (i.e. the number of previous births) is of prominent influence (it is noteworthy that the above groups of mothers were balanced in size and infant sex ratio, as well as in newborns' birth weight and gestational age, and in mothers' age, labour duration and time to first breastfeeding). The impact of parity is indeed omnipresent in the maternal physiology and behaviour of mammals, including humans (e.g. Thoman et al. 1970; Fleming 1990; Hrdy 1999). In particular, first-time mothers appear less optimal in their assistance to the newborn, especially in the first episodes of nursing (Dewey et al. 2003; Michel et al. 2007), leading their infants to be more contingent upon their own sensitivity and behavioural efficiency to achieve successful nipple localization and latching. In this context, primiparous mothers endowed with more AG (compared with primiparae endowed with less AG) may be more efficient in their (chemo)sensory guidance to the nipple.

A logical consequence of the above results would be that, if AG activate nursing infants, they should also thrive more efficiently. Indeed, infants of mothers having higher AG counts exhibit lesser average weight loss between birth and day 3 as compared to infants of mothers with lower AG number. Thus, the amount of AG is tied to fitness consequences in terms of infants' weight regain after birth, an effect that is expectedly again qualified by parity (Schaal et al. 2006; Doucet et al. 2012): Passive (areolar odour) and active (experience-dependent care) affordances of the maternal organism interact in the infants' breastfeeding competence, modulating early postnatal body weight fluctuations. This link between maternal AG and neonatal short-term weight gain can be understood as resulting from the reciprocal action of infant's and mother's physiology/behaviour: more AG leads to more efficient sucking, which leads to extra nipple stimulation, commanding earlier onset of lactation, increased release of milk, and finally enhanced infant growth, which in turn feeds back onto previous processes. Data from two studies confirm indeed that the AG count correlates negatively with the timing of lactation stage 2 onset: the more mothers bear AG, the earlier they do evince 'coming in' of milk (Schaal et al. 2006; Doucet et al. 2012). Finally, through their reactogenic power on newborn infants and the mediation of induced sucking, chemical cues emanating from the areolar-nipple regions may orchestrate in parallel lactational physiology and adaptive effects that favour empathetic feelings and bonding on the part of mothers (Bourvis et al. 2018).

7 Conclusion: Variability and Regularity in the Human Mammary Chemosignalling System

The above account reveals the polymorphism of the human mammary phenotype regarding traits such as total number of AG, number of secretory AG, distribution of AG on the areolae, which all may participate in areolar chemosignalling. On the other side, there is also variability/regularity in the behavioural activity that these volatile compounds elicit in newborn infants.

7.1 Variability/Regularity in Areolar Chemo-Emission

Three replication studies showed that the amount and spatial patterning of AG varies between women. Despite this phenotypic variability, the majority of women in the studied samples (85–90%) bore 1 to more than 40 AG on each areola. In about 1 in 4 or 5 mothers (depending on the study), some of these AG were seen to emit a secretion in minute amounts (several tenths of μL between two breastfeeds). These secretory AG appear located 'strategically' under the nose of infants in typical nursing position (i.e. over the external/upper quadrant of the areolar disc), a coincidence suggesting their potential involvement in communication.

However, the chemosignalling service of AG may be ancillary to other basic functions encompassing integrity of areola-nipple against sucking-induced pain, soreness and corrosion, as well as creation of the seal permitting the negative pressure of sucking. Thus, if any, the communicative function of areolar chemistry must be understood in the wider context of these mechanical or protective roles. One may expect that a glandular system that assigns conjointly protective, sealant and signalling functions to the interface structure that delivers milk to offspring be of highest survival value. For the sake of species perenniality, such an interface structure should be positively selected and, hence, an optimally designed AG pattern should be well conserved across individuals.

The current state of research makes it hard to draw an optimum AG endowment in either amount, arrangement, activity or timing. Limited evidence indicates that a certain amount of AG has fitness consequences in terms of initial infant growth and the onset of stage-2 lactation. But, although AG secretions are especially reactogenic for infants, we have no insight on the number of secretory AG necessary to elicit adaptive responses *in the nursing newborn*. Probably only one, well-positioned AG would be enough to boost orientation, mouth gaping, latching and sucking. In an optimal AG design, one may also expect intra-individual phenotypic plasticity of emission of AG secretions, in the sense that their activity should be maximal right after partum in order to boost infants' responses at the initial breastfeed attempts. Such an early adaptive consequence of AG could also work on the mother's side, improving preservation of the papillary epidermis when it is maximally exposed to sucking-related stress. All these points need further observational and experimental scrutiny.

The reasons and mechanisms underlying the variability in areolar skin structure and functioning are unclear. They could rest first on methodological issues, such as our sampling of secretory AG made outside episodes of breastfeeding, their activity (and the odour-amplifying thermal properties of the areola) being partly conditional upon infant's physical presence. Another limitation of current investigation may reside in the restriction of extant studies to Caucasian participants. One cannot exclude that certain ethnic groups may express higher variability in areolar features than others (e.g. in a similar way that axillary glandular endowment differs between Asiatic, African and Caucasian populations; e.g. Rawlings 2006; Schaal and Porter 2001; Wang 2018; cf. also Prokop-Prigge et al. 2015, 2016). More distal explanations of human AG variability may be sought in an evolutionary relaxation of selective pressure on areolar structure and functions. The variable glandular endowment of the mammary outlet may indeed reflect biocultural compensation of suboptimal areolae by the enrolment of allomothering or wet nurses along hundreds of generations (e.g. Badinter 1982; Hrdy 2009; Roulin and Heeb 1999) and, since the domestication of dairy species 8,000–10,000 years ago (e.g. Vigne and Helmer 2007; Evershed et al. 2008), the use of heterospecific milks and substitutive milk-delivery devices (e.g. Delahaye 1990; Dasen 2003). Thus, we hypothesize that biocultural evolution may have buffered the adverse effects of lower extreme cases of variability of the areolar-papillary structure, especially in populations consuming dairy products collected from the cow or other mammals.

Future studies on AG and related secretions should consider comparing populations of different genetic and cultural backgrounds. Based on the above argument, one may hypothesize that non-medicalized hunting-gathering populations could have a different AG design than populations relying on dairy farming. Also, whether there is a particular AG design that is more effective for mother-to-infant chemosignalling may be addressed in studying extreme cases of AG numbers. Mothers (especially primiparae) bearing AG-defective areolae could thus be investigated in terms of infant's breastfeeding and growth performances or, on the maternal side, nipple integrity, course of lactation, delay to supplement the infant needs with nonhuman milk-feeds. Another point for future studies would be whether AG function at a higher rate (i.e. with more secretory AG) during the colostral period, when breastfeeding is initiated and nipples/areolae need both greater protection and olfactory advertisement to infants; alternatively, does AG function extend much longer than the initial days/weeks/months of lactation? Such a case of intra-individual phenotypic plasticity in mothers is of great theoretical interest as it relates to events that are both causal and consequential on the infant's activity. Finally, it would be of comparative interest to analyse whether other primate lactating females, especially anthropoids, have also evolved infant-directed chemosignalling mechanisms around, on or within their nipples.

7.2 Variability/Regularity in Neonatal Response to AG Secretion

In the so far single study to assess neonatal response to the odour of pure AG secretion (Doucet et al. 2009), 12 on 19 (63%) were reactive according to the response criterion. Although this is a notable proportion, it also points that between- and within-individual variability occurs in neonatal responsiveness to mammary odour cues. This highlights the difficulty in designing an optimal functional assay for olfaction in human newborns.

The behavioural responses elicited in neonates by the volatiles emitted by the lactating breast pertain to several categories, including attention (temporary inhibition of crying, eye opening), head orienting, whole-body approach and activation of the face, mouth, and tongue. These basic responses are not all expressed in experimental conditions that do not mimic the context of nursing. However, several studies, among which the aforementioned study by Doucet et al. (2007), show that all these items are sequentially displayed when the behavioural testing occurs in ecological conditions, i.e. when motivated infants are positioned in proximity to the breast or a representative odour stimulus (see also Varendi et al. 1994; Mizuno and Ueda 2004). However, feeding-ready infants are tricky to assess for choice or preferences, as their response repertoire promptly ends in disorganized fussing and crying (and then the ability to put an end to crying may be another criterion of efficiency for a given odour stimulus). Psychophysiological measurements (e.g. heart and respiratory parameters, metabolic or electrical brain activity) are less compatible with such ecological testing, as movements generally induce recording 'artefacts' that mitigate interpretation of autonomic or central variables. These latter variables can however be assessed in sleeping infants as indices of detection and differential processing of odour stimuli (e.g. Soussignan et al. 1997). Thus, infant odour bioassays encompass a range of behavioural measurements that are variably expressed depending on the ecological validity of the test setting. In sum, convergent ecological and non-ecological approaches are needed to establish a complete or optimal multi-bioassay for human newborns.

Another point is that inter-individual variability in responsiveness to mammary odour cues is not exceptional in mammalian newborns, even in case of species which neonates do exclusively depend on olfaction to locate a nipple (e.g. Hudson and Distel 1995; Schaal et al. 2003; Schaal 2010). For example, 8.7 and 7.2% of rabbit newborns do not respond when experimentally exposed to the mammary pheromone on post-partum days 1 and 3, respectively (Coureaud et al. 2007), although they are critically dependent on it to survive. In contrast to rabbit neonates that are exclusive olfacters (their auditory and visual tracts being not functional), sensorily precocial human infants perceive the environment through olfaction in the same time as through the other sensory systems including audition and vision (Schaal and Durand 2012; Durand et al. 2013). Thus, the early multisensory ability that is typical of human infants may be another inherent source of response variability to areolar odour cues.

In sum, future studies are needed to replicate human neonatal responses to areolar or lacteal chemosignals, using multiple indices of attention, motivation and selective appetence (see also Loos et al. 2019). One may expect that species with precocial newborns, like those of humans who have a complete, although immature sensorium, are more variable in their responsiveness to such maternal cues. *In fine*, the plasticity range of sensory drivers of neonatal behaviour may be a determining factor of the structure of the species-specific maternal milk-transfer interface.

Another point of interest for future studies would be the impact of AG on infants beyond the colostral period: do they influence infant behaviour only during a limited postnatal window ensuring the transition until infants engage other sensory or cognitive adaptive means, or do they provide a prolonged stimulating effect during weeks or months of breastfeeding? In addition, do AG secretions have a role in the maintenance of sucking activity during the whole breastfeeding episode rather than only guiding the infant to the nipple and stimulating onset of sucking?

In any case, the areolar polymorphism of human lactating females evidenced here reveals the considerable plasticity of human infants to adapt to their nursing mother's breast. One point will be to establish how an earlier maturing sensory modality such as olfaction (relative to later-maturing senses like vision) contributes to this initial plasticity in the ways of acquiring the life-saving colostrum and milk. Another point relates to current theoretical debates relating inter-individual variability of a bodily feature and the function of it, with the frequent postulate that high morphological variability of a feature implies a lack of function or of selection thereof (e.g. Kelly et al. 2018). In contrast, Houle (1992) suggests that morphological traits supposed to be under strong selection tend to exhibit more variability than those assumed to be under weak selection. If this principle is relevant for the phenotypic variability of physiological or behavioural traits, the interindividually variable endowment in skin glands' of the human areola during lactation may relate to functionality and strong selection for functionality.

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