ISI-1 Changes in cognitive and anxiety-like behaviors induced by two separate ways of olfactory deprivation in mice

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Introduction: A close link is proposed between smell impairment and Alzheimer’s disease (AD) pathogenesis, pointing to the possibility that damaged olfaction may lead to cognitive deterioration. As a step to evaluate this possibility in rodent models, we used behavioral test battery to investigate whether cognitive and anxiety-like behaviors are altered in mice deprived of olfaction. Affective behavior was tested because cognitive deterioration, the canonical symptom of AD, is often accompanied by emotional symptoms called the behavioral and psychological symptoms of dementia (BPSD).

Method: For olfactory deprivation, bulbectomy or methimazole-induced epithelial degeneration was used. Then, mice were subjected to behavioral test battery.

Results: After olfactory deprivation, anxiety-like behavior emerged, with severer manifestation in bulbectomized than methimazole-treated mice. Avoidance behavior from 2MT, a synthesized derivative of a fox urine component, was suppressed by bulbectomy but exaggerated by methimazole treatment, which suggests that these two procedures differentially impact on olfactory information processing as is implied from the markedly different modes of anatomical damage after these two treatments. Novel object recognition test revealed that cognitive performance was not impaired by either treatment. However, Morris water maze (MWM) test, in which cognition was assessed in a wet, stressful environment, showed that both deprivation procedures worsened cognitive performance.

Conclusion: We conclude that the suppressing influence on MWM performance by olfactory deprivation may be related to an elevated vulnerability to stressful environment, drawing the inference that emotional effects of smell impairment might play an important part in the proposed, smell-linked cognitive impairment in AD.
Introduction: Sniffing, as a natural mean to efficiently sample odorants, has been shown to activate the olfactory cortex, even when sniffing odorless air. Some patients with hyposmia/anosmia regain their olfaction by sniffing odors regularly as an olfactory training, in which the role of sniffing still unsettled. Therefore, this study aimed to profoundly investigate how the brain network changes in response to sniffing, especially for patients with olfactory loss. We chose to recruit congenital anosmia (CA) patients to highlight the difference in brain network as compared to normal subjects (NS).

Method: We recruited 9 patients in CA group and age- and sex- matched 15 volunteers in NS group (29.9 ± 6.2 years old). Functional MRI with block-designed sniffing paradigm were undertaken. In brief, the participants followed the visual cues to sniff in sniffing blocks (ON) and to breath smoothly in breathing blocks (OFF). Each block lasted for 32 seconds, and totally ten blocks made one session. The head motion was well controlled by pre-scanning instruction and training for the participants. Chest wall expansion was monitored to make sure the differentiations between both blocks. The functional and structural data were subjected to preprocessing, first level within-subject analysis (ON-OFF), and second level group comparison. We also conducted independent component analysis (ICA) to identify sniffing induced networks. The number of independent components (IC) was estimated by minimum description length criterion. The ICs were identified by the temporal relevance to the sniffing paradigm and the spatial distribution of activation areas. Two-sample t-test was employed for between-group analyses. Significance was set at the uncorrected voxel level p < 0.001 followed by FWE-corrected cluster level p < 0.05.

Results: Upon group level analysis, CA group shared a spatially similar pattern but less intensive activation than NS, although the between-group contrast displayed no significant voxel surviving. In group ICA, it yielded 34 ICs. By sorting with the temporal relevance to sniffing task, we can further identify primary/secondary olfactory network, olfactomotor, somatosensory and integrative networks. After between-group analysis of the ICs, we did not find any evidence of compensatory network activation in CA. On the contrary, the NS presented a more intensive activation in the integrative network and in another temporally irrelevant somatosensory network. This finding reflected that NS may take advantage of an integrative network activated by sniffing, during which the central processing of olfaction was enhanced.

Conclusion: The current study highlighted the pertinent role of signal integration and network cross-talk in sniffing. It may also imply that through the stimulation of the odors and the repeating acts of sniffing, olfactory training can improve or rebuild olfactory integrative network and ultimately achieve restoration of olfactory functionality.
ISI-3 Dramatic olfactory improvement after sinus surgery in a case of CRS with Parkinsonism

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This is a 65 year-old female who had olfactory disorder for more than 20 years. In addition, she had Parkinson’s disease for 15 years, which is known to lead to olfactory disorder. At the clinic, sinus endoscopy revealed that she had bilateral low grade nasal polyposis in anterior ethmoid sinus and olfactory cleft, Lund Mackay score is 4. The tentative diagnosis is a special type of CRSwNP: central compartment atopic disease (CCAD). In respect to olfactory function, she scored 15 out 48 in Taiwan olfactory test (TIBSIT), categorized as severe hyposmia. She tried a one-month course of ICS and oral corticosteroid treatment, but received limited improvement. Researches showed that patients of Parkinson’s disease had progressive decline of olfactory function in pre-clinical phase, and this patient had mild degree of nasal polyposis; hence, we speculated that olfactory function improvement after sinus surgery would be limited. Despite that, she was willingful for bilateral functional endoscopic sinus surgery. Remarkably, her TIBSIT score increased from 15 to 31 in just two weeks after surgery. Due to an unexpected olfactory outcome, this case is proposed for further discussion.
**International session 1**

**ISI-4**  
**IL-4 decreases multiciliated cell numbers via the loss of deuterosomal cells in human nasal epithelium**

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**Introduction:** Allergic inflammation affects the epithelial cell populations resulting in goblet cell hyperplasia and decreased ciliated cells. Recent advances in single-cell RNA sequencing (scRNAseq) have enabled the identification of new cell subtypes and genomic features of single cells. In this study, we aimed to investigate the effect of allergic inflammation in nasal epithelial cell transcriptomes at the single-cell level.

**Method:** We performed scRNAseq in cultured primary human nasal epithelial (HNE) cells and in vivo nasal epithelium. The transcriptomic features and epithelial cell subtypes were determined under IL-4 stimulation, and cell-specific marker genes and proteins were identified.

**Results:** We confirmed that cultured HNE cells were similar to in vivo epithelial cells through scRNAseq. Cell-specific marker genes were utilized to cluster the cell subtypes, and FOXJ1+-ciliated cells were sub-classified into multiciliated and deuterosomal cells. PLK4 and CDC20B were specific for deuterosomal cells, and SNTN, CPASL, and GSTA2 were specific for multiciliated cells. IL-4 altered the proportions of cell subtypes, resulting in a decrease of multiciliated cells and loss of deuterosomal cells. The trajectory analysis revealed deuterosomal cells as precursor cells of multiciliated cells.

**Conclusion:** The effects of IL-4 appear to be mediated through the loss of the deuterosomal population, resulting in the reduction of multiciliated cells. This study also newly suggests cell-specific markers that might be pivotal for investigating respiratory inflammatory diseases.

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International session 1

ISI-5    An evolving trend in rhinosinusitis in hematologic patients receiving hematopoietic stem cell transplantation: a ten-year cohort study

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Introduction: Rhinosinusitis is a crucial issue in treating hematologic patients receiving hematopoietic stem cell transplantation (HSCT). However, there is currently no consensus on the management for rhinosinusitis in patients receiving HSCT. Therefore, we reviewed these cases and their outcomes in search of the guidance of management.

Method: The nested case-control study included hematologic patients receiving HSCT and diagnosed with rhinosinusitis across a ten-year period (from April 2011 to April 2021). We collected detailed data on demographics, smoking status, hematological diseases, and features of rhinosinusitis for descriptive analysis. Additionally, we investigated the association with control of rhinosinusitis and overall survival using logistic regression and Cox regression, respectively.

Results: There was a total of 1553 patients receiving HSCT in this cohort study, and 81 of them diagnosed as rhinosinusitis. Fifty-eight of them patients were included in this study and another 116 HSCT patients without rhinosinusitis were selected as controls. We found that allergy and reduced-intensity conditioning therapy were risk factors for higher risk of post-transplant RS but not pre-transplant RS, while smoking for both pre- and post-transplant RS. The multivariable logistic analysis indicated that endoscopic sinus surgery was an independent prognostic factor for better control of rhinosinusitis. The survival was exclusively associated with hematologic related factors, including autologous HSCT, myeloablative conditioning and remission.

Conclusion: The epidemiology of rhinosinusitis among hematologic patients receiving HSCT evolved spatially and temporally and thus the management could be accordingly tailored. Sinonasal evaluations should target the high-risk group and endoscopic sinus surgery is an effective way for the management of rhinosinusitis in HSCT patients. Nevertheless, treating rhinosinusitis in HSCT patients may not contribute to improvement in overall survival or rate of sepsis.

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ISI-6  Microbiota dysbiosis in secondary chronic rhinosinusitis

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Introduction: Chronic rhinosinusitis (CRS) is a multifactorial upper airway disease. Environmental and host factors both play a key role in rhinosinusitis development. The local microbiome is one of the critical environmental factors. However, the role of bacterial microbiota in various phenotypes of CRS is still not thoroughly understood.

CRS was classified as primary and secondary subtypes in EPOS 2020 (European Position Paper on Rhinosinusitis and Nasal Polyp 2020). Secondary CRS such as odontogenic rhinosinusitis and fungal rhinosinusitis were highly influenced by local pathology and with possible deep connection with local microbiome. However, secondary CRS was less discussed comparing with primary CRS. Therefore, we conducted next generation sequencing (NGS) methods to determine differences in microbiome between secondary CRS (fungal rhinosinusitis and odontogenic rhinosinusitis) and control group as well as the interplay between the involved bacteria have not been explored.

Methods: Endoscope-guided swabs were used to collect samples from the lesion site of consecutive CRS patients. DNA was extracted as well as investigated through 16S rRNA amplification. Secondary CRS was classified according to EPOS 2020 guidance. Odontogenic and fungal rhinosinusitis were subdivided from secondary CRS on the basis of their unique clinical, image and pathologic characters.

Results: Bacterial community dysbiosis was more apparent in fungal rhinosinusitis samples comparing with non-fungal rhinosinusitis. Shannon diversity was significantly lower in those from fungal rhinosinusitis group (p = 0.029). Fungal rhinosinusitis samples also exhibited a distinct distribution of taxon relative abundance, which involved not only the absence of rhinosinusitis-associated commensal Corynebacterium and Fusobacterium but also a significant increase in Haemophilus prevalence and abundance. On the other hand, significant differences were also revealed by the Shannon diversity index (p = 0.0003) between odontogenic and non-odontogenic rhinosinusitis groups. Anaerobic bacteria such as Porphyromonas, Fusobacterium, and Prevotella were significantly dominant in the odontogenic rhinosinusitis group.

Conclusion: Our findings demonstrate that microbiota dysbiosis revealed in secondary CRS such as odontogenic and fungal rhinosinusitis and the interplay between specific bacteria may a major cause of this subtype of rhinosinusitis.
International session 1

ISI-7   Airway Medicine & biologics for global airway disease

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Eosinophilic chronic rhinosinusitis (ECRS) is a serious, chronic inflammatory disease that predominantly displays a type 2 inflammatory signature. AR/CRS and asthma, COPD and bronchiectasis are frequent comorbidities, as up to 67% of patients with ECRS have comorbid asthma. Global airway disease is the new concepts of total care for both airway, advocated in EPOS2020. ECRS with BA is definitely the systemic disease of airway, although the patients are treated separately with ENT doctor and respiratory medicine doctor.

As a rational therapeutic strategy, we focused on the ICS exhalation through the nose (ETN) treatment for asthmatics with ECRS. We have been treated the patients with ECRS have comorbid asthma, with ENT & Internal Medicine doctor in the same room of our clinic. Airway medicine is the concepts for the total airway treatment with ICS ETN combined with full-house ESS. The endpoints for the surgical therapy is to make a drug delivery root for sinuses and the reduction of the inflammatory mucosa and eosinophilic mucin to control the airway inflammation. Although airway medicine is reasonable and the half recurrence rate compared to JESREC study, the additional therapy is required for severe cases. Biologics, including anti IgE, anti IL-5, anti IL-5Ra, and anti IL-4Ra have strong efficacy to control of type2 airway inflammation.

Here, we present our strategy for type2 upper and lower airway inflammation based on the concepts of airway medicine in this presentation.