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Review Article

The Scent of Neurogenesis: Refurbish Your Brain the Pleasurable Way

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1. Abstract

Neurogenesis in adult mammals is prominently observed in two specific brain regions: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Neurons born in the SVZ migrate through the rostral migratory stream (RMS) to the olfactory bulb (OB), where they differentiate into interneurons. This migration is important for the sustenance and functional adaptation of the olfactory system, which is unique in its constant turnover of sensory receptor cells. The olfactory system, by its very design, maintains a direct link with the areas of the brain responsible for controlling various behaviors and emotional responses, making it a key component in the sensory-behavioral paradigm influencing adult neurogenesis. This discussion explores the mechanisms through which odors may influence the regeneration and migration of neuronal stem cells to the olfactory bulb (OB) and, consequently, affect neurogenesis.

Keywords: Rostral Migratory Stream; Neural Stem Cells; Neurogenesis; Fragrance; Aromatherapy

Abbreviations

SVZ: Sub Ventricular Zone; SGZ- Subgranular Zone; RMS: Rostral Migratory Stream; NG: Neurogenesis; OB: Olfactory Bulb; EO: Essential Oil; AOB: Accessory Olfactory Bulb

2. Introduction

Till quite recently, brain regeneration was not thought possible. Medical textbooks expounded the dogma that a human child was born with a certain number of neurons, which remained either constant in number throughout life, or declined with age. The teaching was that new neurons could not be formed, since the brain had no stem cell reservoir. Recent studies have turned this dogma on its head, by indicating that neurogenesis (NG) does keep occurring throughout the human life-time and is not confined to only a few regions in the brain [1]. Rather, it is more widespread, though the magnitude of the new brain cells being produced is comparatively low, as compared to the intra-uterine phase [2]. The intimate neural linkages of the olfactory system to the primary regions involved in neurogenesis connote a very important role of olfaction as a mediator in the process of production, migration, maturation and integration of neuronal stem cells into the mainstream brain circuitry [3].

Since olfaction is all about odours, delightful aromas which are pleasing to the human soul may have a key role to play in facilitating neurogenesis. The Indian cultural and religious traditions are replete with practices entailing use of fragrances and scented flowers. In fact, the preparation of pure fragrance concentrates was pioneered in India. Commonly known by the Arabic term 'attar,' these floral concentrates have been a part of Indian religious rituals since times immemorial, because various attars were proffered to different deities in devotion. During the 'nava griha pooja' when all nine planets are worshiped, or during the veneration of different deities at one time, each deity is offered

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a different, designated fragrance or ‘sugandhi tailam’ (fragrant essential oils). In India, there is no worship without the charm of fragrance. Like the sun and light, worship is inseparable from fragrance in the Indic spiritual thought process. Be it praying before grand sacred fires (yagyas and havans) or daily household ‘pooja’ rituals, fragrance forms the soul of spiritual practices. In houses, shops and temples, the most popular modality of accessing aromas is by lighting Agarbattis (Figure 1). Agarbattis are very thin and long, inflammable spike-like sticks, which are lighted to produce fragrant smoke.

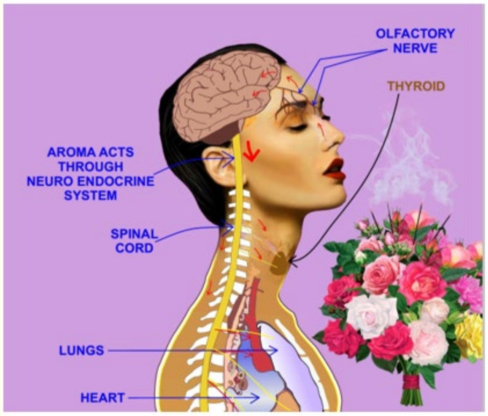

Figure 1: A popular modality for enjoying fragrance is by lighting Agarbattis, which are incense sticks having floral aromas. Fragrance compounds are perceived by the olfactory nerve, and can also enter the brain directly through the cribriform plate, promoting neurogenesis and exerting systemic effects through the neuro-endocrine axis.

3. Effect of odors on newborn neuronal survival, integration and function

Odors, once detected by the olfactory epithelium, initiate a complex series of neuronal activations, leading to the migration of neural progenitors from the SVZ to the OB [4] (Figure 2). This migration is impacted by the olfactory environment; an enriched olfactory environments has been shown to enhance neurogenesis in the OB by promoting the survival of newly born neurons [5-7]. Conversely, olfactory deprivation can lead to a decrease in the survival rates of these neurons during critical developmental windows [8]. Moreover, the role of odors extends beyond the physical migration and integration of neurons; it also includes functional aspects such as learning and odor discrimination. Studies have shown that olfactory learning tasks can modulate the survivability of newborn neurons in the OB, indicating a selective process that might be based on the function or engagement of these neurons in odor-related tasks [9,10]. This suggests a complex relationship between olfactory exposure, learning, and the maintenance of a balanced neuronal population in the OB. Further, the continuous influx of new neurons into the OB is essential not just for replacing older neurons but also for optimizing olfactory discrimination. This ongoing neurogenesis ensures the OB’s adaptability to new odors or complex olfactory environments, thereby maintaining the efficiency and precision of the olfactory system [9,11,12]. Studies given below (section 5) suggest that the selective survival and integration of these neurons is seemingly modulated by their exposure to specific odors, indicating towards a feedback loop where olfactory experiences shape the neurogenic process. These key findings highlight the significance of sensory experiences in shaping the brain’s structure and function, including neurogenesis. They also demonstrate an interesting aspect of neuroplasticity, where environmental stimuli directly influence the regeneration and integration of neurons in brain areas.

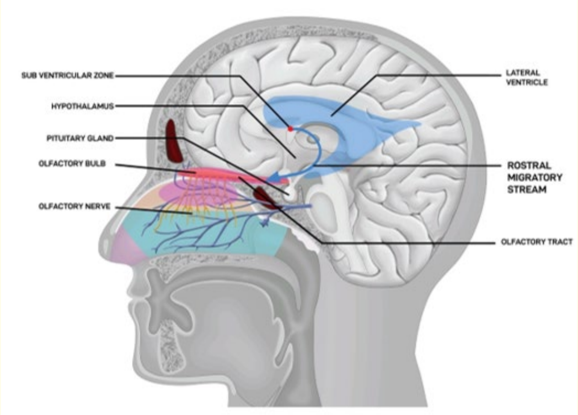

Figure 2: Neural progenitor cells migrate from the sub-ventricular zone to the Olfactory Bulb along the Rostral Migratory Stream (RMS). This migration of neural stem cells is influenced by olfactory stimulation from the olfactory pathway (Section 8). During migration, newly born neural stem cells can deviate from the RMS, and refurbish vital areas in the proximity of RMS, such as the hypothalamus, pituitary, amygdala and hippocampus.

4. Affect of odor cues in specific brain regions

4A. The Olfactory Cortex: Integration of newborn neurons into existing neural networks

The olfactory cortex (see section 8), with its principal projection site being the piriform cortex, plays a key role in processing olfactory information. This area, known for its phylogenetically ancient structure and widespread synaptic organization, is important in the integration and mapping of olfactory sensations [13]. Notably, newborn neurons have been observed in various structures of the olfactory cortex across different mammalian species, including rodents, rabbits, and monkeys [14-21]. A fraction of neurons originating from the SVZ diverge from the RMS and migrate towards the olfactory cortex through specific pathways. This migration is not just a matter of relocating; it's about integrating these cells into existing neural networks where they can contribute to the olfactory processing [15]. The fact that these neurons can be derived from local progenitor cells or through migration from the SVZ adds another layer of complexity to the regulation of neurogenesis in the olfactory system. These observations highlight the dynamic nature of the olfactory system, capable of integrating new neurons into its circuitry, a process potentially influenced by olfactory stimuli.

4B. Olfactory enrichment: Promoting neurogenesis in the olfactory system

The influence of olfactory enrichment on neurogenesis is significant. Studies have demonstrated that exposing the olfactory system to a variety of scents (olfactory enrichment) not only promotes the differentiation and survival of newborn neurons in the olfactory cortex, but also enhances neurogenesis in the olfactory epithelium and OB [5,22]. This suggests that sensory experiences, particularly through odors, can modulate the neurogenic process, providing a mechanism for the olfactory system to adapt and respond to new stimuli. Further, the detection of pheromones, a critical aspect of mammalian behavior, is linked to the olfactory system, particularly through the accessory olfactory bulb (AOB) [23,24]. Neurogenesis within the AOB can be influenced by exposure to pheromonal stimuli, as seen in studies where exposure to male pheromones increased neurogenesis in the AOB of female mice. This suggests that social and environmental cues, including odor can directly impact the neurogenic processes within the olfactory system. The ability of odors and pheromones to steer the migration, differentiation and integration of neuronal stem cells into the olfactory bulb and cortex highlights the plasticity of the brain and its capacity to adapt to new sensory inputs.

4C. The amygdala's neurogenesis: Influence of olfactory inputs

Interestingly, the amygdala, a central node in the processing of emotional responses, receives substantial input from the olfactory bulb, indicating a direct link between olfactory perception and emotional regulation [25]. Neurogenesis within the amygdala, although occurring at a smaller scale compared to other regions like the hippocampus, plays a potentially significant role in emotional and affective behaviors. Studies have shown that the amygdala can both generate new neurons locally and receive migrating neurons from the SVZ [15,26,27], suggesting a dynamic interplay between local neurogenesis and olfactory inputs in making emotional responses. The influence of olfactory inputs on amygdala neurogenesis has been shown in various research studies. For example, olfactory bulbectomy, which disrupts the normal olfactory input to the amygdala, has been observed to alter neurogenesis patterns within this region [28-30]. Furthermore, pheromonal stimuli, whether through direct olfactory input or via the AOB have been shown to affect neurogenesis in the amygdala. The reception of pheromonal signals, influencing neurogenesis within the amygdala, thus links social and reproductive behaviors to olfactory cues [31-33]. This highlights the amygdala's sensitivity to olfactory stimuli and its potential role in modulating emotional states through neurogenesis. The locations of the Orbito frontal cortex, Olfactory tubercle, Hypothalamus, Pituitary gland, Amygdala, Striatum and the Hippocampus are illustrated in Figure 3.

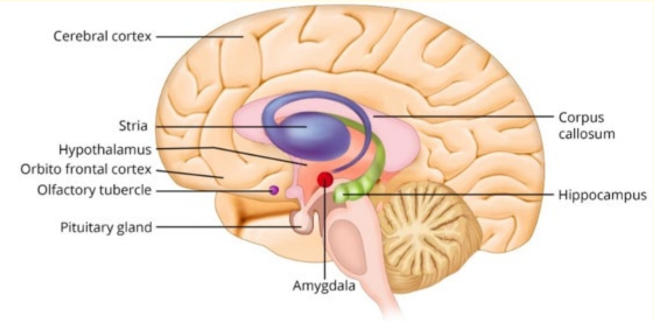

Figure 3: Olfactory information received by the Olfactory bulb is conveyed to large parts of the brain via the Olfactory Pathway. The main parts of the Olfactory Pathway are shown, including the Orbito frontal Cortex, Olfactory Tubercle, Amygdala, Striatum and Hippocampus.

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4D. The Striatum and Olfactory-Induced Neurogenesis

The striatum, integral to the brain's reward system, also exhibits neurogenesis and is influenced by olfactory stimuli. New neurons in the striatum are thought to be generated both locally and from migrating neurons originating from the SVZ [34]. This neurogenesis is modulated not only by intrinsic factors but also by external stimuli, including olfactory cues. Research studies suggest that growth factors and hormones can significantly influence striatal neurogenesis, indicating a pathway through which olfactory stimuli might affect the reward circuitry of the brain. This appears plausible since the Olfactory Tubercle, which is a part of the Striatum and receives olfactory input, has a rich neurochemical composition, including neurotransmitters, neuromodulators and hormones [35]. This is particularly relevant in understanding how odors can modulate behaviors related to motivation and reward, such as feeding and reproduction [36,37].

By influencing striatal neurogenesis, olfactory stimuli have the potential to affect the reinforcement of behaviors. Also, the entorhinal cortex, located along the lateral olfactory tract, serves as a key hub for processing olfactory information before it is relayed to the hippocampus and amygdala [38,39]. Its role in encoding the timing of events adds a temporal dimension to olfactory signals, which is important for integrating these sensory inputs with memories and emotional responses. The discovery of neurogenesis within the entorhinal cortex highlights its dynamic nature and its potential to adapt to new olfactory stimuli by incorporating newly generated neurons into its processing circuits [14,26,40].

4E. The Hippocampus: Olfactory inputs modulating neurogenesis

The hippocampus, known for its key role in memory consolidation and retrieval, exhibits a unique capacity for neurogenesis throughout life. The complex process of memory formation is influenced by various factors, including environmental stimuli and, notably, olfactory inputs. The connection between the olfactory system and the hippocampus allows for the integration of sensory experiences with memory and emotional states. Studies have shown that specific olfactory stimuli can either enhance or inhibit neurogenesis in the hippocampus, indicating that the nature of the odor -- whether it be non-pheromonal environmental odors, pheromones associated with social interactions [41-50], or stress-inducing odors [51] -- play a significant role in modulating this process [52-57]. For example, exposure to certain pheromones can enhance neurogenesis, potentially influencing behaviors such as mate selection, parental care, and social interaction. This suggests a biological mechanism whereby olfactory stimuli can directly influence brain structure and function to support adaptive behaviors. Conversely, aversive odors, such as those associated with predators, may inhibit neurogenesis, which could be a response mechanism to stress, and mediated through hormonal changes.

4F. Intrinsic bulbar plasticity and olfactory-induced neurogenesis

An alternative pathway for neurogenesis induced by olfactory stimuli in humans may be the intrinsic plasticity within the olfactory bulb. This process involves progenitor cells already present within the OB, which contribute to the turnover of neural cells [58]. The isolation of neural stem cells from the adult human OB suggests a direct effect of olfactory stimuli on local neurogenesis, a process that occurs independently of cell migration from distant neurogenic regions. The influence of olfactory stimuli on neurogenesis is twofold: it can promote the development of new neurons and affect the survival and integration of these neurons into existing neural networks [58]. Beneficial outcomes may result from the activation of neurogenic pathways that are sensitive to specific olfactory signals, leading to increased neural proliferation, differentiation, and integration. On the other hand, negative impacts could arise from exposure to harmful substances or environmental stressors, leading to impaired neurogenesis or neuronal damage.

5. Olfactory deprivation and its effects on neuronal survival

Sensory experiences, including those mediated by odors, significantly influence the survival and maturation of new neurons, particularly in the OB and hippocampus. One of the earliest pieces of evidence regarding this came from studies showing that sensory deprivation led to a decrease in the number of granule cells in the OB due to increased apoptosis [59]. Conversely, sensory enrichment, or the exposure to a variety of odors, promoted the survival of newly formed bulbar interneurons, suggesting that olfactory input plays a crucial role in neurogenesis by modulating cell survival rates [5]. Further experiments have revealed that not only does the sensory experience affect the survival of new neurons, but it also influences their integration into existing neural circuits. For instance, the reopening of a nostril after occlusion in newborn rats, or olfactory enrichment in adults, has been found to promote the survival of these neurons by enhancing their synaptic integration and functional relevance within the olfactory system [60]. On the flip side, the absence of olfactory stimulation or deprivation has been linked to reduced proliferation rates in the SVZ, alterations in the RMS, and increased cell death, highlighting the importance of sensory input for maintaining a healthy rate of neurogenesis [61]. These findings highlight how apoptosis and proliferation in the olfactory neurogenesis pathway are closely regulated by sensory experiences, with odors acting as critical external cues that influence these processes. Moreover, the temporal dynamics of sensory-dependent plasticity indicate that the survival and integration of new neurons in the OB are sensitive to olfactory activity within specific time windows [61]. This suggests that the newly generated neurons require timely and appropriate sensory experiences to fully integrate and contribute to the olfactory circuitry.

6. Chemotaxis and olfactory modulation of neurogenesis

The chemotaxis process (see section 8) supports the role of odors in modulation of neurogenesis in different brain regions. Chemotaxis directs the migration of cells towards or away from chemical signals, including the guidance of neuronal stem cells to various parts. In the adult brain's SVZ, chemotaxis is particularly evident as progenitor cells travel via the RMS to the olfactory bulb, where they differentiate into interneurons [62,63]. This migration is guided by chemotactic cues, among which Slit (a secreted extracellular matrix signaling protein) and vascular endothelial growth factor (VEGF) play significant roles. Slit serves as a chemorepulsive agent, propelling cells away from the SVZ and along the RMS, while VEGF acts as a chemoattractant, attracting cells towards the olfactory bulb [62,63]. These molecules ensure the orderly movement of neural progenitor cells, demonstrating the role of chemotaxis in brain development and repair mechanisms in the central nervous system. The influence of aromas on the chemotactic response, especially regarding the migration and integration of neuronal stem cells, remains a relatively unexplored frontier. However, the chemotactic mechanisms used by SVZ progenitor cells point towards the potential of specific odors and chemical gradients in impacting cell migration. Given the progenitor cells' expression of various chemokine receptors and their ability to respond to chemotactic ligands like CXCL12, it is conceivable that certain aromas could modulate these chemotactic pathways [62,63]. While direct research on aromas influencing stem cell migration is limited, the foundational understanding of chemotaxis and its role in neuronal cell migration sets the stage for investigating how different sensory inputs, including specific odors, might impact neurogenesis and brain repair mechanisms.

7. Olfactory neuroepithelium and its role in neurogenesis

The continuous regeneration within the olfactory neuroepithelium is a key process by which olfactory stimuli may affect neurogenesis [64,65]. This epithelium maintains a population of proliferative progenitor cells, which give rise not only to neurons but also to their associated glial and support cells, indicating a dynamic state that is receptive to olfactory signals. Olfactory receptor neurons, which are in immediate contact with the external environment, are vulnerable to harm from pollutants, pathogens, or injury, thus necessitating their constant regeneration. This renewal process is important for preserving the sense of smell and implies a direct mechanism by which olfactory stimuli can modulate neural proliferation and cell survival. Another significant source of neural plasticity is the generation of neuroblasts from the SVZ of the lateral ventricle, which migrate towards the OB where they differentiate into interneurons [64,65]. This process is thought to contribute to complex behaviors such as olfactory memory formation and odor discrimination. In rodents and primates, this pathway is well-established, indicating a clear mechanism through which olfactory stimuli can promote neurogenesis and neural integration within the OB, potentially enhancing olfactory functions and cognitive processes related to the sense of smell.

8. Discussion

Neurogenesis, the process which is responsible for formation of new neurons in the brain, occurs predominantly in three brain regions: the subventricular region situated on the outside wall of each lateral ventricle, the olfactory bulb and the subgranular zone of the dentate gyrus of the hippocampus [66]. The SVZ is the region having maximum neuronal progenitor activity, the probable reason for this being that the neighboring lateral ventricle is a ready source of nutrients and growth factors, as well as having guidance cues for neuroblast migration such as 'slit' proteins (see section 6). Freshly generated offsprings of neural stem cells in the SVZ travel along the rostral migratory stream (RMS) to the olfactory bulb (OB), where they differentiate into interneurons [67,68]. This migration is important to sustain the function of the olfactory system, which bears continuous loss of sensory cells concerned with olfaction (see section 7). The olfactory system is directly linked to the areas of the brain processing behavior, emotional responses and memories, making it a significant factor in the holistic functioning of the human brain. The experimental studies described in the preceding sections make it abundantly clear that fragrances and odors have the ability to influence adult neurogenesis, probably using the mechanisms of chemotaxis [68,69] (Figures 3,4).

Chemotaxis (from chemo- + taxis) is one of the most primeval sensory functions found in single celled organisms. It can be defined as the movement of a cell or organism in response to a chemical stimulus in their environment. Somatic cells, bacteria, and other single-cell or multicellular organisms direct their movements according to the concentration gradient of particular chemicals in their vicinity. In humans, leukocytes are able to seek out and home in to areas of inflammation and infection due to their chemotactic abilities. In fact, chemotaxis is essential for the functioning of the immune system, since immune cells can detect and migrate towards the source of the chemical stimulus. Odour molecules are also chemicals, and can similarly affect several immune cell types, including monocytes, neutrophils and macrophages, as also migrating stem cells, whether hematopoietic or neural [70,71].

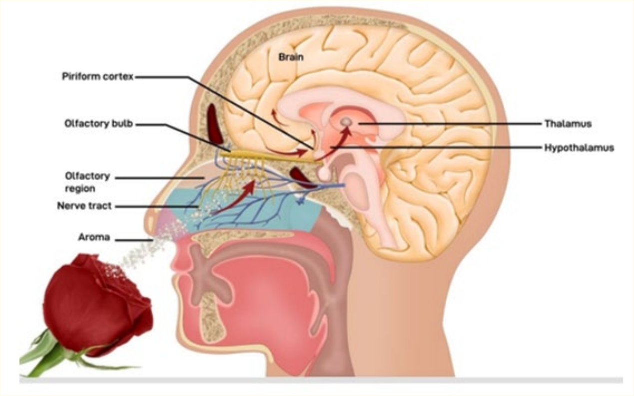

Figure 4: Aroma compounds are perceived by the nerves in olfactory region of the nasal cavity, and also directly enter the brain through the cribriform plate. From the region of the olfactory bulb, the odor information is transmitted via the olfactory pathway to large areas of the brain, including the limbic system, stimulating them and affecting the production, migration and survival of neural stem cells.

In India, since ancient times, scented flowers and aromatic substances have played a central role in the cultural and religious traditions. Amongst the most popular forms of inhaling fragrance in Indian spiritual practices, is the use of incense sticks, commonly called 'agarbatti'. On setting them alight, the incense sticks produce fragrant smoke. These agarbattis are so called, because traditionally, pure powdered Agarwood (*Aquileria agallocha*) was used to make incense sticks. Today because of its high cost, incense sticks made from pure Agar wood are a rarity, and a variety of aromatic agarbattis are available at reasonable cost. These are used anywhere and everywhere, such as in shops, carts, homes and even offices.

A similar combustible fragrant widget is dhoop, which is also so named because it was originally produced from the scented wood of the dhoop tree (*Canarium strictum*). Agarbattis and dhoops are ignited and proffered to deities during all rituals and religious festivals. Burning incense forms an indispensible part of various religious ceremonies, poojas (worship) in temples, and even at funerals. Flowers are also the devotee's essential offering while visiting temples. Apart from roses and marigolds, a large variety of indigenous fragrant flowers including those from the jasmine family are offered to the deity [72]. This prolific use of fragrances in the Indian cultural tradition is nothing short of olfactory enrichment, a vital modality for promoting life-long neurogenesis (see sections 3 and 5).

The Olfactory Cortex is the part of the cerebral cortex that processes the sense of smell. Located mainly in the temporal lobe and receiving input directly from the olfactory bulb, it includes the Uncus, Piriform cortex**,** Amygdala**,** Olfactory tubercle, and the Parahippocampal gyrus. The olfactory tubercle is connected to numerous areas, namely amygdala, thalamus, hippocampus, hypothalamus, brain stem, retina and the auditory cortex. The Stria terminalis functions as the information pathway between the amygdala and hypothalamus, as well as the hypothalamus and pituitary gland. The hippocampus receives almost all of its olfactory information via the amygdala. From the olfactory cortex, odor information is conveyed to the orbitofrontal cortex via the dorsal medial nucleus of the thalamus. All of these regions mentioned above form the Olfactory Pathway (Figure 3). The orbitofrontal cortex is that portion of the prefrontal cortex which is located on the underside of the frontal lobe and overlies the eye orbit. Odor information is also sent to portions of the hypothalamus and brainstem . It is obvious that olfactory information is received in some or the other form by large parts of the limbic system that exerts control over vital functions, such as regulation of thirst, hunger, mood, reward processing, habit formation, movement and learning. Thus, aromas can affect all these parts of the brain, influencing their function.

9. Conclusion

It is evident from the above discussion that smells and fragrances, including pheromonal odors, have the capacity to modulate neurogenesis across various regions of the adult brain. Recent findings support and strengthen the intimate connection between the olfactory system and several brain regions where neurogenesis is observed, reinforcing the proposition that aromas and odors play an important role in modulating neurogenesis within areas tied to emotion (such as the amygdala), reward (like the striatal system), as well as learning and memory, notably the hippocampus and entorhinal cortex. Neural stem cells deviating from the RMS under chemotactic stimuli, can also reach the endocrine master glands, namely the hypothalamus and pituitary, refurbishing these areas with fresh neuro-endocrine cells, resulting in a revitalized neuro-endocrine axis (Figures 2&3). As is evident from above explanations, aromas play a vital role in cognitive functions and in maintaining the satisfactory performance of the brain. The ancient practice of perfumery may thus not be just a cosmetic adornment, but rather a specialized craft to enrich the

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