Complete Olfactory Neural Pathway Hypothesis and Modeling

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Abstract

Investigation of olfactory neural pathways constitutes the foundation of olfactory research and likewise holds multifaceted significance for brain science research. By synthesizing extant relevant research findings, this study proposes a hypothesis regarding the complete olfactory neural pathway. This neural pathway comprises an anterior component centered on the olfactory bulb layer, an intermediate component centered on the entorhinal cortex, and a posterior component centered on the dentate gyrus. Upon this foundation, the present paper constructs a comprehensive structural model of the olfactory neural pathway and conducts a preliminary analysis.

Full Text

Hypothesis and Modeling of Complete Olfactory Neural Pathway

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Abstract: Research on the olfactory neural pathway forms the foundation of olfactory studies and holds multifaceted significance for brain science. By synthesizing existing relevant research, this paper explores a hypothesis regarding the complete olfactory neural pathway. This pathway comprises a front-end section centered on the olfactory bulb layer, a middle section centered on the entorhinal cortex, and a rear section centered on the dentate gyrus. Based on this hypothesis, we construct a complete structural model of the olfactory neural pathway and conduct preliminary analysis.

Key words: olfactory neural pathway; olfactory bulb; entorhinal cortex; dentate gyrus; bionic model

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When it comes to olfaction, it is remarkable that nearly all organisms respond to odors in their external environment. This perceptual capacity provides highly specific and useful information about food, danger, mating, territory defense, and more. Consequently, research on olfactory neural pathways is essential for understanding the series of organismal activities triggered by odorants.

Researchers typically construct bionic models of olfactory neural pathways based on their layered characteristics. Representative models include the K-series models, Li model, Liljenstrom model, and various biophysical models. The Liljenstrom model [**?**] simulates a three-layer olfactory cortex, from superficial to deep: Layer I—a feedforward inhibition unit layer (NI layer) containing inhibitory interneurons and afferent fibers from the olfactory bulb; Layer II—an excitatory unit layer (NII layer) primarily comprising excitatory pyramidal cells; and Layer III—a feedback inhibition unit layer (NIII layer) containing both pyramidal neurons and interneurons. The Li model [**?**] is a coupled model of the olfactory bulb and cortex, where odor information from the olfactory epithelium is encoded as oscillatory patterns in the olfactory bulb layer. When an odor pattern from the bulb matches a stored odor memory pattern in the olfactory cortex, these patterns generate resonant oscillations, enabling odor recognition by the model. In recent years, biophysical models have gained favor among researchers. These models incorporate realistic cellular morphology, synaptic properties, and the dynamics of various ion channels, typically employing multicompartmental models. A compartmental model discretizes a spatially continuous neuron into multiple interconnected compartments to describe the neuron' s spatiotemporal dynamics [**?**]. Linster et al. constructed a multicompartmental model from the olfactory bulb to the olfactory cortex to investigate how the olfactory system separates target odors from background odors [**?**]. De Almeida et al. also built a multicompartmental model from bulb to cortex to study how cholinergic inputs to these regions modulate odor representation [**?**]. Li and Cleland attempted to construct a general multicompartmental model of the olfactory bulb to generate gamma oscillations that influence mitral cell spike timing [**?**]. The K-series models progressively simulate the olfactory nervous system from low to high levels, including K0, KI, KII, and KIII models [**?**, **?**]. Among these, K0, KI, and KII models serve as basic components of the KIII model, which realistically simulates the entire olfactory nervous system. However, these models are limited to simulating odor information processing and do not involve brain regions associated with higher-level activities triggered by odor information.

Based on anatomical knowledge, this paper summarizes the neural transmission mechanisms of olfactory pathways to higher brain regions, dividing them into three components: front-end, middle, and back-end, and conducts modeling studies on the key components of each section.

1 Construction of the Olfactory Neural System Pathway

This paper reviews the neural pathway from the olfactory system to the temporal lobe, as illustrated in Figure 1 [Figure 1: see original paper], which can be divided into three parts: front-end, middle, and back-end. The front-end constitutes the basic olfactory nervous system, responsible for fundamental odor information processing. Odor molecules act on the olfactory epithelium (OE), which converts chemical signals into electrical signals transmitted to the olfactory bulb (OB). The bulb encodes odor information, which is then further processed by the olfactory cortex (OC) to prepare for odor perception and memory formation. The front-end olfactory cortex primarily refers to the anterior olfactory nucleus (AON) and piriform cortex (PC). The middle section, also part of the olfactory cortex, includes the amygdala and entorhinal cortex (EC), receiving projections from both the olfactory bulb and piriform cortex. The amygdala triggers a series of emotional responses based on odor information [**?**]. For example, when smelling sweet floral fragrances, the amygdala modulates positive emotional responses, creating a pleasant mood. The entorhinal cortex processes odor information in preparation for memory formation in the hippocampus. The back-end refers to the hippocampus, primarily composed of the dentate gyrus (DG), CA3, and CA1, which is the site of memory formation. Finally, CA1 returns information to the entorhinal cortex via the subiculum. The entorhinal cortex then projects memory information to relevant brain regions for storage, though the specific storage process requires further investigation. Research indicates that long-term memory is not stored in the medial temporal lobe but rather, after encoding and processing by this region, returns to neocortical areas that initially processed the sensory information [**?**]. Since the amygdala' s emotional modulation process is not directly related to olfaction itself, the neural pathways associated with the amygdala are omitted in this study of olfactory neural pathways, focusing instead on the memory formation process in temporal lobe regions after odor information entry.

1.1 Front-End Olfactory Neural Pathway

Based on laminar organization, the front-end olfactory neural pathway consists of the olfactory epithelium, olfactory bulb, and olfactory cortex from outer to inner layers. As shown in Figure 2 [Figure 2: see original paper], after odor molecules enter the nasal cavity, they bind to odorant receptors (OR) on specific olfactory receptor cells (ORC, also called olfactory sensory neurons, OSN) in the olfactory epithelium. Multiple odorant receptors distributed on a single olfactory sensory neuron belong to the same type. Activated odorant receptors transmit odor information via olfactory nerves to glomeruli (GL) in the olfactory bulb, either directly or after preprocessing by periglomerular cells (PG). Notably, olfactory sensory neurons expressing the same odorant receptor converge onto the same glomerulus. Activated mitral cells (M) and granule cells (Gr) in glomeruli interact to generate local oscillations, transforming odor information into spatial distribution patterns of glomerular activity [**?**]. Mitral cells

transmit processed odor information via the lateral olfactory tract (LOT) to the anterior olfactory nucleus and piriform cortex, subsequently reaching olfactory centers to trigger odor perception and other higher-level brain activities. The anterior olfactory nucleus and piriform cortex generate feedback to the olfactory bulb via the medial olfactory tract (MOT), and the piriform cortex can also send feedback to the anterior olfactory nucleus through the MOT.

Currently, definitions of olfactory cortical regions reached by the LOT remain ambiguous without specific consensus, broadly including the anterior olfactory nucleus, piriform cortex, amygdala, entorhinal cortex, olfactory tubercle (OT), and other regions [**?**]. Among these, the piriform cortex is the largest olfactory cortical area receiving direct projections from the olfactory bulb.

The piriform cortex comprises pyramidal cells (P), semilunar cells (SL), and various interneurons. Pyramidal cells include two types: superficial pyramidal cells (SP) and deep pyramidal cells (DP), which serve as the primary input and output neurons of the piriform cortex. The apical dendrites of both pyramidal cell types and the dendrites of semilunar cells receive projections from the lateral olfactory tract and other piriform cortex cells. However, only the axons of both pyramidal cell types project to regions outside the piriform cortex, such as the olfactory bulb, amygdala, and entorhinal cortex, whereas semilunar cell axons only target the somata of the two pyramidal cell types [**?**]. Interneurons are mainly divided into two categories: those mediating feedforward inhibition (FF) within the piriform cortex and those mediating feedback inhibition (FB).

1.2 Middle Olfactory Neural Pathway

The temporal lobe primarily contains the middle and back-end components of the olfactory neural pathway. Based on functional mechanisms of the temporal lobe, olfactory-related structures include the amygdala, parahippocampal gyrus, and hippocampus, with the entorhinal cortex and subiculum in the parahippocampal gyrus providing main inputs to the hippocampus. Excluding the amygdala' s emotional modulation process, the middle olfactory neural pathway primarily comprises projection pathways from the olfactory bulb and piriform cortex to the entorhinal cortex, along with feedback projections from the entorhinal cortex [**?**]. Some literature also mentions that the piriform cortex, located at the temporal lobe margin, merges various odor features into odor objects projected to the entorhinal cortex [**?**].

The entorhinal cortex is typically divided into six layers, with Layers I, II, and III as superficial layers and Layers IV, V, and VI as deep layers. After receiving inputs from various cortical regions in the superficial layers, the entorhinal cortex primarily projects to the hippocampus from Layers II and III. The hippocampus returns processed information to the deep layers of the entorhinal cortex, which then project to other cortical regions. More specifically, Layer II mainly provides input to the dentate gyrus and CA3, Layer III primarily projects to CA1 and the subiculum, and outputs from CA1 and subiculum

mainly project to the deep layers of the entorhinal cortex [**?**]. Reference [**?**] notes that when studying entorhinal inputs and outputs, olfactory information inputs are selectively projected to Layers I and II of the entorhinal cortex.

Additionally, based on unique cytoarchitecture and connectivity patterns, the entorhinal cortex can be divided into medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC). MEC plays a crucial role in spatial navigation, while LEC provides sensory-related information to the hippocampus [**?**]. References [**?**] specifically note that projections from the olfactory bulb and piriform cortex to the entorhinal cortex concentrate in LEC. As shown in Figure 3 [Figure 3: see original paper], two neuron types in the entorhinal cortex closely related to hippocampal projection circuits are stellate cells and pyramidal cells [**?**]. Stellate cells are located in Layer II and primarily project to the dentate gyrus and CA3. Pyramidal cells not only provide input to CA1 and subiculum but also project to brain regions beyond the hippocampus. Both stellate and pyramidal cells are excitatory neurons, while various inhibitory interneurons are also distributed throughout the entorhinal cortex, interacting with excitatory neurons to form local oscillatory circuits.

The middle section, primarily composed of the entorhinal cortex, serves as a bridge connecting the front-end and back-end olfactory neural pathways. The olfactory bulb and piriform cortex are critical components in the neural pathway projecting olfactory information to the temporal lobe. Considering only major projection relationships while ignoring minor ones, it is essential to clarify the projection process from the olfactory bulb and piriform cortex to the entorhinal cortex to construct this olfactory neural pathway completely. However, projections from the olfactory bulb and piriform cortex to other brain regions remain ambiguous, with relatively few studies providing specific descriptions of neuronal projection circuits, making it impossible to determine the exact neuronal connectivity patterns. Despite these unclear projection circuits, we can attempt to hypothesize the connectivity patterns from the olfactory bulb and piriform cortex to the entorhinal cortex based on existing research and validate these hypotheses through experiments.

The principal projection neurons in the olfactory bulb and piriform cortex are mitral cells and pyramidal cells, respectively. In the entorhinal cortex, stellate cells primarily receive various sensory inputs and project to the dentate gyrus. During construction of neuronal connections, common approaches include one-to-one connections, full connections, and random connections. However, in real neural pathways, neuronal connections are specific rather than fully connected to all neurons, making full connectivity inappropriate. Random connections merely simulate seemingly random connectivity patterns and do not imply chaotic organization. By selecting the three main neuron types—mitral cells, pyramidal cells, and stellate cells—we can attempt to construct connections from the olfactory bulb and piriform cortex to the entorhinal cortex using either one-to-one or random connection patterns.

1.3 Back-End Olfactory Neural Pathway

The back-end component involves the neural pathway for olfactory memory formation, primarily concerning hippocampal structures in the temporal lobe. As shown in Figure 4 [Figure 4: see original paper], the projection circuits within the hippocampus [**?**] receive major cortical input from the entorhinal cortex. Among numerous internal hippocampal projection circuits, the most classic and primary is the "trisynaptic circuitry" : Synapse 1—projection from entorhinal cortex to dentate gyrus, known as the perforant path (PP); Synapse 2—projection from dentate gyrus to CA3, known as mossy fibers (MF); Synapse 3—projection from CA3 to CA1, known as Schaffer collaterals (SC). Additionally, the entorhinal cortex can directly project to CA3, CA1, and subiculum; CA3 sends feedback to the dentate gyrus and possesses recurrent projections. The subiculum is the main output structure of the hippocampus, transmitting information back to the entorhinal cortex, while CA1 can also directly project to the entorhinal cortex. In studies of neural pathways, the primary projection circuit is typically selected: EC→DG→CA3→CA1→subiculum→EC.

In this primary circuit, the dentate gyrus is the first hippocampal structure to receive information, possessing pattern separation functionality. It is generally considered the initial stage for processing information ultimately used in memory formation, separating neural representations of similar memories through different circuits to optimize memory storage and subsequent retrieval [**?**]. In other words, the dentate gyrus acts as an information preprocessor preparing for subsequent CA3 processing, playing a crucial role in memory formation. When the current input pattern shares components with a past pattern, responses to common components are suppressed, achieving pattern separation. This allows the hippocampus to create unique representations of similar experiences, minimizing interference with specific memory storage and retrieval [**?**]. The dentate gyrus enables organized memory formation, allowing memorization of many similar scenes and objects. Therefore, when studying memory formation mechanisms, the dentate gyrus is the primary research target.

The principal neurons of the dentate gyrus are granule cells, which mainly receive projections from the entorhinal cortex. Granule cell axons project not only to certain interneurons such as basket cells and mossy cells but also converge into fiber bundles leaving the polymorphic layer, extending to the stratum lucidum of CA3 to establish synaptic connections with CA3 pyramidal cells. Moreover, granule cell projection to CA3 is the sole output pathway from the dentate gyrus to external brain regions. Additionally, granule cells lack mutual connections, achieving indirect interactions only through connections with other cell types.

2 Olfactory Neural Pathway Model

Based on the preceding analysis of the olfactory neural pathway, ignoring minor structures and connections, we constructed the olfactory neural pathway model shown in Figure 5 [Figure 5: see original paper]. The front-end includes the

olfactory epithelium, olfactory bulb, anterior olfactory nucleus, and piriform cortex; the middle section comprises the entorhinal cortex; and the back-end includes the dentate gyrus. Connections from the olfactory bulb and piriform cortex to the entorhinal cortex are hypothesized as either one-to-one or random connections.

Both the front-end and middle models are constructed based on neural mass theory, proposed by Professor Freeman, which states that groups of similar neurons form cell clusters with similar functions and consistent properties that can serve as building blocks of the entire nervous system [**?**]. Freeman' s K-series models are based on this theory, where the K0 model is the basic module representing cell clusters of similar neurons with consistent functions and properties. Beyond the K0 model, higher-level models contain modules composed of lower-level models. The KI model consists of two interconnected K0 models, the KII model comprises two interconnected KI models, and both KI and KII models generally serve as basic modules rather than standalone analytical models. The KIII model is formed by K0, KI, and KII models through feedforward and delayed feedback connections, simulating the entire front-end olfactory neural pathway.

2.1 Front-End Model Based on KIII

Based on Freeman' s research, this paper constructs a front-end olfactory neural pathway model using the KIII model as the foundation, as shown in Figure 6 [Figure 6: see original paper]. The KIII-based front-end model covers key components of the front-end olfactory neural pathway. R corresponds to olfactory receptors receiving odor information, P corresponds to periglomerular cells preprocessing odor information, M and G correspond to mitral cells and granule cells respectively, jointly completing spatial transformation of odor information, E and I correspond to excitatory and inhibitory neurons in the anterior olfactory nucleus, and key components of the PC layer correspond to different parts of the piriform cortex. Specifically, Ff corresponds to interneurons mediating feedforward inhibition, Py corresponds to pyramidal cells providing major input and output of the piriform cortex, and Fb corresponds to interneurons mediating feedback inhibition. Additionally, connections and delays are incorporated between different model components. Each R represents one class of olfactory receptors projecting to a single glomerulus, either directly or via P. Stettler et al.' s optical imaging of piriform cortex odor responses revealed that each neuron in the piriform cortex responds only to specific odors, with projections from mitral cells in the olfactory bulb showing no obvious spatial preference, displaying discontinuous receptive fields where different odors activate unique, discrete sets of piriform cortex neurons [**?**]. Therefore, random connections can be used to simulate the projection process from M to Py. Within the PC layer, Ff also receives projections from M to modulate excitatory input from M. Py sends excitatory connections, Fb sends inhibitory connections, and local mutual connections between Py and Fb form oscillatory circuits. Feedback from the

PC layer to the AON and OB layers is implemented through projections from Pr to I and G, respectively.

2.2 Middle Model Based on Neural Mass

The middle olfactory neural pathway structure primarily consists of the entorhinal cortex. Based on neural mass theory, this paper constructs an entorhinal cortex-centered middle olfactory neural pathway model, as shown in Figure 7 [Figure 7: see original paper]. This entorhinal cortex model covers major neuron types in the entorhinal cortex. Stellate cells in the entorhinal cortex receive sensory information input and project to the dentate gyrus, interacting with interneurons to form local oscillatory circuits. In the model, S corresponds to stellate cells and I corresponds to interneurons.

2.3 Back-End Model Based on Dentate Gyrus

The back-end olfactory neural pathway primarily involves hippocampal structures, and hippocampal memory formation has long been a research challenge. Therefore, hippocampal research can follow a stepwise approach from simple to complex and from local to whole. This paper focuses on modeling the first structure receiving hippocampal input: the dentate gyrus, as shown in Figure 8 [Figure 8: see original paper]. Based on bionic principles, the dentate gyrus model includes granule cells (GC), mossy cells (MC), basket cells (BC), and hilar cells with axonal projections to the perforant path (HIPP). The first two are excitatory neurons, while the latter two are inhibitory neurons. These four neuron types constitute the vast majority of all neurons in the dentate gyrus, with limited physiological data available for other neuron types [**?**]. The model comprehensively simulates internal neural pathways of the dentate gyrus. GC are the main input neurons of the dentate gyrus, with all GC receiving input from the entorhinal cortex, along with all BC and 15% of MC. However, no direct connections exist between GC, which achieve indirect interactions through connections with other neuron types. Additionally, the model contains rich internal connections: mutual connections exist among these four neuron types except for BC not projecting to HIPP, and both MC and BC have connections within their own cell types.

This paper systematically summarizes the neural transmission mechanisms of the olfactory neural pathway, dividing it into front-end (olfactory epithelium, olfactory bulb, anterior olfactory nucleus, piriform cortex), middle (amygdala, entorhinal cortex), and back-end (hippocampus, subiculum) sections. The projection process from the olfactory bulb and piriform cortex to the entorhinal cortex remains unknown, and we hypothesize neuronal connection patterns as either one-to-one or random connections. Subsequently, we propose an olfactory neural pathway model and conduct modeling studies from front-end, middle, and back-end perspectives. The KIII-based front-end model improves upon Freeman' s KIII model by expanding the basic units for piriform cortex simulation. The neural mass-based middle model focuses on the entorhinal cortex,

constructing a distributed KII model incorporating major entorhinal neuron types. The dentate gyrus-based back-end model considers connectivity among major neuron types.

The proposed olfactory neural pathway model focuses on key components of this pathway and has not yet covered all structures. Moreover, the actual connectivity patterns from the olfactory bulb and piriform cortex to the entorhinal cortex remain unknown. Future work will follow advances in neurophysiological research on this olfactory neural pathway to determine connectivity patterns, neuronal ratios, and other parameters. Additionally, we will refine the structures of the front-end, middle, and back-end models, determine model parameters using neurophysiological data, integrate the three model components, and conduct optimization studies using small-world network theory and EEG synchronization indices. We will analyze the dynamic characteristics of the model, evaluate its biomimetic fidelity, and ultimately apply the model to multiple domain scenarios to analyze its functional features.

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Note: Figure translations are in progress. See original paper for figures.