Henkin et al., J Clin Exp Pathol 2018, 8:5
DOI: 10.4172/2161-0681.1000358

Journal of Clinical & Experimental Pathology

Research Article Open Access

# Phantageusia and its Inhibition by Repetitive Transcranial Magnetic Stimulation

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## Abstract

**Background:** Phantageusia is an unpleasant, commonly persistent oral taste occurring without any oral stimulus. It is commonly experienced by patients subsequent to loss of taste acuity (hypogeusia). There is currently no defined treatment. We wished to describe phantageusia and efficacy of its treatment with repetitive transcranial magnetic stimulation (rTMS).

**Methods:** An open label controlled clinical trial of 30 patients with phantageusia of two months to six years duration. Phantageusia was judged subjectively on a 0-100% scale with 100 indicating greatest phantageusia intensity before treatment and changes measured on the same scale after treatment. Patients were initially treated with rTMS and followed after treatment initially for periods of 2-4 months and subsequently for 1-10 years.

**Results:** rTMS inhibited phantageusia from a mean 58% before treatment to a mean 30% after treatment. Twenty-four of these 30 patients responded with significant phantageusia inhibition with six with total inhibition. Inhibition persisted for months-years without recurrence. These patients were labeled responders. Six of these 30 patients did not respond with significant phantageusia inhibition and were labeled non-responders. Repeated rTMS two or three additional times in some non-responders inhibited phantageusia similar to initial inhibition in responders.

**Conclusions:** rTMS is an effective method to inhibit phantageusia. Inhibition in 80% of patients persisted for months to years after rTMS suggesting that placebo responses did not contribute significantly to this inhibition. Activation of brain gamma-aminobutyric acid (GABA) and synaptic and cortical plasticity by rTMS may play roles in this inhibition.

**Keywords:** Phantageusia; Repetitive transcranial magnetic stimulation; Taste distortion; Sensory hallucinations; Hypogeusia

## Introduction

Phantageusia describes an unpleasant, distorted taste in the oral cavity in the absence of any oral stimulus. It was described in the 19th century by Jackson [1] and Gowers [2] usually as an aura associated with onset of an epileptic seizure usually of a complex, partial type and considered a phantom or hallucination similar to description of phantom limb [3].

We observed this type of hallucination as a chronic condition in patients subsequent to a loss of taste acuity related to some systemic disorder, e.g., a viral-type illness [4], a metabolic disorder such as hypothyroidism [5] or several other disorders [4]. It is usually orally global. No patient exhibited any myoclonic activity.

We classified phantageusia into three types – torquegeusia [4], i.e., salty, bitter, sour, metallic or chemical, cacogeusia [4], i.e., rotten or fecal or less commonly mixed, a combination of these two types [4]. While it can be intermittent, it is more commonly persistent without remission. It occurs commonly subsequent to taste loss (hypogeusia) occurring usually days, weeks or months after onset of initiating pathology [4]. It occurs less commonly independent of any known pathology (idiopathic). Initiating pathology varies widely such as an influenza-like illness [4], allergic rhinitis [4], head injury [6] or systemic illness related to an endocrine deficiency (e.g., hypothyroidism) [5], vitamin deficiency (e.g., vitamin B12, vitamin E), neurological (e.g., multiple sclerosis, stroke, Parkinson's disease) or other clinical disorders [7]. Some patients perceived its intensity and persistence as a type of constant oral pain.

We reported this symptom occurring in about 60% of patients who experienced some type of hypogeusia [4]. Since many patients experience taste loss due to systemic disorders noted above [4], phantageusia is a common but underrecognized occurrence. Dentists, neurologists and otolaryngologists encounter patients with phantageusia but are usually unfamiliar with its character, etiology or treatment. Many practitioners have encountered patients with unpleasant taste distortions related to the intake of food or fluids, termed dysgeusia or aliageusia [4], but phantageusia occurs unrelated to intake of any food or fluid.

While etiology of phantageusia is diverse, once it appears, it usually persists although it may wax and wane in intensity. Patients stated that phantageusia was very disturbing to their ability to follow their usual life patterns. It was usually less severe in the morning but greater in the afternoon or evening. Sleep diminished phantageusia intensity. Phantageusia was exacerbated by oral presence of spicy, overly salty or bitter foods or beverages (allodyngeusia) [4]. Phantageusia was masked by bland or cold food or beverages, chewing gum or sucking on hard candies but it always returned once this activity was terminated.

To understand more about this symptom we systematically evaluated these patients. We performed a complete medical history

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**Received:** November 28, 2018; **Accepted:** December 05, 2018; **Published:** December 12, 2018

**Citation:** Henkin RI, Abdelmeguid M, Potolicchio SJ (2018) Phantageusia and its Inhibition by Repetitive Transcranial Magnetic Stimulation. J Clin Exp Pathol 8: 358. doi:10.4172/2161-0681.1000358

[4] and systematic tests of taste function [4] in patients who presented to The Taste and Smell Clinic in Washington, DC for evaluation and treatment of this symptom.

We also studied these patients using functional magnetic resonance brain imaging (fMRI) [8]. Results indicated that patients, when asked to "imagine" their phantageusia while in the scanner, activated not only brain regions associated with taste function but also other brain areas not usually associated with taste function [8], regions involving emotion, pain and memory. No prior studies identified such diverse brain activation [8].

We also used magnetic resonance spectroscopy (MRS) in which several brain neurotransmitters was quantitated [9]. They revealed that brain gamma-aminobutyric acid (GABA) levels were significantly diminished from normal levels in the same brain regions previously activated by "imagination" of phantageusia [9]. These results suggested that one mechanism associated with this symptom was that GABA levels were diminished allowing perception of usually inhibited sensations. Because of diminution of this inhibitory neurotransmitter, we treated patients with GABA ergic drugs [10]. MRS studies after treatment demonstrated increased brain GABA levels in the specific regions in which they were previously decreased; subjective responses indicated significant inhibition of phantageusia [11]. These changes were documented symptomatically by placing patients back into the scanner and by use of fMRI asking patients to "reimagine" their phantageusia; following this GABA increase, repeat fMRI studies showed little or no activation [8].

We previously demonstrated that repetitive transcranial magnetic stimulation (rTMS) improved taste and smell function and inhibited sensory distortions in a small group of patients who had taste and smell loss and phantageusia [10,11]. These results, along with animal [12] and human [13,14] studies and our prior studies [9,11], suggested that rTMS might increase brain GABA, enhance synaptic and brain plasticity [15,16] and inhibit phantageusia.

To test this hypothesis we measured brain GABA levels using MRS in two patients with phantageusia before and after rTMS [11]. We found GABA levels before treatment were lower than normal and after rTMS GABA levels increased to normal with associated phantageusia inhibition [11].

Although we have previously reported on some characteristics of this symptom [17] and use of rTMS in treatment of a small group of these patients [10], we have not previously dealt in any systematic manner with either the fully characterized nature of phantageusia or its treatment using rTMS.

The purpose of our study is to describe details of phantageusia and specific responses to its treatment with rTMS in a carefully studied group of patients over a prolonged time period.

## Methods

### Patients

Thirty patients, aged 22-83 y [62 ± 3 y (Mean ± SEM)], 13 men, aged 22-83 y (63 ± 5 y) and 17 women, aged 23-83 y (61 ± 3 y) were studied. The patients were 28 Caucasians and 2 Blacks. Each patient came to The Taste and Smell Clinic in Washington, DC for evaluation and treatment of a persistent, unpleasant taste in their oral cavity independent of presence of any oral stimulation (Table 1).

Distortions were described as present globally in the entire oral cavity and not limited to any oral structure or location. Patients were each patient who presented to The Taste and Smell Clinic in Washington, DC with this symptom between 2005-2014 in whom rTMS was applied.

Physical examination of head and neck was within normal limits in each patient. Examination of the oral cavity was normal in each patient. Computed tomography and/or magnetic resonance imaging scans of the head were normal in each patient.

Patients described their phantageusia (Table 1) as either salty (six patients, 20%), salty/metallic/bitter (three patients, 10%), metallic only (three patients, 10%), metallic/bitter/chemical (five patients, 17%), chemical only (one patient, 3%), bitter only (three patients, 10%), rotten only (three patients, 10%), sour only (two patients, 0.7%), sour/bitter (three patients, 10%) or chalky (one patient, 0.3%) (Table 1).

Phantageusia was persistent lasting two months to six years (2.1 ± 0.3 y) at initial evaluation (Table 1).While occasionally it waxed and waned in intensity, it was always present. Some patients (10 patients, 33%) developed phantageusia spontaneously (i.e., idiopathic) without defined antecedent illness. However, phantageusia more commonly followed a specific pathological process which initiated taste loss with subsequent taste distortion onset [in 20 patients (67%)] (Table 1). No patient exhibited any myoclonic activity.

Before treatment, patients graded phantageusia intensity daily on a scale of 0-100 with 100 indicating their most intense oral distortion. After rTMS, they graded distortions down from 100 to 0 with 0 indicating phantageusia absence. Records were reviewed prior to rTMS by one investigator (RIH) to insure understanding of symptom grading but investigators were masked after treatment.

### Measurement techniques

Taste acuity was measured using gustometry by a standard three stimuli forced choice staircase technique [4]. Detection (DT) and recognition (RT) thresholds and magnitude estimation (ME) for four tastants [NaCl (salt), sucrose (sweet), HCl (sour) and urea (bitter)] were obtained and results compared to reference values previously established for normal subjects [4,18]. DT-defined abnormalities in taste receptor function, RT-abnormalities in brain function, ME-abnormalities in taste receptor number and Hedonics-abnormalities in interactions between receptor and brain function. All DT and RT for tastants were converted into bottle units (BU) [4,19]. ME was determined on a 1-100 scale by methods previously described, calculated for mean intensity (in percent) for each stimulus and compared to previously established standards [4,18]. Reliability of techniques was confirmed by studies performed in a previously published controlled double blind clinical trial [19] and in other controlled clinical trials [4,18]. Hedonic measurements (H) related to tastant tasting either pleasant, unpleasant or neutral. Mean values of pleasantness, unpleasantness or neutral responses were calculated arithmetically for each tastant and mean responses determined [4].

The battery of sensory measurements was obtained at initial patient visit and repeated prior to and after each rTMS trial. This battery was also repeated at variable intervals after each rTMS trial. Each test battery and rTMS trial was performed independent of knowledge of any prior result. The study was approved by the IRB of the George Washington University Medical Center.

### Treatment protocol

rTMS was performed with a Cadwell (Kennewick, WA) magneto-

| Gender | Diagnosis | Type of Phantageusia | Length of Distortion (y) |
|---|---|---|---|
| M | Renal failure | Salty, Metallic | 3 |
| F | Trigeminal neuralgia | Sour | 1 |
| M | Allergic rhinitis | Metallic | 0.6 |
| F | Trigeminal neuralgia | Sour, Bitter | 1 |
| M | Post-influenza-like hyposmia and hypogeusia | Bitter, Metallic | 0.8 |
| F | Post anesthesia | Sour, Bitter | 2.5 |
| F | Idiopathic | Metallic | 0.5 |
| F | Head injury | Bitter | 2 |
| F | Idiopathic | Sour | 3 |
| F | Idiopathic | Biter | 1.5 |
| M | Idiopathic | Salty | 0.8 |
| M | Idiopathic | Salty | 0.8 |
| F | Multiple Sclerosis | Metallic | 0.8 |
| M | Idiopathic | Salty | 6 |
| F | Idiopathic | Salty | 3 |
| F | Post-influenza-like hyposmia and hypogeusia | Chemical | 0.8 |
| F | Post anesthesia | Metallic | 2 |
| M | Idiopathic | Bitter | 2 |
| M | Post-influenza-like hyposmia and hypogeusia | Bitter, Metallic | 2 |
| F | Post treated Hodgkin's disease | Salty | 5.5 |
| M | Post-influenza-like hyposmia and hypogeusia | Rotten | 0.9 |
| F | Idiopathic | Rotten | 0.9 |
| F | Multiple myeloma renal failure | Bitter, Salty | 5 |
| M | Post anesthesia | Bitter, Salty | 0.6 |
| M | Post-influenza-like hyposmia and hypogeusia | Bitter, Metallic | 0.2 |
| F | Hypothyroidism | Sour, Bitter | 1 |
| F | Post-influenza-like hyposmia and hypogeusia | Metallic, Chemical | 0.9 |
| M | Head injury | Chalky | 6.3 |
| F | Idiopathic | Metallic, Chemical | 0.5 |
| M | Idiopathic | Salty | 6 |

**Table 1:** Clinical description of phantageusia.

electric stimulator MES-10 monitored by a TECA TD20 (Pleasantville, NY) wave form generator. Stimulation was applied by use of a single circular 5 cm (internal diameter) coil.

Three consecutive stimulation procedures were used at each rTMS trial. The first two were sham procedures, the third was the real trial [16]. The first procedure, a sham procedure, applied 20 stimuli at intervals of 1-5 seconds at 30-40% maximal output [30-40% of 1.5 T or ~0.4-0.8 T] to three regions: a) the anterior left shoulder, [at the lateral acromial process of the clavicle (near Erb's point)] then b) anterior right shoulder (near Erb's point) and then c) to the back of the mid neck (at the level of C5-8). Moderate muscle flexion of arm and hand muscles (shoulder stimulation) and neck, strap and facial muscles (neck stimulation), respectively, followed stimulation at each respective site and was visually monitored.

The second procedure, another sham procedure, consisted of applying 20 stimuli at intervals of 1-5 seconds at 5-10% maximal output (5-10% of 1.5 T or ~0.08-0.15 T, a subthreshold stimulus) to four skull regions in a fixed sequence (left temporoparietal, occipital, right frontoparietal, frontal). No subjective or peripheral muscle response occurred in response to these stimulations.

The third procedure, the real trial, consisted of applying 20 stimuli at intervals of 1-5 seconds at 40-55% maximal output (~0.8-1.1 T) sequentially to each skull location as in the second sham procedure noted above. Mild right/left thenar and/or phalangeal flexion occurred after left/right temporoparietal stimulation, respectively. Mild facial muscle flexion occurred after occipital stimulation. Bilateral eye blinking occurred after frontal stimulation.

After each sham procedure and real rTMS trial changes in intensity and character of phantageusia was recorded on the descending 100-0 scale. If any change in sensory distortion occurred, stimulation at that location at that same intensity was repeated two-six times until no further change occurred.

## Outcome measures

After each rTMS procedure patients graded changes in sensory distortion intensity on the same descending 100-0 scale used previously with any decrease in phantageusia intensity considered consistent with its inhibition. Patients were reevaluated at several intervals after initial stimulation. All patients were evaluated by telephone, e-mail or return visit to The Clinic weekly and at two to six weekly intervals after initial stimulation. Most patients were also reevaluated by telephone, e-mail or return visit to The Clinic four to six months after initial stimulation. Patients were also reevaluated at yearly intervals after initial stimulation.

Measurements of taste function were also repeated with DT, RT, ME and H calculated and significance of differences compared to responses before rTMS. Differences were calculated using paired t tests with significance determined by Student t test with differences of $P<0.05$ considered significant. Results of all 16 taste tests [DT, RT, ME and H (for four tastants)] were evaluated before and after stimulation by $X^2$ with results after treatment compared to pre-treatment and to responses previously obtained in normal subjects [9,11,18].

## Results

Distortion intensity in all patients prior to treatment varied from 10-100%, mean intensity, 58 ± 5% (Table 2).

No patient responded with phantageusia diminution to either of the two sham procedures. After stimulation, phantageusia intensity among all treated patients was significantly inhibited to 30 ± 5% (Table 2). Phantageusia intensity measured four to six weeks after initial rTMS remained inhibited (Table 2). However, when measured four to six months after initial rTMS, inhibition decreased (to 49 ± 5%) but levels were still below onset levels. When analyzed by gender prior to rTMS women initially demonstrated a significantly greater degree of phantageusia intensity than did men (Table 2). After initial rTMS phantageusia was inhibited in both men and women but overall inhibition in women was proportionately greater than in men.

More detailed analysis revealed that inhibition differed among patients with inhibition occurring in 24 patients (80%), labeled responders (Table 3).

Of these patients, 13 (aged 51-83y) were women (54%) and 11 (aged 22-83y) were men (46%) (Table 3). Clinical diagnoses were head injury (one patient, 4%), idiopathic phantageusia (11 patients, 46%), post-influenza-like infection (six patients, 25%), renal failure (two patients, 8%), trigeminal neuralgia (one patient, 4%), post general inhalation anesthesia (two patients, 8%) and hypothyroidism (one patient, 4%).

Among responders there was a slight increase in men with respect to women (13 to 11).

Among responders phantageusia decreased significantly after rTMS (Table 3). This inhibition continued not only for four to six weeks after rTMS but also for four to six months post stimulation. Among responders phantageusia in six patients [(three men, three women) (20% of patients)] was totally inhibited (response intensity graded as 0). Their diagnoses were idiopathic phantageusia (three patients), post-influenza-like infection (two patients) and post general inhalation anesthesia (one patient). This inhibition continued in some patients studied for as long as four to six years.

Both genders responded to rTMS with a consistent decrease in phantageusia intensity which persisted for the four to six month follow-up. However, analysis by gender indicated that women responded with a proportionately greater inhibition than men (Table 3).

Six patients (20%) labeled non-responders did not respond with significant inhibition of phantageusia (Table 3). More women than men were non-responders. Of these non-responders, initial phantageusia intensity prior to rTMS was significantly less than in responders (Table 3).

Among non-responders initial phantageusia intensity was less than in responders and no significant inhibition of phantageusia occurred after rTMS; this lack of inhibition also continued for the initial four to six month follow-up interval.

No change in phantageusia occurred among non-responders when analyzed by gender.

Prior to treatment measurements of taste function in all 30 patients were significantly impaired with respect to normal subjects (Table 4).

Reanalysis of initial taste function studies performed among all patients revealed that in responders who successfully inhibited phantageusia their taste loss prior to rTMS was significantly impaired with respect to normal or to the total group (Table 4). However, among

| Patients | Pre Treatment | Immediately Post Treatment | Four To Six Weeks Post Treatment | Four To Six Months Post Treatment |
|---|---|---|---|---|
| All (30) | 58 ± 5* [10-100] | 30 ± 5[a] [0-70] | 32 ± 4[a] [0-70] | 49 ± 5 [0-95] |
| Men (13) | 45 ± 6 [10-80] | 25 ± 7[c] [0-68] | 28 ± 6[e] [0-68] | 42 ± 11 [2-85] |
| Women (17) | 68 ± 8[e1] [10-100] | 33 ± 6[b] [0-70] | 35 ± 6[b] [0-70] | 57 ± 8 [20-95] |

( ) Patient number
*Mean ± SEM of subjective response (in percent)
[ ] Range of distortion intensity (in percent)
With respect to pre treatment
a p<0.001
b p<0.005
c p<0.01
e p<0.05
With respect to men
e1 p<0.05

**Table 2:** Changes in phantageusia inhibition after Repetitive transcranial magnetic stimulation (rtms).

| Responders | Pre Treatment | Immediately Post Treatment | Four to Six Weeks Post Treatment | Four to Six Months Post Treatment |
|---|---|---|---|---|
| All Responders (24) | 64 ± 6*[,e2] [10-100] | 29 ± 6[a] [0-70] | 31 ± 5[a] [0-70] | 27 ± 6[a] [0-50] |
| All Non-Responders (6) | 35 ± 6 [20-50] | 31 ± 6 [15-48] | 36 ± 6 [20-50] | 38 ± 6 [20-70] |
| Men Responders (11) | 47 ± 6 [10-80] | 24 ± 7[d] [0-68] | 27 ± 7[d] [0-68] | 22 ± 7[d] [0-50] |
| Women Responders (13) | 78 ± 8[c1] [10-100] | 34 ± 8[a] [0-70] | 34 ± 8[a] [0-70] | 27 ± 6[a] [0-60] |
| Men Non-Responders (2) | 35 | 33 | 35 | 31 |
| Women Non-Responders (4) | 35 ± 7 [20-50] | 31 ± 6 [20-48] | 36±7 [20-50] | 40 ± 7 [20-75] |

( ) Patient number
*Mean ± SEM of subjective response (in percent)
[ ] Range of distortion intensity (in percent)
With respect to pre treatment
a p<0.001
d p<0.02
With respect to men
c1 p<0.01
With respect to non-responders
e2 p<0.05

**Table 3:** Changes in phantageusia inhibition after rtms in responders and non-responders.

non-responders while taste responses prior to rTMS were still impaired with respect to normals they were not as consistently impaired compared to responder responses in whom each taste test result was significantly impaired with respect to normals ($X^2$, $P<0.05$) (Table 4).

Following rTMS there were significant increases in taste function sensitivity among all patients (Table 5) with taste responses (DT, RT, ME) for all tastants exhibiting improvement over pre-treatment responses and Hs for NaCl, HCl and urea were perceived as more unpleasant and sucrose perceived as more pleasant.

Characterized by diagnosis, inhibition intensity did not decrease consistently in each patient group (Table 6).

Phantageusia in patients with idiopathic phantageusia, post-influenza-like infection or post anesthesia decreased significantly and stayed inhibited over the four to six month follow-up period, but phantageusia in patients with multiple sclerosis, Hodgkin's disease and allergic rhinitis did not perceive any diminution in phantageusia (Table 6).

| | Taste Function Pre Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Detection Thresholds | | | | Recognition Thresholds | | | | Magnitude Estimation | | | | Hedonics | | | |
| | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea |
| **Patients (30)** | | | | | | | | | | | | | | | | |
| Mean | 4.4[a] | 4.4[a] | 4.9[a] | 5.6[a] | 5.4[a] | 4.9[a] | 5.8[a] | 6.3[a] | 47[b] | 40[a] | 49[d] | 42[a] | -33[d] | 17[d] | -45[e] | -41 |
| SEM | 0.4 | 0.4 | 0.4 | 0.5 | 0.6 | 0.4 | 0.6 | 0.5 | 5 | 4 | 5 | 5 | 5 | 6 | 4 | 5 |
| **Normals (55)** | | | | | | | | | | | | | | | | |
| Mean | 2.3 | 2.5 | 3.1 | 3.2 | 3.1 | 3.2 | 3.5 | 3.4 | 68 | 60 | 66 | 68 | -18 | 35 | -58 | -49 |
| SEM | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 3 |

| | Taste Function Pre Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Detection Thresholds | | | | Recognition Thresholds | | | | Magnitude Estimation | | | | Hedonics | | | |
| **Responders (24)** | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea |
| Mean | 4.5[a] | 4.6[a] | 5.2[a] | 5.8[a] | 5.5[b] | 5.2[a] | 5.6[c] | 6.5[a] | 46[b] | 40[a] | 48[d] | 42[a] | -37 | 13 | -43 | -41 |
| SEM | 0.5 | 0.5 | 0.5 | 0.6 | 0.7 | 0.5 | 0.7 | 0.6 | 6 | 5 | 5 | 5 | 6 | 8 | 5 | 6 |

| | Taste Function Pre Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Non-Responders** | Detection Thresholds | | | | Recognition Thresholds | | | | Magnitude Estimation | | | | Hedonics | | | |
| **(6)** | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea |
| Mean | 3.7 | 3.7 | 3.8 | 4.7[e] | 5.0[d] | 3.8 | 6.5 | 5.8 | 48 | 43 | 54 | 41 | -15 | 30 | -53 | -39 |
| SEM | 0.2 | 0.2 | 0.3 | 0.2 | 0.8 | 0.2 | 1.3 | 1.0 | 10 | 7 | 12 | 10 | 10 | 8 | 12 | 11 |

( ) Patient Number
With respect to normals
a p<0.001
b p<0.005
c p<0.01
d p<0.02
e p<0.05

**Table 4:** Taste changes in patients with phantageusia before rtms.

| | Taste Function Post Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Detection Thresholds | | | | Recognition Thresholds | | | | Magnitude Estimation | | | | Hedonics | | | |
| **Patients (30)** | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea |
| Mean | 3.6 | 3.4 | 3.5[c] | 4.1[e] | 4.1 | 4.0 | 4.4[b] | 4.6[d] | 57 | 46 | 55 | 45 | -40 | 23 | -50 | -43 |
| SEM | 0.3 | 0.4 | 0.3 | 0.4 | 0.4 | 0.3 | 0.3 | 0.4 | 5 | 4 | 4 | 5 | 6 | 7 | 4 | 5 |

| | Taste Function Post Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Detection Thresholds | | | | Recognition Thresholds | | | | Magnitude Estimation | | | | Hedonics | | | |
| **Responders (24)** | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea |
| Mean | 3.8 | 3.5 | 3.7 | 4.3[e] | 4.2 | 4.1 | 4.3 | 4.8 | 54 | 46 | 54 | 45 | -40 | 20 | -49 | -44 |
| SEM | 0.4 | 0.5 | 0.3 | 0.5 | 0.5 | 0.4 | 0.4 | 0.5 | 5 | 5 | 4 | 5 | 7 | 9 | 5 | 5 |

| | Taste Function Post Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Non-Responders** | Detection Thresholds | | | | Recognition Thresholds | | | | Magnitude Estimation | | | | Hedonics | | | |
| **(6)** | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea | NaCl | Sucrose | HCl | Urea |
| Mean | 3.2 | 3.0 | 2.8 | 3.7 | 3.5 | 3.8 | 4.8 | 3.7 | 65 | 43 | 55 | 45 | -42 | 35 | -54 | -41 |
| SEM | 0.3 | 0.4 | 0.5 | 0.2 | 0.2 | 0.2 | 0.5 | 0.2 | 12 | 8 | 10 | 12 | 20 | 6 | 10 | 12 |

( ) Patient Number
With respect to pre treatment
b p<0.005
c p<0.01
d p<0.02
e p<0.05

**Table 5:** Taste changes in patients with phantageusia after rtms.

| Etiology | Pre Treatment | Immediately Post Treatment | Four to Six Weeks Post Treatment | Four to Six Months Post Treatment |
|---|---|---|---|---|
| Idiopathic (11) | 68 ± 7* | 24 ± 8[a] | 27 ± 7[a] | 27 ± 6[a] |
| Post-influenza-like hyposmia and hypogeusia (6) | 33 ± 13 | 11 ± 5[e] | 8 ± 5 | 10 ± 6[e] |
| Post anesthesia (3) | 57 ± 23 | 20 ± 12 | 33 ± 7 | 18 ± 8[d] |
| Trigeminal neuralgia (2) | 73 | 48 | 58 | 46 |
| Head injury (2) | 48 | 43 | 43 | 46 |
| Renal Failure (2) | 83 | 60 | 55 | 49 |
| Multiple Sclerosis (1) | 25 | 30 | 30 | 30 |
| Hodgkin's disease (1) | 50 | 48 | 50 | 50 |
| Hypothyroidism (1) | 90 | 70 | 70 | 70 |
| Allergic rhinitis (1) | 50 | 50 | 50 | 50 |

( )Patient number
*Mean ± SEM of subjective response (in percent)
With respect to pre treatment
a p<0.001
d p<0.02
e p<0.05

**Table 6:** rtms treatment of patients with phantageusia.

## Discussion

These results indicate that phantageusia can occur in patients who exhibit hypogeusia and that can be inhibited by rTMS. Its onset usually occurred after taste loss associated with a number of etiological entities similar to onset of phantom limb after amputation of a significant portion of a limb [3]. Its inhibition by use of rTMS was effective in 80% of patients.

Once phantageusia was inhibited by rTMS in responders, inhibition continued over time indicating that changes associated with rTMS were long lasting and persistent. On the other hand if rTMS treatment were ineffective there appears to be little change over time. Nevertheless in the six non-responders repeat rTMS inhibited phantageusia in one of the two patients in whom the procedure was used. This type of response also occurred with prior patients in whom sensory distortions of this type occurred [10,11]. In a third non-responder further rTMS stimulation inhibited phantageusia. The three other patients did not undergo repeat rTMS.

Patients with phantageusia, regardless of etiology exhibited taste loss as measured by gustometry. Following rTMS taste loss improved albeit more robustly in the responders.

Mechanisms underlying this symptom are complex. MRS studies, which indicated decreased brain GABA associated with phantageusia onset, demonstrated that increase of this neurotransmitter was associated with phantageusia inhibition [9,11,17]. Increases of this neurotransmitter in our studies suggest that brain levels of GABA are important in onset and inhibition of phantageusia [9,11]. However, rTMS may initiate multiple other neurochemical changes reported to play a role in inhibiting this symptom [9,11] including changes in synaptic [16] and cortical [16,17] plasticity as well as effects of specific neurotransmitters including brain-derived neurotrophic factor [20], beta-adrenergic and 5-HT2 receptor activity [21], increased expression of striatal dopamine release [22] and cholecystokinin mRNA [23]. Indeed, mechanisms by which rTMS influences cognition has been extensively reviewed [24]. In one study, rTMS was reported to inhibit auditory hallucinations [25].

The study has some limitations. Although we have used two sham procedures to control placebo effects and no patient responded with phantageusia inhibition with sham procedures, a placebo response is always possible with any subjective response. However, efficacy of rTMS with phantageusia inhibition in such a large number of patients with inhibition persistence lasting months or even years tends to decrease a significant placebo response.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of Interest

Robert I. Henkin is a member of the board of directors of Cyrano Therapeutics. None of the other authors has a conflict of interest, financial or otherwise with respect to the publication of this manuscript.

## Disclosure

All authors have read and approved the final article.

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