



Early Interplay of Smell and Sight in Human Development: Insights for Early Intervention With High-Risk Infants

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Accepted: 2 November 2023 / Published online: 27 November 2023
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Abstract

Purpose of Review In this narrative review, the early interplay between olfaction and vision is analysed, highlighting clinical effects of its manipulation in typical subjects and in presence of visual disorders. In addition, new methods of early intervention, based on this multisensory interaction, and their applications on different infant populations at risk of neurodevelopmental disabilities are discussed.

Recent Findings Multisensory processes permit combinations of several inputs, coming from different sensory systems, playing a key role in human neurodevelopment, and permitting an adequate and efficient interaction with the environment. In particular, during the early stages of life, the olfactory and the visual systems appear to interact to facilitate the adaptation and the mutual bond with the caregiver and to mediate the development of social attention of the infant, although, at birth, the olfactory system is much more mature than the visual system.

Summary Although the results from this line of research are promising, mechanisms at the basis of this interlink between sight and smell are unclear, so more work needs to be done before concluding that a multisensory approach, based on visual and olfactory stimulations, is applicable in clinical practice.

Keywords Vision · Olfaction · Sensory processing · Development · Multisensory

Introduction

Development of multisensory integration (MI) begins early in human life and continues to develop after birth through an individual's interaction with their physical/social environments. Simultaneously, MI capacity plays a key role in human neurodevelopment by progressively enriching our sensory experiences and increasing the accuracy of our judgements of environmental events [1, 2].

During the first periods of life, olfactory stimulation (odour of the mother's skin, odour of the breastmilk, odours of different people or environments) acts a

particularly important function in the adaptation to the surrounding world. Specifically, olfactory stimulation is vital for the survival of newborns in postnatal life, because it promotes a range of early regulatory functions and motor responses [3]. About this, it is well known that during this period, the mother is one of the most important sources of sensory and multisensory experiences for the infant, regulating physical growth and promoting neural maturation of brain structures involved in cognitive functions [4]. In particular, the olfactory and the visual systems appear to interact early during the neonatal period and this interaction continues through childhood, mediating the development of communication and social attention [5].

In line with this knowledge, this review is aimed at (i) examining the role of the interplay between olfactory and visual stimulation in neurodevelopment, (ii) highlighting the differences in these multisensory processes in children and adults with visual disorders, and (iii) exploring the clinical implications for early intervention of infants at risk of neurodevelopmental disabilities.

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Visual-Olfactory Interaction in Human Development: a Bridge From Intra-Uterine to Extra-Uterine Life

Evidence of prenatal olfactory function primarily comes from animal models, but it is known that olfaction is one of the most precocious sensations; in a human foetus it is functioning from around 29 weeks of gestational age (see Fig. 1) [6]. In fact, at birth, the olfactory system is much more mature [3, 7•], than the other sensory systems, for example the visual system [8]. Therefore, in the early postnatal period the sense of smell plays a meaningful role in the mediation of neonates' adaptive behaviour and well-being. For example, it was shown that 3-day-old newborns are capable to respond selectively to the odour of their mother's amniotic fluid from that of another mother [9]. Moreover, several authors suggested maternal odour might therefore be an important guiding factor in emotional learning in infancy. On the other hand, olfaction also depends on experience to improve, as early postnatal experiences are crucial for the development of olfaction from the early stages of life to the adolescence [3, 7•]. In line with this thought, Romantshik et al. [10] found that the first hour after birth is a sensitive period for olfactory learning by human neonates. Indeed, behavioural evidence of efficient olfactory learning in newborns was only found when the exposure to olfactory stimulation occurred shortly after birth, but not when it occurred 12 h after birth. Taken together,

these findings suggest that prenatal experiences influence the earliest olfactory preferences in the breast-feeding human neonate but also that these capacities rapidly change thanks to postnatal stimuli. About this, in a recent review, Shafer and Croy [11] emphasise the significance of smells in parent-child communication, not just during infancy but throughout the entire developmental period. However, body odour expression and perception evolve over time, leading to reduced olfactory reinforcement of bonding.

Few studies have investigated the possibility that olfaction may interact with other sensory modalities, facilitating the extra-uterine adaptation of newborn, although the interaction between vision and olfaction seems active from birth. This interaction seems to play a key role in the progressive adaptation and knowledge of the environment's elements. For example, Doucet et al. [12] explored the hypothesis that the breast odour might modulate visual input in newborns. In this study, the authors examined the behavioural responses of infants facing their mother's breast, manipulating the natural olfaction stimuli. Newborns were presented their mother's breast in two consecutive trials: a scentless condition (breast entirely covered with a transparent film) paired with one odorous condition. According to these findings, the duration of eye opening was longer when the newborns were facing the odorous breast condition compared to the scentless breast condition. In addition, the infants' behaviours to the visual "landscape" of the breast were different when the corresponding natural odours were present. In fact, when the

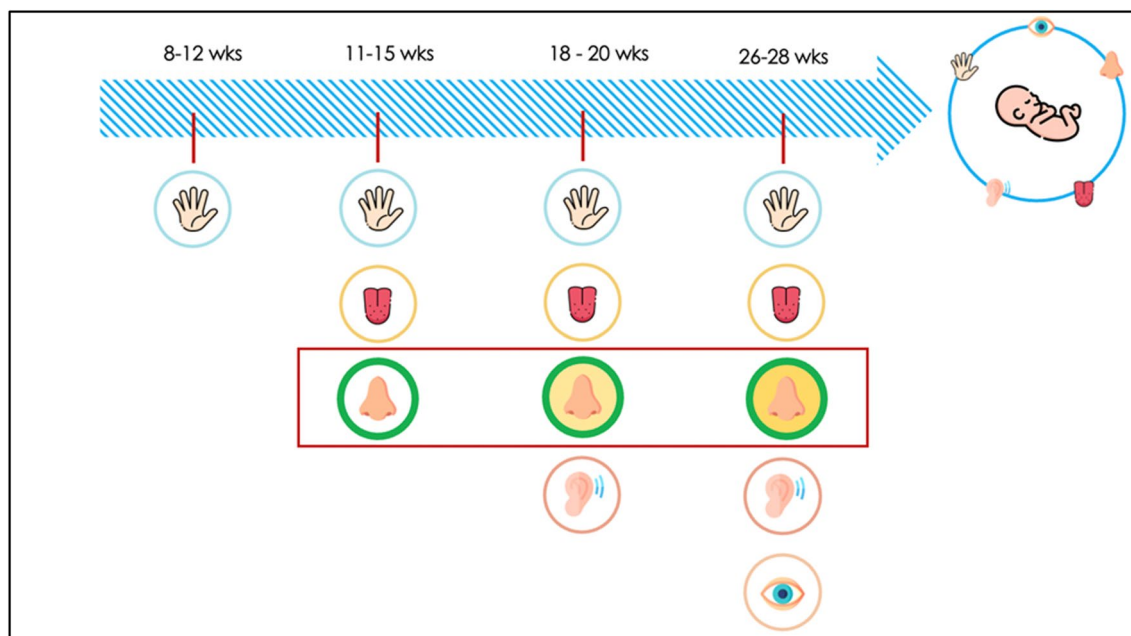


Fig. 1 What role does smell play in sensory development? A schematic timeline of senses' development before birth, underlining the precocity with which the sense of smell develops before that of sight.

The red rectangle highlights the evolution of olfactory structures and skills: from the development of the ciliated neuroreceptors (11–15 weeks) to the responses to chemical stimuli (26–28 weeks)

newborns saw the breast in a nursing-like position but with an absence of odours, the infants began crying more rapidly.

Given the importance that smell [13] and sight [14] have in the early mother-infant bonding, some research has focused on the role of their interplay in development of social attention. Durand et al. [5] investigated visual behaviour of 4-month-old infants to social (faces) and non-social (cars) stimuli in association with two olfactory conditions (familiar odour vs control odour). They found that infants exhibited a spontaneous preference for faces and that this preference significantly increased when the human face was associated to a familiar human odour. These findings were supported by the results of Leleu et al. [15••]. These authors used a neurophysiological approach to test the hypothesis that, in 4-month-old infants, visual categorisation of human faces is shaped by another human-related input from the olfactory system, which is the mother's body odour. They observed that the concurrent body odour inputs from the mother actively shape face categorisation, by enhancing a face-selective response in individual infant brains, especially over the right occipitotemporal cortex. More recently, the same research group suggested also that adding maternal body odour caused a significantly increased response to face stimulus and shift in the brain response over to the right hemisphere, which is dominant for face categorisation in the mature brain [16]. This suggests that early multisensory visual-olfactory processes are critical for cognitive and social development in developing human brain.

In line with these findings, it was found that infants are able to match affective affordances carried by olfactory and visual inputs [17]. Specifically, it was demonstrated that these intersensory matching abilities are active in 3-month-old infants, but they disappear between 5 and 7 months of age. Thus, although in typical neurodevelopment olfaction might affect visual behaviour, several variations during perceptual development could produce changes to the interaction of these two sensory systems.

In fact, it is true that individuals use olfaction to interact with the environment, but during the lifespan the role of olfaction progressively changes, which allows for an increase in the use of the other sensory stimuli (which eventually become primary, e.g. vision). It was observed that some associations between odour and pitch, odour and shape, and odour and tactile properties were more likely to be observed in older children (from 10 years old), than younger children, suggesting a progressive maturation during the school age of these cross-modal correspondences [18]. At the same time, Arshamian et al. [19] found that mental imagery of smell and taste remains equally poor for adults and children in comparison to the other sensory imageries, even though within this age range there is evidence of a developmental maturation (e.g. more vivid imagery for sight and hearing especially coming into adulthood). However, in adults,

olfactory information processing deactivates the default mode network as evidenced by fMRI analysis, which suggests that olfactory perception may draw cognitive, attentional, and memory resources during odour processing [20].

Finally, according to Rekow et al. [21], the disambiguating function of visual-olfactory integration persists also in adulthood due to congruent odours facilitating neural visual categorisation when the interpretation of the visual input is equivocal. Overall, body odour helps in categorising ambiguous face-like stimuli, confirming the importance of olfactory stimuli in social adaptation.

How Much Does the Sense of Smell Weigh on Other Sensory Channels? A Focus on Olfactory Skills in Children and Adults With Visual Impairment

It is well known that olfaction represents the sense that, along with taste, develops first in humans and it plays a pivotal role as early as the gestational age [22]. But despite numerous works on how important the sense of smell is during the first stages of neurodevelopment, there are not many studies focused on what happens to the olfactory system in the event of impairment to one of the other sensory channels, especially the sight. A lot of literature shows that congenitally blind people exhibit impairments in specific auditory or tactile spatial tasks [23, 24]. However, other studies have argued that in the absence of vision, our brain tends to give more weight to sensory estimates obtained from the other intact senses, therefore leading to a greater reliability to spatial non-visual cues [25]. Hence, here we discuss the second aim of this review which is to summarise evidence in the literature regarding the development of olfactory skills in visually impaired people.

A recent review by Sorokowska et al. [26] highlights rather heterogeneous data in this regard: they found contradictory results in studies conducted since the beginning of the twentieth century on olfaction, probably due to the variability of the samples considered and to the different olfactory abilities tested. Notwithstanding, the authors argued that olfactory abilities in blind and sighted people are similar overall [26]. The earliest works regarding this issue date back to 1986 when Murphy and Cain [27] examined olfactory identification abilities in 20 blind adults. Those authors administered a threshold test and an identification test with olfactory stimuli to both sighted and blind subjects. They found that sighted people had significantly better sensitivity but were unable to perform the identification task. Meanwhile, blind individuals were able to name 31% more odours than sighted people. Conversely, in a more recent study conducted by Luers [28], it was shown that there was no significant difference between blind and sighted subjects

as regards olfactory threshold and in the identification and discrimination performance. Some years later, Sorokowska et al. [29] confirmed comparable results, using a new protocol in which an odour identification test in addition to extensive psychophysical testing and self-assessed olfactory performance were combined. The authors highlighted that sensory compensation in the visually impaired sample did not occur with regard to olfactory abilities. Overall, these results suggest that olfactory abilities of blind people are similar to those of sighted people, regardless if they were born blind or developed blindness later in life.

There are several studies that explored the possibility that smelling abilities can support and integrate other sensory information to promote adaptive behaviour, even in case of early-onset visual disorders. An example of this is work from Manescu et al. [30] that showed only patients with congenital, and not late, blindness outperformed sighted individuals in an olfactory localization task by extracting spatial information from chemosensory stimuli. Therefore, the authors suggested that visual impairment at birth can lead to an improvement in spatial skills mediated by another sensory modality, in addition to touch and hearing. Even fewer studies have been conducted regarding the effects of visual impairment on social assessments and on the possible compensation of other sensory channels. One such study [31] explored the importance of non-visual sensory modalities in the assessments of opposite-sex strangers, in the context of mate selection. They observed that in the absence of sight, the importance of hearing increases in social assessment tasks, but this does not happen for the other sensory modalities, including olfactory. However, taking a neurobiological point of view, it is widely documented that in people with early-onset blindness, adaptive neuroplastic changes are active with regard to the processing of non-visual cues, in particular tactile and auditory [32, 33]. Moreover, few studies have investigated the neural correlates of olfactory processing in adults with visual impairment. One recent example from Kupers et al. [34••] exhibited stronger recruitment of the occipital cortex during odour detection. This finding expands the current knowledge about the supramodal function of the visually deprived occipital cortex in people who are blind from birth.

Likewise, some research has been conducted on the development of olfactory skills during infancy and childhood in subjects with visual disability. It is known that children with visual impairment do not always benefit from multisensory integration. For example, one study [35] showed that visually impaired children do not rely on visuo-haptic integration to perform an object recognition task. While many studies have investigated how visual impairment impacts the cross-sensory calibration of vision and touch, less is known about what happens to the olfactory sense in case of visual disorders. A study conducted by Rosenbluth

et al. [36] indicated that young children with very early-onset blindness showed an advantage for some olfactory tasks, but not for others. Specifically, in a task involving the self-generation of odour labels, they performed better compared to sighted controls. But in an olfactory sensitivity task, in which they had to choose the correct odour from an array of labels, they performed similarly to controls. Another example from scientific literature is the study conducted by Wakefield et al. [37]. They investigated the cognitive factors associated with the ability to name a familiar odour by comparing early blind, late blind, and sighted children (12–16 years old). More precisely, these authors proposed to the children of the three groups (i) two olfactory tasks, which were an odour-naming task and an odour-sensitivity task with a 2-alternative forced-choice, (ii) three paired-associate memory tasks, each using a different type of association—odour-word, word-word, and sound-word, (iii) a story recall task, to evaluate the capacity to memorise and retell short stories, and (iv) a sound-naming task to evaluate the directed attention. Finally, after each task, the authors recorded the strategy chosen by the children for the paired-associate tasks, by asking “How did you remember which smell/sound/word went with which word?” Based on children’ answers, strategies were categorised into “no strategy”, “visualisation”, “word association”, and “remembering the order of presentation of the stimuli”. They demonstrated that visually impaired and sighted children had an equal ability to identify odours, yet the blind children achieved higher results on cognitive tasks that did not require the use of visualisation to improve their performance. This was particularly pertinent in the case of children who experienced blindness from the earliest stage of development. To be exact, early blind children scored significantly better than sighted controls on the non-visualisable word pairs task and sound-word pairs task and performed better in the direct attention task; in contrast, such a significant difference was not found in the memory task for a story or for visualisable word pairs.

Recently, a study used questionnaires to investigate the awareness and reactivity to olfactive stimuli in sighted and visually impaired children [38]. These authors found that children with visual impairments reported that they paid more attention and reacted more often to odours than sighted children.

So, in the current review we observed a strong heterogeneity of the obtained results regarding the role of olfaction in sensory calibration in case of visual impairment. Therefore, since it is known that during the early stages of life, smell plays a pivotal role in the adaptation to the surrounding environment, it would be interesting to conduct more focused studies on the weight of olfactory during the first days of life in children with visual impairment. These studies are needed in order to implement even more targeted rehabilitation plans from the earliest periods of development.

Clinical Implication and Future Directions for Neurorehabilitation of Children at Risk of Neurodevelopmental Disabilities

Despite growing awareness of the potential therapeutic benefits of early multisensory intervention for infants and children at risk of neurodevelopmental disabilities [39, 40], the combination of olfactory stimulation with other sensory stimulation is rather underused in this context.

To our knowledge, the first study that investigated the use of olfactory stimulation in daily care routine of infants at risk of neurodevelopmental disabilities is that of Goubet et al. [41]. During this research, they explored the possibility that a familiar odour might alleviate a premature infant's pain during and after blood collection procedures. Although the underlying mechanism was not completely clear, authors demonstrated that infants who were presented with a familiar odour during venipuncture showed no significant increase in crying and grimacing during the procedure compared to baseline levels before blood collection. Moreover, infants presented with an unfamiliar odour or with no odour at all during procedures of blood collection had a significant increase in crying and grimacing. Finally, when the pain was milder and a concomitant familiar odour was presented, infants showed little to no crying. Successively, similar results were obtained also by Badiee et al. [42] that found that breast milk odour had better ability to control the pain in comparison with formula milk odour in preterm infants, suggesting analgesic effects in premature infants of the breast milk odour: babies who were exposed to the smell of milk of their mothers during painful procedures had lesser increases in salivary cortisol levels than the group that was exposed to formula milk odour.

Interesting results also come from Khodagholi et al. [43] who have administered an intervention based on Non-Nutritive Sucking (NNS) combined with olfactory stimuli in a group of preterm infants born between the gestational age of 28 and 32 weeks. The olfactory stimulations added to NNS were performed with cotton pads impregnated with breast milk from the infant's mother and held around 2–3 cm from the infant's nose. This approach, in comparison with the exclusive NNS intervention, demonstrated an acceleration in the sucking function of infants and the transition from tube to oral feeding, promoting a faster discharge from the hospital. Similar results were obtained also by Yildiz et al. [44], who found that preterm infants exposed to breast milk odour during gavage feeding made a transition to oral feeding sooner, had increased weight gain, and were discharged from the hospital earlier than infants in the control group who did not receive such stimulation.

Based on these studies, Neel et al. [45] recently proposed a randomised control trial to investigate the causal effects of multisensory stimulation on neurodevelopmental outcomes in preterm infants. This includes tactile stimulation (holding and light pressure, using the kangaroo position), auditory stimulation (exposure to the mother's voice), olfactory stimulation (exposure to a cloth scented with a parent's scent), and vestibular stimulation (exposure to carefully regulated therapist breathing and movement). The trial is aimed at studying the changes in neural processing that mediate these outcomes.

Even fewer studies have investigated the use of such approach in clinical settings for children with neurological or neurodevelopmental disorders [46, 47], and results about its efficacy are very limited.

It is evident that results about the integration of olfactory stimuli within early multisensory interventions are very few, so it is impossible to give concluding feedback on its efficacy. Indeed, to support the evidence in favour of these interventions and to include the olfaction between the sensory stimulations useful for these populations, it is necessary to implement future investigations, ensuring the use of validated instruments and consistent blinding. It is also true that scientific knowledge about the early interplay of olfaction with visual stimuli for social adaptation suggests that this practice might benefit infants and children.

Conclusion

This line of research offers interesting insights and new ideas in the study of multisensory integration as it includes a yet underinvestigated sensory modality such as smell. Currently, knowledge regarding the role that olfaction plays in the development of other senses is still quite heterogeneous due to the complexity of devising paradigms that involve the use of odours. This review is also aimed at investigating the evidence in the field of olfactory skills in people with visual impairment. Notwithstanding results regarding this topic are disparate. What primarily emerges is that, during the early years of life, the sense of smell may play an important role in social adaptation to the surrounding environment [21] and thus it can be integrated into multisensory stimulation interventions in infants at risk of neurodevelopmental disabilities [39, 40]. For this reason, further well-designed and larger experimental studies are needed to strengthen the generalizability of these findings and the use of smell in early rehabilitation protocols.

Author Contributions All authors drafted, reviewed, and approved this manuscript.

Funding Open access funding provided by Università degli Studi di Milano - Bicocca within the CRUI-CARE Agreement.

Compliance with Ethical Standards

Conflict of Interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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