The Laryngoscope

Empty Nose Syndrome: Limbic System Activation Observed by Functional Magnetic Resonance Imaging

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Objectives/Hypothesis: Empty nose syndrome (ENS) patients have a persistent sense of impaired nasal patency despite radical resection of nasal turbinates. The aim of this study was to elucidate differences in cerebral activation during free breathing and after inhalation of a fragrance (lemonene) and a pseudodecongestant (menthol) over a nasofacial mask. Our hypothesis was that menthol would be perceived as beneficial and that cerebral activation would show differences in areas corresponding to emotional suffering and air hunger in ENS patients.

Study Design: Prospective, controlled intervention with lemonene and menthol during functional magnetic resonance imaging (f-MRI) experiment.

Methods: Ten right-handed ENS patients were compared to 15 controls using f-MRI and fully automated data analysis with SPM software. Nasal patency was measured with rhinomanometry and rated on a four-point scale.

Results: Despite similar objective nasal flow, ENS patients rated nasal patency significantly worse than did controls. Menthol was perceived to increase nasal patency. In patients, f-MRI data showed different activation of temporal cortex areas after inhalation of menthol. The comparison of patients and controls showed ENS-specific activation of temporal and cerebellar areas and amygdala during the rating task itself.

Conclusions: Our experiments showed different cerebral processing of the feeling of nasal patency in ENS patients with prominent activation of areas belonging to the limbic system. The beneficial effect of menthol seems to correspond to activation differences in the temporal pole. These results demonstrate a neuronal substrate for both symptoms and their relief in ENS patients.

Key Words: Empty nose syndrome, nasal patency, menthol, functional magnetic resonance imaging, limbic system.

Level of Evidence: 3b.

***Laryngoscope,* 000:000–000, 2011**

INTRODUCTION

Empty nose syndrome (ENS) results from radical resection of the nasal turbinates performed due to complaints of restricted nasal patency. In these cases, the main nasal functions (humidifying, warming, and clearing the inspired air) are deteriorated by a significant reduction of respiratory mucosa. The loss of respiratory mucosa drastically diminishes the number of mechanosensitive, tactile, and temperature receptors. It is known from a previous study[1] that the intranasal climate in ENS patients shows a lower humidity and a higher temperature and that the nasal airway resistance is actually lower in ENS. On the whole, the nose in ENS is dry, crusted, and too wide. Strikingly "paradox nasal obstruction" is the leading symptom in these patients.[1] The pathophysiology is only partly understood, and the question remains why only a subgroup of patients presenting with subjective nasal obstruction ends up with chronic symptoms despite multiple interventions.

Here it can be speculated that central processes are involved that prevent a simple local solution of the symptoms. Other chronic diseases with important central components include pain syndromes such as complex regional pain syndrome, fibromyalgia, or irritable bowel syndrome, where functional imaging of the brain has shown changes of central processing in patients.[2–5]

In regard to possible central components of ENS, several aspects seem to be important: ENS patients describe nasal congestion, even though airway resistance is lower than normal. Perhaps mechanisms concerning the rating of nasal patency are changed or the valence of efferents from the nasal mucosa has changed.

The reduction of nasal function tissue or altered flow characteristics (laminar vs. turbulent) might affect processing of olfactory stimuli.

Air hunger or decreased ability to breathe has been shown to lead to activation of brainstem, cerebellar, and limbic areas[6]; frontal and limbic system/temporal pole activation as a sign of processing of the emotional valence of stimuli[6,7] has been shown. Piriform cortex and amygdala activation, however, have been shown in olfactory functional magnetic resonance imaging (f-MRI).[8]

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Editor's Note: This Manuscript was accepted for publication May 4, 2011.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.21903

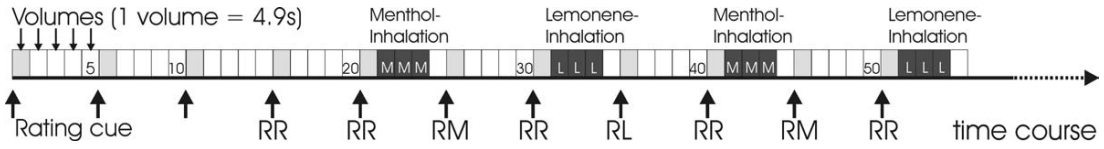

Fig. 1. Stimulation paradigm. The time course of the experiment is depicted. At the beginning, for 20 volumes (nearly 100 seconds) there is free room-air breathing. All white boxes correspond to rest (R = condition of free room-air breathing without a task). Every 5 volumes, a rating cue is applied (arrow), and the following volume (marked light grey) is analyzed for cerebral activation. The rating cues are marked as follows: RR = rating after room air, RM = rating after menthol, and RL = rating after lemon aroma. The first three cues are not labeled; they belong to the RR condition. For the purpose of analysis, the volume after the rating cue is analyzed; it contains the activity linked to the rating process.

To date there is no proven cure for these symptoms. Established treatment may consist of saline irrigation or implantation of materials to normalize nasal airflow. Experimental procedures currently tested include injection of Botulinum toxin into the dilator nasalis muscle.[9]

Decongestants are known to relieve symptoms from swollen turbinates in the short term. Instead of decongestants, sometimes menthol is used to relieve symptoms of nasal congestion. However, the effect of menthol on nasal patency seems to be due to a sensory illusion[10,11] rather than changed airflow.[12]

To elucidate differences in cerebral activation between ENS patients and controls, we conducted an f-MRI experiment involving the rating of nasal patency during free breathing and after a pseudodecongestant (menthol) or an odor (lemonene). We expected a beneficial effect of menthol inhalation. We furthermore expected differences in cortical activation during our experiment. Because ENS patients suffer during normal breathing and show symptoms of air hunger and have decreased nasal function (as stated previously), we expected differences in amygdala, piriform cortex, and temporal pole activation in comparison to controls.

MATERIALS AND METHODS

Subjects and Patients

After approval of the study by the local ethics committee and in accordance to the Declaration of Helsinki, 15 healthy subjects (controls) and 10 patients with ENS were recruited. Inclusion criterion for the patients group was the diagnosis empty nose syndrome.

The diagnosis and symptom assessment was based on the clinical manifestations of ENS by the participating ear, nose, and throat (ENT) specialist (M.O.S.). For reasons of standardization, only ENS patients who had undergone a resection of both middle and inferior turbinates were included. Inclusion criterion for the controls was absence of ENT-related pathology, including operations of the turbinate.

Exclusion criteria were current neurologic illness and contraindications for MRI or the inability to smell menthol and lemonene.

The olfactory function was tested according to the Guidelines of the Smell and Taste Working Group of the German ENT Society using Sniffin' sticks (Burghart Messtechnik, Wedel, Germany). Patients and controls were asked to smell 12 differently defined substances with eyes closed. Each side was tested separately. The trigeminal function was tested with ammonia.

Data Acquisition

F-MRI data were acquired on a 1.5-T MRI machine (Magnetom Symphony; Siemens, Germany). A standard f-MRI sequence was used (for details, see supplementary material).

Experimental Protocols

Subjects were placed supine with head forward into the MRI machine. A facial mask covering mouth and nose was fitted snugly with straps around the head. Attached to the mask was a wide diameter tube protruding out of the head coil cage.

This tube was placed so that one experimenter could easily attach a standard paper respiration filter to it. Two filters were loaded, one with l-menthol (10% solution in peanut oil) and the other with high-grade lemon oil, whose active ingredient is lemonene. Lemonene was chosen, because it has a fresh fragrance but no known properties concerning subjective nasal patency, so it was thought to contrast menthol by giving a similarly perceived fragrance (fresh and healthy) but producing no pseudodecongestant effect.

To rule out changes in airway resistance or olfaction due to the ongoing inhalation of menthol or lemonene, the experimental condition (block design) was the rating of the airway patency under influence but after cessation of substance inhalation. The conditions were named according to the context: free breathing without instruction (R), rating after room air (RR), rating after menthol (RM), rating after lemonene inhalation (RL) (Fig. 1).

The order of stimulation was presented on a personal computer, running ERTS software (BeriSoft AG, Frankfurt, Germany) synchronized with the MRI machine.

Psychophysical Data Collection

Bilateral airflow was measured using active anterior rhinomanometry, according to the recommendations of the International Committee for Standardization.[13] The device used was the Rhino 4000 M (Homoth Medizin Elektronik, Hamburg, Germany). This objective measurement produced flow rates measured in cubic centimeters per second.

Furthermore, subjective nasal patency was rated on a four-point scale where the following ratings were possible: 1 = better patency than usual, 2 = normal patency, 3 = worse patency than usual, and 4 = very bad patency. The patency score was recorded by means of a custom four-key keyboard placed on the right thigh. Blind input was practiced just before the scan. The rating procedure was performed with the right hand of the subject every time a rating cue was delivered; the cue was a touch of the right thigh by an experimenter observing the ERTS monitor through the scanner window.

Data Analysis

For the data analysis, the fully automated software package SPM 5 (Wellcome Department of Imaging Neuroscience,

TABLE I.
Rating of Nasal Patency.

	Healthy Subjects (90 Ratings)			Patients (60 Ratings)		
Rating	Rest, %	Menthol, %	Lemonene, %	Rest, %	Menthol, %	Lemonene, %
1 (Better)	10.1	46.7	27.8	22.3	31.7	28.3
2 (Normal)	74.9	41.1	60.0	29.5	33.3	21.7
3 (Worse)	11.6	11.1	7.8	27.7	28.3	41.7
4 (Very bad)	3.4	1.1	4.4	20.5	6.7	8.3

London, UK) was used with standard settings (for details see supplementary material) with the aim of identification of activated areas.[14]

To compare the psychophysical data concerning nasal patency, χ^2 testing was used. Results with an error $P < .05$ are seen as significant.

Activation and Deactivation

In the brain, a resting network activity[15] exists, meaning that even in "resting" conditions, there is brain activity. Therefore, any stimulation in comparison to (this already partially active) rest may evoke relative activation or relative deactivation.

The analysis with SPM only shows activation. Thus the question regarding which brain areas are active during the rating process (compared to rest) will be answered in the contrast RR-R. However it may be useful to compute the inverse contrast R-RR even if it has no logical background: By definition, the resting state should show no activation over any task. But if there exists suppression of brain activity during the task, it will be apparent in this contrast as "activation" that is stronger in the resting state than during the rating process. This may be interpreted as relative deactivation during the task.

In our experiment, we have taken the controls as the norm, thereby classifying activation occurring in inverse contrasts as relative deactivation occurring in patients.

RESULTS

Psychophysical Data

The ENS group consisted of five men and five women. The median age was 55 years. The control group consisted of eight men and seven women with a median age of 32 years. Thirteen of 15 controls had a normal sense of smell, two of 15 were hyposmic. In the ENS group, eight of 10 had a normal sense of smell, and two of 10 were hyposmic.

The trigeminal function was tested with ammonia. Both the control and the ENS group proved to have normal trigeminal function. The sense of smell for menthol and lemonene in both groups was tested and was normal.

In the ENS group, a median bilateral inspiratory flow of 593 cm^3/s (126–762 cm^3/s) was measured. In the control group, a median bilateral inspiratory flow of 700 cm^3/s (212–865 cm^3/s) was measured. There was no significant difference of nasal airflow between the two groups ($P > .05$).

Regarding the feeling of nasal patency (subjective rating), the details are given in Table I. Comparing nasal patency of controls and patients, significantly more patients than controls rated their feeling of patency worse than normal (each χ^2 test $P < .00001$) in every condition (rest, after menthol or lemonene). Comparing the conditions, controls noted a significant benefit regarding nasal patency from both menthol and lemonene ($P < .00001$). Empty nose patients also regarded nasal patency better after inhalation of menthol ($P = .04$) or lemonene ($P = .01$). Controls rated the effect of menthol significantly better than that of lemonene ($P < .00001$), and patients reported no significant difference between the substances ($P = .08$).

F-MRI Data

Controls. Assessing the rating task itself was done with the contrast RR-R. Here, widespread and robust bilateral cerebellar activation as well as activation of bilateral amygdala and parahippocampal gyrus (Supplementary Table I and Fig. 2) and caudate/septal nuclei and left-sided middle occipital gyrus (MOG) was detected, also of the superior colliculi of the brainstem.

Comparing the effects of menthol and room air on the feeling of nasal patency, there were no brain regions more active after menthol inhalation than after room air (Supplementary Table I). But there were brain regions with reduced activity after menthol: bilateral caudate nucleus as well as bilateral temporal and superior frontal cortex.

After lemonene inhalation, there again were no activated brain areas to be detected. But deactivations included bilateral caudate body, bilateral cerebellum, frontal cortex, and paracentral lobule adjacent to anterior cingulate cortex and posterior cingulate cortex.

Comparing the effect of menthol and lemonene, there were no areas activated more after limonene, but several brain areas were activated more after menthol: bilateral middle frontal gyrus/superior frontal gyrus being Brodmann's area (BA) 6, left MOG, and hippocampus.

Patients. The rating task itself (RR-R) produced caudate/septal nuclei and (left-sided) cerebellar activation (Supplementary Table II and Fig. 3), extending to the amygdala and weaker activation of the superior colliculi. Also, bilateral temporal activation of middle temporal gyrus (MTG)/BA 21 and superior temporal gyrus (STG)/BA 38 was shown.

As in controls, there was no activation detected after menthol inhalation (Supplementary Table II), but deactivation of bilateral temporal cortex, bilateral caudate nucleus, right insula and left precentral gyrus (Broca's area). Also after lemonene, there was no activation, but deactivation of bilateral caudate nucleus,

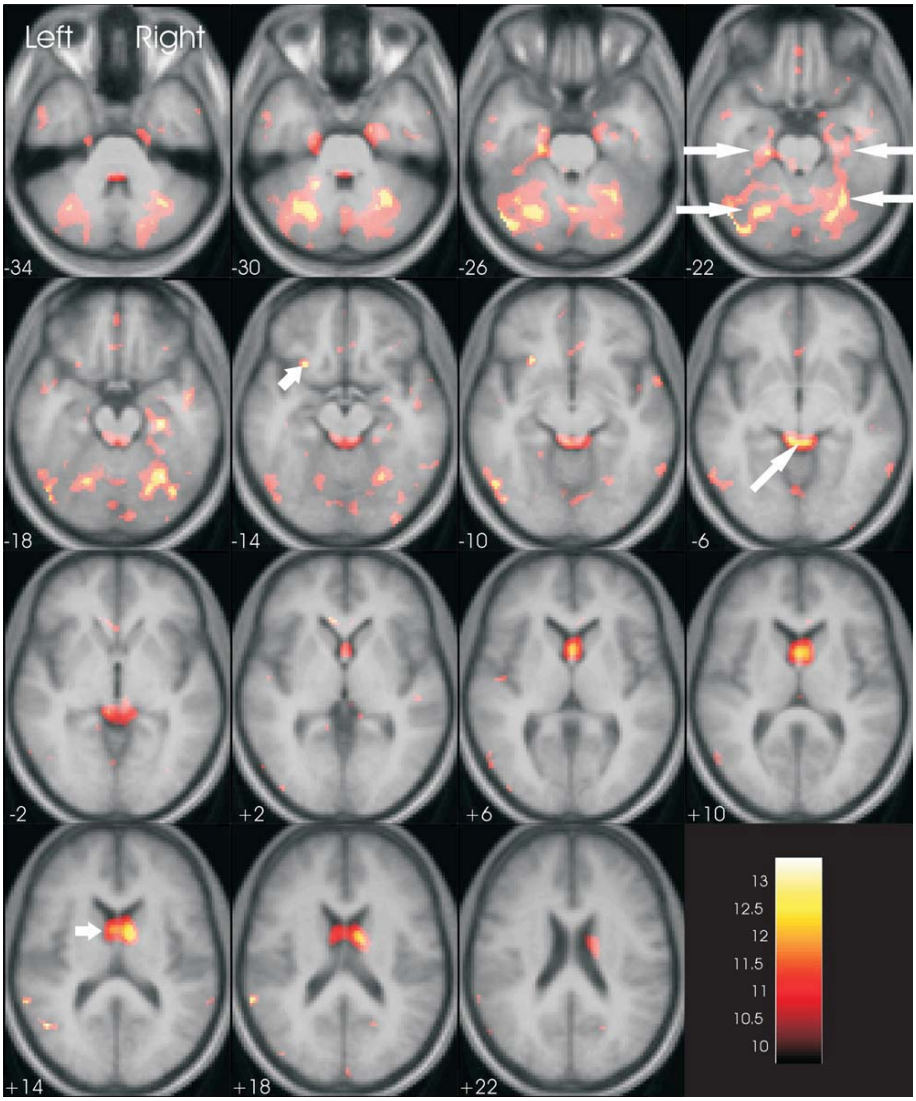

Fig. 2. Activation during the rating task (RR-R), i.e. rating of nasal patency during respiration of room air compared to rest of the controls. The colored blobs (Supplementary Table I) are projected on transversal slices (neurological convention, the right side of the image referring to the right side of the brain) from a template created from all controls and patients. Z-axis values are given in the lower left hand corner of each slice. The horizontal arrow points to the bilateral cerebellar and amygdala activation, the diagonal arrow points to activation of the superior colliculi and the short horizontal arrow points to activation of the caudate/septal nuclei and the diagonal short arrow points to the left inferior frontal gyrus.

bilateral middle frontal gyrus, and bilateral STG. Comparing menthol and lemonene, there were no areas more active after menthol, but after lemonene there was activation of right STG and insula.

Patients and controls. Supplementary Table III shows cortical activation discerning patients and controls. The comparison of the rating task itself (RR-R) led to specific activation in ENS of the left cerebellum / amygdala and bilateral dorsolateral prefrontal cortex and right MTG/BA 21 (Fig. 4).

After menthol inhalation there was no specific activation to be seen in patients that was not apparent in controls. Specific deactivation in patients occurred in bilateral STG (BA 38+10) as well as Broca's area and left precuneus. After lemonene inhalation, no specific activation was evident, but there was deactivation of right STG (BA 38) and bilateral inferior frontal gyrus in BA 45 and sensorimotor areas in BA 5,6, and 9.

The comparison of the effects after menthol and lemonene showed "activation" only after lemonene inhalation. This activation occurred in the bilateral MTG, left STG, right insula and posterior cingulate cortex, and right MOG.

DISCUSSION

In an f-MRI experiment employing inhalation of menthol and lemonene in comparison to room air, ENS patients were compared to controls. Despite similar results of rhinomanometric measurements, the subjective nasal patency was rated to be worse for ENS patients than for controls and to be better after menthol or lemonene inhalation.

The rating of nasal patency activated areas belonging to the limbic (emotional brain circuitry) system in both patients and controls. Deactivation (compared to rest) proved to be the dominant feature after inhalation of menthol or lemonene. Patients are distinguished by specific deactivation of bilateral (paralimbic) temporal cortex and Broca's area.

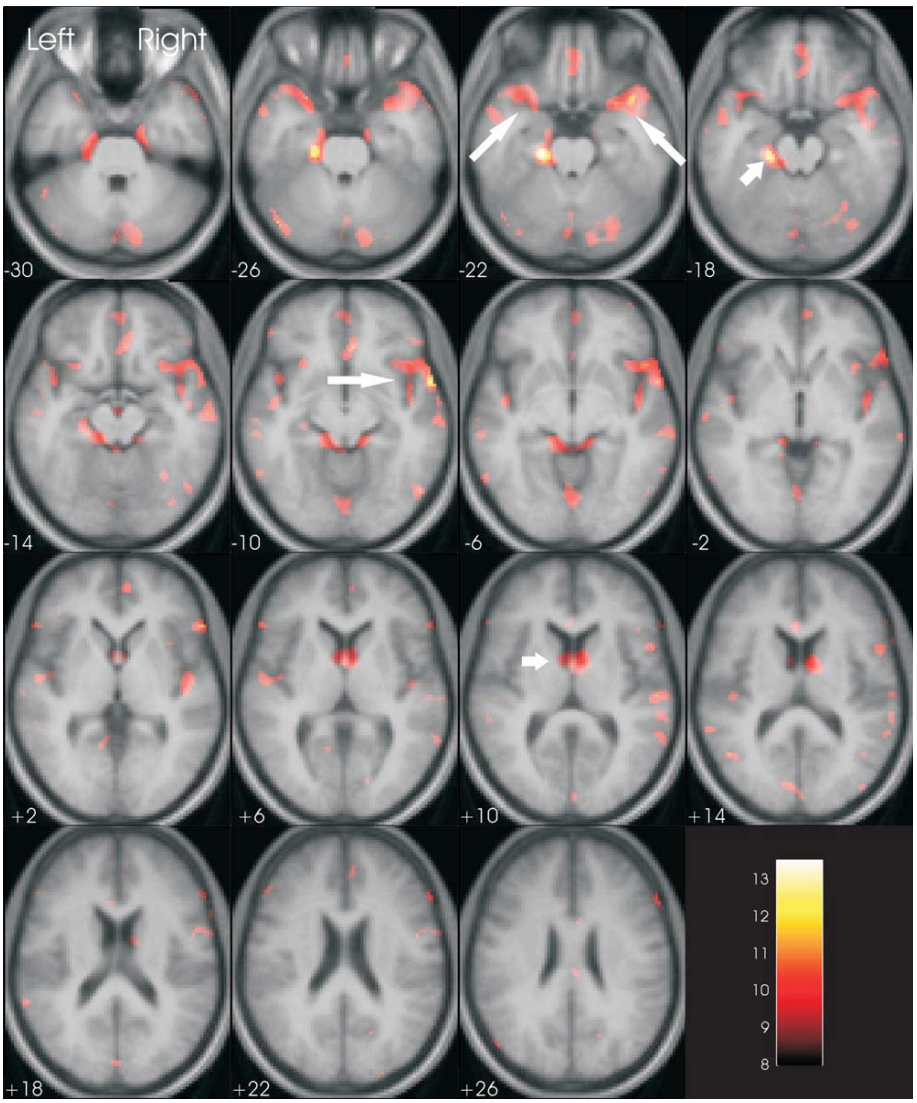

Fig. 3. Activation during the rating task (RR-R) of the patients. The colored blobs (Supplementary Table II) are projected on transversal slices (neurologic convention, the right side of the image referring to the right side of the brain) from a template created from all controls and patients. Z-axis values are given in the lower left-hand corner of each slice. Like in Figure 2, there is some superior colliculi and cerebellar activation. The horizontal arrow points to the right insula, the diagonal arrow points to activation of the temporal pole (BA 38+21), the short horizontal arrow points to activation of the caudate/septal nuclei, and the diagonal short arrow points to the left amygdala.

Nasal Airway Resistance Measurements

Despite the resection of turbinates the rhinomanometric measurements showed no advantage for the ENS patients. This may be ascribed to the loss of laminar flow and to distress-induced altered cooperation in ENS patients.

Psychophysical measurements showed different responses of controls and ENS patients concerning the rating of nasal patency during/after inhalation of room air: Despite similar objective airflow measurements, patients rated their subjective nasal patency significantly worse than controls (Table I).

For this clinical situation, the term "paradox nasal obstruction" was coined.[1] This phenomenon is caused by several interacting factors: 1) reduced nasal airway resistance, 2) disturbed airflow, 3) loss of respiratory mucosa (the true nasal organ), and 4) reduced contact interval in between air and mucosa. This situation outlines the distinct difference between nasal patency, the data of rhinomanometric measurement, and the individual feeling of nasal breathing in ENS patients. They simply cannot feel the air flowing through their nose, because they cannot perceive it at the interface between the air and mucosa. This is due to the functional imbalance between the intranasal volume and the mucosal surface.

Thus the difference in the subjective perception of nasal patency is not rooted in objective airway resistance differences but rather may be attributed to loss of nasal mucosa. Bearing this in mind, it becomes clear why further resection of nasal turbinates will only worsen the perception.

The Rating Task

The rating task itself (contrast RR-R) yielded widespread and robust bilateral cerebellar activation as well as activation of bilateral amygdala and parahippocampal

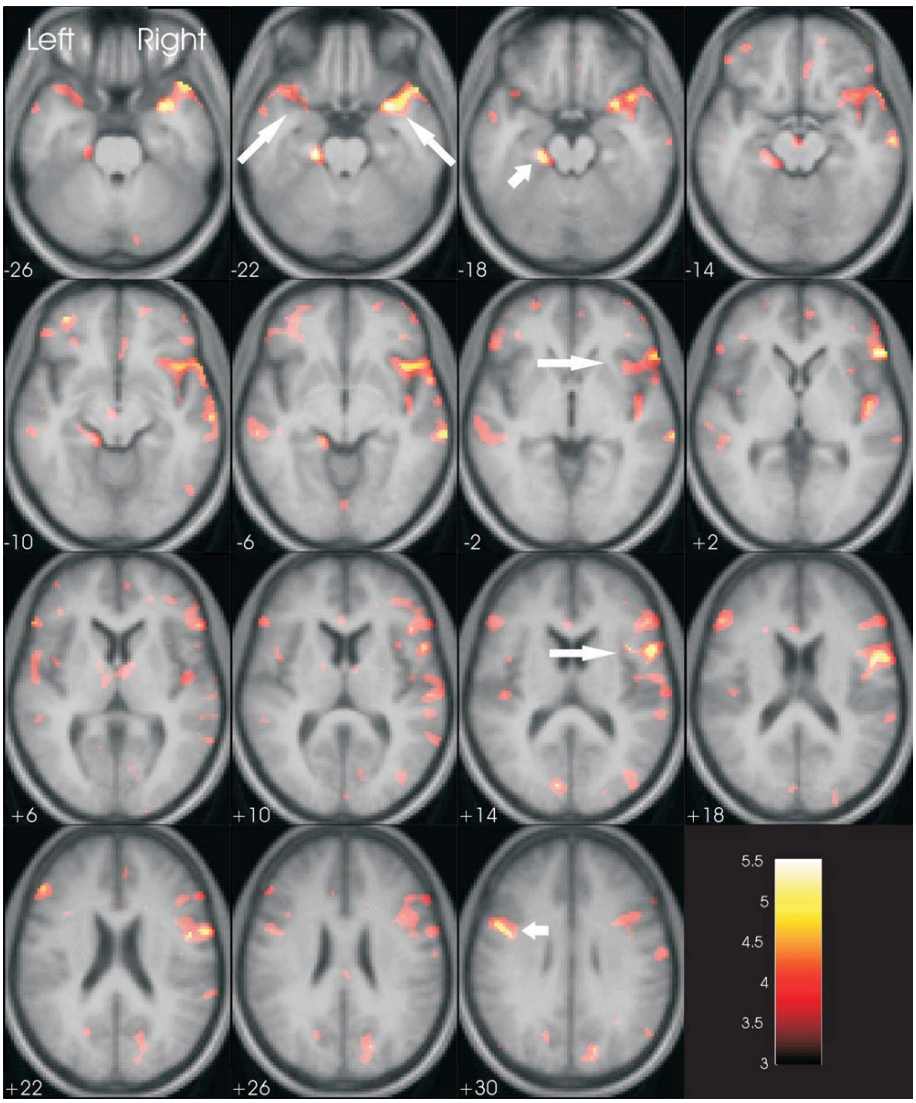

Fig. 4. Activation of the group comparison of patients and controls during the rating task (RR-R). The colored blobs (Supplementary Table III) are projected on transversal slices (neurologic convention, the right side of the image referring to the right side of the brain) from a template created from all controls and patients. Z-axis values are given in the lower left-hand corner of each slice. The horizontal arrow points to the right inferior frontal gyrus, the diagonal arrow points to activation of the temporal pole (BA 38+21 and uncus), the short horizontal arrow points to activation of the left inferior frontal gyrus, and the diagonal short arrow points to the left amygdala.

gyrus and caudate/septal nuclei and left-sided MOG (see also supplementary material).

The temporal pole as well as the amygdala belongs to the limbic system normally involved in emotional processing. The described temporal activation has also been detected in an experiment involving respiratory distress.[16] This parallel possibly indicates distress in empty nose patients in the "resting" condition. In another experiment involving air hunger during CO_2 inhalation, similar cerebellar and prefrontal activation was present.[6]

Thus the activation discerning patients from controls could point to the feeling of respiratory distress in the "resting" condition of the empty nose patients.

Menthol Inhalation

Psychophysical measurements show similar subjectively positive responses of controls and ENS patients concerning the rating of nasal patency after inhalation of menthol. Because of this, menthol has been labelled a pseudo decongestant.[11,17]

Patients reported less benefit concerning subjective nasal patency after menthol than controls. This may be due to the fact that ENS patients possess less nasal mucosa or that the menthol simply does not reach the olfactorial areas because of pathologic laminar air flow.

During f-MRI of controls, no activation but strong deactivation (mainly of areas belonging to the olfactory network) could be shown in the contrast comparing menthol and rest: There was caudate and cerebellar activation as well as prefrontal and temporal activation.

In patients also, only deactivation could be detected after menthol inhalation. Specific deactivation (Supplementary Table III) included mainly the bilateral temporal pole (BA 38). These areas have been shown to activate in emotional context of various stimuli[7,18] and are thought to constitute a paralimbic region. The deactivation in patients may point to higher resting level

activation: During rating of the nasal patency after menthol inhalation, this persistent resting-level emotional component is diminished.

Lemonene Inhalation

Psychophysical measurements show similar positive responses of controls and empty nose patients concerning the rating of nasal patency after inhalation of lemonene. However, although the effect of menthol was rated to be significantly stronger than lemonene by controls, this difference was only a trend ($P = .08$) for patients.

During the rating task after inhalation of lemonene there could be shown no activation, but strong deactivation in cerebellar regions reckoned to belong to the olfactory network. Also caudate and prefrontal (BA 6) deactivation was detected. These regions have been shown to activate during intravenous presentation of odors[19] or during "verbal" odor presentation.[20]

Patients selectively deactivated (Supplementary Table III) prefrontal areas including a secondary sensory area so that this can be interpreted as patients showing less sensory processing of the lemonene stimulus. This in turn might be related to diminished capacities for odor detection.

CONCLUSION

Despite similar objective measurements, ENS patients perceive less nasal patency than controls. Both, however, profit more from the effect of menthol than lemonene.

The robust activation of areas belonging to the olfactorial network in the "empty" rating procedure (RR-R) shows that the main workload of our experiment results from the rating process itself, and it may actually be easier to rate after the interventions. Activation of structures belonging to the limbic system demonstrates the connection of olfactory and limbic processes.

Specific activation in ENS patients hints at ongoing suffering during the resting condition as observed in experimental air hunger. The beneficial effect of menthol inhalation may correspond to the decreased activation of paralimbic temporal pole areas. Menthol indeed was beneficial in that it alleviated the distress of ENS patients. Thus it is proposed to incorporate menthol into treatment plans, perhaps as an additive to nasal ointments.

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