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The microbiome-nose-brain axis in health and disease

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Abstract

Growing evidence implicates the bacterial populations in the nose as an important factor for personal and global health. Here, we provide a brief overview of the nasal microbiome, and speculate on its potential roles in olfactory processing and neurodegeneration, with a particular focus on Parkinson's disease.

Main text

Our environment-exposed body surfaces, namely the skin, respiratory tract, and gastrointestinal tract, are colonized from birth by microorganisms. These environmental microbes form various symbiotic communities in our organism, constituting the systemic microbiome. Growing preclinical and clinical evidence implicates altered microbiome composition in the pathogenesis of neurological and neurodegenerative disorders, including for instance a suspected role of the gut microbiome in Parkinson's disease (PD). Strikingly, the nose offers a shortcut for microbiota signals to reach the brain through the olfactory system, raising questions about the potential roles of the nasal microbiome in nervous system function. In this article, we first offer a brief overview of the nasal microbiome, and its emerging potential role in olfactory processing. We then speculate on the potential relevance of dysbiosis of the nasal microbiome in neurodegeneration, with particular focus on PD pathogenesis.

The nasal microbiome

The human nose is colonized by billions of microbes, including bacteria, viruses, fungi, and archaea. Collectively, these constitute the nasal microbiome, which is increasingly recognized as essential to our personal and collective health. Bacteria are the main component of the nasal microbiome, and the diversity of communities of the human nasal microbiome is estimated at approximately 10^4 unique strains of bacteria, with about 2 to 10 species making up to 90% of an individual's nasal microbiome. Microbial colonization of the nose is thought to emerge from patches of single bacterial strains seeding the surface of the nasal epithelium. Most of the strains are likely symbiotic, but some are opportunistic pathobionts that may cause various illnesses. Symbiotic microbes colonize the nose from birth and develop during the first year [1]. The profiles (species) and abundances of the different microbial communities continue to evolve slightly thereafter, according to the seasons and lifestyle. Schematically, Proteobacteria and Firmicutes are overrepresented in children, while Actinobacteria are overrepresented in adults [1]. Potential bacterial pathogens may sometimes be part of the nasal microbiota, including *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella*

catarrhalis (three species of bacteria associated with upper respiratory tract infections) [2].

The various microbial communities (in the skin, gut, and respiratory tract) share common components within a single human organism, especially along the respiratory system, from nose to lung. In particular, there is a large overlap between microbiome of the anterior nares and superior-posterior portions of the nasal cavities, despite differences in local temperatures, acidity and salinity [2].

The composition of the nasal microbiome is influenced by various lifestyle determinants including geographical factors and proximity to animals [3]. Other factors which may play important roles in microbiota composition include climate, air quality, drinking water composition, prevalence of infectious diseases, and diet, but future research is needed to explore these potential contributions in more detail. Conversely, the human nasal microbiome influences the composition of the environmental microbiota by sculpting the microbiome shared for instance by household occupants and co-residents in health-care facilities [4]. Among host determinants, age and immunity are two major factors influencing nasal microbiota composition, while host genetics appears to play a minor role in the context of microbial and environmental encounters [1].

Impact of the nasal microbiome on olfaction

While recent studies suggest that nasal microbial communities are involved in maintaining a healthy microenvironment by limiting pathogen colonization and modulating the host-immune response to respiratory-tract infections and disease severity [1], the influence of the nasal microbiome on olfactory performance remains largely understudied [5, 6]. The nasal microbiome may play a key role in the physiology of the nasal epithelium, as odorant responses recorded by electro-olfactogram have a stronger amplitude and are faster for most odorants in axenic (germ-free) mice [5]. Interestingly, the amplitude of odorant-evoked responses and the speed of odorant detection (depolarization and repolarization phases) are differentially affected according to the odorant nature in nasal microbiota-free mice [5]. Thus, we suggest that changes in the nasal microbiome may have important consequences for health, given that olfaction influences nutrition [7] and general well-being.

In mammals, odorants are sensed by olfactory sensory neurons (OSNs), located in the olfactory epithelium of the posterior nasal cavity. The cilia of OSNs emerge within the olfactory epithelium, whereas the axons of OSNs project into the brain to reach the olfactory bulb. Interestingly, a study in healthy adult subjects suggests that the nasal microbiota may influence human olfaction [6]. The subjects, aged 18-46 years, were classified into three groups presenting either good sense of smell, normal olfactory function, and poor olfactory function (*i.e.*, hyposmia), as established by an olfactory test aiming at scoring odor threshold, discrimination, and identification [6]. The most abundant bacteria at genus level in all subjects were *(i) Corynebacterium, (ii) Staphylococcus, (iii) Dolosigranulum* and *(iiii) Peptoniphilus.* Of note, odorant threshold and discrimination but not identification were associated with microbial community composition [6]. Interestingly, the mere presence of butyric-acid producing bacteria in the nasal microbiota correlated with alterations in the olfactory functions [6]. Extending these investigations to a larger group of healthy subjects, including older adults, and to studies in animal models (e.g. axenic mice colonized with selected microbiota strains), would allow testing the broader potential relevance of these initial findings.

Implications of the nasal microbiota for neurodegenerative diseases

The question arises whether the nasal microbiota might be involved in certain neurological diseases, for instance by affecting OSNs or activating local immune responses which can then spread to the brain. OSNs are highly vulnerable to environmental factors such as microbes (e.g. coronaviruses, *Staphylococcus* bacteria) and toxins (herbicides, pesticides), which could trigger mitochondrial damage, oxidative stress, and inflammation-induced axon damage. Ultimately, this could result in a dysfunction of the olfactory bulb innervated by the altered OSNs. Of note, olfactory deficits are often found in inflammatory, neuro-inflammatory, and neurodegenerative diseases, such as COVID-19, Zika, multiple sclerosis, Alzheimer's disease, and PD. These olfactory deficits could result from nose-colonizing microbiota, particularly for idiopathic PD which has a strong environment component (**Figure 1**).

PD is primarily characterized by loss of dopaminergic neurons in the *substantia nigra pars compacta*. PD pathogenesis implicates interactions between genetic and environmental factors, with the latter including exposures to toxic and

infectious agents. When it comes to the microbiome, so far, major emphasis has been placed on gut microbiota alterations and their potential role in the development of PD through the gut-brain axis. Somewhat surprisingly, given the well-established involvement of olfactory alterations in PD, the nasal microbiome has received relatively little attention in this context. Olfactory dysfunction is often reported early in PD progression. It is conceivable that the nasal microbiome might be involved in the neuronal accumulation of misfolded alpha-synuclein (aSyn), a protein which is strongly expressed in OSNs. Misfolded aSyn is the major component of Lewy bodies – neuronal inclusions which represent a hallmark of PD pathology in most patients. Putatively, local inflammation induced by chronic nasal dysbiosis could exacerbate the neurodegenerative damage of OSNs, with subsequent neuronal accumulation of misfolded aSyn. This pathological process might then propagate to the olfactory bulb, the *substantia nigra pars compacta* and possibly other brain regions to eventually produce motor, cognitive and psychiatric manifestations in PD patients consistently with Braak's description of the disease's stages [8].

In keeping with our hypothesis, misfolded aSyn is often found in the neuroepithelium and olfactory bulb tissue samples collected from PD patients. Familial (genetic) forms of the disease hint at intriguing potential links between aSyn and olfactory dysfunction. Specifically, patients with PARK-*SNCA*, who carry pathogenic variants in the *SNCA* gene that encodes aSyn, frequently have early olfactory dysfunction and are more prone to develop cognitive alteration than sporadic PD. By contrast, PARK-*Parkin* patients, who carry the relatively rare variants in *PRKN* (another PD-linked gene, encoding Parkin) typically have neither olfactory dysfunction nor aSyn pathology, and are less prone to develop cognitive alteration.

So far, the potential influence of the nasal microbiome on PD has been largely overlooked [9-12]. In the few studies that explored this link, the characterization of nasal microbiota composition was insufficiently comprehensive, we would argue, to reach definitive conclusions. When it comes to comparison of PD and control groups, many of the findings reported so far has been negative. In a Finnish case-control study, the dominant genera in the nasal cavity were *Corynebacterium* and *Propionibacterium,* followed by *Moraxella and Staphylococcus*, with no difference in genus abundance noted between the PD and control groups [9]. Both Chinese [10] and German [11] case-control studies also found the same genera in the nasal

cavity, with no difference between the PD and the control groups after adjusting for age, sex, and body mass index. However, nasal dysbiosis has been reported to be associated with PD in a recent US case-control study, using nostril swabs collected under endoscopic guidance [12]. In this study, the deep nasal microbiome in PD patients was distinct when compared to either spousal or random healthy controls, with changes characterized by increased relative abundances of bacteria belonging to the phylum Proteobacteria, including *Moraxella catarrhalis* opportunistic pathobiont [12]. Comparison across studies is hampered by differences in sampling nasal fluids [11] or nasal swabs [9, 10, 12], and the sampling site being either superficial or deep [12], but also the use of different variables regions of the 16S rRNA gene to characterize the bacterial microbiome, DNA extraction, library generation and sequencing platform. Overall, except the recent US study [12], notable differences in the nasal microbiome between PD and healthy controls were not found [9-11]. However, these negative findings do not rule out possible relevance of the nasal microbiome in PD. Indeed, one can speculate that early dysbiosis, playing a role as part of the triggers for the disease, is rebalanced later during disease progression. More refined methodologies in longitudinal follow-up studies with *de novo* PD patients and healthy controls may report more subtle changes, not seen so far. In addition, potential confounders such as dietary intake, medications, or age-related factors need to be comprehensively analyzed and considered. It is also crucial to generate dedicated experimental models, by transplanting human nasal microbiota from patients in dedicated mice models, and to analyze whether these mice would develop some features reminiscent of PD.

Concluding remarks

Emerging research on the human microbiota offers unique opportunities to further understand the interplay between environmental factors and neurodegeneration. The nasal microbiome plays an important role in human health, and it is conceivable that changes in its composition may promote early PD symptoms such as loss of smell. Imbalance of the nasal microbiome might be involved in the local initiation of aSyn aggregation and associated neurodegenerative processes, that may in turn propagate to adjacent brain areas through the nose-brain axis. A better understanding of the role of the microbiome–nose–brain axis in PD

development and progression would help in identifying novel targets for early interventions and neuroprotective strategies.

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Figure 1.

The putative microbiome-nose-brain axis in Parkinson's Disease. The olfactory mucosa (left) contains olfactory sensory neurons, which are in direct contact with the brain, thought the olfactory nerve. Nasal dysbiosis might contribute to accumulation of the neurotoxic alpha Synuclein in the olfactory mucosa, which could then propagate to the olfactory bulb and other brain structures (right).

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