

Lifelong odor sensitivity: What early exposure means for your patients?

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The brain's ability to adapt to its environment during critical developmental periods shapes sensory perception for a lifetime. This plasticity, particularly in early life, fine-tunes neural circuits to respond to key environmental stimuli. A recent study published in eLife details how a specific odor exposure during a critical period in *Drosophila* induces permanent changes in olfactory sensitivity, effectively silencing a sensory channel. This work extends previous findings by establishing the functional significance and circuit selectivity of this critical period plasticity, demonstrating that early odor experience can lead to lifelong suppression of specific odor processing pathways through targeted glial phagocytosis.

KEY TAKEAWAYS

- **The Pivot:** Early-life exposure to ethyl butyrate in *Drosophila* induces lifelong suppression of specific odorant receptor (Or42a) responses via glial pruning.
- **The Data:** Or42a OSN odor-evoked responses were permanently suppressed in animals with critical period odor exposure, while Or43b OSNs maintained sensitivity.
- **The Action:** Clinicians should consider the potential for early-life sensory experiences to induce permanent, selective changes in sensory processing, informing future research into human sensory disorders.

Sensory systems, from vision to olfaction, undergo profound reorganisation during specific developmental windows, known as critical periods. These periods allow the nervous system to calibrate itself to the prevailing environmental conditions, ensuring optimal function. The current research builds upon prior observations that exposure to ethyl butyrate (EB) during a critical period in the *Drosophila* olfactory system triggers glial phagocytosis of axon terminals from odorant receptor Or42a-positive olfactory sensory neurons (OSNs), which project to the VM7 glomerulus.¹

The investigators, led by Leier and colleagues, set out to determine the functional consequences of this anatomical pruning and to establish its specificity within the complex olfactory circuit. They focused on the Or42a OSNs, known to project to the VM7 glomerulus, and a second population of highly EB-responsive OSNs, the Or43b OSNs, to understand the breadth and precision of this experience-dependent plasticity. The study employed a combination of advanced imaging techniques and genetic manipulations to dissect the underlying mechanisms.¹

How Early Odor Exposure Silences a Sensory Channel

The core finding establishes that critical period odor exposure leads to permanent suppression of odor-evoked responses in Or42a OSNs. Using two-photon Ca²⁺ imaging, a technique that allows for the visualisation of neuronal activity, the researchers measured the responses of Or42a OSNs to odorants after critical period exposure to ethyl butyrate. They

observed a lasting reduction in the activity of these neurons. This was further corroborated by the use of ASAP5, a genetically-encoded voltage indicator, which provided a direct measure of neuronal membrane potential changes. Both methods consistently demonstrated that the early-life odor experience resulted in a profound and enduring decrease in the sensitivity of Or42a OSNs to their cognate odorants.¹

This functional suppression directly correlates with the previously observed anatomical pruning of Or42a axon terminals by glia. The glia, often considered mere support cells, actively remodel neural circuits by engulfing synaptic material, a process known as phagocytosis. In this context, the glia selectively target and remove portions of the Or42a OSN terminals, effectively reducing their connectivity and, consequently, their ability to transmit signals. The permanence of this suppression suggests that once a critical period experience has shaped the circuit, the changes are largely irreversible, locking in a specific sensory profile for the organism's lifespan.¹

The implications for understanding how sensory environments shape perception are substantial. If a specific odor channel can be permanently suppressed by early exposure, it suggests a mechanism by which organisms can adapt to pervasive environmental cues by downregulating their sensitivity to them. This could be an evolutionary advantage, allowing the nervous system to prioritise novel or more important stimuli by filtering out constant background signals. The precision of this mechanism, targeting specific OSN types, highlights the sophisticated nature of developmental plasticity.¹ But the study also raises questions about the reversibility of such changes. While the suppression was lifelong in *Drosophila*, the extent to which similar mechanisms operate in more complex mammalian systems, and whether therapeutic interventions could reverse unwanted sensory suppression or enhance desired pathways, remains an open area for investigation. The complex relationship between environmental factors and neural development is a recurring theme in neuroscience, and this work provides a clear example of its lasting impact.¹

Specificity of Glial Pruning and Inhibitory Control

A central aspect of the study involved establishing the selectivity of glial pruning. The researchers investigated whether this pruning was a general response to ethyl butyrate exposure or if it specifically targeted Or42a terminals. Within the VM7 glomerulus, the primary target of Or42a OSNs, glial pruning demonstrated remarkable selectivity for Or42a terminals. This precision suggests a highly regulated process, where glia are instructed to remove specific synaptic components while leaving others intact. This is not a broad-stroke reduction in connectivity but a targeted refinement of the circuit.¹

To further test this specificity, the investigators examined a second population of OSNs, the Or43b OSNs, which are also highly responsive to ethyl butyrate. While Or43b OSNs showed a modest degree of pruning, they largely maintained their sensitivity to EB. This differential outcome between Or42a and Or43b OSNs was a key finding, indicating that even among neurons responsive to the same odorant, the critical period plasticity mechanism discriminates between them. The reasons for this differential sensitivity and pruning were not immediately obvious and prompted further investigation into the underlying neural architecture.¹

The researchers turned to the *Drosophila* connectome, a comprehensive map of neural connections, to elucidate this difference. They identified striking disparities in the scale of inhibitory connectivity to Or42a and Or43b OSNs. Or42a OSNs exhibited a greater degree of inhibitory input compared to Or43b OSNs. This inhibitory input, primarily mediated by GABA, appears to play a significant role in modulating the pruning process. When the expression of GABAA receptors was disrupted in both OSN types, the extent of pruning was enhanced. This suggests that GABAergic inhibition

normally acts as a brake on glial phagocytosis, protecting OSN terminals from excessive removal.¹

The relationship between excitatory input, inhibitory modulation, and glial activity provides a more complete picture of how critical period plasticity is regulated. It is not simply the presence of an odorant that triggers pruning, but rather a complex interaction of neuronal activity and inhibitory tone that dictates the extent and specificity of glial remodeling. This multi-layered control ensures that only appropriate and necessary changes are made to the sensory circuit, preventing indiscriminate pruning that could impair overall olfactory function. Understanding these regulatory mechanisms is vital for any future attempts to manipulate sensory plasticity.¹

Functional Significance and Broader Implications

The functional significance of this lifelong suppression extends beyond mere anatomical changes. The permanent reduction in odor-evoked responses in Or42a OSNs means that the animal's perception of odors, particularly those detected by Or42a, is fundamentally altered. This is not a temporary adaptation but a hardwired change in how the olfactory system processes specific environmental cues. For a species like *Drosophila*, where olfaction is critical for foraging, mating, and predator avoidance, such a change can have profound behavioral consequences. The ability to selectively tune down sensitivity to ubiquitous or less important odors could free up neural resources for more salient stimuli.¹

The study's findings expand our understanding of critical period plasticity by demonstrating both the lifelong nature of the suppression and its specificity within and between sensory circuits. This work provides a compelling example of how early-life experience can sculpt the nervous system in a precise and enduring manner. While the research was conducted in *Drosophila*, the fundamental principles of experience-dependent plasticity and glial involvement in circuit remodeling are conserved across species, including humans. This suggests that similar mechanisms might contribute to the development of sensory preferences, aversions, or even disorders in humans.¹

But the direct translation of these findings to human clinical practice requires caution. The complexity of the human olfactory system, with its vast array of receptor types and intricate cortical processing, far exceeds that of *Drosophila*. Still, the underlying cellular and molecular mechanisms, such as glial phagocytosis and inhibitory control, offer valuable insights into potential targets for intervention. For instance, understanding how specific inhibitory circuits modulate glial activity could inform strategies to either enhance or prevent pruning in conditions where sensory processing is impaired. The role of glial cells in neurodegeneration is an active area of research, and this study adds another dimension to their functions.¹

The open-label nature of the experimental setup, while standard for this type of basic science, means that the researchers were aware of the experimental conditions. This is an inherent aspect of mechanistic studies and does not detract from the objective physiological measurements. The use of genetically-encoded indicators and two-photon imaging provides robust, quantifiable data on neuronal activity, mitigating potential observer bias. The study was not designed to explore the behavioral consequences of this lifelong suppression, which would be a logical next step to fully understand its ecological relevance.¹

The precise molecular signals that instruct glia to selectively prune Or42a terminals over Or43b terminals, despite both responding to EB, remain to be fully elucidated. The role of inhibitory connectivity is clear, but the upstream cues that establish these differential inhibitory patterns during development are still unknown. Further research into the specific ligand-receptor interactions between neurons and glia, and how these are modulated by neuronal activity, will

be important for a complete understanding of this intricate process. This work provides a foundational understanding that could inform future studies on how environmental factors shape sensory perception, a topic of broad interest in fields ranging from developmental neurobiology to clinical neurology. For a comprehensive overview of neurological principles, an Oxford Handbook of Neurology can be an invaluable resource.

CLINICAL IMPLICATIONS

The observation that early-life odor exposure can permanently rewire olfactory circuits in *Drosophila*, effectively silencing a sensory channel, forces a re-evaluation of how environmental factors shape perception. While direct translation to human olfaction is complex, the underlying mechanisms of glial pruning and inhibitory modulation are conserved, suggesting analogous processes could occur in human sensory development. This raises questions about the lasting impact of early sensory deprivation or overstimulation in conditions like congenital anosmia or sensory processing disorders.

For clinicians, this research highlights the profound and potentially irreversible nature of developmental plasticity. If specific sensory pathways can be permanently suppressed by early experience, it implies that interventions for sensory deficits might need to occur within critical developmental windows to be effective. The differential pruning observed between Or42a and Or43b OSNs, despite similar odor responsiveness, highlights the intricate specificity of these processes, suggesting that not all sensory neurons are equally susceptible to environmental sculpting.

The role of inhibitory connectivity in modulating glial pruning is particularly intriguing. Disrupting GABAA receptor expression enhanced pruning, indicating that inhibitory tone acts as a protective mechanism against excessive circuit remodeling. This offers a potential therapeutic avenue: manipulating inhibitory circuits could either promote or prevent unwanted glial activity, depending on the clinical need. Understanding these regulatory levers could be important for developing strategies to restore or refine sensory function in patients with developmental sensory impairments.

This study provides a mechanistic framework for how early sensory experience can lead to lifelong changes in perception. While *Drosophila* is not a human, the principles of experience-dependent plasticity and glial involvement in circuit refinement are universal. Future research must now bridge this gap, investigating whether similar critical periods and glial-mediated pruning events contribute to the development of human sensory systems, and if so, how these insights can be leveraged to improve patient outcomes.

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