A Critical Period in Postnatal Neuroplasticity of Olfaction
A Pediatric Tracheostomy Model

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IMPORTANCE There is controversy over whether a critical period in the development of olfaction exists, as there is in hearing and vision, whereby early stimulation of the olfactory nerve is necessary for normal olfactory performance later in life. Children who undergo tracheotomy early in life are deprived of airflow through the nasal cavity during a critical period of development. Persistent olfactory dysfunction in this patient group after decannulation would provide evidence that postnatal stimulation of the olfactory nerve is critical to normal development.

OBJECTIVE To determine whether children who undergo early tracheotomy have persistent olfactory dysfunction following decannulation and to validate a prior study showing olfactory deficits in cannulated patients.

DESIGN, SETTING, AND PARTICIPANTS This was a cross-sectional study of smell function in pediatric patients with either long-term tracheostomy (cannulated), decannulated patients after long-term tracheostomy, and healthy age- and sex-matched controls, conducted in a tertiary care academic referral center, using data that were collected between 2013 and 2015. All patients were without coexisting nasal abnormalities or developmental delay that would prevent completion of testing.

INTERVENTIONS Administration of a validated pediatric smell test to all 3 patient groups.

MAIN OUTCOMES AND MEASURES Mean percentage correct on a validated pediatric smell test.

RESULTS In 18 patients ages 6 to 18 years, there was a statistically significant difference (P = .007) in mean percentage of correct responses on the smell test between cannulated (67%; 95% CI, 54%-79%, N = 6), decannulated (61%; 95% CI, 42%-80%, N = 6), and age-matched controls (94%; 95% CI, 90%-99%, N = 6). Analysis between groups showed statistically significant differences between both control and cannulated patients (P = .002) and between control and decannulated patients (P = .006). There was no significant difference between scores in the cannulated and decannulated groups (P = .64).

CONCLUSIONS AND RELEVANCE This pilot study suggests that olfactory deficits from early chronic tracheostomy persist following decannulation and provides early data suggestive of a critical period in the postnatal development and neuroplasticity of olfaction.
he process of olfaction is highly complex and involved in the discrimination of taste and odors, requiring the integration of several processes to yield chemosensory perception. Airflow-dependent odorant trafficking to chemosensory receptors on the cribriform plate leads to stimulation of receptors and activation of central pathways that ultimately facilitate complex pattern recognition used for subsequent smell identification.1-2 Despite important research on the mechanics of olfaction, relatively few studies exist on the development of mammalian olfaction when compared with other sensory modalities, such as hearing and vision.

It is well established that other sensory systems, such as hearing and vision rely on a critical period of development, during which sensory input is mandatory for subsequent sensory development and function later in life.3 However, controversy exists over a possible critical or sensitive period for olfaction,4 wherein stimulation of the olfactory nerve is essential during early olfactory development. To date, there have been relatively few studies exploring the effects of early olfactory stimuli deprivation on subsequent olfactory performance. In one murine study, Yamaguchi et al5 found increased apoptotic granular cells in the olfactory bulbs of mice deprived of olfactory input. Furthermore, the study6 found that at days 14 to 18 of life, granular cells were most susceptible to apoptotic cell death in the absence of olfactory stimuli, suggesting a critical period in the development of murine olfaction whereby granular cells undergo apoptosis in the absence of olfactory stimulation.

The only study7 in humans to assess a possible critical period in human olfaction was conducted in newborns exposed to various odorants within 1 hour of life or after 12 hours of life. The study7 found that newborns displayed a head turn preference for odorants exposed within 1 hour of life, but those exposed after 12 hours did not.7 Based on these data, the authors suggest that a critical or sensitive period may exist in human newborns.

Beyond the newborn period, the ethical study of prolonged olfactory stimuli deprivation early in life becomes untenable, except in the unique model of long-term pediatric tracheostomy patients. Studies8 have demonstrated that patients with tracheostomy tubes experience anosmia because air does not pass over the olfactory epithelium. Furthermore, Rothschild et al9 established that pediatric patients with long-term placement of tracheostomy tubes experience significant hyposmia when compared with age-matched healthy controls. However, Rothschild et al9 did not study decannulated patients, and there remains a dearth of information concerning the long-term effects of chronic olfactory stimuli deprivation. Pediatric patients who require long-term placement of tracheostomy tubes at an early age may not have received adequate stimulation of the olfactory nerve prior to tracheostomy, and thus may experience permanent anosmia or hyposmia following decannulation. Such a finding would lend support to the hypothesis that adequate stimulation of the olfactory nerve during a critical period is necessary for normal olfaction.

The study of pediatric patients with long-term placement of tracheostomy tubes not only allows a better understanding of postnatal olfactory development but also has the added benefit of allowing the study of clinical effects of smell deprivation once the tube is removed. Patients with anosmia, such as those with tracheostomy tubes, report changes in food intake and preference,9 report lower quality of life than those with intact smell, and are prone to developing anxiety and depression.10 Anosmia can also have life-threatening consequences, because patients with anosmia lack the ability to smell smoke or hazardous chemicals.11 In studying this population, further insight into clinical symptoms may prove useful in designing treatments to mitigate long-term consequences of tracheostomy and improve patient quality of life.

The present study evaluates the effects of tracheostomy on olfaction in high-functioning pediatric patients ages 6 to 18 years with long-term placement of tracheostomy tubes, decannulated patients who have previously had tracheostomies for more than 6 months, and age-matched healthy controls. We hypothesized that cannulated patients will have decreased performance on the smell tests compared with healthy, age-matched controls. Furthermore, if early stimulation of the olfactory nerve is necessary for normal development of olfaction, we hypothesize that decannulated patients will exhibit decreased olfactory function compared with age-matched healthy controls.

Methods

Participants

Following institutional review board approval, 18 children, ages 6 to 18 years, were recruited from the otolaryngology clinic at the Children’s Hospital of Philadelphia between August 2013 and March 2015. Verbal assent was received from all children and written informed consent was received from their parents. No compensation was provided for participation. Patients were classified into 1 of 3 groups: current tracheostomy (cannulated), decannulated, or age-matched healthy controls. All patients were without coexisting nasal abnormalities or developmental delay that would prevent completion of smell testing. All patients, including those with current tracheostomy and those who were decannulated were taking a full, per-oral diet and were not taking any medications with hyposmia or smell disturbance as a listed adverse effect.

Patients in the cannulated group all underwent tracheostomy at or before age 4 years and had been cannulated for at least 6 months at the time of testing. Patients in the decannulated group all underwent tracheostomy before age 4 years, had been cannulated for at least 6 months, were decannulated for at least 1 month prior to testing, and underwent tracheostomy capping at least 2 months prior to testing to allow sufficient odorant exposure before smell test administration. All patients in the decannulated group had undergone reconstruction prior to decannulation to resolve underlying airway pathologic abnormalities. Furthermore, if decannulated patients had a tracheocutaneous fistula or stoma, these were occluded and children were breathing transnasally during test administration. Control patients were recruited from the otolaryngology clinic, had never had a tracheostomy tube, and were...
Smell Test Administration
The Pediatric Smell Wheel, a validated 11-item smell test, was used for this study. The test includes commonly encountered olfactory stimuli, such as bubblegum, soap, onion, peppermint, cherry, chocolate, smoke, cinnamon, and banana. Administration of the test was performed as specified by Cameron and Doty. In brief, patients self-administered the test by scratching an odorant patch and filling in the multiple-choice answer that corresponded to the test odorant.

Data Analysis
Statistical analysis was performed using a 1-way analysis of variance test between all 3 groups and student’s t test for post hoc analysis. Statistical significance was defined as a P < .05. In accordance with Cameron and Doty, the odorants of rose and popcorn were excluded from analysis because of poor identification in the initial validation study.

Results
A total of 18 patients were recruited for the study from the pediatric otolaryngology clinic. Characteristics of the cannulated and decannulated populations are listed in Table 1. Six control patients were matched for age (mean age, 7.8; range, 6.5-15.0 years) and sex (83% were male) to the cannulated and decannulated groups. Subglottic stenosis represented the indication for tracheostomy in most tested patients (Table 2).

The mean percentage correct on the smell test for cannulated (67%; 95% CI, 54%-79%), decannulated (61%; 95% CI, 42%-80%), and age-matched control patients (94%; 95% CI, 90%-99%) was found to have statistically significant variance between the 3 groups (P = .007) (Figure 1). Statistically significant differences in scores of the smell test were found between cannulated patients and control patients (P = .002) and between patients who had been decannulated and controls (P = .006). Importantly, there were no significant differences in smell test scores between patients with cannulated and those who had previously been decannulated (P = .64).

Decannulated patients were then stratified by time since decannulation, and no significant trends were found with respect to time since decannulation and smell test score (Figure 2), (R² = 0.12). Furthermore, mean percentages correct on the smell test between decannulated patients with tracheocutaneous fistula (59%; n = 3) and those without tracheocutaneous fistula (63%; n = 3) were similar.

Table 1. Characteristics of Cannulated and Decannulated Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range)</th>
<th>Cannulated (n = 6)</th>
<th>Decannulated (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td></td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>7.2 (6.0-8.8)</td>
<td>8.7 (6.7-16.4)</td>
</tr>
<tr>
<td>Testing</td>
<td></td>
<td>0.3 (0.0-4.0)</td>
<td>0.4 (0.0-1.0)</td>
</tr>
<tr>
<td>Cannulation</td>
<td></td>
<td>6.6 (3.9-16.3)</td>
<td></td>
</tr>
<tr>
<td>Length of tracheostomy, y</td>
<td></td>
<td>6.0 (1.5-8.4)</td>
<td>5.8 (3.4-16.3)</td>
</tr>
<tr>
<td>Time since decannulation, y</td>
<td></td>
<td>2.0 (0.1-5.2)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Indication for Tracheostomy

<table>
<thead>
<tr>
<th>Indication for Tracheostomy</th>
<th>Patients, No.</th>
<th>Cannulated</th>
<th>Decannulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subglottic stenosis</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bilateral vocal cord paralysis</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Complete tracheal ring</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Mean Percentage Correct on the Pediatric Smell Wheel by Patient Group

Figure 2. Percentage Correct in Decannulated Patients as a Function of Time Since Decannulation

R² represents coefficient of determination from the best-fit line, which was generated from the data points in the figure.
Discussion

The process of olfaction is dependent on airflow through the nasal cavity as well as odorant binding and stimulation of an associated chemosensory receptor.13 Plausible explanations for olfactory dysfunction include both conductive and sensorineural deficits. It is well established that patients with partially obstructive nasal pathologic abnormalities such as turbinate hypertrophy experience hyposmia, which is subsequently reversed following surgical correction of obstruction.14 Furthermore, patients who undergo procedures that limit nasal airflow, such as laryngectomy, have been shown to have hyposmia, providing support for the idea of conductive olfactory dysfunction.15 However, these patient models have 2 major limitations in assessing long-term outcomes of olfactory stimuli deprivation: olfactory deprivation is incomplete, as with partially obstructive nasal abnormalities, or deprivation of olfactory input is irreversible, as with patients who have undergone total laryngectomy. The pediatric tracheostomy model addresses both of these limitations, because many patients are cannulated early in life and tracheostomy is often reversible, allowing restoration of normal nasal airflow.

Few studies have examined the possibility of a critical period in human olfactory neuroplasticity, though there has been some research on short-term olfactory deprivation and subsequent neural changes. Wu et al16 showed that a 7-day olfactory input deprivation could induce changes in odor-evoked responses in the orbitofrontal cortex. However, these changes were reversible, and the study was conducted in adults, suggesting that short-term olfactory deprivation in adults is unlikely to produce lasting olfactory performance changes.

In the present study, we validated a prior study by Rothchild et al10 showing that pediatric patients with long-term tracheostomy demonstrate statistically significant hyposmia as compared with age-matched healthy controls. Importantly, we also show that decannulated patients exhibit persistent olfactory dysfunction even after the restoration of normal nasal airflow, which suggests that early olfactory stimulation is important in establishing subsequent olfactory function. Furthermore, our data suggest that deficits persist long after decannulation, because there was no correlation between time since decannulation and percentage correct on the smell test.

To our knowledge, the present study is the first to examine long-term effects of chronic olfactory stimuli deprivation early in life and provide early evidence that long-term stimuli deprivation may produce irreversible olfactory deficits. Though olfactory sensory neurons are continually regenerated throughout life,17 changes in the orbitofrontal cortex may no longer be reversible after a critical period of time. This pilot study suggests that deprivation of olfactory sensory input for more than 6 months via tracheostomy may be sufficient to induce irreversible changes in olfactory sensation, possibly through changes in the orbitofrontal cortex. Furthermore, both duration of deprivation and age at deprivation may be important to subsequent olfactory performance after stimulus reexposure. Most of the patients in the study required tracheostomy before they were 1 year old, suggesting that tracheostomy early in life may have a more profound impact on subsequent olfactory performance than tracheostomy later in childhood. Future longitudinal studies examining olfactory performance in patients before tracheostomy, with current tracheostomy, and after decannulation will be instructive in differentiating these possibilities.

Though this study provides strong evidence of olfactory deficits in both cannulated and decannulated patients, it has several limitations. Olfactory deficits seen in the cannulated and decannulated groups may be due to limited olfactory nerve stimulation but also may include other aspects of cannulation, including chronic changes in nasal airflow, humidification, and temperature, which may affect olfaction. Furthermore, the sample size in each patient group is small and there were few female patients tested. Despite the small sample size, the study was sufficiently powered to detect the large differences noted in group performance. In addition, 3 of the patients in the decannulated group had tracheocutaneous fistulae, which could potentially limit nasal airflow and thus have an impact on olfactory exposure and smell test performance. However, smell test scores between decannulated patients with and without tracheocutaneous fistulae were similar. Also, though patients included were without underlying nasal abnormalities that would preclude testing, they or their caregivers were not specifically queried about recent upper respiratory infections, which could have an impact on olfactory performance. One other limitation of the study is that patients were not tested longitudinally, preventing definitive conclusions from being drawn about potential changes in olfaction over time. Future longitudinal cohort studies will provide more robust data about the long-term effects of olfactory stimuli deprivation on subsequent olfactory function.

Given the clinical implications of poor olfaction, strategies to maintain stimulation during critical periods of development should be considered. One possibility is therapy designed to maintain olfactory stimuli during tracheostomy, potentially through intranasal odorant exposure. Other treatments, such as olfactory epithelial transplantation,18 are early in development but may also prove useful as future interventions for these patients.

Conclusions

This pilot study suggests that olfactory deficits from early chronic tracheostomy persist following decannulation and provides early data suggestive of a critical period in the postnatal development and neuroplasticity of olfaction.
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Statistical analysis: Kennedy, Lewis.
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Conflict of Interest Disclosures: None reported.

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REFERENCES