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Neurobiological mechanisms involved in recognition of olfactory signature of the young in sheep

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RÉSUMÉ

Cet article passe en revue les mécanismes neurobiologiques impliqués dans l'apprentissage de la signature olfactive du jeune chez la brebis à la parturition. Les stéroïdes et la stimulation vaginocervicale, consécutive à l'expulsion du fœtus, induisent des changements électrophysiologiques et neurochimiques dans le bulbe olfactif qui sont impliqués dans les mécanismes d'apprentissage de l'odeur individuelle du jeune, permettant l'établissement d'un lien sélectif entre la brebis et son agneau. En particulier, on observe une augmentation du nombre de cellules mitrales (principales cellules du bulbe olfactif) qui répondent aux odeurs d'agneaux. Ce phénomène est accompagné d'une modification des interactions entre les cellules mitrales et les interneurones et également de leurs interactions avec les systèmes centrifuges. Les changements intervenant dans les interneurones les rendraient plus sensibles au glutamate et ainsi pourraient accroître l'inhibition en retour des cellules mitrales. Cependant, du fait de l'augmentation de l'inhibition des interneurones par le système centrifuge noradrénergique aidé en cela par la libération d'ocytocine, il en résulterait un changement dans l'équilibre de l'unité mitrale-interneurone qui conduirait à une augmentation de l'activité de décharge des cellules mitrales. L'activation d'une sous-population de cellules mitrales pour lesquelles les fibres centrifuges exerceraient une désinhibition plus importante par le jeu de la régulation présynaptique gabaergique pourrait rendre compte de la spécificité de la réponse de certaines unités mitrales vis-à-vis de l'odeur de l'agneau familier. Ces mécanismes se mettraient en place lors de la première mise-bas et dans les 6 premières heures d'échanges avec l'agneau. Ainsi l'expérience maternelle induirait un processus de maturation dans le bulbe olfactif qui faciliterait l'efficacité de la libération de neurotransmetteurs.

SUMMARY Olfactory recognition of the young in sheep

The following review focuses on neurobiological mechanisms responsible for the individual recognition of the olfactory signature of the young by the ewe at parturition. Steroids and vaginocervical stimulation are responsible for neurochemical and electrophysiological changes within the olfactory bulb that are part of the learning mechanisms of the individual lamb odour, thus allowing the establishment of a selective bond between the ewe and her lamb. There is an increase in the number of mitral cells, the principal cells of the olfactory bulb that respond to lamb odours, which is associated with increased release of glutamate and gamma-aminobutyric acid from the dendrodendritic synapses between the mitral and granule cells. The relation between the release of the two transmitters after birth suggests an increased efficacy of glutamate evoked gamma-aminobutyric acid release. Parturition is also accompanied by increased oxytocinergic, cholinergic and noradrenergic neurotransmitter release that are essential for selective recognition of lambs. These increases in transmitter release depend on maternal experience, so that greater amounts have been found in multiparous than primiparous ewes. Therefore maternal experience seems to induce a neural maturation process that facilitates effective transmitter release in the olfactory bulb.

Maternal behaviour presents a wide variety of patterns among the mammals which depend mainly on the degree of precocity of the young at birth, but also on the social structure of the species and their ecology.

Sheep are seasonal breeders and lambing typically occurs in early spring, during a relatively short period of time, thereby affording the young a maximal period of growth and development. Amongst wild sheep, as well as domestic sheep living in free-ranging conditions, adult females and their suckling young form flocks whose members share a common home range (Grubb & Jewell, 1966; Geist, 1971). These matriarchal flocks may also include yearling offspring and mothers of adult ewes. These social groups are constantly on the move in search of food and it is vital that young are well enough developed to follow their mothers. Indeed new-born lambs are highly precocial with their senses as well as their capacities for thermoregulation and motor control. Thus, the demands of maternal care for precocial mammals could be somewhat different from altricial mammals.

Because of the co-occurence of own and alien young in the same flock, nursing ewes potentially risk having their limited maternal resources usurped by lambs that are not their offspring. Indiscriminate acceptance of any lambs that approach the udder and attempt to suck might result in the ewe having insufficient milk for her own young and therefore have drastic negative consequences for her reproductive success. A strategy has evolved for guarding against costly misdirected maternal investment, consisting for ewes to become rapidly familiar with the salient phenotypic traits of their own neonates (*i.e.*, learned individual recognition). Subsequently mothers develop discriminative maternal care with those young alone, allowing them to suck while rejecting any alien young that may approach the udder. In this respect, the establishment of a selective bond between the ewe and her lamb within the first hour after parturition represents one of an essential characteristic of maternal behaviour in this mammal.

Another intriguing characteristic of the sheep maternal behaviour is the primary importance of olfactory cues provided by the newborn. Olfaction is involved both in the attractiveness of any neonate for the parturient ewe and in the individual recognition of the lamb that permits the formation of the exclusive bond. Consequently, sheep constitute an alternative model for investigating the neurobiology of olfactory memory in a natural context. Indeed, this recognition is established at a very particular period, parturition and is effective after a very short time of mother-young contact. Also, this learning is of great value for the survival of the offspring and thus for the species. Our neurobiological studies were focused on the involvement of the olfactory bulb (OB) in the processing of this olfactory information. These studies lead us to the view, shared with other groups of researchers (Holley, 1991; Gervais *et al.*, 1988, 1990; Keverne & de la Riva, 1982), that this brain structure is able to show plastic changes during learning and has to be integrated in forebrain circuits underlying olfactory memory.

OLFACTORY MEDIATION OF LAMB RECOGNITION

Although olfactory cues may be less salient than the lamb's visual appearance and voice for distal recognition (Lindsay & Fletcher, 1968; Poindron & Carrick, 1976; Walser *et al.*, 1981), numerous experimental studies consistently indicate that the sense of smell plays a primary role in ewes' selective acceptance of lambs for nursing (Poindron *et al.*, 1993; Porter & Lévy, 1994).

When ewes or does suffer experimentally induced olfactory deficits prior to parturition, via bulbectomy (Bouissou, 1968; Baldwin & Shillito, 1974), sectioning the olfactory nerve (Morgan *et al.*, 1975), or irrigating the olfactory mucosa with zinc sulfate solution (Lévy *et al.*, 1995a; Poindron, 1976; Romeyer *et al.*, 1994), they subsequently show no evidence of recognizing their neonate, but accept alien young as well as their own. It should be pointed out that the anatomically distinct accessory olfactory system does not appear to be implicated in lamb recognition, since severing the nerves of the accessory olfactory system does not prevent ewes to be selective (Lévy *et al.*, 1995a). In related experiments, the degree of mother-offspring contact during the first 12 hours following birth was systematically manipulated (Poindron & le Neindre, 1980). Ewes that had been exposed to their lamb confined in a double-walled mesh cage that prevented physical contact, nonetheless developed a selective bond with that lamb. In contrast, few ewes subsequently accepted their lamb if it had been kept in an airtight transparent box (thereby eliminating olfactory cues) during the exposure period.

There have been few investigations of either the chemical nature or the source (site of production or emission) of the odours by which ewes distinguish between familiar and unfamiliar lambs. As mentioned above, ewes tend to focus on the lamb's ano-genital region for identification at close quarters, but odour cues from other areas of the body surface may also be sufficient for maternal recognition (Alexander, 1978). Odours associated with amniotic fluid appear not to be implicated in selective maternal acceptance. Ewes that already become bonded to their familiar offspring rejected alien young coated with amniotic fluid, regardless of whether that substance came from their own or an alien lamb (Porter *et al.*, 1994).

Arbitrarily selected scents such as thyme and lavender may not be as salient as the lamb's natural biological odour for mediating learned maternal recognition. In tests of maternal selectivity conducted several hours postpartum, ewes rejected equal numbers of alien lambs anointed with a novel scent and those bearing a familiar artificial odour that had been applied to their offspring at birth (Porter *et al.*, 1994). None of those ewes rejected their own (scented) lamb, however. It was concluded that artificial odour do not impede learning of the lamb's natural olfactory phenotype, nor do they substitute effectively for that odour. Moreover, ewes may be predisposed to learn a limited range of biological odours associated with conspecific neonates. Alternatively, ewes in the above experiment may have recognized unique mixtures of odours (mosaics) composed of the lamb's individual biological signature plus the artificial scent. The artificial odour would thus constitute a component of the mosaic signature rather than serve as that recognisable phenotype per se.

NEUROBIOLOGICAL MECHANISM OF LAMB ODOUR RECOGNITION

A mother's interest in lambs and her ability to selectively recognize her own offspring depend not only on odour, but also on *parturition* triggering her interest in these sensory cues (Keverne *et al.*, 1983). Neural signals resulting from stimulation of the vagina and cervix feedback to the brain to induce recognition process bringing about changes in the olfactory sensory processing system (Kendrick *et al.*, 1992). The mechanisms by which parturition bring about changes in the processing of olfactory signals involves the OB, the first relay of olfactory information, and are influenced by maternal experience.

Changes in the sensory processing of olfactory signals induced by birth in sheep

The importance of the VCS was shown by mimicking birth of a second new-born lamb 2 hours after parturition in mothers of single lamb. In these experimental conditions, 5 min of experimental vaginal stimulation are sufficient for eliciting the acceptance of an alien lamb in 80 % of the ewes which have rejected this same lamb few minutes before (Keverne *et al.*, 1983). This stimulation is efficient for fostering alien new-born lambs during the first day after parturition (Basiouni & Gonyou, 1988; Kendrick *et al.*, 1991). For these reasons, we decided to analyse electrophysiological and neurochemical activities of the OB in response to lamb odours before and after parturition. Additional pharmacological studies helped us to understand the functional importance of some of these changes.

Electrophysiological recordings were made from mitral cells in the same conscious ewes before and after they gave birth (Kendrick *et al.*, 1992). In recordings made during the last 2 months of pregnancy, none of these cells responded preferentially to lamb or amniotic fluid odours. Indeed, in only 11 cells (10 %) were these odours capable of eliciting any significant change in firing rate. The majority of cells (72 %) responded preferentially to food odours. Some 3 days after birth, there was a dramatic increase in the number of cells, from this region of the bulb, that now responded preferentially to lamb odours (60 %). However, the majority of these cells that responded to lamb odours (70 %) did not differentiate between the odour of the ewe's own lamb, and that of an alien lamb and were remarkably resistant to habituation. Nevertheless, a proportion of the cells (30 %) did respond preferentially to the odour of the ewe's own lamb. A small proportion of cells was also found that responded preferentially to amniotic fluid odours (11 %), while a large reduction was recorded in the number of cells that responded primarily to food odours. These results indicate that, although the odour of lambs have almost no influence on the activity of OB neurons during the period before birth, when lambs have no behavioural attraction, they provide a very potent olfactory stimulus in the period after birth, when the recognition of lamb odours has a very behavioural priority. Moreover, a proportion of cells respond differentially to the odour of the lamb with which the ewe has formed a selective bond.

The OB is a relatively simple trilaminar structure, and its network comprises three basic neural types (Shepherd, 1972). The mitral cells, which show this increased responsiveness to lamb odours after birth, receive and transmit olfactory signals, and their activity is modulated at their apical dendrites by periglomerular cells and at their lateral dendrites by granule cells. Intrinsic connections within this network contain both excitatory and inhibitory amino acid transmitters and dopamine. Transmissions among neurons in the network is further influenced by centrifugal projections from noradrenergic, cholinergic, and serotonergic neurons that come from the locus coeruleus, the horizontal limb of the diagonal band of Broca or the raphe respectively (Shipley *et al.*, 1985; Godfrey *et al.*, 1980; Gervais *et al.*, 1984). To further understand how the mitral cells increase their responsiveness to lamb odours, we used *in vivo* microdialysis to measure their effect on the release of acetylcholine, amino acid, and monoamine transmitters in the OB before and after birth (Kendrick *et al.*, 1992). Before birth, lamb odours produced no changes in the neurotransmitter release that could be detected using microdialysis. After parturition, when ewes had established a selective bond with their lambs, the odours of these lambs, but not those of alien ones, increased the release of both the excitatory amino acid glutamate and the inhibitory gamma-aminobutyric acid (GABA). Release of another intrinsic transmitter, dopamine, was not influenced by lamb odours. These changes in glutamate and GABA release occurred only during the first 5 min of exposure to the lamb odour, and the increase of GABA after birth was significantly greater than that of glutamate. Basal release of GABA and glutamate in the period after birth was also significantly higher than in the period before birth and, again, this change in GABA release was significantly higher than that of glutamate. Because the GABA-containing granule cells are intrinsic bulbar neurons excited by mitral cells and provide feedback inhibition to the mitral cells by way of reciprocal dendrodendritic synapses, the proportionately higher release of GABA compared to glutamate might be explained in terms of a changed efficacy of glutamate at these synapses after birth. Glutamate and GABA release were correlated both before and after birth in all animals, but the regression slopes for the two periods were significantly different. The overall increase in both glutamate and GABA release in the period after birth is synonymous with more mitral cell activity in response to lamb odours, whereas the significant shift in the regression slope may be a result of an increased efficacy of glutamate in promoting GABA release.

Such enhancement of efficiency at the granule to mitral cell synapses was also revealed in the accessory OB of mice during the memorisation of the odour of the stud male (Brennan *et al.*, 1995) and in the main OB in rat pups conditioned to an odour (Wilson *et al.*, 1987).

This mechanism is not a simple correlation of olfactory learning and the GABAergic modulation may play an important role. Indeed, infusion of an antagonist of $GABA_A$ receptors, bicuculline, in the OB prevents recognition of the familiar lamb, once the bond has been formed (Kendrick, 1994). Similar infusion in the accessory OB of mice precludes the memorisation of the odour of the stud male (Brennan *et al.*, 1990). It appears that nitric oxide mediates synaptic changes during memory formation that allow odours of familiar lamb to stimulate glutamate and GABA release. Drugs targeting the NO signalling pathway prevent rise of both transmitters when own-lamb odours are presented for a 10-min exposure (Kendrick *et al.* 1997).

At the present time, all the steps involved in olfactory memory formation are not known. Other studies on olfactory learning, but involving different behavioural contexts have shown that the selective increase of activity of the OB to significant odours could be the consequence of a centrifugal modulation and in particular of noradrenergic and cholinergic systems (Gervais *et al.*, 1988, 1991; Holley, 1991; Keverne & de la Riva, 1982; Sullivan *et al.*, 1992). In sheep, we hypothesized that one of the first stage leading to olfactory recognition of lambs is that VCS during birth evokes noradrenaline release at the centrifugal synapses with granule cells which acts at ß-adrenergic receptors. Using microdialysis, we have shown that there is a peak of noradrenaline for the first 4 hours after parturition which corresponds to the learning period of the olfactory signature of the lamb (Lévy *et al.*, 1993). This activation is of primary importance since blockade of β-adrenergic receptors of the OB during this period prevents the formation of the olfactory memory (Lévy *et al.*, 1990a). This effect concerns only mechanisms underlying memory formation since experimental ewes do not display any disturbances of maternal behaviour or any deficits of olfactory perception. The importance of noradrenergic transmission in the OB seems to be a common feature to different forms of olfactory learning either in the mice, sheep and neonatal rats. Microdialysis studies have shown that NA levels are also increased in the AOB of mice after mating (Brennan *et al.*, 1995), and in the OB of neonatal rats in response to tactile stimulation (Rangel & Leon, 1995). In each case, olfactory learning is prevented by the infusion of noradrenergic antagonists directly into the olfactory structure (Kaba & Keverne, 1988; Sullivan *et al.*, 1992). Noradrenaline has been proposed to promote learning-dependent changes in the OB by disinhibiting mitral cells (Jahr & Nicoll, 1982). In sheep, release of NA at parturition would reduce GABA release at the granule to-mitral cell synapses and therefore relieve the inhibition of the mitral cells. Although the activation of the locus coeruleus concerns all the noradrenergic terminals, a selective action of NA at the level of the OB could be achieved by a presynaptic mechanism involving GABA receptors on nordrenergic terminals (Gervais *et al.*, 1987). Therefore, mitral cells activated by the lamb odours would stimulate indirectly noradrenergic terminals via the activation of granule cells. This would result in the differentiation of the mitral cells responding to the lamb's odours so that their output may be more easily decoded by secondary and tertiary olfactory processing brain regions.

Birth also evokes acetylcholine rise in the OB, similarly to noradrenaline (Lévy *et al.*, 1993). Knowing the contribution of the cholinergic system to learning and memory processes, and in the context of olfactory learning, the fact that infusions of scopolamine, a muscarinic antagonist, within the OB impaired short-term memory (Ravel *et al.*, 1994), prompted us to investigate the role of acetylcholine in olfactory recognition of the lamb. We now have several lines of evidence indicating that the whole basal forebrain cholinergic system, rather than the cholinergic innervation of the OB itself, is involved in this type of memory. Indeed, infusion of scopolamine within the OB at the time of parturition does not prevent the olfactory recognition of lambs (unpublished data). However, peripheral injections of scopolamine during the first 4 hours post-partum impaired olfactory lamb recognition whereas methylscopolamine, an antagonist that does not cross the blood-brain barrier, did not so (Lévy *et al.*, 1997). This central effect may involve muscarinic receptors in projection areas of basal forebrain cholinergic neurons. To address this issue, we developed the use of an immunotoxin, ME20.4 IgG-saporin, that is specific to basal forebrain cholinergic neurons (Ferreira *et al.*, 2001b). Combined immunotoxin injections into ventricles and the nucleus basalis produced a near complete loss of cholinergic neurons (80-95 %) in each nucleus and their respective limbic, olfactory and cortical targets. Such an extensive lesion performed two months before parturition severely impaired olfactory recognition of the lamb whereas this performance was unaffected in animals for which loss of basal forebrain cholinergic neurons was less than 75 % (Ferreira *et al.*, 2001a). Therefore, since only extensive lesions affect performance, this indicates that the basal forebrain cholinergic system possesses substantial reserve capacity to sustain olfactory memory.

Influence of maternal experience on neurochemical activity of the OB contingent on olfactory memory

Behavioural differences between inexperienced and experienced ewes in maternal care at parturition are well recognized (Poindron *et al.*, 1988). Maternal experience also influences the duration time for which the olfactory memory is formed. Whereas 90 % of the multiparous ewes are selective after 2 hours of contact with the young, only 15 % of the primiparous mothers are so (Kendrick, 1994). Also, the mechanisms by which VCS, which mimics parturition, induces maternal recognition in multiparous ewes, are ineffective in nulliparous ewes. However, these differences decrease with time. A significant improvement of maternal care occurs in primiparous females during the first 3 hours postpartum (Poindron *et al.*, 1984). In addition, the ability of genital stimulation to stimulate adoption of alien lambs at 6 hours postpartum is equivalent in primiparous and multiparous ewes (Kendrick *et al.*, 1991). It would seem, therefore, that the neural changes underlying maternal recognition have been produced within 6 hours following parturition. These changes are long term and facilitate recognition of lambs at all subsequent births. In order to test this proposition, neurotransmitter changes at mitral granule-cell reciproqual synapses, as well as the centrifugal inputs of the OB, were compared between nulliparous and multiparous sheep at parturition. In ewes giving birth for the first time there is no measurable increase in glutamate or GABA release in the OB at parturition whereas these neurotransmitters show significant increases in experienced ewes (Keverne *et al.*, 1993). In addition, potassium challenges produce greater increases in glutamate or GABA release in multiparous than in nulliparous ewes. This would suggest the existence of an enhanced activity across the reciprocal mitral to granule cell synapses in experienced mothers only, that would be important for the recognition process. Thus, it is possible that the first maternal experience induce long-term changes at the level of this synapse. When VCS was given at 6 hours postpartum, no difference in glutamate and GABA release was observed between primiparous and multiparous mothers (Keverne *et al.*, 1993). Thus, the first parturition would induce a neural maturation process that takes place within the first 6 hours after birth.

Experience is also important for the release of noradrenaline and acetylcholine at birth itself, because only after the first birth experience can significant changes in acetylcholine transmitter be detected, while noradrenaline shows a fivefold increase at birth in experienced ewes (Lévy *et al.*, 1993). Potassium challenges induce greater increases in noradrenaline and acetylcholine release in multiparous than in nulliparous ewes. Thus, maternal experience would increase the control of the reciprocal synapse between mitral and granule cells by the centrifugal inputs resulting in a better characterisation of the olfactory information. This regulation would take place very rapidly after the first hours of contact with the lamb. Indeed, an experimental genital stimulation undergone 6 hours after parturition reveals no more difference in noradrenaline release between primiparous and multiparous mothers (Lévy *et al.*, 1993).

The cellular mechanisms underlying this general increase of neurotransmitter release, observed in experienced mothers, could be a consequence of an increase of synaptic density or of the number of synaptic vesicles. This also could be due to a change of neuronal-glial relationships allowing juxtaposition and association of neuronal elements as it occurs at parturition in the hypothalamic and neurohypophysial oxytocinergic system of the rat (Theodosis & Poulain, 1987; Tweedle & Hatton, 1987). Neural changes could also involve a local regulation of release through presynaptic mechanisms. Infusion of muscimol, a $GABA_A$ agonist, into the OB enhances the release of NA in experienced but not in naive ewes (Lévy *et al.*, 1993). On the other hand, parturition induces oxytocin release in the OB and this increase is less pronounced in inexperienced ewes (Lévy *et al.*, 1995a). Oxytocin also modulates the release of noradrenaline in the OB but only in experienced mothers (Lévy *et al.*, 1995b). Hence, the first parturition and interactions with the young would also induce changes involving interactions between neurotransmitters. An increase of receptor expression as a result of maternal experience, as it was demonstrated for oxytocin receptor expression (Broad *et al.*, 1999) could account for these changes.

CONCLUSION

The data reviewed in this article underline the importance of neural changes occurring at the level of the OB for learning the olfactory signature of the lamb. The question arises whether this neural plasticity is particular to the type of learning that happens during a sensitive period or reflects normal processes of learning in everyday contexts. For instance, the spatial pattern of the bulbar EEG, in adult rabbits, changes during aversive conditioning to an odour but not when an odour is presented without an reinforcement (Freeman & Schneider, 1982). These modifications of the bulbar EEG are prevented in the case of infusions of a β-adrenergic antagonist in the OB (Gray *et al.*, 1986). Also, using a pseudo-odour paradigm in the rat, Mouly *et al.* (1993) have shown that olfactory learning, in which natural stimuli were replaced with multisite electrical stimulations, induces neural changes critical for long-term retention. Moreover, using a classical conditioning procedure to establish an olfactory discrimination in mice, Brennan *et al.* (1998) found similar changes in the gain of synapses between mitral neurons and their inhibitory interneurons as is found in pheromonal learning in newly mated female mice (Brennan *et al.*, 1995). Therefore, it appears that significant structural changes in the OB , which indicate important abilities of plasticity in the adult animal, are a general feature of olfactory learning. In this respect, the OB differs from the majority of other brain structures in that neurogenesis continues throughout life (see Lledo *et al.*, this volume). This plasticity is associated with olfactory performance: enriched odor-exposure enhances the number of inhibitory interneurons and in parallel extends the olfactory memory (Gheusi *et al.*, this volume). In the context of maternal behavior in sheep, one could hypothesize that parturition and lactation could be a particular period of increased neurogenesis with consequent influences on olfactory recognition of the young.

The OB is certainly not the sole repository for olfactory learning. This structure establishes connections to brain areas strongly implicated in learning and memory. Of particular relevance are connections to the hippocampus via the entorhinal cortex which contribute to the representation of relations among odour so that they can use these representations in new contexts (Eichenbaum *et al.*, 1989). Another pathway involves the mediodorsal nucleus of the thalamus which projects to the frontal cortex. This pathway is claimed to participate to complex olfactory learning set problems (Slotnick & Kaneko, 1981). Direct projections to the corticomedial amygdala contribute to the acquisition of olfactory fear conditioning (Otto *et al.*, 2000). Investigations of the respective role of these pathways would further increase our understanding of the mechanisms by which lamb odour is memorised.

Mothers also develop recognition of their lamb through other sensory modalities, i.e. vision and audition, as early as 8 hours postpartum (Terrazas *et al.*, 1999). This recognition can be established independently of the memorization of the lamb's smell. Anosmic ewes are as efficient in developing early visual and auditory recognition of their lamb as are intact ewes (Ferreira *et al.*, 2000). Consequently, the neural networks responsible for the memorization of the lamb's visual and auditory cues may be activated separately from the neural networks involved in the memorization of lambs' odors to allow the establishment of maternal selectivity. However, this does not mean that intermodal sensory processing between olfactory and other cues is not important for recognition of the lamb. At one month postpartum, differential behavior of anosmic ewes toward their own versus an alien lamb at the udder, a situation in which acceptance is based on the learning of olfactory cues, suggests that vision and audition may compensate for the loss of olfaction (Ferreira *et al.*, 2000). Thus, some compensatory mechanisms may exist between the different sensory modalities. How the brain processes these mechanisms is an important area for further investigations.

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