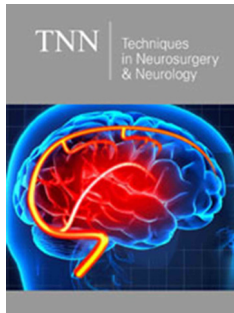


# Olfactory Dysfunction, GNAL Signaling and PI3K $\delta$ Dysregulation: A Hypothesis on Schizophrenia Pathophysiology

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## Abstract

Olfactory dysfunction is one of the most consistent and earliest sensory abnormalities observed in schizophrenia, often preceding the onset of overt psychotic symptoms and reflecting central neural circuit dysfunction rather than peripheral sensory loss. Growing evidence suggests that olfactory deficits may provide a unique window into the molecular and cellular mechanisms underlying disease vulnerability. In this hypothesis-driven framework, we propose that schizophrenia arises, in part, from the convergence of disrupted GNAL-mediated signaling, impaired inhibitory G $\alpha$ i/o pathways and inflammation-associated dysregulation of phosphoinositide 3-kinase delta (PI3K $\delta$ ). We suggest that altered GNAL-dependent cAMP signaling contributes to deficits in sensory and dopaminergic amplification, while impaired G $\alpha$ i/o signaling represents a primary driver of excitatory/inhibitory imbalance underlying cognitive and psychotic symptoms. Concurrently, chronic inflammatory states may destabilize PI3K $\delta$  signaling, indirectly influencing olfactory and cortical neural function. Impaired neural resilience within olfactory circuits, including reduced Sirt1-dependent neurogenic support and genomic stability, may further exacerbate early olfactory dysfunction. Together, this integrative model provides a testable mechanistic link between peripheral inflammatory processes, olfactory system vulnerability and central inhibitory signaling deficits in schizophrenia, with implications for early biomarker development and novel therapeutic targeting.

**Keywords:** Olfactory dysfunction; GNAL signaling; G $\alpha$ i/o inhibitory pathways; PI3K $\delta$  dysregulation; Schizophrenia pathophysiology

## Introduction

Schizophrenia is a complex neuropsychiatric disorder characterized by cognitive deficits, affective disturbances and psychotic symptoms. Among the earliest detectable abnormalities are olfactory deficits, including impaired odor identification and altered hedonic perception. Epidemiological evidence suggests that environmental pollutants and chronic inflammatory conditions of the upper respiratory tract may increase susceptibility to schizophrenia, potentially through peripheral inflammatory mechanisms impacting the olfactory system [1].

Olfaction is uniquely positioned among sensory modalities due to its direct connections with frontal and temporal brain regions, which are central to cognitive and emotional processing in schizophrenia. Consequently, olfactory dysfunction may serve as an early biomarker of disease vulnerability, reflecting structural and functional alterations in neural circuits that contribute to cognitive and affective deficits [2].

The GNAL gene encodes G $\alpha$ olf, a stimulatory G-protein essential for odorant signal transduction in Olfactory Sensory Neurons (OSNs). G $\alpha$ olf couple's olfactory receptors to Adenylyl Cyclase 3 (ADCY3), initiating cAMP production and generating action potentials in response to odorants. Mutations or loss of GNAL function result in severe olfactory impairment, highlighting its critical role in sensory perception [3,4]. Beyond olfaction, G $\alpha$ olf is highly expressed in the basal ganglia, where it mediates dopaminergic and adenosinergic signaling through coupling to Adenylyl Cyclase 5 (AC5). Disruption of G $\alpha$ olf impairs dopamine-stimulated cAMP production, contributing to motor and cognitive dysfunction [5].

Inhibitory G-proteins (Gai/o) regulate dopamine and GABA neurotransmission and their dysfunction contributes to excitatory/inhibitory (E/I) imbalances central to schizophrenia pathology. Reductions in Gai/o subunits, DARPP-32 and GABAergic interneuron function have been documented in schizophrenia, linking impaired inhibitory signaling to cognitive and positive symptoms [6-9]. Within this framework, disrupted GNAL-mediated signaling may contribute to sensory and dopaminergic amplification deficits, whereas impaired Gai/o signaling represents the primary driver of inhibitory imbalance underlying cognitive and psychotic symptoms.

In olfactory sensory neurons, inhibitory Gai/o pathways also modulate odorant signaling via phosphoinositide 3-kinase regulation [10]. PI3K $\delta$ , a class IA PI3K with a catalytic p110 $\delta$  subunit encoded by PIK3CD, plays a critical role in immune regulation. Chronic inflammatory states, such as sinusitis, may destabilize PI3K $\delta$  activity, indirectly influencing neuronal and olfactory signaling and increasing schizophrenia vulnerability [11-13]. Evidence of elevated PIK3CD expression in patients supports a mechanistic link between peripheral immune dysregulation and central neural circuit dysfunction [14-16].

Chronic eosinophilic inflammation, tightly regulated by PI3K $\delta$ , has been associated with psychological stress, anxiety and depressive symptoms, highlighting a pathway through which immune dysregulation may influence neuropsychiatric outcomes [17-19]. Preclinical studies further demonstrate that the p110 $\delta$  subunit regulates eosinophil trafficking and airway inflammation, reinforcing the connection between PI3K $\delta$ -driven immune states and systemic conditions capable of modulating brain function.

## Hypothesis

We propose that schizophrenia arises, at least in part, from the convergence of impaired inhibitory signaling and immune-mediated vulnerability within neural circuits. Specifically:

- A. Dysfunctional inhibitory Gai/o signaling in cortical and olfactory neurons impairs excitatory/inhibitory balance, contributing to cognitive deficits and psychotic symptoms.
- B. Chronic inflammation-induced dysregulation of PI3K $\delta$  (p110 $\delta$ ) disrupts immune-olfactory signaling pathways, increasing susceptibility to neural circuit instability.

Impaired PI3K $\delta$  function in the olfactory system may contribute to early sensory deficits, while concurrent cortical inhibitory signaling deficits underlie cognitive and psychotic manifestations. Olfactory dysfunction reflects central abnormalities in frontal, temporal and striatal circuits rather than peripheral sensory impairment. Experimental evidence further indicates that olfactory function depends on continuous neurogenic support and genomic stability within subventricular zone-derived neural stem cells, maintained by Sirt1 activity. Integrating these findings, we hypothesize that impaired neural resilience in olfactory circuits interacts with disrupted GNAL-mediated cAMP signaling and deficient inhibitory Gai/o pathways, while chronic inflammation-

associated PI3K $\delta$  dysregulation destabilizes these networks, linking early olfactory deficits to widespread inhibitory imbalance and cognitive dysfunction [20,21].

## Conclusion and Recommendations

This hypothesis integrates olfactory dysfunction, GNAL-mediated signaling and PI3K $\delta$  dysregulation into a unified mechanistic framework for schizophrenia pathophysiology. To test this model, future studies should:

- a) Characterize Gai/o and G $\alpha$ olf signaling in olfactory sensory neurons and basal ganglia circuits from schizophrenia patients.
- b) Assess PI3K $\delta$  expression and stability in both peripheral immune cells and central nervous system tissues.
- c) Evaluate chronic inflammation and eosinophil activity as modulators of neural signaling.

Elucidating these pathways may identify novel biomarkers for early disease detection and highlight PI3K $\delta$  signaling and inhibitory G-protein pathways as potential therapeutic targets, offering a mechanistic rationale for interventions that address both neural and immune contributions to schizophrenia.

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