

Glial and Neurogenic Targets for Pharmacological Modulation of Chemosensory Circuit Plasticity

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Abstract

Chemosensory systems exhibit substantial plasticity that supports adaptive perception, sensory learning, and behavioral responses to changing environmental and physiological conditions. Although synaptic mechanisms have traditionally been viewed as the principal basis of chemosensory plasticity, accumulating evidence indicates that adaptive sensory function depends on coordinated interactions among circuit modulation, glial regulation, metabolic and inflammatory state, and structural remodeling. This review synthesizes experimental findings showing how cortical feedback reshapes olfactory and broader chemosensory representations, how astrocytes and microglia regulate synaptic, metabolic, inflammatory, and remodeling environments, and how neurogenic and other structural mechanisms contribute to longer-term adaptation in experimental olfactory systems. On this basis, the review proposes an integrated multiscale framework in which cortical, glial, metabolic, inflammatory, genetic, and structural processes act as interconnected regulators of chemosensory plasticity rather than isolated contributors. Pharmacologically relevant entry points include neuromodulatory control of cortical feedback, astrocytic glutamate handling, purinergic signaling, metabolic support, microglial inflammatory responses, complement-associated synaptic remodeling, and neurotransmitter-dependent regulation of neurogenic niche dynamics. The framework also considers sirtuin 1 (SIRT1) as a candidate genetic and metabolic regulator linking cellular energy state, inflammation, oxidative stress, autophagy, synaptic plasticity, aging, and neurodegeneration, while emphasizing that its direct role in human chemosensory recovery remains unproven. Because smell and taste disturbances are prominent in aging, neurodegenerative disease, metabolic disorders, and post-viral conditions, this framework provides a basis for identifying context-dependent therapeutic strategies that may support sensory adaptation and recovery while avoiding disruption of beneficial inflammatory or remodeling responses.

Keywords: Chemosensory plasticity, Neuropharmacology, Olfactory dysfunction, Astrocytes, Microglia, Neuroinflammation, Pharmacological modulation, SIRT1

Introduction — Chemosensory Plasticity Beyond Synapses: Toward Pharmacological Modulation

Chemosensory systems, encompassing olfaction and gustation, exhibit substantial plasticity that allows sensory perception and behavior to adapt to environmental stimuli, prior experience, and physiological state. This plasticity supports odor and taste discrimination, sensory learning, food-related decision making, hazard detection, and context-dependent behavior. Traditionally, chemosensory plasticity has been explained primarily through synaptic mechanisms, including long-term potentiation, long-term depression, and activity-dependent changes in synaptic strength within the olfactory bulb, piriform cortex, and gustatory cortex [1,2].

However, synaptic plasticity alone does not fully explain the persistence, flexibility, and disease vulnerability of chemosensory adaptation. Chemosensory circuits are continuously influenced by cortical feedback, neuromodulatory signaling, glial regulation, inflammatory state, metabolic support, and structural remodeling. Experimental studies increasingly show that these mechanisms interact across biological scales rather than acting independently. Cortical feedback modifies early sensory processing and sensory representations [3–8], astrocytes regulate neurotransmitter handling and metabolic support, microglia influence inflammatory signaling and synaptic remodeling [7,9], and neurogenic or structural remodeling contributes to longer-term circuit adaptation in experimental olfactory systems [5,10].

The central problem is that these mechanisms are often considered separately, making it difficult to explain how chemosensory circuits maintain adaptive plasticity or why that plasticity fails during aging, inflammation, metabolic stress, viral injury, and neurodegenerative disease. Existing reviews commonly emphasize individual mechanisms such as synaptic plasticity, neuroinflammation, glial function, or neurogenesis, but less attention has been given to how these processes interact as a coordinated regulatory system.

This review addresses that gap by proposing an integrated framework in which cortical feedback, glial regulation, and structural remodeling operate as interconnected regulators of chemosensory plasticity. Within this framework, cortical feedback shapes circuit activity and sensory gain, astrocytes and microglia regulate the synaptic, metabolic, and inflammatory environment, and neurogenic or other structural mechanisms support longer-term remodeling in experimental systems where these processes remain active. The emphasis is therefore not simply on identifying individual mechanisms, but on understanding how their interactions determine whether chemosensory plasticity remains adaptive, becomes impaired, or supports recovery.

This integrated view has direct pharmacological relevance. Chemosensory dysfunction occurs in aging, neurodegenerative disease, metabolic disorders, inflammatory states, and post-viral conditions, yet therapeutic options remain limited. Potential pharmacological entry points include neuromodulatory control of cortical feedback, astrocytic glutamate handling, purinergic signaling, metabolic support, microglial inflammatory responses, complement-associated synaptic remodeling, and regulation of neurogenic niche dynamics in experimental systems. The therapeutic challenge is therefore not simply to increase plasticity or suppress inflammation, but to restore conditions that support normal sensory adaptation while preserving beneficial circuit remodeling.

Accordingly, this review has three aims. First, it synthesizes experimental evidence on cortical feedback, astrocytes, microglia, and neurogenic or structural remodeling in chemosensory plasticity. Second, it examines how these mechanisms interact across molecular, cellular, circuit, and structural levels. Third, it identifies pharmacologically relevant pathways that may influence chemosensory adaptation, recovery, and disease-associated dysfunction, while considering the translational limitations of experimental models.

Review methodology

This article was developed as a narrative and integrative review rather than a systematic review or meta-analysis. Relevant literature was identified through targeted searches of PubMed and Google Scholar and through examination of

reference lists from pertinent primary studies and reviews, with the literature updated through July 2026. Searches focused on combinations of terms related to chemosensory and olfactory plasticity, cortical feedback, sensory learning, astrocytes, microglia, neuroinflammation, metabolic regulation, neural stem cells, adult neurogenesis, olfactory bulb circuitry, pharmacological modulation, aging, neurodegeneration, and post-viral chemosensory dysfunction.

Priority was given to peer-reviewed experimental studies that directly addressed mechanisms of chemosensory circuit plasticity, glial regulation, activity-dependent remodeling, neurogenic or structural plasticity, or pharmacologically relevant pathways. Recent studies were emphasized where available, while established earlier studies were retained when necessary to define foundational mechanisms. Reviews were used primarily to provide broader context and to identify relevant primary literature. Evidence from experimental animal models was distinguished from evidence applicable to humans, particularly for adult SVZ-derived olfactory neurogenesis, where substantial species differences limit direct translation.

The selected literature was organized according to the major mechanistic levels examined in this review, including circuit regulation, glial regulation, structural remodeling, and their interactions. It was then evaluated in relation to pharmacological targets, disease-associated chemosensory dysfunction, and translational relevance.

Chemosensory Circuit Architecture as a Plastic Substrate

Organization of chemosensory circuits

Chemosensory processing is mediated by distributed neural circuits that transform chemical stimuli into perceptual and behavioral outputs. In the olfactory system, sensory information originates in olfactory receptor neurons, which project to the olfactory bulb, where inputs are organized into discrete glomerular units based on receptor identity [6,11]. Within the olfactory bulb, principal neurons (mitral and tufted cells) relay processed signals to higher-order regions, most notably the piriform cortex, which serves as a primary olfactory cortical area [6,11]. Unlike other sensory systems, olfactory pathways bypass thalamic relay nuclei and project directly to cortical and limbic structures, enabling rapid integration with memory, emotion, and behavioral circuits [6,12].

A distinguishing feature of chemosensory systems, particularly within the piriform cortex, is the absence of strict topographic organization. Unlike visual or somatosensory systems that rely on spatially ordered maps, olfactory representations are encoded through distributed and

associative activity patterns across neuronal populations [8,12]. This organizational principle supports flexible and context-dependent encoding of odor information. Although gustatory pathways involve brainstem and thalamic relays prior to reaching the gustatory cortex, similar principles of distributed representation and adaptive coding apply across chemosensory modalities [2,13].

The major organizational features of chemosensory circuit architecture discussed in this section are summarized in **Figure 1**.

Recurrent connectivity and feedback pathways

As illustrated in **Figure 1**, chemosensory circuits are organized as distributed and highly interconnected systems in which feedforward, recurrent, and top-down pathways jointly shape sensory processing. A defining feature of chemosensory circuits is the presence of extensive recurrent and feedback connectivity. In the olfactory system, the piriform cortex sends dense corticofugal projections back to the olfactory bulb, forming feedback pathways that modulate early sensory processing [6,8]. These projections target both excitatory and inhibitory neuronal populations, enabling dynamic regulation of signal gain, contrast enhancement, and temporal coordination within the bulb [6,8,14].

Local recurrent circuits further contribute to network dynamics. In the olfactory bulb, inhibitory interneurons such as granule and periglomerular cells mediate lateral inhibition and synchronize mitral and tufted cell activity, shaping odor representations [11,14]. In the piriform cortex, recurrent excitatory connections support associative processing, enabling pattern completion and the retrieval of learned odor representations from partial or degraded inputs [12,15]. Together, these recurrent and feedback interactions establish chemosensory circuits as highly interconnected systems in which information flow is continuously shaped by internal network states and prior experience.

Activity-dependent circuit reconfiguration

Chemosensory circuits exhibit substantial activity-dependent plasticity at multiple levels, including synaptic strength, connectivity patterns, and network organization. Experimental studies have demonstrated that sensory experience, learning, and environmental exposure can modify synaptic efficacy within both the olfactory bulb and piriform cortex, leading to changes in odor tuning, discrimination, and perceptual sensitivity [8,12,16,17]. These modifications include long-term potentiation and depression, as well as shifts in inhibitory–excitatory balance that influence circuit output and stability [6,8,16].

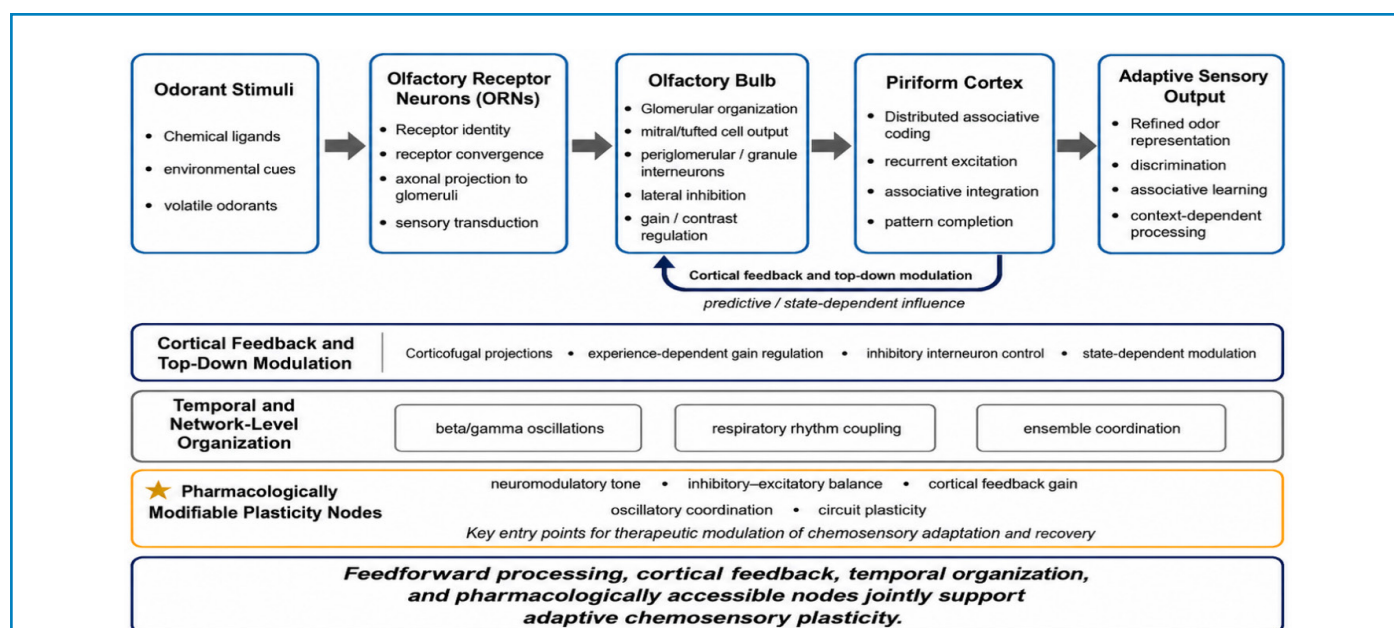


Figure 1. Chemosensory circuit architecture as a plastic substrate. Schematic overview of major circuit features that support chemosensory plasticity, with emphasis on the olfactory system. Odorant information is transmitted from olfactory receptor neurons to the olfactory bulb and then to the piriform cortex, where distributed associative coding supports adaptive odor representation. Cortical feedback provides top-down modulation of olfactory bulb activity, while temporal network mechanisms, including beta/gamma oscillations, respiratory rhythm coupling, and ensemble coordination, further shape sensory processing. The figure also highlights pharmacologically accessible nodes, including neuromodulatory tone, inhibitory–excitatory balance, cortical feedback gain, oscillatory coordination, and circuit plasticity, which may influence chemosensory adaptation and recovery. This figure was created by the author for the present manuscript and was not reproduced or adapted from another source.

In addition to synaptic changes, activity-dependent processes can alter connectivity patterns and influence the recruitment of neuronal ensembles during sensory processing. Repeated odor exposure or associative learning refines neuronal population responses, enhancing selectivity and improving signal-to-noise ratios in odor representations [8,12,17]. Chemosensory processing is also strongly shaped by temporal dynamics, including oscillatory activity in the beta and gamma frequency ranges and coupling to respiratory rhythms, which organize neuronal firing and influence odor representation and discrimination [18–20]. These temporal features provide an additional dimension through which circuit activity is structured and modulated by experience.

Together, feedforward processing, recurrent connectivity, cortical feedback, and activity-dependent reconfiguration allow chemosensory circuits to update sensory representations according to experience, internal state, and behavioral context [6,8,12,16–18]. These circuit properties are further shaped by glial regulation and longer-term structural remodeling.

Experience-Dependent Plasticity in Chemosensory Systems

Behavioral and circuit-level adaptation to sensory experience

Chemosensory experience modifies detection, discrimination, preference, and learned associations. Repeated exposure can produce habituation, whereas perceptual or associative learning can improve discrimination and assign behavioral significance to odors or tastes [4,12,21]. These behavioral changes are accompanied by altered neuronal responsiveness, tuning, ensemble recruitment, and temporal coordination within the olfactory bulb, piriform cortex, gustatory cortex, and related chemosensory circuits [4,12,22].

Attention, behavioral relevance, reward, and internal state all influence experience-dependent plasticity. Chemosensory learning therefore changes circuit activity according to context rather than producing a fixed response to repeated sensory input [23].

Molecular and cellular mechanisms underlying experience-dependent plasticity

At the molecular and cellular levels, sensory activity engages calcium-dependent signaling, transcriptional regulation, neuromodulatory pathways, and changes in synaptic efficacy and neuronal excitability [5,24]. Cholinergic and other neuromodulatory systems help link plasticity to attention, reward, and behavioral state.

Glial regulation and, in experimental olfactory systems, neurogenic remodeling extend these effects beyond neurons.

Astrocytes and microglia shape neurotransmitter availability, metabolic support, inflammatory signaling, and synaptic remodeling, whereas sensory experience can influence the survival and integration of newly generated neurons [5,7,10]. These mechanisms are examined in greater detail in the following sections.

Cortical Feedback as a Driver of Circuit Reconfiguration

Anatomical and functional organization of cortical feedback pathways

Cortical feedback is a major feature of chemosensory circuit organization, particularly in the olfactory system. The piriform cortex sends dense corticofugal projections to the olfactory bulb, targeting principal neurons and local interneurons, including granule and periglomerular cells [6,8,25]. Through these targets, cortical inputs regulate lateral inhibition, neuronal synchronization, and the temporal structure and specificity of mitral and tufted cell output [26–28]. These feedback pathways are modified by learning and repeated sensory exposure, allowing cortical control of early sensory processing to be tuned by prior experience and behavioral relevance [6,8,29].

Mechanisms of cortical modulation of sensory processing

Cortical feedback modifies chemosensory processing partly through regulation of inhibitory interneurons. Cortical inputs to olfactory bulb granule cells alter lateral inhibition and thereby adjust the contrast, selectivity, and gain of odor representations produced by mitral and tufted cells [8,29,30].

Corticofugal projections also influence the temporal organization of sensory activity, including beta- and gamma-frequency oscillations associated with odor processing and learning [8,31,32]. By modifying the timing and coordination of neuronal firing, cortical feedback helps organize how complex sensory information is encoded.

These effects are further shaped by cholinergic, noradrenergic, and other neuromodulatory inputs, which regulate the gain and plasticity of corticofugal signaling [19,24,33]. Through these neuromodulatory influences, cortical feedback can enhance behaviorally relevant signals, reduce responses to less relevant inputs, and adjust sensory processing according to attention, arousal, reward, and behavioral context [8,12,30,32,33].

Cortical feedback in learning and predictive processing

Cortical feedback contributes to learning-dependent plasticity by transmitting experience- and context-related

signals from higher-order regions to early chemosensory circuits. During associative learning, these signals can modify olfactory bulb activity and refine sensory representations according to prior experience and behavioral relevance [8,12,34]. Predictive-processing models further suggest that cortical pathways convey expectations about incoming sensory input, although the precise mechanisms remain under investigation [35–37]. Experimental findings nevertheless support a role for cortical feedback in enhancing relevant representations, suppressing less informative signals, and improving odor discrimination and learning [8,12,34].

Cortical feedback therefore links experience, behavioral state, and sensory context to early chemosensory processing. Because these pathways are regulated by cholinergic, noradrenergic, and other neuromodulatory systems, they provide pharmacologically accessible mechanisms for modifying sensory gain, discrimination, learning, and adaptive circuit responses [19,24,33].

Glial Regulation of Chemosensory Circuit States as Pharmacological Entry Points

Astrocytes in chemosensory circuit modulation

Astrocytes are integral components of chemosensory circuits, contributing to the regulation of synaptic transmission, metabolic support, and extracellular homeostasis. Within the olfactory bulb and piriform cortex, astrocytes are positioned in close proximity to synapses, forming part of the “tripartite synapse,” in which pre- and postsynaptic neuronal elements are functionally integrated with astrocytic processes that regulate synaptic transmission and plasticity [38–40]. Through uptake and recycling of neurotransmitters such as glutamate and GABA, astrocytes regulate synaptic signaling and prevent excitotoxicity, thereby maintaining circuit stability [41–43].

These astrocytic functions are pharmacologically relevant because glutamate clearance, GABA–glutamate balance, transporter activity, and extracellular homeostasis directly shape neuronal excitability and plasticity. In chemosensory circuits, altered astrocytic regulation could influence sensory gain, discrimination, and vulnerability to inflammatory or metabolic disruption [18,44,45]. Thus, astrocyte-mediated neurotransmitter handling represents a potential entry point for modulating chemosensory circuit stability and maladaptive sensory processing.

In addition to neurotransmitter clearance, astrocytes modulate synaptic transmission through the release of gliotransmitters, including ATP, D-serine, and glutamate, which can influence synaptic strength and plasticity [40,46,47]. Astrocytes also play a key role in providing metabolic support to neurons by regulating glucose uptake, lactate production, and energy distribution within neural circuits [48–50].

Astrocyte–neuron metabolic coupling, including lactate shuttling, provides an additional mechanism through which glial cells support activity-dependent plasticity [48,49,51]. These functions are particularly relevant in chemosensory systems, where continuous sensory input requires efficient metabolic coordination between neuronal activity and energy supply.

From a therapeutic perspective, astrocyte–neuron metabolic coupling may be especially important in aging, metabolic disorders, and neurodegenerative disease, where impaired energy support can reduce circuit resilience [52,53]. Pharmacological strategies that influence astrocytic metabolism, lactate signaling, or activity-dependent energy supply may therefore affect the capacity of chemosensory circuits to maintain adaptive plasticity under physiological stress.

Experimental studies have demonstrated that astrocytic activity is dynamically regulated by sensory experience and can influence neuronal responsiveness and circuit function [54–56]. Changes in astrocytic calcium signaling and gliotransmission have been associated with modulation of synaptic efficacy and network activity in response to sensory stimulation, indicating that astrocytes contribute both to maintaining baseline circuit function and to experience-dependent modulation of chemosensory processing.

These observations position astrocytes not simply as supportive cells but as pharmacologically accessible regulators of sensory circuit state. Astrocytic calcium signaling, purinergic signaling, gliotransmission, glutamate handling, and metabolic support may each provide mechanisms through which drug action could influence chemosensory adaptation, recovery, or dysfunction.

Microglial roles in synaptic remodeling and immune signaling

Microglia serve as the primary immune cells of the central nervous system and play an active role in shaping neural circuits through synaptic remodeling and immune-related processes. In chemosensory systems, microglia continuously survey the local environment and respond to changes in neuronal activity, injury, or inflammation [57–59]. One of their key functions is the selective elimination of synaptic elements through activity-dependent pruning, which contributes to the refinement of neural circuits [57,60,61].

Experimental evidence indicates that microglia can modulate synaptic connectivity in response to sensory experience, participating in the removal of less active synapses while preserving or strengthening functionally relevant connections [7,58,62]. This process is mediated through molecular pathways involving complement proteins and

other signaling mechanisms that tag synapses for elimination [60,63,64]. Through these actions, microglia contribute to the optimization of circuit architecture and the maintenance of efficient sensory processing.

This remodeling function has direct immunopharmacological relevance. Complement-associated synaptic tagging, microglial pruning, and activity-dependent remodeling are mechanisms through which inflammatory state can alter sensory circuit architecture [63]. In disease contexts, excessive or misdirected microglial remodeling may contribute to impaired chemosensory discrimination, persistent sensory dysfunction, or reduced recovery after injury.

In addition to synaptic remodeling, microglia release cytokines and other signaling molecules that influence neuronal excitability and plasticity [18,59,64,65]. While these immune-related functions are essential for maintaining tissue integrity, excessive or dysregulated microglial activation can disrupt circuit function and contribute to pathological conditions. Thus, microglial activity must be tightly regulated to balance adaptive plasticity with circuit stability. The principal astrocytic and microglial mechanisms that regulate

chemosensory circuit states are summarized schematically in **Figure 2**. Because microglial responses are shaped by cytokine signaling, purinergic pathways, complement activity, and inflammatory priming, they represent an important class of potential immunopharmacological targets. However, therapeutic modulation of microglia requires caution, because suppressing inflammatory signaling indiscriminately may impair adaptive remodeling, while excessive activation may destabilize circuits and promote maladaptive plasticity.

Integrated glial regulation and pharmacological relevance

Astrocytes and microglia regulate complementary features of the local circuit environment. Astrocytes primarily support neurotransmitter handling, extracellular homeostasis, gliotransmission, and metabolic coupling, whereas microglia contribute to immune surveillance, cytokine signaling, complement-associated synaptic tagging, and activity-dependent remodeling [56,57,66]. Together, these cells help determine whether chemosensory circuits remain stable, undergo adaptive remodeling, or develop maladaptive changes.

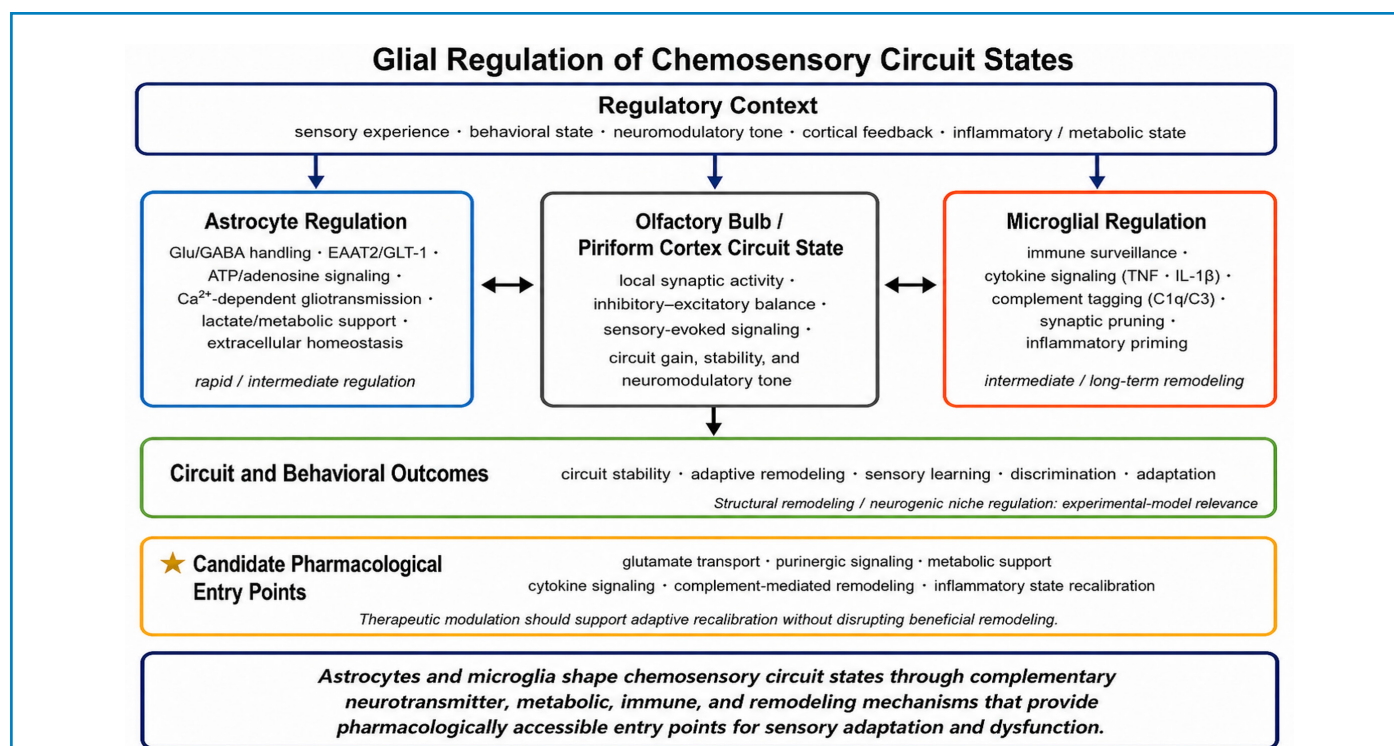


Figure 2. Glial regulation of chemosensory circuit states. Schematic overview of astrocyte and microglial mechanisms that regulate chemosensory circuit function and provide pharmacologically accessible entry points. Astrocytes influence circuit state through glutamate/GABA handling, EAAT2/GLT-1-associated transport, ATP/adenosine signaling, Ca²⁺-dependent gliotransmission, metabolic support, and extracellular homeostasis. Microglia contribute through immune surveillance, cytokine signaling, complement-associated tagging, synaptic pruning, and inflammatory priming. These mechanisms interact with local synaptic activity, inhibitory–excitatory balance, sensory-evoked signaling, circuit gain, and neuromodulatory tone to shape circuit stability, adaptive remodeling, sensory learning, discrimination, and adaptation. This figure was created by the author for the present manuscript and was not reproduced or adapted from another source.

Glial regulation is activity-dependent and context-sensitive. Sensory activity, cortical feedback, neuromodulatory tone, inflammatory state, and metabolic conditions can alter astrocytic and microglial responses [56,57,67–71]. Glial signaling can in turn modify neuronal excitability, synaptic efficacy, circuit gain, and structural remodeling [56,57,66–71]. Glia therefore shape the conditions under which chemosensory plasticity occurs rather than controlling it independently.

These functions identify several pharmacologically relevant pathways, including astrocytic glutamate transport, ATP and adenosine signaling, calcium-dependent gliotransmission, lactate-mediated metabolic support, microglial cytokine signaling, complement-associated remodeling, and inflammatory-state regulation. Treatment should aim to restore conditions that support healthy circuit function rather than broadly suppress glial or inflammatory activity, because these responses can either promote repair or contribute to dysfunction depending on their timing and context.

Neural Stem Cells and Structural Plasticity in Experimental Olfactory Systems

SVZ-derived neurogenesis and species limitations

Adult neurogenesis provides a well-characterized form of structural plasticity in rodent and other experimental mammalian olfactory systems. Neural stem and progenitor cells within the subventricular zone generate neuroblasts that migrate through the rostral migratory stream to the olfactory bulb [72–74]. After reaching the bulb, these cells differentiate primarily into granule and periglomerular interneurons and integrate into local circuits involved in sensory processing [10,75,76]. This pathway allows experimental olfactory circuits to modify their cellular composition in response to developmental, environmental, and activity-dependent signals.

The relevance of this pathway differs substantially across species and developmental stages. SVZ-to-olfactory-bulb neurogenesis is robust in adult rodents, whereas in humans it is prominent early in life but becomes sharply attenuated thereafter and appears extremely limited as a major source of ongoing olfactory bulb interneuron replacement in adulthood. Adult olfactory neurogenesis should therefore be interpreted here primarily as an experimental model of structural plasticity rather than as an established mechanism of adult human olfactory circuit renewal.

Activity-dependent and neurotransmitter regulation

Neurogenic output is regulated by interactions among intrinsic programs, local niche signals, and neural activity. The SVZ niche contains ependymal, vascular, extracellular-matrix, and glial components that influence stem-cell quiescence,

activation, proliferation, and differentiation [77–79]. Sensory enrichment and learning can promote the survival and integration of newly generated neurons, whereas sensory deprivation can reduce neurogenic output and alter olfactory circuit composition [80–82]. Activity-dependent selection therefore helps retain neurons that become functionally engaged within active circuits [5,76,80].

Neurotransmitter systems provide major links between circuit state and stem-cell behavior. GABAergic signaling helps maintain quiescence and regulate the size and activity of the stem-cell pool [83–85]. Cholinergic inputs can promote activation of quiescent stem cells and increase proliferation through receptor-dependent mechanisms [86,87]. Dopaminergic and serotonergic pathways also contribute to niche regulation, although their effects depend on cell state, receptor expression, and experimental context [88–90]. Together, these signals allow short-term circuit activity and sustained sensory experience to influence proliferation, survival, differentiation, and neuronal integration.

Integration into olfactory circuits and sensory function

After migration to the olfactory bulb, adult-born neurons undergo synaptic maturation and integrate primarily into inhibitory granule and periglomerular cell networks. During a critical period of maturation, these neurons display heightened synaptic responsiveness and are preferentially recruited into active circuits [76,91,92]. Their survival and stabilization depend partly on sensory experience and local network activity, linking neuronal integration to functional demand [75,93].

Adult-born interneurons can influence inhibitory control, excitation–inhibition balance, synchronization, and the temporal organization of olfactory bulb activity [75,81,94]. Experimental disruption of adult neurogenesis can impair discrimination between similar odorants, whereas increased survival or recruitment of adult-born neurons has been associated with improved pattern separation, odor learning, and novelty encoding [81,94,95]. These findings support a role for newly generated neurons in refining sensory representations and updating circuit function in experimental models.

The relationship between circuit activity and neurogenesis is bidirectional. Sensory experience, cortical and subcortical activity, neuromodulatory signaling, and local inhibitory networks influence the neurogenic niche [86,87,96,97]. Once integrated, adult-born interneurons modify the same circuit activity that helped regulate their production and survival [75,81,94,98–100]. Neurogenesis therefore functions as an activity-coupled form of structural remodeling in experimental systems where this pathway remains active.

The relationship among circuit activity, neurogenic-niche regulation, neuronal integration, and sensory function is summarized in **Figure 3**.

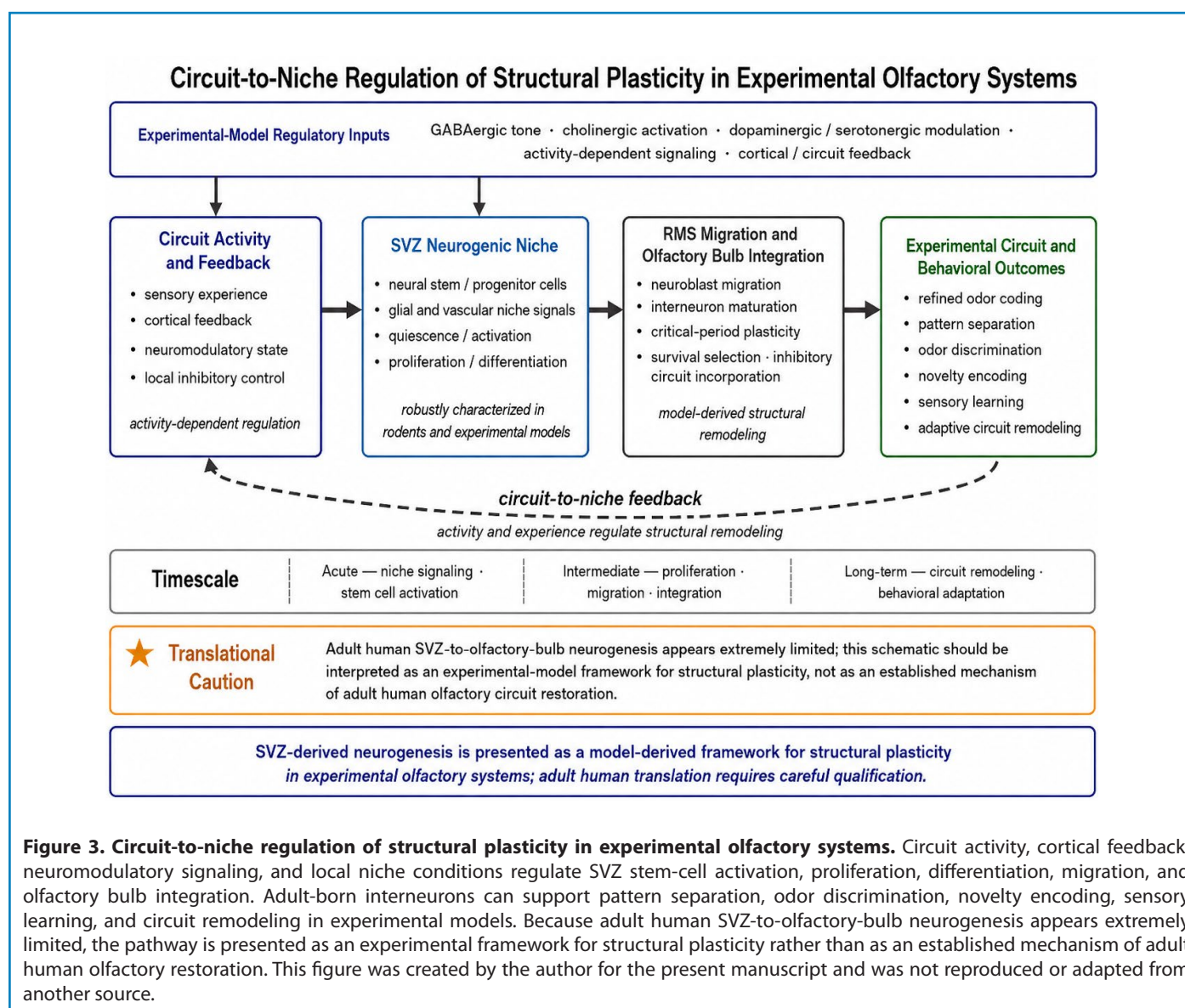
Translational interpretation

SVZ-derived olfactory neurogenesis is a robust mechanism of structural plasticity in rodents and other experimental mammalian models, but it should not be presented as an established restorative mechanism in adult humans. Its principal translational value lies in demonstrating how neural activity, neurotransmitter signaling, glial state, inflammation, metabolism, and niche biology can regulate structural remodeling and repair capacity across species and disease contexts. Pharmacological investigation of this pathway should therefore focus on general principles of

niche regulation and structural plasticity rather than assume that robust adult human olfactory bulb neurogenesis can be therapeutically restored.

Integrated Framework for Chemosensory Plasticity

The evidence reviewed above supports an integrated model in which chemosensory plasticity emerges from interactions among circuit regulation, glial state, and structural remodeling. Cortical feedback rapidly modifies sensory gain, inhibition, temporal coordination, and context-dependent processing. Astrocytes and microglia regulate the synaptic, metabolic, and inflammatory conditions under which these circuit changes occur. In experimental systems where neurogenic remodeling remains active, neural stem cell-derived neurons provide a slower form of structural adaptation.



These mechanisms operate over different but overlapping timescales. Circuit modulation can occur rapidly, glial regulation can alter intermediate cellular, metabolic, and inflammatory conditions, and structural remodeling can support longer-term changes in circuit composition and function. Activity-dependent signaling, neuromodulatory pathways, metabolic coupling, inflammatory mediators, and niche-regulatory mechanisms connect these levels rather than allowing them to operate independently [6,8,9,45,55].

The effect of a drug will depend on the condition of the sensory circuit and its surrounding cellular environment. The same treatment may support adaptation in one setting but interfere with compensation or repair in another. Treatment strategies should therefore consider circuit integrity, glial and inflammatory conditions, metabolic support, disease stage, and whether the relevant form of structural remodeling is active in the experimental model or human tissue being studied.

The principal components and timescales of this framework are summarized in **Table 1**.

Neuropharmacological and Therapeutic Implications

The mechanisms reviewed above provide several possible targets for pharmacological intervention. At the circuit level, cholinergic, noradrenergic, dopaminergic, serotonergic, and GABAergic systems can alter cortical feedback, sensory gain, inhibition, attention, and learning. At the glial level, candidate targets include astrocytic glutamate transport, purinergic signaling, metabolic coupling, microglial cytokine responses, and complement-associated remodeling. In experimental neurogenic systems, neurotransmitter- and niche-regulatory pathways may also influence longer-term structural adaptation.

Circuit and neuromodulatory targets

Neuromodulatory systems provide pharmacological access to circuit-level plasticity. Cholinergic signaling can influence attention-dependent sensory processing and cortical feedback, whereas dopaminergic and noradrenergic pathways can modify salience, reward association, learning, and state-dependent responsiveness [66,104–108]. Serotonergic and GABAergic pathways may further regulate excitability and inhibitory–excitatory balance. Modulation of these systems could therefore affect odor and taste discrimination, sensory learning, predictive processing, and the recovery of sensory circuit function [40,109,110].

The effects of circuit-directed treatments are unlikely to be uniform. Their outcomes may depend on behavioral state, prior sensory experience, disease stage, and the integrity of inhibitory, glial, and metabolic support systems. In experimental olfactory models, neurotransmitter signaling can also regulate neural stem-cell activation, survival, and integration, providing a possible mechanism for longer-term structural adaptation [81,94,111]. However, this experimental mechanism should not be presented as an established method for restoring adult human olfactory bulb neurogenesis.

Glial, inflammatory, and metabolic targets

Astrocytic glutamate transport, GABA–glutamate balance, ATP and adenosine signaling, calcium-dependent gliotransmission, and lactate-mediated metabolic support represent candidate targets for modifying synaptic stability, circuit gain, and resilience [40,109,110]. Microglial cytokine signaling, inflammatory priming, complement-associated synaptic tagging, and activity-dependent pruning may influence whether circuits undergo adaptive refinement or maladaptive remodeling [49,64,112–114].

Table 1. Integrated components of chemosensory plasticity.

Component	Principal function	Predominant timescale	Role in the integrated framework
Cortical feedback	Regulates sensory gain, inhibition, temporal coordination, and context-dependent processing [6,8,9,16,19,45,100]	Rapid to intermediate	Adjusts circuit activity according to experience, behavioral relevance, and internal state
Astrocytes	Regulate neurotransmitter handling, extracellular homeostasis, gliotransmission, and metabolic support [9,45,55,100]	Rapid to intermediate	Shape the synaptic and metabolic conditions under which circuit plasticity occurs
Microglia	Mediate immune surveillance, cytokine signaling, complement-associated tagging, and synaptic remodeling [58,101,102]	Intermediate to long-term	Influence circuit refinement, inflammatory state, and the balance between adaptive and maladaptive remodeling
Neurogenic and structural remodeling in experimental systems	Supports activity-dependent neuronal integration and longer-term changes in circuit composition [45,58,76,81,94,100–103]	Long-term	Provides a model of structural adaptation regulated by circuit activity, glial state, inflammation, metabolism, and niche biology; adult human extrapolation remains limited

These pathways require context-sensitive modulation. Inflammation and glial activation are not uniformly harmful; they may support debris clearance, tissue repair, synaptic remodeling, and recovery under some conditions. Indiscriminate suppression could therefore interfere with beneficial responses, whereas excessive or persistent activation could destabilize circuit function. Similarly, interventions targeting metabolism may support circuit resilience but can also produce broad systemic effects. The therapeutic goal should be to restore glial, inflammatory, and metabolic conditions that support healthy sensory function rather than simply suppress these processes.

SIRT1 as a genetic and metabolic regulatory target

Genetic and epigenetic regulation may influence chemosensory plasticity by controlling the inflammatory, metabolic, and synaptic conditions under which sensory circuits adapt or recover. One candidate regulator is sirtuin 1 (SIRT1), an NAD⁺-dependent deacetylase encoded by the SIRT1 gene. SIRT1 links cellular energy status to transcriptional regulation and has been implicated in mitochondrial function, oxidative-stress responses, inflammatory signaling, autophagy, neuronal survival, and synaptic plasticity. These functions place SIRT1 at the intersection of several mechanisms already discussed in this review, including glial regulation, metabolic support, circuit resilience, aging, and neurodegeneration [115,116].

Direct evidence connecting SIRT1 to chemosensory recovery remains limited but is biologically relevant. In an experimental model of excitotoxic olfactory-bulb injury, recovery of

olfactory function was associated with increased expression of SIRT1 and SIRT4 in the olfactory bulb. This association does not establish that increased sirtuin expression caused recovery, but it suggests that sirtuin-dependent metabolic and stress-response pathways may participate in tissue remodeling or functional restoration after olfactory injury [117]. SIRT1 may therefore provide a mechanistic link among metabolic state, inflammation, synaptic plasticity, and recovery-related circuit remodeling.

Pharmacological activation of SIRT1 has shown anti-inflammatory, antioxidant, metabolic, autophagic, and neuroprotective effects in several preclinical settings, whereas SIRT1 inhibition or loss of function can disrupt these protective pathways. However, the consequences of SIRT1 modulation are likely to depend on cell type, dose, timing, disease stage, and metabolic context. Current evidence does not establish that SIRT1 activators improve human olfactory or gustatory function, nor that SIRT1 inhibitors directly cause chemosensory impairment. SIRT1 should therefore be considered a candidate regulatory target for mechanistic investigation rather than a validated treatment for chemosensory dysfunction.

The principal candidate targets, potential outcomes, and translational cautions are summarized in **Table 2**.

Context, timing, and combination strategies

The effect of a pharmacological intervention will depend on the origin, location, duration, and stage of chemosensory dysfunction. Olfactory or gustatory impairment may result from peripheral receptor or epithelial injury, altered central

Table 2. Candidate pharmacological entry points for chemosensory plasticity and disease-associated dysfunction.

Target domain	Candidate pharmacological entry points	Primary biological role	Potential relevance to chemosensory plasticity or dysfunction	Translational caution
Neuromodulatory control of cortical feedback	Cholinergic, dopaminergic, noradrenergic, serotonergic, and GABAergic signaling	Regulates sensory gain, inhibitory–excitatory balance, attention, reward association, cortical feedback, and state-dependent plasticity	May influence odor and taste discrimination, salience assignment, sensory learning, predictive processing, and recovery-related circuit recalibration	Effects are likely context-dependent and may vary by disease stage, behavioral state, and circuit integrity
Astrocytic neurotransmitter handling	Glutamate uptake, GABA–glutamate balance, transporter activity, extracellular ion regulation	Maintains synaptic stability, prevents excitotoxicity, and regulates neuronal excitability	May affect sensory gain, discrimination, synaptic plasticity, and vulnerability to maladaptive circuit activity	Excessive modulation could disrupt normal synaptic signaling or compensatory circuit adaptation
Purinergic and gliotransmission pathways	ATP/adenosine signaling, astrocytic calcium signaling, D-serine, glutamate release	Couples glial activity to synaptic function, plasticity, and neuron–glia communication	May regulate experience-dependent plasticity, adaptation, and local circuit responsiveness	Purinergic signaling can support both adaptive repair and pathological inflammation depending on context

Target domain	Candidate pharmacological entry points	Primary biological role	Potential relevance to chemosensory plasticity or dysfunction	Translational caution
Astrocyte–neuron metabolic support	Glucose utilization, lactate signaling, mitochondrial support, activity-dependent energy supply	Coordinates neuronal activity with metabolic demand and circuit resilience	May influence plasticity under aging, metabolic stress, neurodegeneration, or post-injury recovery	Metabolic interventions may have broad systemic effects and require disease-specific interpretation
SIRT1-dependent genetic and metabolic regulation	SIRT1 expression and activity; NAD+–dependent deacetylation; experimental SIRT1 activators or inhibitors	Links cellular energy state with transcription, mitochondrial function, oxidative-stress responses, inflammation, autophagy, neuronal survival, and synaptic plasticity	May influence metabolic resilience, inflammatory state, injury responses, synaptic remodeling, and recovery-related mechanisms in experimental chemosensory circuits	Direct evidence in human olfactory or gustatory dysfunction is lacking; effects may depend on cell type, dose, timing, and disease stage
Microglial inflammatory state	Cytokine signaling, inflammatory priming, immune surveillance, microglial activation state	Regulates immune tone, neuronal excitability, synaptic remodeling, and tissue response to injury	May contribute to persistent chemosensory dysfunction, post-viral impairment, aging-related decline, and neurodegenerative sensory deficits	Inflammation is not uniformly harmful; indiscriminate suppression may impair repair or adaptive remodeling
Complement-associated synaptic remodeling	Complement signaling, synaptic tagging, microglial pruning	Refines circuit architecture by removing selected synaptic elements	May influence circuit refinement, maladaptive pruning, sensory discrimination, and long-term network remodeling	Excessive inhibition or activation may disrupt normal circuit maintenance and plasticity balance
Species-dependent neurogenic and structural remodeling	Neural stem cell niche regulation, neurotransmitter-dependent progenitor control, glial–niche interactions, inflammatory and metabolic regulation of structural plasticity	Supports structural remodeling in experimental olfactory systems where SVZ-derived neurogenesis remains active	Provides a model for long-term adaptation, circuit updating, and structural plasticity constraints across disease contexts	Adult human SVZ-to-olfactory-bulb neurogenesis appears extremely limited; this should not be framed as an established human therapeutic restorative mechanism
Multiscale combination approaches	Pharmacological modulation combined with sensory training, behavioral intervention, metabolic support, or disease-specific treatment	Coordinates circuit, glial, metabolic, inflammatory, and structural mechanisms	May better support adaptive recalibration than targeting one mechanism alone	Combination strategies require careful timing, patient selection, and mechanistic validation

processing, inflammatory or metabolic disruption, or combinations of these mechanisms. The same target may therefore produce different outcomes depending on age, disease stage, inflammatory state, circuit integrity, and whether the underlying response is damaging or compensatory.

Combination approaches may be more effective than isolated pathway modulation. Pharmacological treatment could be combined with sensory training, behavioral intervention, metabolic support, or disease-specific therapy to promote recovery at both circuit and cellular levels. Such strategies will require careful timing, patient selection, and mechanistic validation to avoid increasing maladaptive plasticity or disrupting beneficial repair.

Implications for Chemosensory Dysfunction and Disease

Chemosensory dysfunction can arise from disruption at peripheral, circuit, glial, inflammatory, metabolic, and structural levels. The relative importance of these mechanisms differs across conditions, and the presence of the same sensory deficit does not necessarily indicate the same underlying biological process.

Post-viral and inflammatory dysfunction

Anosmia and hyposmia may involve altered olfactory bulb activity, reduced cortical feedback, disrupted synaptic

organization, and changes in the local glial and inflammatory environment [6,8,30,118,119]. The resulting impairment can affect odor detection, discrimination, and adaptation, although the relative contributions of peripheral injury and central circuit dysfunction vary among patients and conditions.

Post-viral olfactory dysfunction, including that associated with SARS-CoV-2, illustrates this mechanistic complexity. Viral injury can disrupt peripheral sensory and supporting cells while also producing inflammatory changes that may affect central olfactory pathways [120–122]. Persistent anosmia, hyposmia, or distorted odor perception may therefore reflect incomplete peripheral repair, sustained inflammation, altered circuit activity, or interactions among these processes.

Aging and neurodegenerative disease

Aging is associated with declining odor sensitivity, discrimination, and adaptation. Age-related changes in synaptic regulation, glial activity, inflammatory tone, and metabolic support may reduce circuit responsiveness and resilience [123–125]. Reductions in SVZ-derived olfactory neurogenesis are well documented in experimental aging models, although their relevance to adult human olfactory decline remains uncertain [126–128].

Olfactory impairment frequently appears early in Parkinson’s disease and Alzheimer’s disease. In Parkinson’s disease, altered olfactory bulb circuitry and cortical processing occur alongside astrocytic and microglial activation and other inflammatory changes [129–134]. These alterations may

impair odor identification, discrimination, and adaptive sensory processing.

In Alzheimer’s disease, disrupted olfactory pathway connectivity, altered network activity, and glial inflammatory responses may contribute to declining odor recognition [58,127,131–133,135–138]. Structural and neurogenic changes have also been reported in experimental models, but their functional importance and relevance to adult human chemosensory impairment remain incompletely resolved [58,123,127,130,131,139]. Olfactory dysfunction in neurodegenerative disease should therefore be interpreted as a feature of broader disease-associated circuit and cellular disruption rather than as evidence of one isolated mechanism.

SIRT1 may also connect aging and Alzheimer’s-related pathology with chemosensory circuit vulnerability. Experimental and broader neurodegenerative evidence indicates that SIRT1 can regulate inflammatory signaling, mitochondrial and metabolic function, oxidative stress, autophagy, synaptic plasticity, and pathways related to amyloid- β and tau biology [115,140]. These processes are relevant to olfactory dysfunction because aging and Alzheimer’s disease affect many of the same circuit, glial, inflammatory, and metabolic mechanisms discussed in this review. However, direct evidence showing that SIRT1 modulation prevents or reverses chemosensory impairment in patients with Alzheimer’s disease remains insufficient.

The major disease-related alterations are summarized in Table 3.

Table 3. Chemosensory dysfunction through a multiscale and species-aware plasticity lens.

Condition	Circuit-level alterations	Glial / inflammatory features	Species-dependent structural / neurogenic remodeling	Functional chemosensory outcome
Anosmia / hyposmia	Altered olfactory bulb activity, reduced cortical feedback, disrupted synaptic organization [6,8]	Local inflammatory responses and glial activation may impair circuit stability [7,141]	Structural remodeling and repair-related processes may be secondarily affected depending on severity, duration, and site of dysfunction [10,122]	Reduced odor detection, impaired discrimination, diminished sensory adaptation [120,121]
Post-viral dysfunction / SARS-CoV-2	Peripheral sensory disruption with possible secondary central alterations in olfactory pathways [121,122]	Prominent inflammatory and cellular disruption involving peripheral and central mechanisms [118,120]	Potential disruption of reparative, inflammatory, and structural plasticity processes remains under investigation [118,122]	Persistent anosmia, hyposmia, distorted odor perception, delayed sensory recovery [121,142]
Aging	Progressive decline in circuit plasticity, altered synaptic regulation, reduced adaptive responsiveness [123,125]	Age-related changes in glial activity and inflammatory tone [58,125]	Reduced structural plasticity and diminished SVZ-derived olfactory neurogenesis are documented in experimental models; adult human relevance remains uncertain [10,126]	Decline in odor sensitivity, discrimination, and adaptation to novel sensory input [123,125,143]

Condition	Circuit-level alterations	Glial / inflammatory features	Species-dependent structural / neurogenic remodeling	Functional chemosensory outcome
Parkinson's disease	Early alterations in olfactory bulb circuitry and cortical processing; impaired circuit-level plasticity [131,135,137]	Increased microglial and astrocytic activation, neuroinflammatory disruption of local microenvironment [58,132]	Impaired structural remodeling and altered neurogenic capacity have been reported mainly in experimental models, with human relevance requiring careful interpretation [127,137]	Early olfactory dysfunction, impaired odor identification and discrimination [137,143]
Alzheimer's disease	Disrupted olfactory pathway connectivity and altered network activity [129,144]	Neuroinflammatory processes involving astrocytic and microglial responses [133,145,146]	Structural plasticity and neurogenic processes may be altered, though their functional significance and relevance to adult human chemosensory dysfunction remain incompletely resolved [145,147]	Early olfactory impairment, reduced odor recognition, progressive sensory decline [123,144]
Metabolic / systemic disorders	Altered neuronal excitability and impaired integration of sensory signals [50,148]	Hormonal, metabolic, and inflammatory dysregulation affecting local circuit environment [50,58,148]	Potential disruption of adaptive remodeling, metabolic support, and neurogenic niche regulation in experimental systems [10,149]	Altered smell and taste perception, reduced sensory flexibility, impaired adaptive responses [143,148]

Metabolic and systemic conditions

Metabolic and systemic disorders can affect olfactory and gustatory function through altered hormonal signaling, energy regulation, inflammation, and neuronal excitability [150–153]. These changes may impair sensory-signal integration, astrocyte–neuron metabolic support, and adaptive circuit responses. Effects on neurogenic-niche regulation have also been reported in experimental models, but their direct relevance to adult human chemosensory dysfunction requires careful interpretation [154–156].

Across these conditions, changes in circuit activity, glial state, inflammation, metabolism, and structural remodeling may function as causes, consequences, or compensatory responses. Their relative contribution is likely to vary with disease stage, age, and the location and duration of injury. Chemosensory dysfunction may therefore signal disruption across several biological levels rather than identify one specific cause.

Conclusion

Chemosensory plasticity cannot be explained by synaptic modification alone. The evidence reviewed here supports an integrated model in which cortical feedback regulates circuit activity, astrocytes and microglia shape the synaptic, metabolic, and inflammatory environment, and structural remodeling contributes to longer-term adaptation in experimental systems where these mechanisms remain active.

This framework identifies pharmacologically relevant

targets at circuit, glial, inflammatory, metabolic, genetic, and niche-regulatory levels. SIRT1 illustrates how an NAD+-dependent regulatory pathway may connect metabolic state, inflammation, stress responses, synaptic plasticity, aging, and neurodegeneration, although its specific role in human chemosensory recovery remains unproven. The effects of all candidate interventions are likely to depend on disease stage, age, circuit integrity, and the surrounding cellular environment. Therapeutic strategies should therefore aim to restore adaptive sensory regulation rather than simply increase plasticity or suppress inflammation.

Adult SVZ-to-olfactory-bulb neurogenesis remains a valuable experimental model of structural plasticity but appears extremely limited as a restorative mechanism in adult humans. Future studies should link circuit manipulation, glial and inflammatory profiling, metabolic assessment, and behavioral measures to determine which mechanisms support recovery and which sustain chemosensory dysfunction.

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Artificial intelligence generated content declaration

During preparation of this manuscript, the author used Google Gemini solely for language editing and improvement of phrasing. All scientific content, interpretation, organization, and final wording were reviewed and approved by the author, who takes full responsibility for the manuscript. No AI tool was used as an author or to replace the author's intellectual contribution.

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