Psychophysical Evaluation of Descriptors and Tools for Measurement of Urge-to-Cough Sensation in Healthy Young Adults (HYA)

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ABSTRACT

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The studies contained in this dissertation were driven by a desire to improve the methods for sensory testing of cough for clinical research and practice. Two scientific gaps in the cough evaluation literature were identified and investigated using two specific studies on healthy young adult participants. The first study focused on validating an appropriate descriptor for cough sensations (Chapter 2) and the second study (Chapter 3) focused on evaluating magnitude estimation tools to measure cough sensations. The findings of this dissertation make several unique contributions to the cough literature. The first study systematically compared two descriptive responses to cough stimuli (i.e., capsaicin) within subjects in terms of both cough sensory and cough motor outcomes. Findings revealed two types of descriptive responses for capsaicin stimuli, warm/burn and urge-to-cough (UTC). The UTC descriptor was, however, more sensitive and a valid predictor of cough response. The second study systematically compared two magnitude estimation tools, the Modified Borg Scale (MBS) and the generalized Labeled Magnitude Scale (gLMS) to measure the UTC sensations. Findings revealed that both tools were reliable and valid in detecting UTC sensations and predicting cough response. However, a differential effect to detection of UTC sensations across neighboring stimuli concentrations were demonstrated by the two tools. This dissertation provides the first set of normative reference values for UTC responses across a wide range of sensory continua using the conventional metric, the MBS, and an additional metric, the gLMS. Limitations are acknowledged and future work is suggested.

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"Gurur Brahma Gurur Vishnu Gurur Devo Maheshwaraha
Gurur Saaskshat Para Brahma Tasmai Sree Guruvae Namaha"

(Based on a Sanskrit Mantra, where "Guru" refers to the one who dispels the darkness of ignorance. The Guru mantra, Gurur Brahma Gurur Vishnu, pays homage to the Guru who shows us the intellectual path by leading us from darkness to light.)

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Chapter 1

INTRODUCTION

The execution of human cough is an important defensive mechanism which serves to protect the airways and lungs from many damaging irritants, including ingested material and oral secretions. Any impairment in its execution results in dystussia (disordered cough), which may lead to complications such as aspiration pneumonia and mortality. Recent evidence points to dysphagia (disordered swallowing) co-occurring with dystussia in patients with neurogenic disorders such as Parkinson's disease (PD), stroke, and amyotrophic lateral sclerosis (ALS), as well as in older adults with a history of aspiration pneumonia (Hegland, Okun, & Troche, 2014; Pitts et al., 2010; Plowman et al. (2016); Troche, Brandimore, Godoy, & Hegland, 2014; Yamanda et al., 2008). Specifically, it should be noted that even trace amounts of penetration and aspiration over time may result in pneumonia in these vulnerable populations (Butler, Stuart, Markley, & Rees, 2009; Ebihara et al., 2003; McCullough, Rosenbek, Wertz, Suiter, & McCoy, 2007). For this reason, it is postulated that improving airway protective outcomes may be dependent upon awareness and response to sub-threshold (subtle) cough stimuli (Hegland, Troche, Brandimore, Okun, & Davenport, 2016; Troche et al., 2014). Thus, it becomes imperative to evaluate the sensory-motor aspects of cough, with consideration of the subtlety of cough-inducing stimuli and their sensory-perceptual correlates.

The urge-to-cough (UTC) is a human central respiratory sensation preceding the reflex cough (Davenport, Sapienza, & Bolser, 2002). The cognitive perception of UTC, in response to cough-inducing stimuli, motivates humans to behaviorally modulate the cough motor response for adequate airway protection (Davenport, 2009; Farrell, Cole, Chiapoco, Egan, & Mazzone, 2012; Mazzone, McLennan, McGovern, Egan, & Farrell, 2007). Based on cognitive perception and volitional control, an individual may choose to act on the stimuli to generate an effective cough or not to act on the stimuli enabling cough suppression (Hutchings, Eccles, Smith, & Jawad, 1993; Lee, Cotterill-Jones, & Eccles, 2002; Troche et al., 2014). The elicitation of the UTC has been postulated to involve discriminative (awareness of physical magnitude) and affective (awareness of emotional salience) processing of cough stimuli. This is dependent on the integration of respiratory afferent activity, respiratory motor drive, affective state, attention, experience, and learning (Davenport, 2009). The UTC is also known to involve cognitive neural pathways that have properties of stimulus detection, evaluation, and discrimination that aid cough production (Davenport, 2009). Reduced UTC sensitivity has been reported in patients with stroke and PD as well as in older adults with a history of aspiration pneumonia (Hegland, Davenport, Brandimore, Singletary, & Troche, 2016; Troche et al., 2014; Troche, Schumann, Brandimore, Okun, & Hegland, 2016; Yamanda et al., 2008). Thus, for sensorimotor cough evaluation and rehabilitation purposes, the UTC is a very important phenomenon that needs to be measured accurately and studied in detail.

Neural Substrates of the UTC

It is now well known that, although cough can be initiated reflexively, it is subject to modulation by higher brain networks (cortical and sub-cortical) that support the role of consciousness, perception, and emotion in its response execution (Canning et al., 2014; Davenport, 2009; Farrell et al., 2012; Mazzone et al., 2007). The perceptual awareness of cough requires higher-order processing of sensory information that is originating in the airways, which in turn promotes the behavioral cough response based on an individual's perception of the UTC (Davenport, 2009; Davenport et al., 2002). The higher-order networks that process UTC are comprised of complex sensory and motor pathways, which have been explored through studies using functional neuroimaging in humans and neuroanatomical tract tracing in rodents (Driessen, Farrell, Mazzone, & McGovern, 2016; Farrell et al., 2012; Mazzone et al., 2007; McGovern, Davis-Poynter, Farrell, & Mazzone, 2012).

fMRI Evidence

The first description of the neural substrates of the UTC was published by Mazzone et al. (2007). This study performed functional brain imaging on 10 healthy participants during capsaicin inhalation challenge to elicit a modest UTC without a motor cough response. Results identified a core sensorimotor network involving widespread cortical and sub-cortical activations that encompassed sensory, motor, premotor, and limbic structures. Subsequently, a follow-up study was conducted by Farrell et al. (2012) to identify specific neural networks that coded capsaicin stimuli intensity and UTC perception. This investigation led to the identification of three modules to encode UTC perception, comprised of sensory, cognitive, and motor components.

The “sensory module” activates brain regions that receive ascending inputs originating in the airways and encodes the discriminative component of the UTC (either intensity or spatial discrimination). Specific brain areas such as the primary somatosensory cortex and anterior insula are involved in intensity discrimination, and areas such as the posterior parietal cortex and dorsolateral prefrontal cortex are involved in spatial discrimination. More specifically, brain activations also denote the existence of distinct sensory discrimination networks that decode stimuli intensity in a dose-dependent fashion (i.e., anterior insula) and also the magnitude of UTC perception based on an individual’s emotions, focus, and alertness (i.e., primary sensory cortex).

The “cognitive module” is involved in shaping the affective responses to airway irritants. fMRI studies revealed activations in areas such as the orbitofrontal cortex, cingulate cortex, and other limbic regions. Similar brain activations have also been reported in studies related to interoceptive processing such as pain, dyspnea, and esophageal distension. Given the variability in sensory-perceptual responses to different stimuli, it has also been postulated that these networks could be topographically arranged or supplemented by additional neural components to elicit specific behavioral response patterns (Mazzone et al., 2013).

The "motor module" is involved in the process of volitional cough, capsaicin-evoked cough, and/or cough suppression during typical capsaicin-challenge testing. Volitional cough is associated with brain activations in areas such as the sensorimotor cortex, supplemental motor area, and cerebellum. Additionally, differences in pattern of brain activation for reflex and voluntary cough have been identified in the cortical regions (i.e., posterior insula and posterior cingulate cortex) and brainstem regions (i.e., medulla). Cough suppression is known to involve brain areas such as the anterior insula, supplemental motor area, motor cingulate cortex, and right inferior frontal gyrus. Additionally, the right inferior frontal gyrus, along with areas such as pre-supplementary motor area, prefrontal cortex, subthalamic nucleus, and basal ganglia, have been known to be a part of the "inhibitory network" involved in motor suppression.

Neuroanatomical Tracings Evidence

In order to have a better understanding of the sensory-neural pathways and their deeper connectivity to the brain, researchers have recently employed a novel viral tracing system using the herpes simplex virus strain (H129) on a rodent model (Driessen et al., 2016; McGovern et al., 2012). Using this approach, it has been recently demonstrated that tracheal afferent neurons terminate in two brainstem nuclei, the nucleus of solitary tract (NTS) and the trigeminal nuclei. Of these, a significant population of trigeminal neurons have been known to relay airway afferent input to thalamic loci, through trigemino-thalamic tracts. These trigemino-thalamocortical pathways have been speculated to play an important role in encoding perceptual awareness of airway irritation and in the generation of the UTC.

Clinical Utility of the UTC

Effective execution of the reflex cough requires appropriate perception of the sensation preceding the cough. The UTC perception motivates individuals to cough in response to a sensory stimulus for adequate airway protection (Davenport et al., 2002; Mazzone et al., 2007). An impairment in both the sensation and motor execution of cough can contribute to the development of aspiration pneumonia and thus influence length of hospital stays and reduced quality of life, or even death in neurogenic population such as stroke, PD, and ALS (Fernandez & Lapane, 2002; Martino, Martin, & Black, 2012; Tabor, Gaziano, Watts, Robison, & Plowman, 2016). More specifically, the UTC has been reported to be blunted at sub-threshold levels of cough stimuli (i.e., stimuli levels below a cough motor threshold) in clinical populations such as stroke, PD, and older adults with history of aspiration pneumonia (Hegland et al., 2016; Troche et al., 2016; Yamanda et al., 2008). Furthermore, a recent study on patients with PD and dysphagia found the UTC to be an important predictor of airway safety more than disease-specific factors such as disease severity and duration (Troche et al., 2016). Thus, because the UTC has both clinical screening and diagnostic possibilities, it is crucial to evaluate the sensory-motor aspects of cough with consideration of the subtlety of cough-inducing stimuli and its sensory-perceptual correlates.

UTC Measurement Challenges

Despite the aforementioned clinical relevance and utility, the current means of evaluating the UTC are subject to numerous challenges owing to an inherent difficulty in quantifying its absolute perception. This is attributed to a lack of understanding of a human respiratory somatosensory-perceptual experience within the context of a stimulus-sensation-response model of psychophysics (Davenport et al., 2002; Goldstein & Brockmole, 2016; Lawless, 2013). This model takes into account the psychophysical evaluation of stimuli to perceive a sensation, followed by a human decision-making process to execute a response. Existing evaluation protocols do not consistently consider these conversion processes when performing cough evaluations. More specifically, we are currently limited in our understanding of the UTC phenomenon owing to specific challenges related to its sensory description as well as to a valid tool that can quantify its measurement.

Cough Descriptor Challenges

Interestingly, the UTC is the only descriptor that has been used in the testing of the cognitive sensation preceding the reflex cough (Davenport et al., 2002). Although many studies have conventionally measured and reported on subjects' self-reported UTC ratings (Davenport, 2009; Hegland et al., 2016; Troche et al., 2014), it is still unclear if additional sensations/ descriptors can exist for cough-inducing stimuli such as capsaicin (Mazzone et al., 2007). Given the nociceptive and chemoreceptive properties reported for capsaicin stimulus, it can be speculated if warm or burn could be among the sensations perceived other than the UTC (Bennett & Hayes, 2012). Some anecdotal evidence also exists where participants reported of other sensations such as warm, burn, or tickle in addition to the UTC during cough evaluations. An additional speculation is if there exist differential cough sensations that could be stimuli-dependent (Mazzone et al., 2007).

Tool Challenges

Though not specifically reported in the cough literature, the Modified Borg Scale (MBS) (Borg, 1982; Davenport et al., 2002) has all the potential limitations of a category ratio scale, which is widely used for sensory measurements. Category ratio scales (Borg, 1982) have been criticized for categorical labeling behavior by the subjects and dependence on the modality being measured (Bartoshuk et al., 2004). Also, the inconsistency in provision of magnitude estimation instructions to the subjects poses the risk of them only reporting the verbal categories and ignoring the need to make actual numerical judgments of the perceived intensity. More importantly, the MBS does not necessarily capture an absolute intensity of the sensation of interest (i.e., the UTC) as the participants may not rate a sensory magnitude in consideration of all of their sensory experiences. The intensity descriptors used for categorical labeling and anchoring the ends of the scale may denote different perceived intensities to different people depending on their individual sensory experience. This results in subjects' ratings clustered at the lower end of the scale, resulting in significant inter-subject and intra-subject variability (Bartoshuk et al., 2004). Furthermore, it is unknown if the scale can detect subtle differences in UTC perception at sub-threshold concentrations of capsaicin stimuli, and if it can capture a wider dynamic range of UTC responses to a range of stimuli concentration (i.e., low, mid, and high).

Threshold Phenomenon and Magnitude Estimation

Mental events have to be stronger than some critical amount in order to be consciously experienced (Heidelberger, 2003). The critical amount is referred to as "threshold," wherein an observer detects a sensory stimulus at least 50% of the time. Threshold is a statistical entity and not a fixed point, as the sensitivity of an observer's threshold changes from moment to moment.

The fundamental goal of a psychophysical evaluation is to reliably capture this "threshold," which is a representation of sensory-perceptual magnitude so that subjective experiences can be meaningfully quantified using scaling functions. This is achieved through a magnitude estimation task in which subjects are encouraged to give their own impressions of sensory stimuli perception instead of just fixed ratios on a category ratio scale (Stevens, 1959). It is now well known that the magnitude estimation data on the UTC conform to a power function, which is demonstrated by the increased perceptual magnitude of the UTC with an increase in capsaicin stimuli intensity (Davenport, 2009). However, the question still remains regarding the validity and reliability of the magnitude estimation tool which is currently used to capture UTC magnitude.

Magnitude Estimation and Weber's Law

A closer look at the Yamanda et al. (2008) study provides some interesting insights into the drawbacks in magnitude estimation procedures and magnitude estimation tools used for cough evaluation paradigms. This study, conducted with older adults with a history of aspiration pneumonia, reported no difference in UTC ratings between normal and pathological groups at cough threshold, but it did find a difference at sub-threshold concentrations of cough stimuli. However, the study raised four important issues. First, it was unclear if the study results were empirically attributed to Weber's law (Fechner, 1965; Weber, 1834). Weber's law is a phenomenon in which an individual can notice changes to small increments in stimuli intensity at sub-threshold or weak stimuli, but for higher thresholds or strong stimuli, larger increments in stimuli intensity would be required to observe a change. Second, the sub-threshold capsaicin stimuli concentrations used in the study were not determined based on the Weber fraction. Weber's law is often expressed as the Weber fraction, consisting of the ratio between the just-noticeable increment and the base stimulus magnitude. The fraction tends to have a constant value, but rapidly increases at very low stimulus values. Based on the Weber fraction, it is now known that visual and auditory senses are able to discriminate much smaller percentage changes in a stimulus energy level, than touch, taste, or olfaction senses. However, with respect to UTC sensation, this information is unknown. Third, the authors opined that the non-difference in the UTC at cough thresholds between the groups was attributed to the influence of cough response on UTC magnitude. Interestingly, the influence of psychophysical concepts such as dynamic range (i.e., difference between smallest and largest intensity, DR) and just-noticeable-difference (JND) on supra-threshold perception of the UTC based on Weber's law were not speculated from a stimulus-sensation growth point of view. Finally, we do not know if the inability to discriminate normal versus pathological groups at thresholds was due to the limitations of the MBS tool which was used to estimate the UTC magnitude. Therefore, we do not know if the MBS failed to capture a wide range of UTC sensory experiences.

Thus, knowing the importance of assessing the UTC and its subtlety from an airway protective standpoint, it is crucial to have the most appropriate tool to measure it reliably and accurately. Specifically, having a tool to reliably assess the absolute sensation of the UTC (in consideration of all sensory experience) and to capture a wide range of sensory experience is important for making effective comparisons between subjects and across groups. These measurement limitations have been addressed in sensory science literature through the development of novel scales, such as the gLMS (Bartoshuk et al., 2004; Green, Shaffer, & Gilmore, 1993). The gLMS (Green et al., 1993), with its high-end anchor denoting the "greatest imaginable sensation of *any* kind," compares the intensity of the stimulus to any sensory modality and allows independence from the modality measured. The use of the gLMS in sensory testing has been shown to increase the validity of participants' perceptual reporting experience, improve discrimination among subjects, and assist in making group comparisons valid (Bartoshuk et al., 2004).

Scientific Gap

Some pertinent questions still remain regarding an appropriate descriptor and a tool to measure cough sensations when a participant is presented with cough-inducing stimuli such as nebulized capsaicin (the active ingredient in hot chili peppers). We currently do not know if the UTC is indeed a valid descriptor for cough sensation and if we have a valid tool that can reliably assess the absolute sensation of the UTC (in consideration of all sensory experiences) and which can also capture a wide range of human sensory experiences. The validation of the descriptor and the tool will be very useful for making effective valid comparisons between subjects and across clinical groups.

Study Rationale and Overall Research Questions

The *rationale* for this research was that determining an appropriate cough descriptor and a tool for sensory evaluation of cough will lay the foundations for screening, diagnostic, and differential sensorimotor cough psychometrics in healthy and impaired populations. This will then be useful in making valid across-group comparisons.

Our long-term goal was to understand the relationship between respiratory sensations and the somatosensory stimuli which evoke the sensations to promote effective sensorimotor cough diagnostics. In order to achieve this objective, there was a need to probe into the psychophysical and cognitive processes underlying cough perception in response to somatosensory stimuli based on psychophysical models and designs. Effective understanding of respiratory sensations within the context of a stimulus-sensation-response psychophysical model will lead to effective diagnosis and differential diagnosis of sensorimotor aspects of cough between normal and pathological groups. This will aid in early identification and intervention of airway protective deficits.

Thus, in order to determine the best methods for evaluating absolute cough sensitivity controlling for human bias and uncertainty, some pertinent questions regarding type of cough sensations and the reliability and validity of magnitude estimation tools to measure these cough sensations need to be answered. Therefore, we designed two specific studies to address the scientific gaps in the cough literature.

The purpose of the first study was to determine the best descriptor for cough sensations that can be used for psychophysical testing during cough evaluations. We specifically aimed to explore the psychophysical characteristics of capsaicin based on a set of descriptive attributes specific to its perceptual sensation and also evaluate its sensitivity. We designed the study in two phases. In the first phase, we identified the types of sensations reported in response to capsaicin stimuli. We hypothesized that one of the descriptors will be quantifiably superior in describing the cough sensation. Then in phase II, we compared the effects of varying capsaicin concentration on the magnitude of the novel descriptor inferred from phase I, with the conventional UTC descriptor reported by Davenport (2002). We hypothesized that the UTC descriptor magnitude would be more sensitive to varying effects of stimuli and more predictive of cough motor response.

The results of the first study led us to the second study, the purpose of which was to evaluate the efficacy of one existing tool for UTC sensation measurement, the MBS (Borg,1982), in comparison with another tool validated for sensory measurements, the gLMS (Bartoshuk et al., 2004; Green et al., 1993), on the same set of healthy young adult (HYA) subjects. Both of these scales were similar in terms of category-ratio scale type, with intensities represented on quasi-logarithmically spaced semantic verbal labels, but they differed in terms of anchoring type. In a scale like gLMS, the upper bound/anchor of the scale is not domain-specific (i.e., strongest imaginable sensation of any kind), but, in a scale like the MBS, the upper bound/anchor bound is domain-specific (i.e., maximal urge to cough). We hypothesized that compared to the traditional MBS, the gLMS would be more efficient in obtaining the absolute intensity of the UTC;

differentiate UTC perception at low, mid, and high concentration range of capsaicin stimuli; demonstrate a wider dynamic range of human perceptual responses; and provide better between-trial reliability.

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Chapter 2

STUDY 1: VALIDATING THE URGE-TO-COUGH AS A DESCRIPTOR FOR MAGNITUDE ESTIMATION IN COUGH

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VALIDATING THE URGE-TO-COUGH AS A

DESCRIPTOR FOR MAGNITUDE ESTIMATION IN COUGH

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ABSTRACT

Background and Purpose: Appropriate sensation of an airway stimulus is important for cough execution. The ‘urge-to-cough’ (UTC) has been used to quantify the respiratory sensation that precedes the reflex cough. However, it is unclear if there are other descriptors which a participant might use to describe the sensation associated with cough-inducing stimuli. Thus, we sought to determine the best descriptor of cough sensation for psychophysical testing by examining the effects of varying stimuli concentration on magnitude estimations of cough perceptual descriptors in healthy young adults (HYA).

Methods: Twenty HYA (12F) participants completed reflex cough testing in two experimental phases over two days. During each phase, randomized counterbalanced blocks of five different capsaicin stimuli concentrations were delivered upon inspiration. In the first phase, participants were asked to report the most salient descriptor for the capsaicin stimuli. In the second phase, participants rated the magnitude of the predominant somatosensory descriptor (i.e., tickle or warm/burn) determined from phase one, and the UTC descriptor using a Modified Borg Scale.

Results: In the first phase of study, warm/burn was the predominant somatosensory descriptor reported from the qualitative sensory analysis. The magnitude of warm/burn and UTC descriptors were both influenced by varying concentrations of capsaicin stimuli ($F_{(1, 98)} = 93.74$, $p < .001$, $R^2 = 0.489$; $F_{(1, 98)} = 132.50$, $p < .001$, $R^2 = 0.575$). Log magnitude for both warm/burn and UTC descriptors were linearly related to log capsaicin concentration. Warm/burn and UTC descriptors were found to significantly influence cough motor threshold (Cr2) at 200μM ($\chi 2(24) = 14.657$, $p < .001$; ($\chi 2(25) = 24.118$, $p < .001$). The sensitivity slope of UTC was higher than warm/burn ($F_{(1, 4)} = 6.08$, $p < .001$) and explained more of the variance in two-cough motor response (Cr2) at 200μM ($\chi 2(97) = 10.535$, $p < .05$).

Discussion: Healthy participants described the sensation of nebulized capsaicin as either UTC or warm/burn. These descriptors were influenced by varying stimuli concentration. The magnitude of the UTC descriptor was more sensitive to varying stimuli concentration and a better predictor of Cr2. Future studies are required to evaluate tools for reliable measurement of cough sensation.

Key words

cough, urge-to-cough, capsaicin, somatosensation, magnitude estimation

Introduction

Cough is an important defensive mechanism which serves to protect the airway and lungs from many damaging irritants including ingested material and oral secretions. It is now well known that the sensation of an airway stimulus is critical for effective cough production (Davenport, 2009; Driessen, Farrell, Mazzone, & McGovern, 2016). The cognitive sensation that is elicited in response to a cough-inducing stimulus is hypothesized to motivate humans to behaviorally modulate the cough motor response for adequate airway protection (Davenport, 2009; Farrell, Cole, Chiapoco, Egan, & Mazzone, 2012; Mazzone, McLennan, McGovern, Egan, & Farrell, 2007). The cognitive magnitude estimation of the sensation which precedes the cough has been postulated to involve discriminative (awareness of physical magnitude) and affective (awareness of emotional salience) processing of cough stimuli (Davenport, 2009). This experience is thought to be dependent on the integration of respiratory afferent activity, respiratory motor drive, affective state, attention, experience, and learning (Davenport, 2009).

The urge-to-cough (UTC) descriptor rated via a modified Borg scale (MBS) is the only metric which has been used to describe and quantify the respiratory sensation that precedes the reflex cough (Davenport, Sapienza, & Bolser, 2002). The UTC as measured by the MBS has been shown to increase in a log linear fashion with increasing capsaicin stimuli concentrations and there exists a direct relationship between the UTC, total number of coughs, and electromyography (EMG) responses of expiratory muscles (Davenport, Vovk, Duke, Bolser, & Robertson, 2009; Vovk et al., 2007). In terms of clinical utility, the UTC is reported to be blunted in impaired populations, specifically in older adults with a history of aspiration pneumonia (Yamanda et al., 2008), stroke (Hegland, Davenport, Brandimore, Singletary, & Troche, 2016) and Parkinson’s disease (PD; Troche, Brandimore, Godoy, & Hegland, 2014). The UTC has also been demonstrated to be an important predictor of swallowing safety in patients with PD more than PD-specific factors such as disease duration and severity (Troche, Schumann, Brandimore, Okun, & Hegland, 2016).

Until now, the UTC has been studied in response to capsaicin (an active ingredient in hot chili peppers), fog and citric acid (Davenport et al., 2002, 2009, Troche et al., 2014, 2016; Hegland et al., 2016; Yamanda et al., 2008). More specifically, capsaicin has been considered the experimental tussive agent of choice for more than three decades given its ability to elicit cough in a safe, reproducible, and dose-dependent manner (Dicpinigaitis, 2009; Midgren, Hanson, Karlson, Simonson, & Person, 1992). Capsaicin as a chemical irritant has been known to have the specific somatosensory and taste qualities of ‘warm’ and ‘burn’ owing to its nociceptive and chemosensory properties (Bennett & Hayes, 2012; Hammer & Vogelsang, 2007; Lawless & Stevens, 1988). Given this somatosensory quality of capsaicin, one could speculate that warm/burn would be among the sensations perceived in response to capsaicin.

Despite the widespread use of the UTC measure, the current means of evaluating the UTC is subject to numerous challenges owing to an inherent difficulty in describing and quantifying its sensory perception. Sensory research studies in the fields of hearing and taste have reported that humans differ in their sensory-perceptual reporting experiences (Bartoshuk et al., 2004; Lawless, 2013). Given this variability, it can be hypothesized that humans may perceive differential cough sensations other than the UTC in response to cough-inducing stimuli (Hilton et al., 2015; Mazzone, McLennan, McGovern, Egan, & Farrell, 2007). Anecdotal evidence also exists in clinical practice where participants did not necessarily report the sensation of only the UTC in response to cough stimuli, but reported alternative sensations such as warm/burn or tickle.

The aforementioned limitations related to the UTC sensory description may limit the possibility of sensitively measuring change in sensory perception in healthy controls, in populations with disease, and as a therapeutic outcome. Therefore, the question remains as to whether the UTC is the best descriptor for quantifying the human cough sensory experience or if there exists a better descriptor. This study sought to determine the best descriptor for cough sensations that can be used for psychophysical testing based on quantitative sensory analysis methods (Lawless, 2013). We defined specific aspects of descriptors for cough sensations to include both somatosensory quality of the stimuli as well as the urge-to-act perceptions elicited by the sensory stimuli.

We specifically aimed to explore the psychophysical characteristics of capsaicin based on a set of descriptive attributes specific to its perceptual sensation and also evaluate the descriptor's sensitivity. Descriptive attributes of tickle and warm/burn were selected based on the somatosensory qualities frequently reported in the sensory analysis literature as well from clinical cough research for the irritant capsaicin (Bennett & Hayes, 2012; Dicipinigaitis, 2002; Mazzone et al., 2007). Our first aim was to determine the most common somatosensory descriptors elicited for capsaicin stimuli in healthy young adults (HYA). We hypothesized that one of three selected somatosensory descriptors would be predominant in describing the sensation associated with the presentation of the capsaicin stimuli in HYA. Our second aim was to examine the effect of varying capsaicin stimuli concentration on somatosensory and UTC perceptual descriptors in HYA. Based on the literature support that UTC sensitivity was stimulus-dependent (Davenport et al., 2002, 2009), we hypothesized that the UTC would be the descriptor that was most sensitive to varying concentrations of capsaicin more than any other type of somatosensory descriptor in HYA. Finally, we were interested in a descriptor that reflected cough sensitivity by being a predictor of cough motor response. Therefore, as an exploratory aim, we also examined the influence of the magnitude estimation of somatosensory and UTC descriptors on the two-cough motor response (Cr2). We hypothesized that Cr2 would be more strongly associated with increased magnitude of the UTC than the somatosensory descriptor.

Materials and Methods

Participants

This study was approved by the Institutional Review Board of Teachers College, Columbia University. Informed consent was obtained from all participants. Participants were a group of 20 healthy young adults (HYA) with no prior knowledge or experience with reflex cough testing. Inclusion criteria were no history of neurological disease, active respiratory condition, head, neck or chest surgery, smoking in the last 5 years, chronic cough or swallowing difficulty, gastro-esophageal reflux disease (GERD), allergy to capsaicin or hot peppers, and use of ACE inhibitors or cough suppressants such as codeine. Participants were recruited consecutively over a 6-month period (August 2017-January 2018). Demographic information is included in Table 1.

Table 1

Participant Demographics (F, Female; M, male; n, number of participants; SD, standard deviation)

Variable	**Mean ± SD**
Participants	n = 20
Age (years)	F = 26.0 (SD = 5.24); M = 27.5 (SD = 4.17) (Range: 21-25)
Sex	F = 13; M = 7

Study Design

A mixed-method research design was used to study the qualitative and quantitative aspects of the sensory-perceptual responses elicited by capsaicin stimuli. Data collection took place in the Laboratory for the Study of Upper Airway Dysfunction, Teachers College, Columbia

University, New York, New York. The study was completed in two experimental phases (i.e., phase I and phase II) that took place over the course of two different visits, each lasting an hour in duration. Participants completed capsaicin inhalation challenge testing in both of the experimental phases. During experimental phase I, participants were presented with nebulized capsaicin stimuli and instructed to choose the best somatosensory perceptual descriptor for the sensations elicited by capsaicin stimuli from a pre-determined list of descriptors provided by the experimenter. Following experimental phase I, the predominant somatosensory descriptor was determined. For experimental phase II, the same set of participants were presented with nebulized capsaicin stimuli and instructed to report the perceptual magnitude of: (a) the predominant somatosensory descriptor identified from phase I, and (b) the conventional UTC descriptor (Davenport et al., 2002), using an MBS (Borg, 1982). During both of these phases, participants were encouraged to respond naturally to capsaicin stimuli and instructed to "cough if they need to." The details of the methods are described below.

Phase I experimental testing: Determination of the best somatosensory descriptor for capsaicin stimuli. The HYA participants with no prior experience to cough testing participated in experimental phase I to determine the most appropriate semantic descriptor for capsaicin stimuli. The participants described their sensory-perceptual experience by choosing the most predominant descriptor associated with the capsaicin stimulus sensation based on pre-determined list of three alternate-forced choice (3-AFC) responses. The 3-AFC responses provided to participants were: (a) No sensation, (b) Tickle, and (c) Warm/Burn. The definitions of descriptors provided to participants in phase I are included in Table 2.

Table 2

List of Somatosensory Descriptors for Capsaicin Stimuli and Their Definitions Provided to Participants During Task Orientation in Phase I Experiment (Bennett & Hayes, 2012; Breslin, Gingrich, & Green, 2001; Cliff & Green, 1996)

Sensory Descriptor	**Definition**
No sensation	No sensation of any sort
Tickle	Sensation of an itch or scratch in the back of the throat
Warm/Burn	Sensation of heat or sting in the back of the throat

Phase I capsaicin inhalation challenge. The capsaicin inhalation challenge procedures were based on previously established cough-testing methodologies reported in the literature (Davenport et al., 2009; Hegland et al., 2016; Troche et al., 2014, 2016; Vovk et al., 2007). Participants were outfitted with a facemask covering the nose and mouth. The facemask was coupled to a pneumotachograph and differential pressure transducer that had a side port with a one-way inspiratory valve for nebulizer connection. The nebulizer used was a DeVilbuss T-piece connected to a dosimeter that delivered aerosolized solution during inspiration with delivery duration of 2 seconds. Participants were initially seated for 30 seconds of quiet breathing in order to acclimate to the facemask. Then, the capsaicin solution was administered automatically upon detection of a participant's inspired breath and there was a minimum of 1 minute between each trial. The cough airflow signal was then digitized (Power Lab Data Acquisition System) and recorded (Lab Chart 7; AD Instruments, Inc.) on to a desktop computer.

Following the acclimatization, participants completed the capsaicin inhalation challenge. This included the randomized presentation of three blocks of five test capsaicin (molecular mass = 305.41g/mol) dissolved in vehicle solutions (80% physiological saline and 20% ethanol): 0, 25, 50, 100, and 200 μM capsaicin. This method was adopted to prevent order effect and potential participant response bias (Davenport et al., 2002). After each presentation of capsaicin, participants were asked a question about how it felt and to respond by indicating their top choice of perceived sensation from the 3-AFC responses. Participants were then provided water to drink between trials. The experimenter presented the next trial stimulus from the randomized block sequence based on a participant's report of no residual perception of the stimulus in the airway or on the facemask. Following completion of experimental phase II, the data were examined to identify the most predominant descriptor, which was then used in experimental phase II.

Phase II experimental testing: Determination of the best descriptor for cough sensations. The same participants returned for the second study visit after 2 weeks. During phase II, participants completed a capsaicin inhalation challenge, as described below. This time, they were instructed to perform magnitude estimation tasks for the somatosensory descriptor (identified from experimental phase I) and the UTC descriptor using the MBS (Borg, 1982) across varying concentrations of capsaicin stimuli. The definitions of descriptors provided to participants in phase I are included in Table 3.

Table 3

Definitions of Somatosensory and Urge-to-Cough (UTC) Descriptors Provided to Participants During Task Orientation in Phase II Experiment (Bennett & Hayes, 2012; Davenport et al., 2002)

Sensory Descriptor	Definition
Warm/Burn	Sensation of heat or sting in the back of the throat
Urge to Cough	Sensation of need to cough

Phase II capsaicin inhalation challenge. Participants were presented with one trial block and four test blocks of capsaicin stimuli. The trial block included single inhalations of 0, 50, and 200 μM capsaicin stimuli (a total of three presentations) which were provided to acclimatize the participants to the protocol. After this trial block, participants were presented with four randomized blocks of capsaicin stimuli. Blocks were also counterbalanced for test descriptor (i.e., participants rated warm/burn descriptor for two blocks and UTC for two blocks). The same five test solutions from Phase I were used in Phase II (0, 50, 75, 100, and 200 μM capsaicin). Upon inhalation of each of the capsaicin stimulus, participants were instructed to respond naturally to capsaicin stimuli and to “cough if they need to.” After that, they were asked to rate the magnitude of warm/burn or UTC descriptor using the MBS on a range of 0-10, where 0 represented no sensation and 10 represented maximal sensation. Cr2 was observed and recorded within the first 30 seconds following stimuli delivery (Davenport, 2009).

Data Analysis and Statistical Considerations

Statistical analyses were conducted using SPSS (Version 22, Armonk, NY).

Phase I: Qualitative Analysis

Participant responses from the Phase I testing were subject to a qualitative analysis to determine the best somatosensory descriptor associated with capsaicin stimuli. This was done by analyzing percentage distribution of total responses from the 3AFC responses of the three somatosensory descriptors (i.e., no sensation, tickle, and warm/burn) reported across the five different concentrations of capsaicin stimuli (i.e., 3 trials x 5 concentrations x 20 HYA = 300 responses). The descriptor that had the highest frequency count and percentage distribution in the data set was chosen as the predominant somatosensory descriptor.

Phase II: Quantitative Analysis

Mixed-model repeated measures analysis of variance (RM-ANOVA) was performed, with capsaicin concentration as within-subject factor, to explore differences in magnitude of warm/burn and UTC descriptors, respectively, across varying capsaicin concentrations. Linear regression was performed to explore the influence of capsaicin stimuli concentration on warm/burn and UTC descriptor magnitudes. The magnitude estimation data for the warm/burn and UTC descriptors were subject to logarithmic (Log) transformations for regression analyses. The average warm/burn and UTC descriptor magnitude were, respectively, plotted against the corresponding capsaicin concentration using a log-log scale, and a line of best fit was applied to the data set. The warm/burn and UTC descriptor sensitivity to varying concentrations of capsaicin was reported as the slope of the line of best fit. Analysis of covariance (ANCOVA) was performed to see differences in log-log slopes of warm/burn and UTC descriptors. Binomial logistic regression was used to assess the influence of log warm/burn and UTC descriptors magnitude on cough motor response (Cr2). Cr2 was computed as a categorical binary responder/non-responder variable based on the response to 200 μM capsaicin, in at least two trial blocks. In consideration of the existence of gender differences in UTC sensation reported in previous studies (Gui et al., 2010; Morice et al., 2014), gender was included as a covariate in the regression models. Post-hoc analyses with Bonferroni corrections were performed for pairwise comparisons to determine differences in magnitude of warm/burn and UTC descriptors across capsaicin stimuli concentrations. Routine normality tests (Kolmogorov-Smirnov and Shapiro-Wilk) were conducted to verify the normal distribution of data set. A nominal two-sided p-value of <.05 was regarded as statistically significant.

Results

Phase I: Determining the Best Somatosensory Descriptor

Examination of types of somatosensory descriptors. Three types of somatosensory descriptors (i.e., no sensation, tickle, warm/burn) were examined across varying capsaicin concentrations. Results revealed that each capsaicin concentration was predominantly associated with one of the three choices of descriptors. The majority of the participants reported having no sensation for 0 and 25 μM (i.e., 99%), tickle for 50 μM (i.e., 63%) and warm/burn for 100 and 200 μM (i.e., 60% and 90%, respectively) capsaicin concentration (Figure 1). On the basis of frequency distribution analysis, we determined warm/burn to be the best somatosensory descriptor for capsaicin stimuli. Subsequently, we used this warm/burn descriptor to pair with the conventional UTC descriptor (Davenport et al., 2002) to determine the best descriptor for cough sensations in experimental phase II.

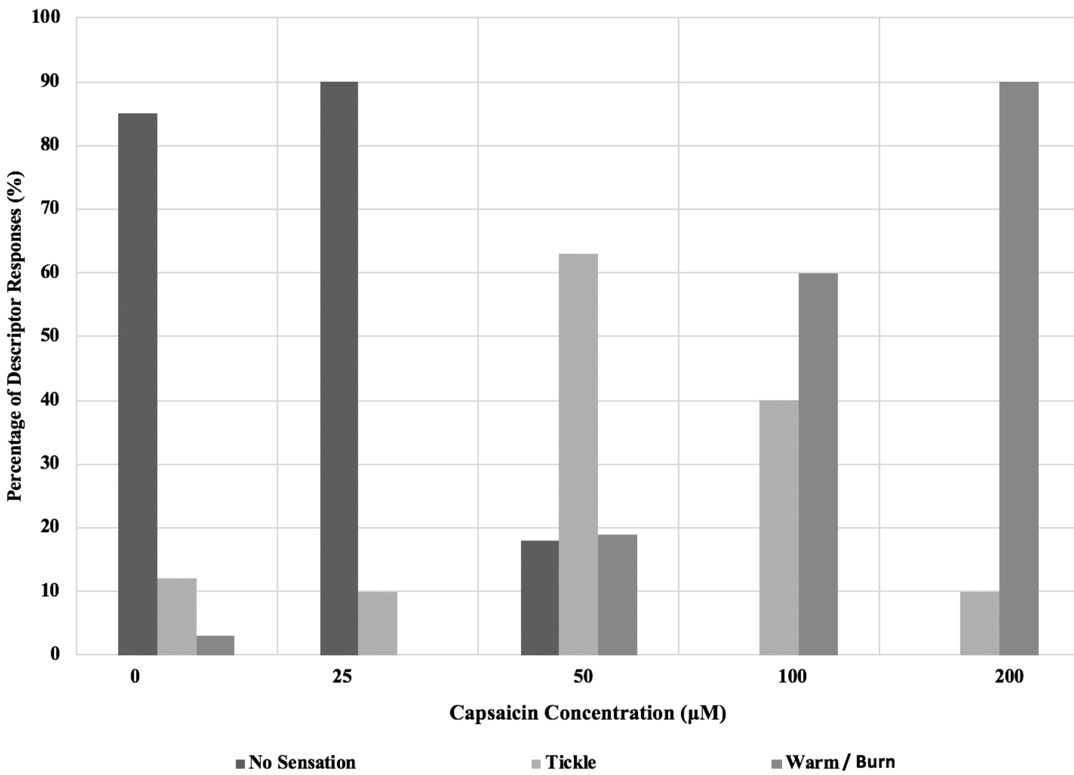

Figure 1. Bar graphs showing percentage frequency distribution of the choices of somatosensory descriptors (i.e., no sensation, tickle, and warm/burn) by the HYA participants (n = 20) across varying capsaicin concentrations.

Phase II: Determining the Best Descriptor for Cough Sensations

Normality tests. Normality tests (Kolmogorov-Smirnov and Shapiro-Wilk) on the magnitude estimation data obtained from the 20 participants revealed a normal distribution for both warm/burn and UTC descriptor magnitude across capsaicin concentrations (df (20), $p > .05$ for 50, 75, 100 and 200 µM, respectively). This suggested that our data were fit for inferential analysis.

Differences in somatosensory and UTC descriptor magnitude across capsaicin concentrations. Table 4 shows the average warm/burn and UTC descriptor magnitude ratings across capsaicin concentrations. Results of omnibus testing from ANOVA revealed significant differences in warm/burn and UTC descriptor magnitude ratings across capsaicin concentrations ($p < .001$, $p < .001$, respectively).

Table 4

Median, Standard Deviation (SD), and Standard Error (SE) of Warm/Burn and Urge-to-Cough (UTC) Descriptor Magnitudes Using the Modified Borg Scale (MBS) Across the Five Different Capsaicin Concentrations

Capsaicin Stimuli (µM)	Warm/Burn Descriptor Magnitude			UTC Descriptor Magnitude		
	Median	SD	SE	Median	SD	SE
0	0.25	0.65	0.15	0.00	0.57	0.13
50	1.25	1.10	0.25	1.00	1.89	0.42
75	2.75	1.79	0.40	2.50	2.12	0.48
100	3.50	2.16	0.48	4.50	2.48	0.55
200	5.50	2.46	0.55	7.00	2.38	0.53

Differences in warm/burn descriptor magnitude across capsaicin concentrations. Multiple pairwise post-hoc comparisons using Bonferroni corrections revealed that the magnitude estimations of the warm/burn descriptor using the MBS were significantly different at majority of capsaicin stimuli concentrations but with the exception of 75 and 100 µM. Figure 2 and Table 5 show the results of the pairwise comparisons of the warm/burn sensory magnitude measured using the MBS for the five concentrations.

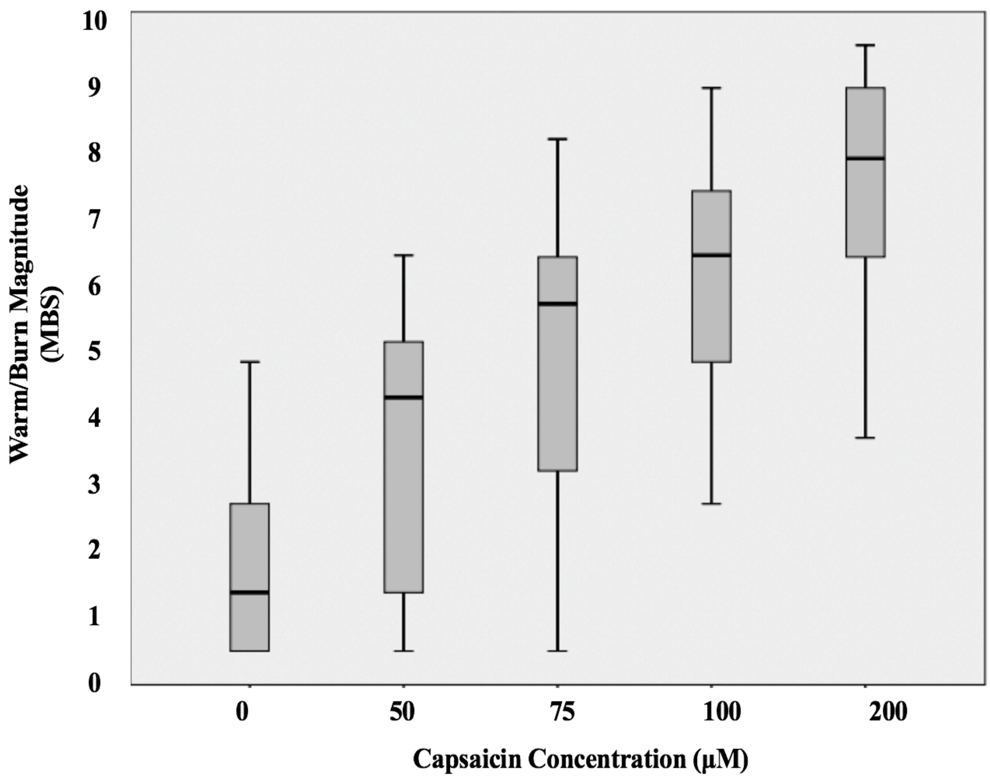

Figure 2. Warm/burn magnitude differences across capsaicin concentrations per Modified Borg Scale (MBS) ratings

Box plots denote the median, lower and upper quartile ranges. X-axis represents the capsaicin concentrations and Y-axis represents warm/burn magnitudes

Table 5

Pairwise Post-hoc Comparisons of Warm/Burn Descriptor Magnitude Differences Across Capsaicin Concentrations (µM)

Capsaicin Concentration (µM)	Warm/Burn Descriptor Magnitude			
	Pairwise Comparison Capsaicin Concentrations (µM)			
0	50 **	75 **	100 **	200 **
50	0 **	75	100 **	200 **
75	0 **	50	100	200 **
100	0 **	50 **	75	200 **
200	0 **	50 **	75 **	100 **

Significant and non-significant statistical p values listed.
** indicates statistical significance of $p<.001$.

Differences in UTC descriptor magnitude across capsaicin concentrations. Multiple pairwise post-hoc comparisons using Bonferroni corrections revealed that the magnitude estimations of the UTC descriptor using the MBS were significantly different at majority of capsaicin stimuli concentrations but with the exception of 0 and 50 µM, 50 and 75 µM. Figure 3 and Table 6 show the results of the pairwise comparisons of the UTC sensory magnitude measured using the MBS for five concentrations.

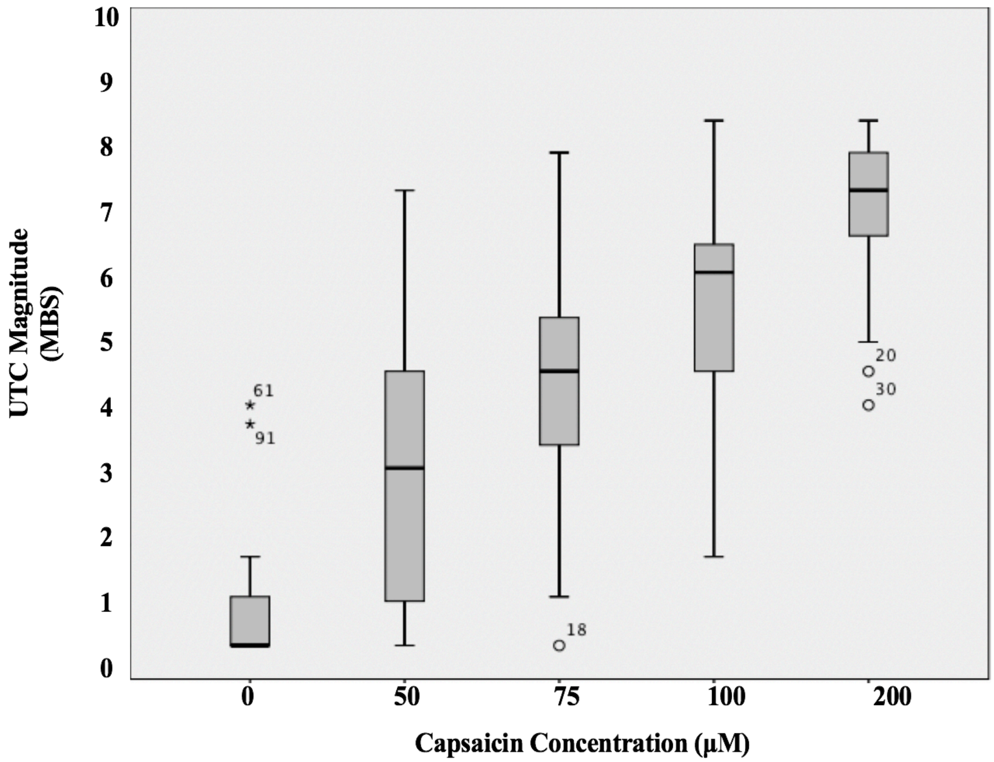

Figure 3. UTC descriptor magnitude differences across capsaicin concentrations per Modified Borg Scale (MBS) ratings

Box plots denote the median, lower and upper quartile ranges. Outliers denoted by asterisk (*) are two times more than inter-quartile range above the third quartile. Outliers denoted by circles (o) are about two times less than inter-quartile range above the first quartile. X-axis represents the capsaicin concentrations and Y-axis represents UTC magnitudes (n = 20).

Table 6

Pairwise Post-hoc Comparisons of Urge-to-Cough (UTC) Descriptor Magnitude Differences Across Capsaicin Concentrations (μM)

Target Capsaicin Concentration (μM)	UTC Descriptor Magnitude			
	Pairwise Comparison Capsaicin Concentrations (μM)			
0	50	75 **	100 **	200 **
50	0	75	100 **	200 **
75	0 **	50	100 **	200 **
100	0 **	50 **	75 **	100 **
200	0 **	50 **	75 **	100 **

Significant and non-significant statistical p values listed.
** indicates statistical significance of p<.001.

Differences between warm/burn and UTC descriptor magnitude. Results of omnibus testing from ANOVA revealed overall significant differences between the magnitude of warm/burn and UTC descriptors ($p < .01$). Pairwise post-hoc comparisons using Bonferroni corrections revealed significant differences between warm/burn and UTC descriptors magnitude at 100 μM ($p < .05$) and 200 μM ($p < .01$), with magnitude of UTC descriptor being significantly greater than the warm/burn descriptor. No significant differences in the magnitude were found between the warm/burn and UTC descriptors for concentrations 0, 50, and 75 μM.

Influence of capsaicin concentration on warm/burn and urge-to-cough (UTC) descriptor magnitude. Linear regression analyses revealed significant influence of increasing log capsaicin concentration on the log magnitude of both warm/burn and UTC descriptor, adjusted for gender ($F_{(1, 98)} = 93.74$, $p <. 001$, $R^2 = 0.489$; $F_{(1, 98)} = 132.50$, $p < .001$, $R^2 = 0.575$, respectively; Figures 4 and 5). This indicates that both the cough sensation descriptor magnitudes are affected by stimuli concentration.

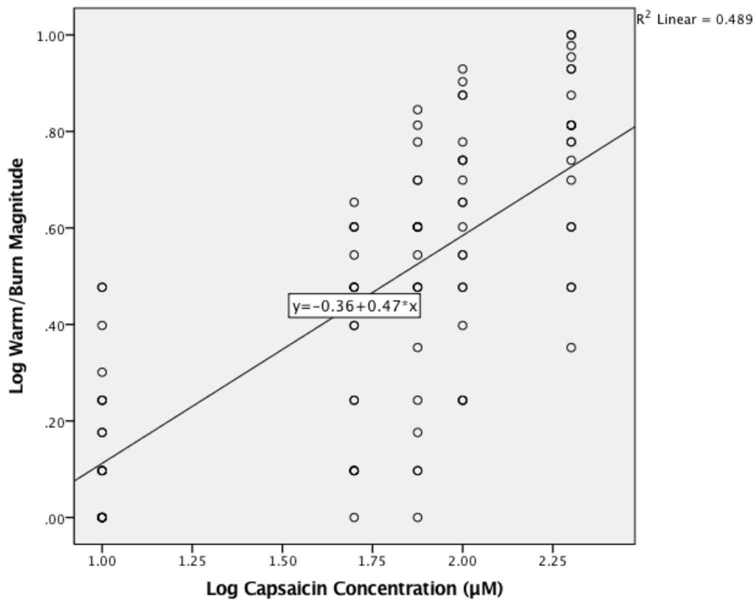

Figure 4. Scatterplots demonstrating the influence of log capsaicin concentration on log warm/burn descriptor magnitude

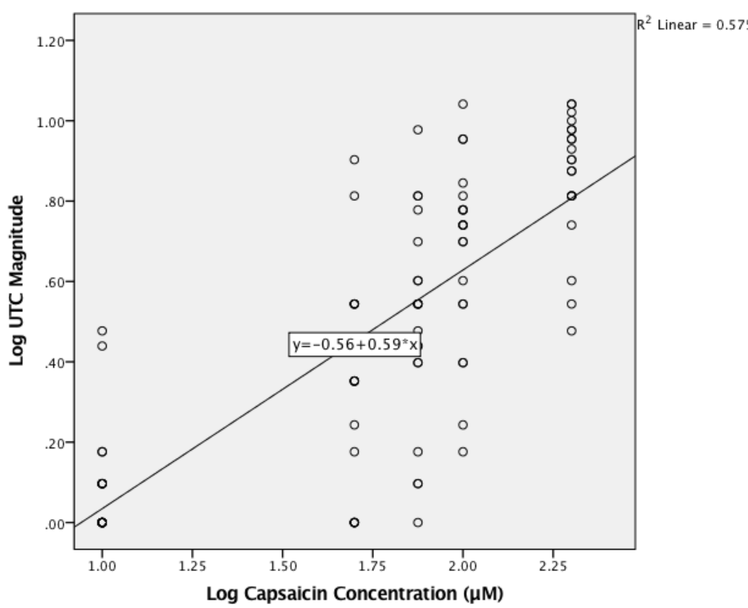

Figure 5. Scatterplots demonstrating the influence of log capsaicin concentration on log urge-to-cough (UTC) descriptor magnitude

Differences in log-log slopes of warm/burn and UTC descriptor magnitude. There were significant differences in the log-log slopes of warm/burn and UTC descriptor, with the magnitude of UTC descriptor being significantly higher than warm/burn descriptor at higher capsaicin concentrations (100 and 200 µM). This was revealed by analysis of covariance (ANCOVA) where UTC was the only significant descriptor affected by capsaicin concentration when warm/burn descriptor was accounted as a covariate ($F_{(1, 4)} = 6.079$, $p < 0.001$, Figure 6). On the contrary, when UTC descriptor was held as a covariate, warm/burn descriptor was not significant ($F_{(1, 4)} = 0.567$, $p = 0.687$).

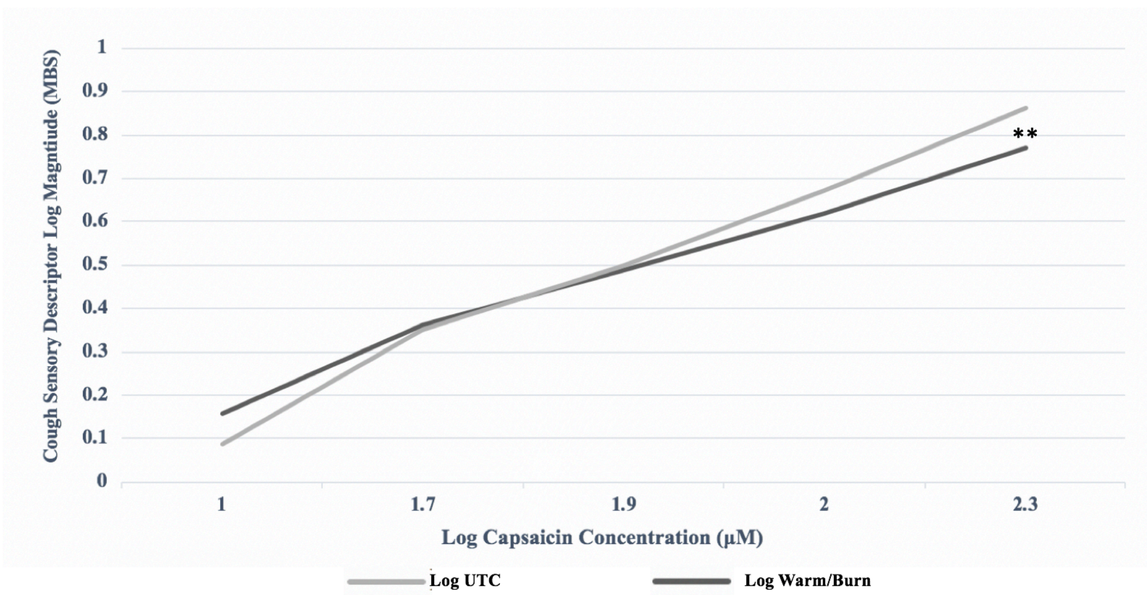

Figure 6. Log-log slopes of magnitude of warm/burn and UTC descriptor for varying capsaicin concentrations
Slopes represents descriptors sensitivity (Warm/Burn and UTC) plotted on linear coordinates (**) denotes significant statistical difference (p <.05) between slopes of warm/burn and UTC descriptors.

Influence of warm/burn and UTC descriptor magnitude on cough motor response. Binomial logistic regression analysis was performed to examine the influence of somatosensory and UTC descriptor magnitude on cough motor response (Cr2). Of the 20 HYA participants, 18/20 (90%) executed a two-cough response in at least two trial blocks for 200 µM capsaicin and were classified as cough responders. Two out of the 20 HYA participants (10%) did not respond with a Cr2 cough response for 200 µM capsaicin and were classified as non-responders. Table 7 shows the percentage distribution (%) of cough responders across capsaicin stimuli in phase II cough testing.

Table 7

Percentage Distribution (%) of Cough Responders Across Capsaicin Stimuli in Phase II Cough Testing

Cough Responders across Capsaicin Stimuli (µM)	Percentage (%)
0	0
50	0
75	45
100	70
200	90
Non-Cough Responders (200 µM)	10

Results of the binomial logistic regression analyses revealed that the magnitude of warm/burn and UTC descriptors significantly influenced the cough motor response (Cr2) at 200 µM ($\chi2(24) = 14.657$, $p < .001$; $\chi2(25) = 24.118$, $p < .001$). More specifically, the magnitude of the UTC descriptor significantly influenced Cr2 at 200 µM, when the magnitude of warm/burn descriptor was accounted as a covariate, and also explained more of the variance ($\chi2(97) = 10.535$, $p < .05$).

Discussion

The aim of this study was to determine the best descriptor for cough sensations that can be used for psychophysical testing during cough evaluations. Our findings revealed that healthy young adults perceived and reported either the UTC or the warm/burn descriptors when presented with nebulized capsaicin and that these descriptors were influenced by increasing stimuli concentration. The magnitude of the UTC descriptor was found to be more sensitive to varying stimuli concentrations and also was a better predictor of cough motor response at 200 μM capsaicin stimuli (Cr2). To our knowledge, this is the first study to compare two descriptors for magnitude estimation of cough sensations elicited by a cough-inducing stimulus such as capsaicin based on the stimulus-sensation-response psychophysical design (Lawless, 2013).

Warm/burn was the predominant somatosensory descriptor reported for capsaicin stimuli. Of the three types of somatosensory descriptors examined in phase I (i.e., no sensation, tickle, warm/burn; Table 1), the incidence of warm/burn was reported to be 56% and tickle to be 38% in our sample of HYA. These findings are in agreement with sensory and cough research studies that also reported higher incidence of warm and burn sensation for capsaicin stimuli in healthy cohorts (Bennett & Hayes, 2012; Davenport et al., 2002; Dicpinigaitis, 2009; Midgren et al., 1994; Lawless & Stevens, 1988). Sensory studies that described the chemical properties of capsaicin stimuli frequently reported warm and burn as two qualities of capsaicin that were found to be perceptually similar by sensory panelists (Bennett & Hayes, 2012; Lawless & Stevens, 1988). Early seminal research on capsaicin-induced cough in humans by Midgren et al. (1994) found that, at a high capsaicin concentration (i.e., 50 μM upon 1-minute inhalation) the majority of the healthy participants perceived a burning taste that was followed by intense coughing. Additional support for this finding also comes from the chemical science literature that reported the transient receptor vanilloid 1 (TRPVI agonist; capsaicin receptor) as distinctly being associated with temperature or nociceptive sensation such as warm, heat, or pain (Bennett & Hayes, 2012; Lawless & Stevens, 1998).

Although warm/burn was the predominant somatosensory descriptor reported at high capsaicin concentrations (i.e., 100 and 200 μM), tickle was the consistent sub-threshold (i.e., 50 and 75 μM) descriptor reported in this study. Mazzone et al. (2007) speculated that a capsaicin stimulus delivered at 50 μM could differentially activate low-threshold mechano-sensors to elicit a tickle sensation, whereas 100 and 200 μM stimuli could activate the chemo-sensors to elicit a nociceptive sensation of warm/burn when approaching a cough motor response. Thus, it could be argued that tickle does not represent the true chemosensory quality of capsaicin but more of a tactile or mechano-sensory quality. Thus, based on the agreement of our results with the sensory analysis literature, we determined warm/burn to be the best somatosensory descriptor for capsaicin stimuli.

The warm/burn descriptor inferred from phase I was then paired with the UTC descriptor (Davenport et al., 2002) to determine the best descriptor for cough sensations in the phase II portion of the study. Results revealed that the magnitude of the warm/burn and UTC descriptors were both influenced by varying concentrations of capsaicin stimuli and conformed to Stevens' (1959) power function. In other words, the log magnitude estimation of the warm/burn and UTC descriptors were linearly related to log capsaicin stimuli concentration. However, closer examination of their log-log slopes revealed significant differences, with the UTC slope being significantly higher than the warm/burn slope, especially when approaching higher capsaicin concentrations (100 and 200 μM). This means that, as much as healthy participants were able to detect differences in both warm/burn and UTC descriptor magnitude with respect to increasing capsaicin concentration, they perceived and reported the UTC descriptor at a higher magnitude than the warm/burn descriptor (especially at higher concentration). This indicates that the UTC descriptor was more sensitive to varying effects of concentration than the somatosensory descriptor.

Finally, we were interested in a descriptor that was able to demonstrate predictive capacity of cough motor response. We found both warm/burn and the UTC descriptors to significantly influence cough motor response (Cr2) at 200µM. However, when we exclusively accounted for warm/burn descriptor as a covariate, the UTC descriptor was the only significant factor that was predictive of Cr2 at 200µM and also explained more of the variance. Thus, based on the results, we reasoned that our hypothesis was correct and that the "urge-to-cough" descriptor was not only more sensitive to varying concentrations of capsaicin stimuli, but also a significant factor in predicting the cough motor response.

Taken together, this study informed us that healthy humans perceive and report both UTC and warm/burn descriptors when provided with cough-inducing stimuli (i.e., capsaicin). As much as these cough sensations can be postulated to be neurophysiologically different, humans psychophysically perceive and report both of these descriptors for a cough-inducing stimulus such as capsaicin. These results are well supported by Jackson, Parkinson, Kim, Schüermann, and Eickhoff (2011) in their viewpoint article on anatomy for urge for action, where they opined that unpleasant body sensations are indeed perceived as an urge for action that are governed by two distinct neural networks. The "motivation for action" network is responsible for behavioral urges and is comprised of limbic sensory and motor regions of the insula and mid-cingulate cortex. The "intentional action" network is responsible for the perception of "willed intention" during the execution of goal-directed actions and is comprised of regions of premotor and parietal cortex.

Thus, it could be that the awareness of the unpleasant warm/burn was actually perceived as a UTC by our healthy participants. This was also supported by neurophysiological models and frameworks for cough which also point to somatosensation and UTC as being an integrated and interdependent phenomenon (Cameron, 2001; Davenport et al., 2002; Rothwell & Edwards, 2011; Troche et al., 2014). However, from a human airway protective standpoint, we were interested in a descriptor that is better predictive of cough. Therefore, we reasoned that the UTC descriptor is in fact unique to the sensorimotor cough behavior and is an appropriate descriptor for cough sensation.

To summarize, based on the alignment of our study findings with the literature and given that UTC is unique to sensorimotor cough behavior and a potential target for cough rehabilitation paradigms (Farrell et al., 2012; Troche et al., 2014), we reasoned that the UTC descriptor is an appropriate outcome measure to test the effectiveness of magnitude estimation (ME) responses of human cough sensations. The next step is to identify an appropriate tool that can reliably capture the magnitude of this UTC descriptor.

Study Limitations

Owing to the pilot study design, the sample size included only 20 participants and power analysis was not performed. However, the normality distribution of our data set indicated that our sample size may have been adequate. Although the research design controlled for the order, adaptation, and residual effects of stimuli presentation, the repeated measures obtained on the same subject could have resulted in selection bias. More specifically, our data may have been skewed towards those participants who were not concerned about the capsaicin stimulus being too aversive. Therefore, for example, the data may not have been representative of participants who may be more sensitive to capsaicin. Our qualitative data could have included more potential descriptors to describe capsaicin stimuli sensation other than warm/burn or tickle. Many different sub-qualities are reported in the sensory science literature for the irritant capsaicin such as sting, prick, itch, and hot and bitter taste (Breslin et al., 2001). However, since we used the 3-AFC method to determine the predominant descriptor, we picked the descriptors that were frequently reported in the sensory science literature for the irritant capsaicin (Bennett & Hayes, 2012). However, future research is required to probe into more sub-irritant qualities of capsaicin as they might potentially be of clinical value. Although we did use the MBS to report sensory magnitude (i.e., warm/burn and UTC), we did not provide consistent and clear instructions to our subjects to control for categorical behavior and perform magnitude estimations. Categorical behavior has been known to influence subjects to focus more on the semantic labels while making magnitude judgments and not report the actual perceived magnitude based on ratio estimations (e.g., 1 = very slight, 3 = moderate, 7 = very very severe).

Though not specifically reported in the cough literature, the MBS has all the potential limitations of a category ratio scale that is widely used for sensory measurements. Category ratio scales (e.g., Borg CR-10; Borg, 1982) have been criticized for being modality dependent and categorical behavior with limited considerations given to the actual numerical estimation procedures (Bartoshuk et al., 2004; Hayes, Allen, & Bennett, 2013). Thus, our participants may have been influenced by the categorical labeling of the verbal descriptors on the scale, ignored numerical estimations, and may not have reported the cough sensory magnitudes in relation to all of their sensory experiences. This could have had an influence on our sensory magnitude group results.

Future Directions

In light of the aforementioned limitations, future studies should include psychophysical evaluations using independent group designs and wider sample representation to overcome selection bias as well as provision of consistency and clarity of instructions for magnitude estimation procedures to overcome response bias. This is especially crucial when it comes to magnitude estimation procedures, where an individual's psychophysical evaluation of sensory stimuli for its physical awareness and an appropriate cognitive judgement are necessary to report a subjective magnitude. Thus, there is a need to develop methods to validate the magnitude estimation of UTC using better scaling methods in order to make effective between-subjects and across-group comparisons. Specifically, studies aimed at evaluating the reliability and validity of magnitude estimation scales that can reliably capture the magnitude of cough sensations are crucial for valid cough diagnostic testing.

Conclusion

The present investigation was the first to systematically compare two descriptive responses to cough stimuli within subjects in terms of both cough sensory and cough motor outcomes. Results demonstrated that healthy young adults perceived and reported either warm/burn or UTC descriptive responses for nebulized capsaicin stimuli in a way that was also sensitive to varying effects of stimuli concentration. The UTC descriptor was more sensitive to varying effects of stimuli concentration and a significant predictor of cough motor response. Future psychophysical studies are required to evaluate tools for the reliable measurement of cough sensation.

Disclosures

None

Ethics Statement

This study was carried out in accordance with the recommendations of the Institutional Review Board of Teachers College, Columbia University. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Teachers College, Columbia University.

Authors' Contributions

AR and MT conception and design of research; AR acquired data, performed experiments, and analyzed data; AR and MT interpreted results of the experiment; AR prepared figures and tables; AR drafted the manuscript; AR and MT edited and revised the manuscript.

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Abbreviations

UTC urge to cough; PD, Parkinson's disease; HYA, healthy young adults; GERD, gastro esophageal reflux disease; µM, micromolar; Cr2, cough motor response at 200 µM; ME, magnitude estimation; MBS, Modified Borg Scale; gLMS, generalized Labeled Magnitude Scale; log, logarithmic; ANOVA, analysis of variance; ANCOVA, analysis of co-variance; 3-AFC, three alternate-forced choice; TRPVI, transient receptor vanilloid 1.

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Chapter 3

STUDY 2: PSYCHOMETRIC EVALUATION OF MAGNITUDE ESTIMATION TOOLS TO ASSESS URGE-TO-COUGH IN HEALTHY YOUNG ADULTS

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PSYCHOMETRIC EVALUATION OF MAGNITUDE ESTIMATION TOOLS

TO ASSESS URGE-TO-COUGH IN HEALTHY YOUNG ADULTS

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ABSTRACT

Background and Purpose: The 'urge-to-cough' (UTC) is a respiratory sensation that precedes the reflex cough and has been recently validated to be the best descriptor for psychophysical cough testing. However, it is still unclear if we have reliable and valid tools to measure UTC. Thus, this study sought to examine the reliability and validity of two tools to measure UTC: the Modified Borg Scale (MBS), and another tool used in sensory sciences, the generalized Labeled Magnitude Scale (gLMS) in healthy young adults (HYA).

Methods: Thirty-four HYA (17 F) participants completed reflex cough testing in two experimental visits over 2 weeks. During each visit, randomized blocks of 11 different capsaicin-stimuli concentrations were delivered upon inspiration. Upon stimuli presentation, participants performed magnitude estimation tasks to rate UTC using both the MBS and the gLMS scales, whose presentation order were randomized and counterbalanced across the two visits.

Results: UTC measured using both the scales (MBS and gLMS) were still affected by capsaicin concentrations when adjusted for gender and age (MBS, $F_{(3, 370)} = 138.852$, $p < .001$, $R^2 = 0.525$; gLMS, $F_{(3, 370)} = 155.754$, $p < .001$, $R^2 = 0.558$). For the MBS, pairwise MANOVA revealed significant differences at majority of concentrations but with the exception of 10 and 20; 30, 40, and 50; 65, 80, and 100 µM. For the gLMS, pairwise MANOVA revealed significant differences at majority of concentrations but with the exception of 40 and 50; 65, 80, and 100 µM; 200 and 300 µM (MBS, $p < .001$; gLMS, $p < .001$). There were no differences in UTC sensitivity slopes obtained from both the scales ($p = 0.48$). UTC magnitude obtained from both scales were found to significantly influence cough motor response (Cr2) at 200µM (MBS; $p < .001$; gLMS, $p < .001$). Peak expiratory flow rate (PEFR) measures obtained from the cough airflow data were not significantly influenced by UTC from both the scales (MBS, $p = .942$; gLMS, $p = .366$). There were no differences between the UTC sensitivity slopes obtained from both scales before and after the cough motor response (Cr2) (MBS, $p = 0.40$; gLMS, $p = 0.59$). Both scales (MBS and gLMS) demonstrated good to excellent between trial reliability in UTC ratings for the majority of the capsaicin concentrations, with the exception of 50 μM on MBS (ICC = 0.34) and 10, 20, 30, 40 μM on gLMS (ICC = 0.5-0.7).

Discussion: The present investigation is the first to validate the use of MBS as well as the gLMS to measure UTC magnitudes. Both scales were reliable and valid in detecting UTC and explaining the influence of UTC on cough response. The MBS was more sensitive and highly reliable in detecting differences for stronger sensory stimuli at and above cough motor thresholds. The gLMS was more sensitive and moderately reliable in detecting differences for weaker sensory stimuli at sub-thresholds of cough. Future studies are required to validate these tools and develop valid cough sensory measures for translational research.

Key words

cough, urge-to-cough, capsaicin, Modified Borg Scale, gLMS, magnitude estimation

Introduction

The urge-to-cough (UTC) is a respiratory sensation that precedes the reflex cough. The cognitive perception of UTC in response to cough-inducing stimuli has been theorized to motivate humans to modulate the cough response for adequate airway protection (Davenport, 2009; Farrell, Cole, Chiapoco, Egan, & Mazzone, 2012; Mazzone, McLennan, McGovern, Egan, & Farrell, 2007). Based on cognitive perception and volitional control, an individual may choose to act on the stimuli to generate an effective cough or not to act on the stimuli enabling cough suppression (Hutchings, Eccles, Smith, & Jawad, 1993; Lee, Cotterill-Jones, & Eccles, 2002; Troche, Brandimore, Godoy, & Hegland, 2014). The elicitation of UTC has been postulated to involve discriminative (awareness of physical magnitude) and affective (awareness of emotional salience) processing of cough stimuli. This is dependent on the integration of respiratory afferent activity, respiratory motor drive, affective state, attention, experience, and learning (Davenport, 2009).

The UTC is known to involve cognitive neural pathways that have properties of stimulus detection, evaluation, and discrimination that aid in cough production (Davenport, 2009; Mazzone et al., 2007). A recent study compared descriptors for cough sensations and validated the UTC as the best descriptor for cough induced by capsaicin (i.e., found in hot chili peppers) in healthy young adults (HYA). Specifically, the study found the UTC descriptor to be more sensitive in response to varying effects of stimuli concentration and also a significant predictor of cough motor response (Rajappa & Troche, in preparation).

The UTC has been conventionally measured using a single metric, the Modified Borg Scale (MBS), based on psychophysical sensory evaluation methods. The fundamental goal of a psychophysical evaluation is to reliably capture a “threshold” (i.e., a representation of sensory perceptual magnitude), so that subjective experiences can be meaningfully quantified using scaling functions. This is achieved through a magnitude estimation task in which subjects are encouraged to give their own impressions of sensory stimuli perception on a category ratio scale such as the MBS (Borg, 1982; Stevens, 1959). The UTC sensitivity (i.e., represented as the slope of the line) has been demonstrated to have a log linear relationship with increasing concentrations of capsaicin cough stimuli (Davenport, Sapienza, & Bolser, 2002). There also exists a direct relationship between UTC sensitivity, total number of coughs (CrTot), and the expiratory muscle electromyography (EMG) response (Vovk et al., 2007).

Reliable and valid quantification of the UTC is very important for translational research. UTC is a sensory measure inferred based on magnitude estimation methods. However, we are currently measuring it only from a gross sensory stimulus detection point of view and not based on psychophysical magnitude estimation models, as used in other sensory sciences such as vison, hearing, and taste. The psychophysical concepts such as dynamic range (i.e., difference between smallest and largest intensity, DR), difference threshold or just-noticeable-difference (JND), Weber fractions, supra-threshold perception, and sensory adaptation have not been explored from a stimulus-sensation growth point of view. More crucially, we still do not know if we even have a reliable and valid tool to measure UTC's sensory magnitude.

Though not specifically reported in the cough literature, the MBS (Borg, 1982) has all the potential limitations of a category-ratio scale that is widely used for sensory measurements. Category-ratio scales (Borg CR-10; Borg, 1982) have been criticized for being dependent on the modality measured with little consideration of the magnitude estimation procedures (Bartoshuk et al., 2004; Hayes, Allen, & Bennett, 2013). The inconsistency in provision of instructions poses the risk of subjects reporting only the verbal categories and ignoring to make numerical judgments of the perceived intensity. More importantly, the MBS does not necessarily capture an absolute intensity of the sensation of interest (i.e., absolute UTC) as the participants may not rate a sensory magnitude in consideration of all of their sensory experiences. The intensity descriptors used for categorical labeling and anchoring the ends of the scale may denote different perceived intensities to different people, depending on their individual sensory experience. This results in subjects' ratings clustered at the lower end of the scale, leading to significant inter-subject and intra-subject variability (Bartoshuk et al., 2004). Furthermore, it is unknown if the scale can detect subtle differences in UTC perception at sub-threshold concentrations of capsaicin stimuli, and if it can capture a wide range of UTC sensory responses to a range of stimuli concentration.

Notably, some of the measurement limitations seen in the traditional MBS have been addressed in sensory science literature through the development of novel scales, such as the generalized Labeled Magnitude Scale (gLMS, Bartoshuk et al., 2004; Green, Shaffer, & Gilmore, 1993). The gLMS, derived from the original labeled magnitude scale (Green et al., 1993), has been empirically tested to evaluate taste sensations based on magnitude estimation methods. The gLMS with its high-end anchor denoting the "greatest imaginable sensation of *any* kind," compares the intensity of the stimulus to any sensory modality and allows independence from the modality measured. Use of the gLMS in sensory testing has been shown to increase the validity of participants' perceptual reporting experience, improve discrimination among subjects, and assist in making group comparisons valid (Bartoshuk et al., 2004).

This leads to the central question of whether a reliable and valid tool to measure UTC magnitude exists. We sought to address the gaps in the literature by psychometrically evaluating the efficacy of an existing tool for UTC measurement, the MBS (Borg,1982), in comparison with another tool validated for sensory measurements, the gLMS (Bartoshuk et al., 2004; Green et al., 1993; see Table 1 for scale comparisons).

Table 1

Comparisons Between the Modified Borg Scale (MBS; Borg, 1982; Davenport, Sapienza, & Bolser, 2002) and generalized Labeled Magnitude Scale (gLMS; Bartoshuk et al., 2004)

Modified Borg Scale		gLMS
1.	Category-Scale (Borg, 1952; Davenport et al., 2002)	Labeled Magnitude Category Ratio Scale (Bartoshuk et al., 2004; Green, Shaffer, & Gilmore, 1993)
2.	Tied to the domain of interest (Assumed that the labels denote the same sensory experience to all participants)	Independent from modality of interest. Top anchor denotes "greatest sensation of any kind"
3.	Ranges from 0-10, 0 being no sensation and 10 being very very severe almost maximal	Ranges from 0-100, 0-no sensation,100-greatest sensation of any kind
4.	Verbal anchors spaced but not based on calibration using ratio scaling	Verbal anchors spaced based on calibration using ratio scaling
5.	Predictive value on cough behavior	Predictive value on food habits but not cough specifically
6.	Criticized for not being valid for group comparisons	Valid for group comparisons based on Taste studies (Bartoshuk et al., 2004)

Our central hypothesis was that compared to the traditional MBS, the gLMS would be more valid in obtaining the absolute intensity of UTC; would differentiate UTC perception at varying concentrations of capsaicin stimuli; would demonstrate a wider dynamic range of UTC perceptual responses; and would yield better between-trial reliability as compared to the traditional MBS.

We evaluated the two scales based on possession of six specific factors unique to the sensorimotor cough behavior (Table 2). The first factor was the ability of the scale to demonstrate log linear relationship between UTC sensation and capsaicin stimuli. The second factor was the ability of the scales to detect subtle differences in UTC sensations across neighboring capsaicin stimuli concentrations. The third factor was the ability of the scales to demonstrate predictive value on the two-cough motor response (Cr2). The fourth factor was the ability of the scales to demonstrate predictive value on cough effectiveness measure (i.e., peak expiratory flow rate, PEFR). The fifth factor was the ability of the scales to demonstrate influence of cough occurrence on UTC magnitude ratings. The sixth and last factor was the ability of the scales to demonstrate higher between-trial reliability of UTC responses across the three trials of each of the 11 stimuli presentations.

Table 2

Specific Scale Evaluation Criteria

	Criteria for Scale Evaluation
1.	Demonstrate log linear relationship between UTC sensation and stimuli
2.	Detect subtle differences in UTC across neighboring stimuli concentrations
3.	Predict cough motor response
4.	Predict cough effectiveness (i.e., peak expiratory flow rate, PEFR)
5.	Demonstrate influence of cough occurrence on UTC magnitude ratings
6.	Demonstrate higher between-trial reliability

Specifically, we attempted to answer three specific aims. The first aim was to evaluate which scale was better at detecting differences in UTC perception across varying capsaicin stimuli concentrations. We hypothesized that the gLMS would be able to detect differences in UTC perception across varying capsaicin stimuli concentrations better than the MBS. Our second aim was to examine between-trial reliability in reporting UTC perception from the two scales. We hypothesized that the gLMS would demonstrate more between-trial reliability than the MBS. Our final aim was to evaluate if one of the two scales demonstrated better influence of UTC magnitude on the two-cough motor response (Cr2) at 200 µM capsaicin as well as on the cough effectiveness measure, the peak expiratory flow rate (PEFR), than the other. We hypothesized that the gLMS would demonstrate better influence of UTC magnitude on the two-cough motor response (Cr2) at 200 µM capsaicin and the PEFR more than the MBS. As an exploratory aim, we also examined if participants rated their UTC magnitude differently for capsaicin presentations that resulted in coughs versus those that did not result in coughs. We hypothesized that the presence of the two-cough motor response (Cr2) would affect UTC magnitude ratings, as demonstrated by a decrease in UTC magnitude at Cr2, and that this effect would be demonstrated more by the gLMS than the MBS.

Materials and Methods

Participants

This study was approved by the Institutional Review Board of Teachers College, Columbia University. Informed consent was obtained from all participants. Participants were a group of 35 healthy young adults (HYA) with no prior knowledge or experience in cough testing. Inclusion criteria were no history of: neurological disease, active respiratory condition; head, neck, or chest surgery; smoking in the last 5 years; chronic cough or swallowing difficulty; gastro-esophageal reflux disease (GERD); allergy to capsaicin or hot peppers; and use of ACE inhibitors or cough suppressants such as codeine.

Data Collection

Data collection took place in the Laboratory for the Study of Upper Airway Dysfunction, Teachers College, Columbia University, New York, New York. Data collected included: a short screening questionnaire, cross-modal ratings of imagined sensations for gLMS and MBS, magnitude estimation ratings of UTC from MBS and gLMS, and cough airflow data. The study was completed in two experimental visits (i.e., I and II) that took place over the course of 2 weeks. Participants completed capsaicin inhalation challenge testing in both visits and performed magnitude estimation tasks using both the MBS and the gLMS scales, whose presentation order were randomized.

Experimental Visit I

Magnitude estimation using either MBS or gLMS (scale order randomized). A group of HYA with no prior experience to capsaicin stimuli or knowledge of cough testing participated in the capsaicin inhalation challenge to determine the most appropriate psychometric tool to measure the magnitude of UTC sensation. Upon presentation of the capsaicin stimuli, the participants were asked to perform a magnitude estimation of their UTC sensation using either of the scales (MBS and gLMS). Participants were instructed to assign numbers in relation to perceptual intensities so that an intensity level that is perceived as twice as intense as the second intensity level was assigned a number twice as large as the first one, and so on.

Scale orientation and cross-modal orientation protocol with verbal instructions. Following the general instructions about magnitude estimation procedures, a comprehensive orientation protocol to the two types of scales was provided verbally to the participants. The protocol included information about scale structure and specific scaling instructions to perform magnitude estimation ratings.

For the MBS, orientation instructions were identical to those provided by Borg (1982). Participants were asked to first determine which descriptor most appropriately described the intensity of the sensation and then fine-tune their rating by choosing a number that corresponded with a descriptor and the next most appropriate one. They were then advised to give their final numerical rating within the range from 0-10, with 0 being no sensation and 10 being almost maximal sensation.

For the gLMS, orientation instructions were identical to those provided by Green (1993) and Bartoshuk et al. (2004). Participants indicated the strongest imaginable sensation they had ever experienced and wrote that at the top of the scale. They were then asked to rate the magnitude of UTC sensation in relation to that strongest imaginable sensation. They had to determine a descriptor that most appropriately described the intensity of the sensation and then fine-tuned their rating by placing a mark on the scale at the proper location between that descriptor and the next most appropriate one. They were advised to give their final numerical rating within the range from 0-100, with 0 being no sensation and 100 being the strongest imaginable sensation of any kind. For both scales, participants were specifically instructed to focus on the numerical rating using ratios for magnitude estimation and not just focus only on the categorical verbal descriptors on the scale.

Prior to the actual rating of UTC sensation on gLMS and MBS, participants were also subjected to a cross-modal orientation protocol. For this task, participants practiced rating intensities of five imagined sensations not related to the sensation of interest (i.e., UTC) using both scales (i.e., MBS and gLMS). This was done to ensure that participants had a standard for normal sensory functioning and checked whether the apparent individual differences in UTC perception were merely the result of how a participant used the scale (Gent, Frank, & Mott, 1997). For MBS, they were asked to rate five imagined sensations unrelated to UTC sensation. For gLMS, they were asked to rate five imagined sensations (unrelated to UTC sensation) in comparison to their strongest imaginable sensation of any kind (e.g., staring at the sun, strongest pain, loudest sound). The imagined sensations provided were based on sensory science methodology used by Hayes et al. (2013). The five imagined sensations that were rated were: loudness of whisper, sweetness of cotton candy, burn of cinnamon gum, pain of tongue bite, and loudest sound.

Capsaicin inhalation challenge. All participants were subjected to the capsaicin inhalation challenge protocol, based on previously established methodologies to induce cough (e.g., Davenport, 2009; Hegland, Okun, & Troche, 2014; Hegland, Davenport, Brandimore, Singletary, & Troche, 2016; Troche et al., 2014; Troche, Schumann, Brandimore, Okun, & Hegland, 2016). They were outfitted with a facemask covering the nose and mouth. The facemask was coupled with a pneumotachograph and differential pressure transducer and had a side port with a one-way inspiratory valve for a nebulizer connection. The nebulizer was a DeVilbuss T-piece connected to a dosimeter that delivered aerosolized solution during inspiration with a delivery duration of 2 seconds. Participants were seated for an initial 30 seconds of quiet breathing to acclimate to the facemask. Then, the capsaicin solution was administered manually upon detection of an inspired breath and there was a minimum of 1 minute between each trial. Participants were instructed to “Breathe in and out through their mouth and cough if you need to.” The cough airflow signal was then digitized (Power Lab Data Acquisition System) and recorded (Lab Chart 7; AD Instruments, Inc.) onto a desktop computer.

Participants underwent four blocks of the capsaicin inhalation challenge, totaling 36 inhalations of capsaicin stimuli of varying concentrations. The first block was comprised of single inhalations of 0, 50, and 200µM capsaicin stimuli (a total of three presentations) that were provided to acclimatize the participants to the protocol. However, this was not factored into the actual analysis as this was just a warm-up trial run. After this initial first block of the trial run, participants entered the actual testing block. This included a pseudo-random presentation of three blocks of capsaicin stimuli presentation that varied randomly in the order of stimuli concentration. This was used to prevent order/position effect and participant response bias A total of 11 test solutions comprised of capsaicin inhalations of 0, 10, 20, 30, 40, 50, 65, 80, 100, 200, and 300µM stimuli (3 trials each) was presented. The presentation order of the 11 individual test solutions were randomized for each block, generating three randomly ordered blocks with only one presentation of each test solution in each block. After the presentation of the capsaicin stimulus, participants were asked to rate the magnitude of UTC using either an MBS (Borg, 1982) or the gLMS (Bartoshuk et al., 2004) to which they were randomly assigned. Participants’ cough motor response (Cr2), defined as the lowest concentration of capsaicin that elicited at least two reliable cough responses in 2/3 trials, were obtained. This was observed and recorded within the first 30 seconds following stimuli delivery (Davenport, 2009). Participants were also provided with water to drink between trials and were cleared for presence of any residual effect from the preceding capsaicin stimulus.

Experimental Visit II

Magnitude estimation using a different scale from Experimental Visit I. The same set of HYA participants from Experimental Visit I came for an additional Visit II after 2 weeks. During this Experimental Visit II, participants were subjected to a capsaicin inhalation challenge similar to Visit I and performed a magnitude estimation task for rating UTC sensation, but using a different scale (i.e., either MBS or gLMS) from Visit I. Prior to testing, they were also provided with a comprehensive orientation protocol to the two types of scales similar to that in Experimental Visit I. The methods and protocol for cough testing and magnitude estimation were the same as Visit I cough testing (Bartoshuk et al., 2004; Borg, 1982; Davenport et al., 2002).

Data Analyses

Data analyses included assessment of UTC magnitude measures and cough airflow measures derived from the two cough Experimental Visits (I and II). UTC measures included median ratings of the magnitude estimation of UTC derived from both scales (i.e., MBS and gLMS). UTC MBS referred to the participant ratings of UTC on a modified Borg rating scale (MBS) following each capsaicin inhalation challenge, where 0 indicated no sensation and 10 indicated very very very severe or almost maximal sensation. UTC gLMS referred to participant ratings of UTC on a generalized Labeled Magnitude Scale (gLMS) following each capsaicin inhalation challenge, where 0 indicated no sensation of UTC in relation to their strongest sensation of any kind and 100 indicated UTC sensation when rated in relation to their strongest sensation of any kind. Cough airflow measures included reflex cough effectiveness measures such as the cough motor response (Cr2) and peak expiratory flow rate (PEFR). Cough motor response (Cr2) was defined as the lowest concentration of capsaicin that elicited the two-cough response in at least 2/3 trials for the capsaicin concentrations (μM). Cr2 at 200 μM was computed as a categorical binary responder/non-responder variable based on the two-cough response observed when a participant was presented with 200 μM capsaicin, in at least two trial blocks. Peak expiratory flow rate (PEFR) referred to the peak volume of air expelled per second during the first cough in a cough epoch (for 200 μM capsaicin stimulus) and was recorded in liters/second (l/s; Figure 1). PEFRs were computed for each participant for the first cough response in a cough epoch for the 200 micromolar capsaicin (μM) for the three trials of capsaicin inhalation challenge. This was completed for cough responses from both Experimental Visits (I and II) and correlated with UTC magnitudes inferred from each of the respective scale ratings (i.e., MBS and gLMS).

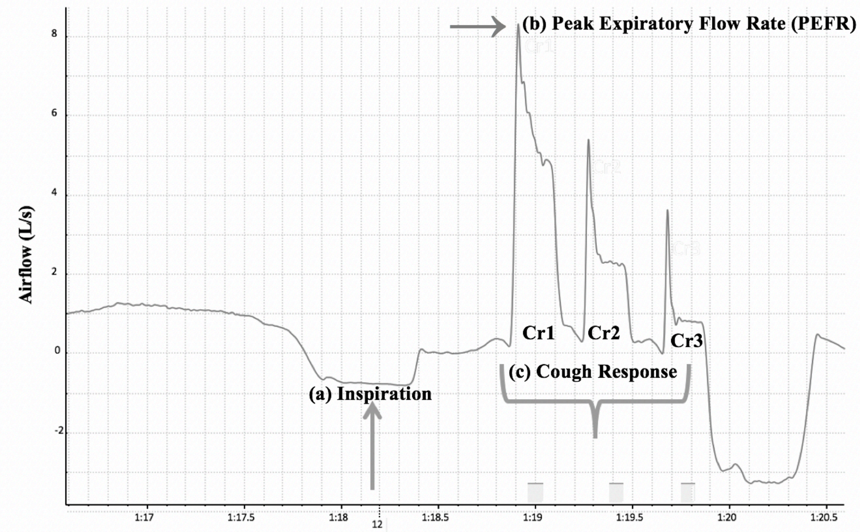

Figure 1. Reflex cough motor response elicited in response to 200 µM capsaicin stimuli by a healthy young adult participant Inspiration (a); Peak expiratory flow rate (PEFR) (b); the first cough response in the epoch (Cr1); second cough response in the epoch (Cr2); third cough response in the epoch (Cr3).

Statistical Analyses

Statistical analyses were conducted using SPSS (Version 25, Armonk, NY).

A quantitative analysis was performed to analyze participants' responses to magnitude estimation of UTC sensations across varying concentrations of capsaicin stimuli between the two scales (i.e., MBS and gLMS) and also to evaluate the correlation between cough effectiveness measures and UTC sensory magnitudes. Multivariate analysis of variance (MANOVA), with capsaicin concentration type as a within-subject factor, was performed to determine overall significant differences in magnitude perception of UTC across varying concentrations of capsaicin stimuli between the two scales. Pairwise comparisons with Bonferroni corrections were performed to determine specificity of differences in UTC magnitudes obtained using both scales (i.e., MBS and gLMS) across the 11 capsaicin concentrations.

Linear regressions were performed to explore the influence of varying capsaicin concentrations on UTC magnitudes as well as the influence of UTC magnitudes on the cough airflow measure (i.e., peak expiratory flow rate, PEFR). The average UTC magnitude was respectively plotted against the corresponding capsaicin concentrations using a log-log scale, and a line of best fit was applied to the data set. The UTC sensitivity to varying concentrations of capsaicin was reported as the slope of the line of best fit. Binomial logistic regressions were performed to explore the influence of UTC magnitudes obtained from both scales (MBS and gLMS) on the cough motor response at 200µM (Cr2 at 200 µM). To examine if participants rated their UTC magnitude differently for capsaicin presentations that resulted in coughs versus those that did not result in coughs, we compared the UTC sensitivity slopes across capsaicin concentrations that did not result in coughs with the slopes that resulted in coughs. Manual hypotheses testing was performed to examine differences in all of the UTC sensitivity slopes obtained using the two scales (MBS and gLMS). Between trial reliability (i.e., between three trials for each capsaicin stimulus), UTC sensory magnitudes were assessed using the intraclass correlation co-efficient (ICC) for both the scale ratings (i.e., MBS and gLMS). Intra- and interrater reliability of the PEFR measure were also assessed using ICC. The ICC classification by Portney and Watkins (2000) was used as reference to classify the strength of reliability.

All analyses were controlled for gender and age effects by including them as covariates in the statistical models. A nominal two-sided p-value of $\leq .05$ was regarded as statistically significant. A sample size of 34 healthy young adult subjects was included based on the power analysis from our pilot data. Based on an estimated small effect size ($d = 0.20$) from our pilot data, the study provided 80% power to detect differences in UTC sensations across varying capsaicin stimuli concentrations.

Results

Demographic Data

A total of 35 HYA participants (18 males) were recruited from in and around Columbia University main campus, New York, New York. One participant did not complete the second visit and was excluded from the study and subsequent analyses. Analyses were completed on the remaining 34 HYA participants (17 males). Age range was 20-35 years (mean: 25.60 years). Aggregate demographic and participant-specific characteristics (age, gender, height, weight, and body mass index) are reported in Table 3.

Table 3

Participant Demographics (F, Female; M, male; N, number of participants; SD, standard deviation)

Variable	Mean ± SD	
Participants	N = 34	
Age (years)	F = 24.94 (SD = 3.54)	M = 26.52 (SD = 5.08)
Sex	F = 17	M = 17
Height (inches)	F = 65.41 (SD = 2.69)	M = 69.17 (SD = 3.01)
Weight (pounds)	F = 135.53 (SD = 28.36)	M = 184.65 (SD = 60.54)
Body Mass Index	F = 22.20 (SD = 4.14)	M = 26.35 (SD = 7.79)

Descriptive Statistics

Table 4 shows the average UTC sensory magnitude obtained from both scales (i.e., MBS and gLMS) reported by the 34 HYA participants across the 11 capsaicin concentrations.

Table 4

Median, Standard Deviation (SD), and Standard Error (SE) of the Urge-to-Cough (UTC) Sensory Magnitude Measured Using the Modified Borg Scale (MBS) and generalized Labeled Magnitude Scale (gLMS) for the 11 Capsaicin Concentrations (n = 34)

Capsaicin Stimuli (µM)	UTC Magnitude MBS Ratings			UTC Magnitude gLMS ratings		
	Median	SD	SE	Median	SD	SE
0	0.00	0.27	0.05	0.50	2.79	0.48
10	0.50	1.13	0.19	3.00	4.03	0.69
20	0.50	1.10	0.19	5.00	4.63	0.79
30	1.00	1.53	0.26	9.00	9.28	1.59
40	1.00	1.06	0.18	13.50	11.10	1.91
50	1.50	1.12	0.19	13.00	11.82	2.02
65	2.50	1.92	0.33	21.00	16.29	2.80
80	2.75	1.71	0.29	25.00	24.13	4.14
100	3.50	2.09	0.36	24.00	23.78	4.08
200	5.50	2.39	0.41	40.00	26.30	0.27
300	7.00	2.41	0.41	50.00	25.20	4.32

Normality Tests

Normality tests (Kolmogorov-Smirnov and Shapiro-Wilk) performed on the UTC magnitude estimation data obtained from both of the scales (MBS and gLMS) revealed a non-normal distribution (df (34), $p < .05$) for the majority of the concentrations. This was mitigated post-log transformation.

Demonstration of log linear relationship between UTC sensation and capsaicin stimuli. Linear regression analyses revealed that the UTC sensory magnitudes measured using both scales (MBS and gLMS) were still affected by capsaicin concentrations when adjusted for gender and age as covariates (MBS, $F_{(3, 370)} = 138.852$, $p < .001$, $R^2 = 0.525$; gLMS, $F_{(3, 370)} = 155.754$, $p < .001$, $R^2 = 0.558$, respectively, Figures 2 and 3).

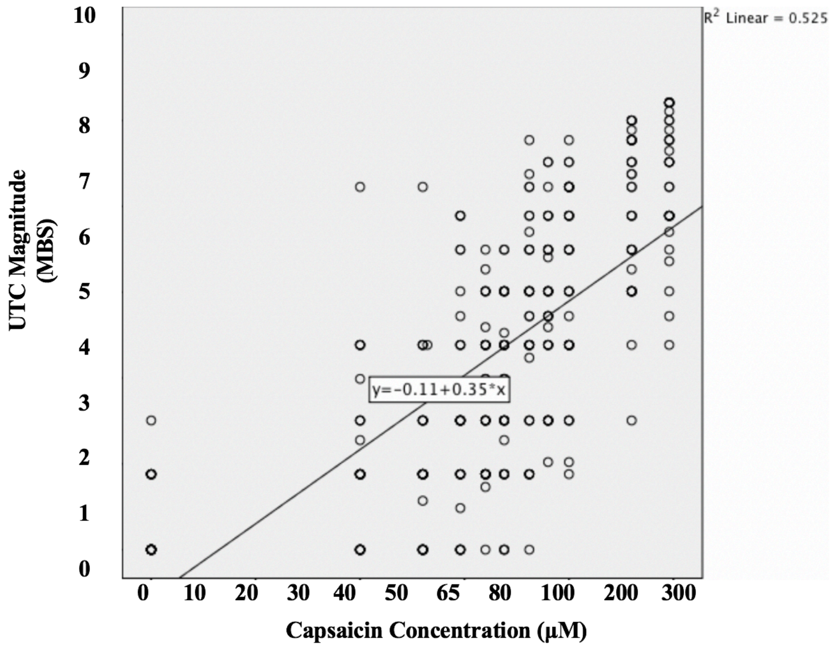

Figure 2. Scatterplots demonstrating the influence of log capsaicin concentration on log Urge-to-Cough (UTC) sensory magnitude measured using the Modified Borg Scale (MBS)

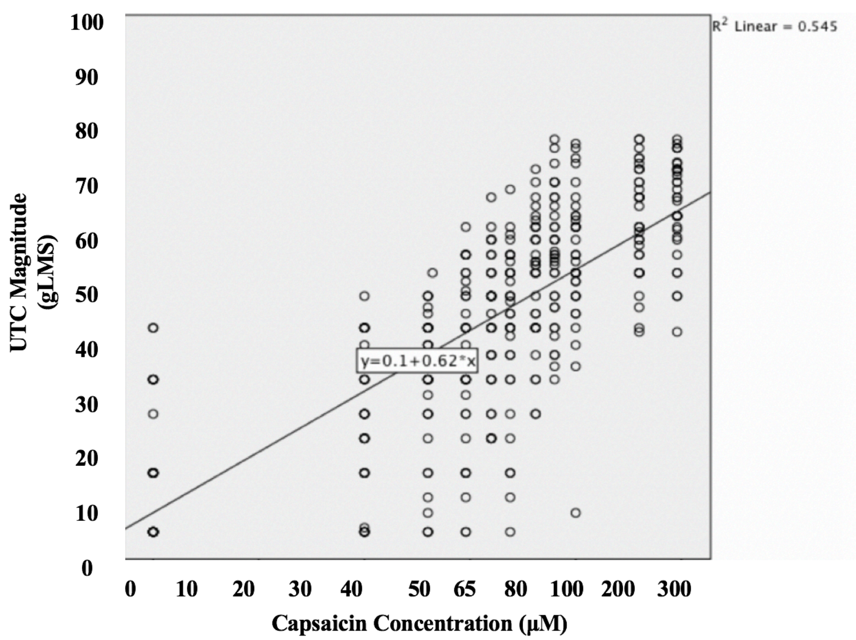

Figure 3. Scatterplots demonstrating the influence of log capsaicin concentration on log Urge-to-Cough (UTC) sensory magnitude measured using the generalized Labeled Magnitude Scale (gLMS)

Evaluation of Log-Log Sensitivity Slopes of UTC Measured Using MBS and gLMS

Hypothesis testing revealed no significant differences in the log-log sensitivity slopes of UTC measured using both scales, MBS and gLMS (p (z > 0.0512 = 0.48). See Figures 4 and 5.

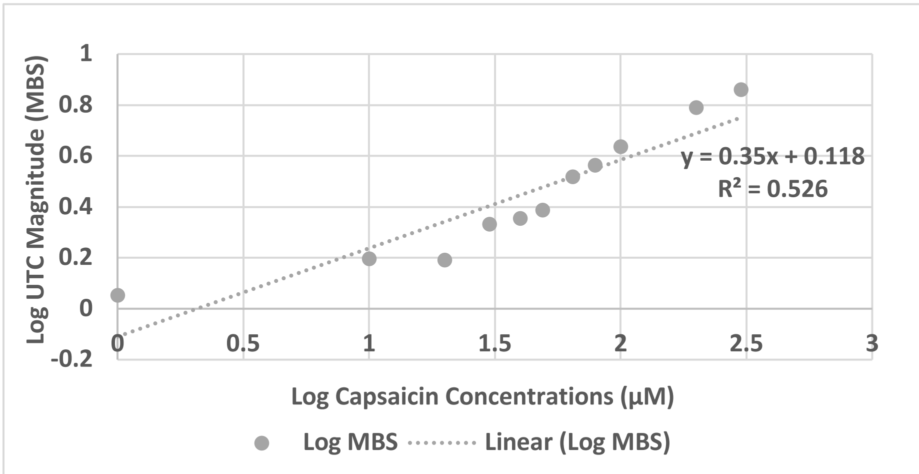

Figure 4. Log-log sensitivity slopes of UTC measured using MBS across capsaicin concentrations

Slopes represents the psychophysical power functions plotted on linear coordinates for log UTC MBS (Trendline equation: $y = 0.35x + 0.118$; $R^2 = 0.526$)

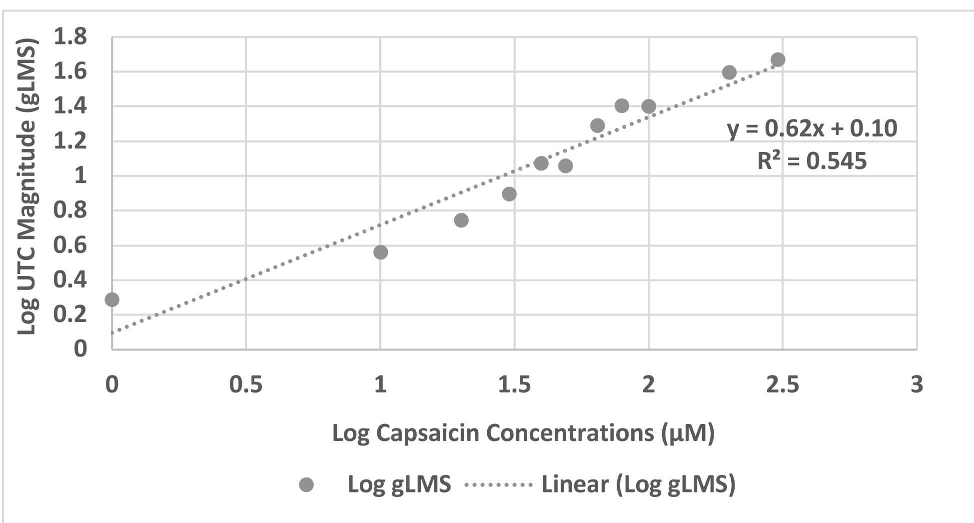

Figure 5. Log-log sensitivity slopes of UTC measured using gLMS across capsaicin concentrations

Slopes represents the psychophysical power functions plotted on linear coordinates for log UTC gLMS (Trendline equation: $y = 0.62x +0.10$; $R^2 = 0.545$).

Detection of subtle differences in UTC across neighboring capsaicin stimuli concentrations. Multivariate analysis of variance (MANOVA) was performed to evaluate mean differences in UTC magnitude across concentrations. Results of omnibus testing revealed a significant effect of concentration on UTC sensory magnitude obtained using both the MBS (Wilk's Lambda = 0.084, $F(10, 24)$, $p < .001$, Eta square: 0.916) as well as the gLMS (Wilk's Lambda = 0.135, $F(10, 24)$, $p < .001$, Eta square: 0.865).

Detection of subtle differences in UTC across neighboring capsaicin stimuli concentrations using MBS. Multiple pairwise post-hoc comparisons using Bonferroni corrections revealed that the magnitude estimation of UTC using the MBS was significantly different at the majority of capsaicin stimuli concentrations, with the exception of 10 and 20; 30, 40, and 50; 65, 80, and 100 µM. Table 5 and Figure 6 show the results of the pairwise comparisons of UTC sensory magnitude measured using the MBS for the 11 concentrations.

Detection of subtle differences in UTC across neighboring stimuli concentrations using gLMS. Multiple pairwise post-hoc comparisons using Bonferroni corrections revealed that the magnitude estimation of UTC using the gLMS were significantly different at the majority of capsaicin stimuli concentrations, with the exception of 40 and 50; 65, 80, and 100 µM; 200 and 300 µM. Table 6 and Figure 7 show the results of the pairwise comparisons of UTC sensory magnitude measured using the MBS for the 11 concentrations.

Table 5

Pairwise Post-hoc Comparisons of Urge-to-Cough (UTC) Sensory Magnitude Differences Measured Using the Modified Borg Scale (MBS) Across Capsaicin Stimuli Concentrations (μM)

Target Capsaicin Concentration (μM)	UTC Magnitude (MBS)									
	Pairwise Comparison Capsaicin Concentrations (μM)									
0	10 *	20 *	30 **	40 **	50 **	65 **	80 **	100 **	200 **	300 **
10	0 *	20	30 **	40 **	50 **	65 **	80 **	100 **	200 **	300 **
20	0 *	10	30 *	40 **	50 **	65 **	80 **	100 **	200 **	300 **
30	0 **	10 **	20 *	40	50	65 **	80 **	100 **	200 **	300 **
40	0 **	10 **	20 **	30	50	65 **	80 **	100 **	200 **	300 **
50	0 **	10 **	20 **	30	40	65 **	80 **	100 **	200 **	300 **
65	0 **	10 **	20 **	30 **	40 **	50 **	80	100	200 **	300 **
80	0 **	10 **	20 **	30 **	40 **	50 **	65	100	200 **	300 **
100	0 **	10 **	20 **	30 **	40 **	50 **	65	80	200 **	300 **
200	0 **	10 **	20 **	30 **	40 **	50 **	65 **	80 **	100 **	300 *
300	0 **	10 **	20 **	30 **	40 **	50 **	65 **	80 **	100 **	200 *

** indicates statistical significance of $p < .001$; * indicates statistical significance of $p < .05$.

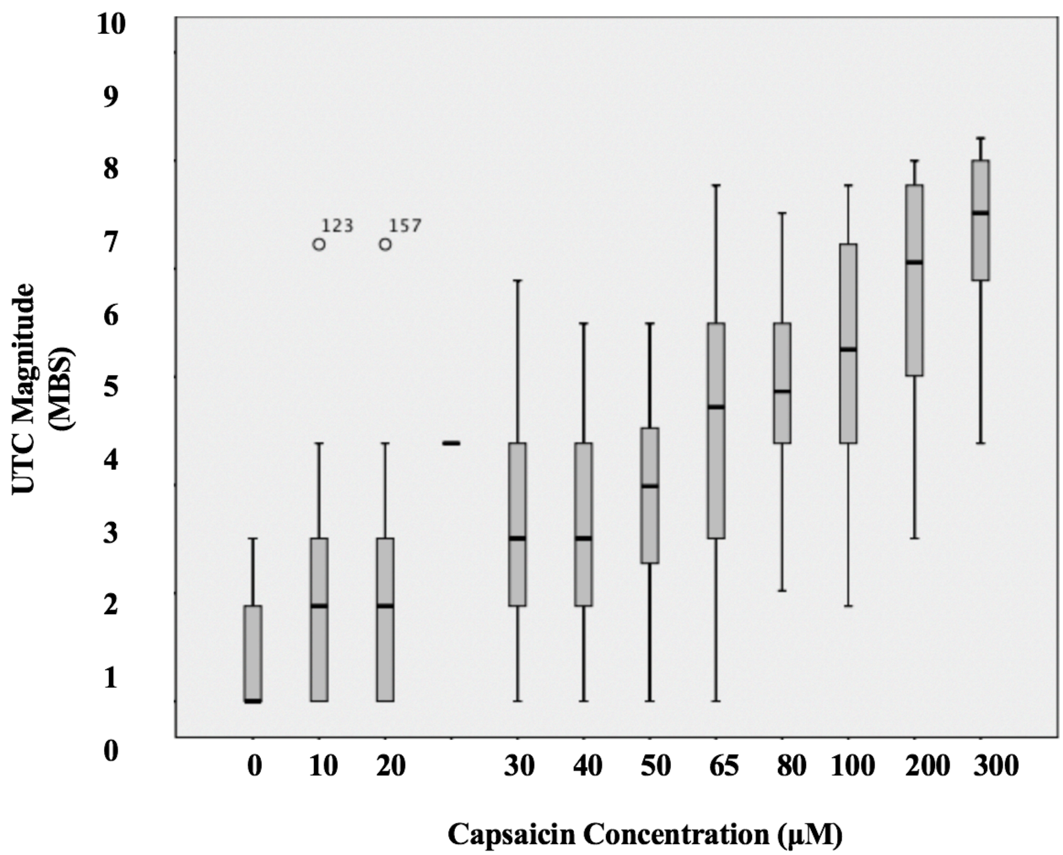

Figure 6. Urge-to-cough (UTC) sensory magnitude across capsaicin concentration (MBS)

Magnitude represents Modified Borg Scale (MBS) ratings; box plots denote the median, lower, and upper quartile ranges. Outliers denoted by circles (o) are two times more than inter-quartile range above the third quartile. X-axis represents the log capsaicin concentrations and Y-axis represents log mean UTC magnitude) (n = 34).

Table 6

Pairwise Post-hoc Comparisons of Urge-to-Cough (UTC) Differences Across Capsaicin Stimuli Concentrations (µM)

Target Capsaicin Concentration (µM)	UTC Magnitude (gLMS)									
	Pairwise Comparison Capsaicin Concentrations (µM)									
0	10 **	20 **	30 **	40 **	50 **	65 **	80 **	100 **	200 **	300 **
10	0 **	20 **	30 **	40 **	50 **	65 **	80 **	100 **	200 **	300 **
20	0 **	10 *	30 *	40 **	50 **	65 **	80 **	100 **	200 **	300 **
30	0 **	10 **	20 *	40 **	50 *	65 **	80 **	100 **	200 **	300 **
40	0 **	10 **	20 **	30 **	50	65 **	80 **	100 **	200 **	300 **
50	0 **	10 **	20 **	30 *	40	65 **	80 **	100 **	200 **	300 **
65	0 **	10 **	20 **	30 **	40 **	50 **	80	100	200 **	300 **
80	0 **	10 **	20 **	30 **	40 **	50 **	65	100	200 **	300 **
100	0 **	10 **	20 **	30 **	40 **	50 **	65	80	200 **	300 **
200	0 **	10 **	20 **	30 **	40 **	50 **	65 **	80 **	100 **	300
300	0 **	10 **	20 **	30 **	40 **	50 **	65 **	80 **	100 **	200

UTC was measured using generalized Labeled magnitude scale (gLMS).
** indicates statistical significance of $p < .001$; * indicates statistical significance of $p < .05$

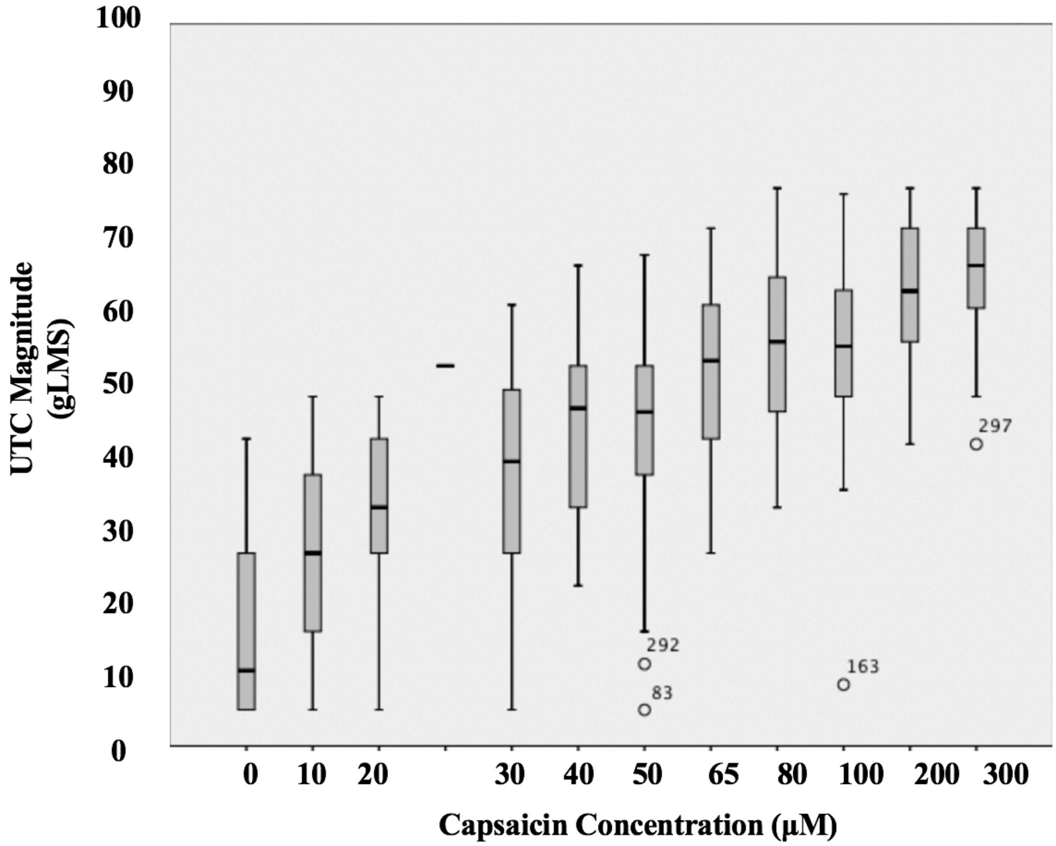

Figure 7. Urge-to-cough (UTC) sensory magnitude across capsaicin concentration (gLMS)

Magnitude represent generalized Labeled Magnitude Scale (gLMS) ratings; box plots denote the median, lower and upper quartile ranges. Outliers denoted by circles (o). For 50 and 100 µM, the outliers denoted by circles (o) are 4 times less than inter-quartile range above the first quartile; For 300 µM, the outlier denoted by circles (o) are 1.5 times less than inter-quartile range above the first quartile; X-axis represents the log capsaicin concentrations and Y-axis represents log mean UTC magnitude) (n = 34).

Prediction of cough motor response (Cr2). Binomial logistic regression analysis was performed to examine the influence of UTC sensory magnitude on cough motor response (Cr2) at 200 µM capsaicin. Cr2 at 200 µM was computed as a categorical binary responder/non-responder variable based on the two-cough response observed when a participant was presented with 200 µM capsaicin, in at least two trial blocks. Those who coughed were classified as cough respondents and those who did not were classified as cough non-respondents. Of the 34 HYA participants, 31/34 (92%) executed Cr2 in at least two trials blocks for 200 µM capsaicin during the first visit of cough testing and 29/34 (85%) during the second visit of cough testing.

Results of the binomial logistic regression analyses revealed that the sensory magnitude of UTC measured using both the Modified Borg Scale (MBS) and the generalized Labeled Magnitude Scale (gLMS) significantly influenced the cough motor response (Cr2) at 200 µM capsaicin ($\chi2(29) = 43.032$, $p < .001$; $\chi2(31) = 40.874$, $p < .001$, respectively).

Prediction of cough effectiveness measure (PEFR). Peak expiratory flow rate (PEFR) measures obtained from the cough airflow data in response to 200 µM capsaicin were not significantly influenced by UTC sensory magnitudes that were measured using both the MBS ($F_{(1, 32)} = .001$, $p = .942$, $R^2 = 3.946E-5$) and the gLMS ($F_{(1, 32)} = .842$, $p = .366$, $R^2 = 0.026$), respectively.

Demonstration of influence of cough occurrence on UTC sensory magnitude. There were no differences between the UTC sensitivity slopes that were obtained from the ratings of MBS and gLMS before and after the participants' cough motor response (Cr2) (MBS, ($p (z > 0.2519) = 0.4005$); gLMS, ($p (z > 0.2519) = 0.599$), Figure 8 and Figure 9).

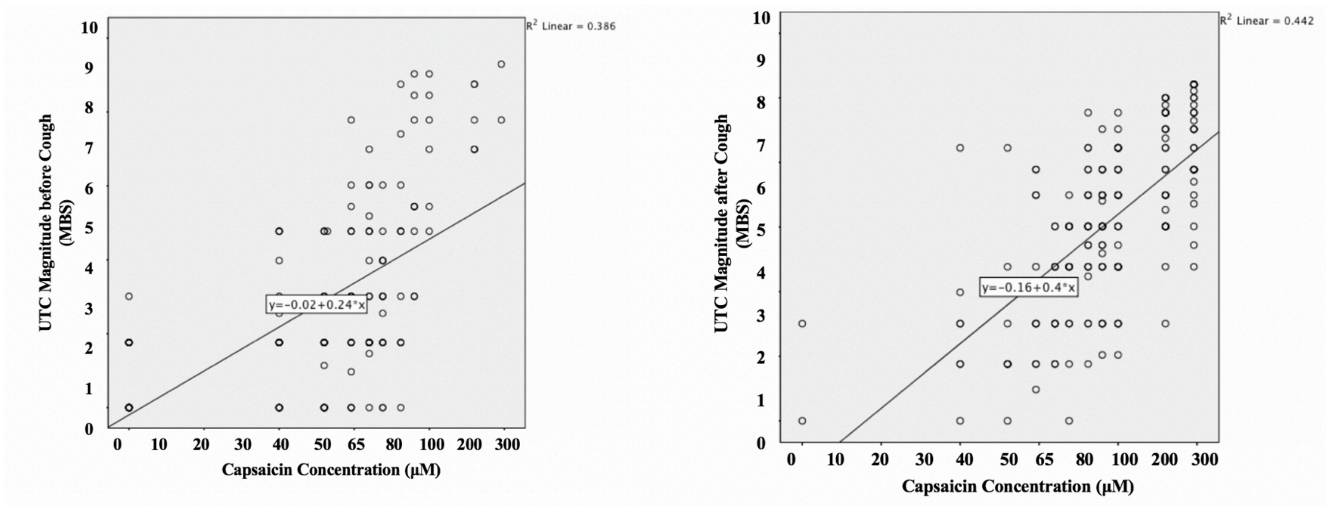

Figure 8. Scatterplots showing the differences in UTC sensitivity slopes before and after cough responses (MBS)

UTC sensitivity slopes represents magnitude estimation ratings from Modified Borg scale (MBS) before and after the two-cough motor response (Cr2).

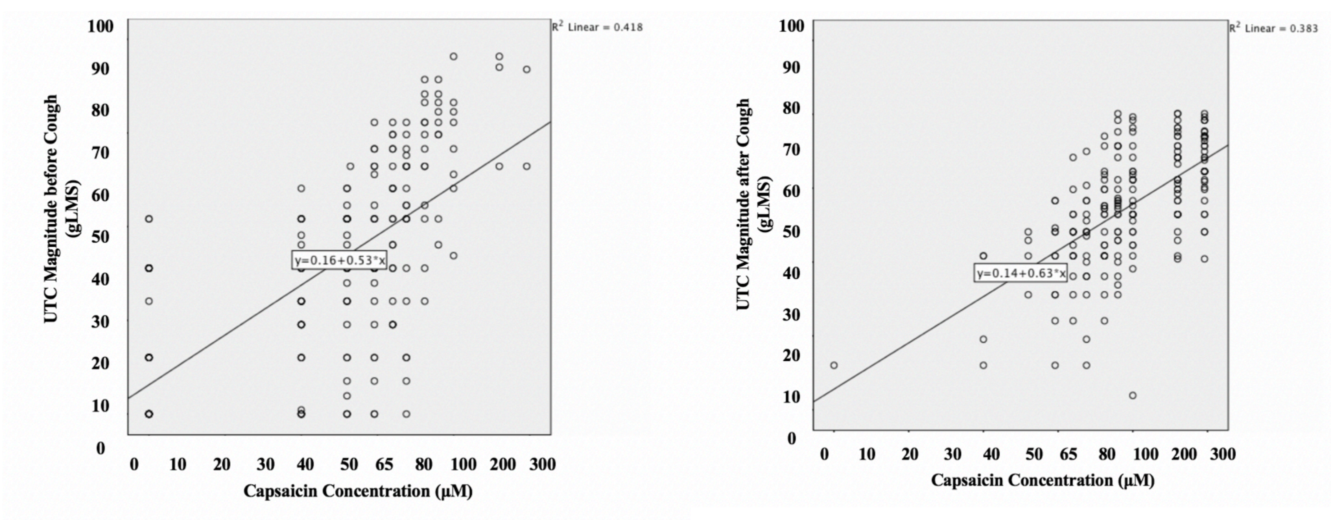

Figure 9. Scatterplots showing the differences in UTC sensitivity slopes before and after cough responses (gLMS)

UTC sensitivity slopes represents magnitude estimation ratings from generalized Labeled magnitude scale (gLMS) before and after the two-cough motor response (Cr2).

Demonstration of higher between-trial reliability. Between-trial reliability of UTC sensory magnitudes obtained from both the scales (MBS and gLMS) were assessed between the three trials for each of the 11 capsaicin stimuli presentations. Results revealed that overall, both scales (MBS and gLMS) exhibited good to excellent between-trial reliability in UTC ratings for the majority of the capsaicin concentrations. Tables 7 and 8 reveal the between-trial reliability determined based on intra-class correlation coefficient (ICC) measures for the two scales (MBS and gLMS).

Table 7

Between-trial Reliability Ratings of Urge-to-Cough (UTC) Measured Using the Modified Borg Scale (MBS) Across Three Trial Blocks of Varying Capsaicin Concentrations

Average Measures	Intra-Class Correlation Coefficient (ICC)	ICC Classification	95% Confidence Interval		F Test with True Value 0			
Capsaicin Concentrations (μM)		(Portney & Watkins, 2000)	Lower Bound	Upper Bound	Value	*df1*	*df2*	Sig
0	0.827	Good	0.695	0.908	5.789	33	66	.000**
10	0.867	Good	0.766	0.929	7.542	33	66	.000**
20	0.863	Good	0.758	0.927	7.298	33	66	.000**
30	0.894	Good	0.813	0.944	9.440	33	66	.000**
40	0.696	Moderate	0.463	0.838	3.290	33	66	.000**
50	0.340	Poor	-.166	0.648	1.516	33	66	.076
65	0.764	Good	0.583	0.874	4.238	33	66	.000**
80	0.833	Good	0.704	0.911	5.977	33	66	.000**
100	0.890	Good	0.805	0.941	9.079	33	66	.000**
200	0.885	Good	0.796	0.939	8.667	33	66	.000**
300	0.930	Excellent	0.877	0.963	14.373	33	66	.000**

Between-trial reliability was assessed using intra class correlation coefficient (ICC). ICC estimates and their 95% confident intervals were calculated using SPSS statistical package version 25 (SPSS Inc, Chicago, IL) based on a mean-rating ($k = 3$), absolute-agreement, 2-way mixed-effects model.
** denotes statistical significance ($p < .001$)

Table 8

Between-trial Reliability Ratings of Urge-to-Cough (UTC) Measured Using the generalized Labeled Magnitude Scale (gLMS) Across Three Trial Blocks of Varying Capsaicin Stimuli Concentrations

Capsaicin Concentrations (μM)	Intra-Class Correlation Coefficient (ICC)	ICC Classification	95% Confidence Interval		F Test with True Value 0			
Average Measures		(Portney & Watkins, 2000)	Lower Bound	Upper Bound	Value	*df1*	*df2*	Sig
0	0.775	Good	0.602	0.880	4.440	33	66	.000**
10	0.546	Moderate	0.199	0.758	2.204	33	66	.003*
20	0.615	Moderate	0.320	0.795	2.599	33	66	.000**
30	0.705	Moderate	0.479	0.843	3.391	33	66	.000**
40	0.599	Moderate	0.292	0.786	2.494	33	66	.001**
50	0.751	Good	0.560	0.867	4.018	33	66	.001**
65	0.867	Good	0.765	0.929	7.503	33	66	.000**
80	0.924	Excellent	0.866	0.959	13.150	33	66	.000**
100	0.914	Excellent	0.848	0.954	11.634	33	66	.000**
200	0.942	Excellent	0.897	0.969	17.187	33	66	.000**
300	0.929	Excellent	0.874	0.962	14.011	33	66	.000**

Intra- and Interrater reliability. Intra- and interrater reliability analyses were completed on 20% of the peak expiratory flow rate (PEFR) measures obtained from the cough airflow data. Results revealed excellent intrarater and interrater reliability (ICC > 0.950).

Discussion

We aimed to determine the best tool for magnitude estimation of the UTC sensation that can be used for psychophysical testing. We compared an existing tool, the MBS, with another tool that is used widely in the sensory sciences, the gLMS. The scales were evaluated for their validity and reliability in measuring the UTC sensation as well as possession of specific factors unique to the sensorimotor cough behavior. Results revealed that both scales demonstrated a log-linear relationship between UTC and capsaicin stimuli, were sensitive in detecting UTC sensations across neighboring capsaicin concentrations, predicted cough motor response, and demonstrated overall good to excellent between-trial reliability. However, the occurrence of the cough motor response did not affect the UTC sensory magnitude ratings of the participants obtained from both scales, and the UTC did not influence the cough effectiveness measure (i.e., PEFR). To our knowledge, this is the first study to evaluate the reliability and validity of magnitude estimation tools to measure the UTC. Table 9 shows the results of the scale performances (MBS and gLMS) based on the evaluation criteria.

Table 9

Results of the Scale Performances Based on the Evaluation Criteria

MBS	Criteria for Evaluation	gLMS
✅	Demonstrate Log-Linear Relationship	✅
❌ ✅	Detect Subtle Differences in UTC	✅ ❌
✅	Predict Cough Response	✅
❌	Predict Cough Effectiveness (i.e., PEFR)	❌
❌	Demonstrate Influence of Cough Occurrence on UTC	❌
✅	Demonstrate Higher Between-Trial Reliability	✅

✅ indicates meeting the criteria and ❌ indicates not meeting the criteria

Closer comparison and careful scrutiny of the results revealed some interesting similarities and differences between the two magnitude estimation tools (MBS and gLMS). First and foremost, the psychophysical scaling functions obtained from both tools demonstrated that the UTC sensory magnitudes were affected by capsaicin stimuli concentrations in a log-linear manner and conformed to Stevens' (1959) classic psychophysical power law. Although the occurrence of this phenomenon has been very well established for the UTC sensation measured using the MBS category tool (Davenport, 2002, 2009), it is important to know that this was also demonstrated by the gLMS tool. It is well known that the gLMS is a valid tool for detecting taste sensations (Bartoshuk et al., 2004; Hayes et al., 2013) and our study results demonstrated that it was as equally valid as the MBS (category scale) tool in detecting UTC sensations.

In terms of UTC sensitivity, both of the tools demonstrated differential sensitivity across the range of 11 capsaicin stimuli concentrations. Specifically, the gLMS tool was more sensitive in detecting subtle differences in neighboring lower concentrations of capsaicin stimuli (i.e., 0, 10, 20, 30, 40 μM) than the MBS. In contrast, the MBS tool was more sensitive in detecting differences at neighboring higher concentrations of capsaicin stimuli (i.e., 200 and 300 μM) than the gLMS. Interestingly, both scales were not able to detect differences between the neighboring concentrations of 40 and 50 μM as well as 65, 80, and 100 μM capsaicin stimuli. Although we can reason that the methodological choice of increments in stimuli concentrations could have influenced scale sensitivity, we contend that scale clustering and scale compression could have also influenced our results because of the category nature of the two scales (Schifferstein, 2012).

The MBS has been criticized as being prone to the clustering effect, owing to the categorical labeling that makes the scale deviate from its original numerical estimation properties, although the MBS has been claimed to generate ratio-level data (Borg, 1982). However, it has not been empirically tested, unlike the original magnitude estimation data by

Stevens (1952) and the labeled magnitude scales developed by Green (1984). The conventional Borg scale (CR-10, Borg, 1952), that was originally created as a categorical ratio scale, has undergone many different modifications both in research and clinical practice. A major drawback was the extensive use of categorical verbal labels to report magnitude and treating the scale as ordinal in nature. Deviance from the numerical ratio properties of the scale has been demonstrated to have a significant effect on the psychophysical sensory magnitude exponent (Moskowitz, 1977). Examination of the seminal work on UTC reported by Davenport et al. (2002) and existing UTC measurement literature revealed that a "Modified Borg-Category" Scale has been used with predominant ordinal properties to rate sensory magnitude. This being the case, we do not know what kind of cognitive operational strategy participants used to report UTC sensory magnitude and if there was an influence of categorical behavior on participant ratings that resulted in a clustering effect.

The gLMS has been criticized as being prone to the compression effect. A recent study comparing the taste sensitivity using the gLMS and the generalized Visual Analogue Scale (gVAS) found that the gLMS failed to identify the difference between two highest taste concentrations. The authors attributed that to the scale compression by the gLMS, owing to its generalized top anchor, and opined that the internal verbal anchor "very strong" could act as a false ceiling. This led to ratings of stimuli being pushed to the bottom half of the scale (Hayes et al., 2013). Although we could not completely eliminate the influence of compression in our study, we specifically attempted to control for categorical labeling by giving magnitude estimation instructions to our participants and encouraged them to use the full range of the scale, report any number they wanted, and not focus only on the verbal descriptors. Scale compression accompanied by smaller variance has been reported to preserve the ability to find differences (Lawless, Popper and Kroll, 2010). However, the gLMS data from our study did not show this.

Hayes et al. (2013) reported that the compression from gLMS is not worrisome if it reduces ceiling effects. Interestingly, the gLMS data from our study did not show such ceiling effects as the majority of the participants rated the UTC in relation to their strongest sensory experience at the top anchor and denoted that with a numerical rating of 100. The UTC ratings for higher capsaicin concentrations of 200 and 300 μM were instead given a numerical median rating of 40 and 50, respectively, and the majority did not report their maximum UTC experience closer to their strongest sensation ever experienced. The gLMS anchors actually have been proven to improve the ability to make valid comparisons across individuals (Snyder & Fast, 2004) who differ in physiology or genetics (Hayes et al., 2008).

The ability of the gLMS tool to detect subtle differences in weak cough stimuli with moderate reliability is still an important finding from our study. It has particular relevance for and clinical utility in the sensory evaluation of cough, where subtle detection of any given sensory stimulus is important for effective cough generation for human airway protection (Ebihara et al., 2003; Hegland et al., 2014; Troche et al., 2014; Yamanda et al., 2008). Blunted perception of UTC, as demonstrated by a decrease in UTC sensitivity with a subsequent impairment in execution of cough motor response, has been reported in clinical populations such as older adults with a history of aspiration pneumonia and patients with Parkinson's disease, (PD) and stroke (Hegland et al., 2016; Troche et al., 2016; Yamanda et al., 2008). Therefore, valid UTC detection by the gLMS tool lends further support to this existing theoretical framework that highlights the importance of the detection of sub-threshold cough stimuli for effective cough diagnostic and rehabilitative purposes in the clinical population. We reason that the ability of gLMS to capture the absolute sensation of UTC (in consideration of all sensory experiences) by being independent from the modality of interest (i.e., UTC) is what increased the validity of the participants' perceptual reporting experience and brought out the difference in

UTC magnitude at sub-thresholds. Participants rating UTC using the gLMS were able to perceive more UTC differences at the lower sensory continuum when they were comparing UTC to their own maximum sensory experiences of any kind. Since the MBS was tied to the domain of interest (i.e., UTC) and also prone to a clustering effect due to categorical labeling, our participants were not able to perceive the differences in UTC magnitude at lower capsaicin concentrations.

The ability of the MBS tool to detect UTC sensory magnitude differences in high concentrations is equally relevant from a motor cough execution point of view. Given that our HYA participants were able to perceive differences in higher concentrations when using the MBS, this finding makes the MBS a valid tool for a patient population whose sensory responses at and above cough threshold (i.e., 200 and 300 μM) are important diagnostic and prognostic indicators of airway protection. Although the perception of sub-threshold cough stimuli is equally valid for clinical groups, we reason that sub-threshold or weaker cough stimuli (i.e., 10, 20, 30, 40 μM from our study) will be even more blunted in such clinical groups because of disease processes; even if MBS fails to detect differences in such lower ranges of sub-thresholds, it may not affect its clinical utility. This is, however, subject to speculation given that we do not completely understand the peripheral and central processing mechanisms of cough. In addition, the sub-thresholds of UTC reported in the literature have been elicited at concentrations two times the dilution of concentrations that elicit Cr2 and Cr5 (i.e., Cr2/2 and Cr5/2; Yamanda et al., 2008) and not at such lower ranges as used in our study.

UTC magnitudes measured from both magnitude estimation tools (MBS and gLMS) were found to influence the cough motor response (Cr2) significantly. These findings supported the cognitive motivational model of UTC and strongly supported that the capsaicin-elicited cough has a sensory-motor process with UTC sensation preceding the reflex cough (Davenport, 2009).

Interestingly, as much as UTC magnitude influenced the presence of the cough motor response (Cr2), it did not have an effect on the cough effectiveness measure, peak expiratory flow rate (PEFR). We reasoned that once the reflex cough is elicited, it is not physiologically possible for a continued linear increase in PEFR with capsaicin concentration. Given that the cough is a sensorimotor experience and a behavioral urge can modulate it, we also assessed whether having coughed changed the manner in which participants rated the UTC. That is to say, did people rate UTC differently when they were not coughing to the capsaicin versus when they were coughing to capsaicin? The results of our study showed that coughing did not change the rate of increasing UTC magnitude estimation.

With respect to scale reliability, the MBS tool demonstrated good to excellent reliability for the majority of the capsaicin concentrations, except for 50 μM. The gLMS tool demonstrated good to moderate reliability for the majority of lower concentrations and excellent reliability for the majority of higher concentrations. As stated earlier in the discussion, aside from the psychophysical science point of view, we also attribute differences in reliability to the potential effects of scale compression for the gLMS tool and clustering for the MBS tool as well as the influence of methodological choice of chosen capsaicin concentrations in the study.

Furthermore, in terms of ease of scale usage, our participants verbally reported that both scales were easy to understand and use. The warm-up scale orientation procedure and practice ratings with imagined sensations helped the participants understand scale usage, regardless of the differing structure and randomizations. However, we did not formally test or compare the scales for their ease of use based on a standardized questionnaire.

Finally, the scaling functions inferred from both scales (MBS and gLMS) conformed to Stevens' (1959) classic psychophysical power law from a stimulus-sensation growth perspective. However, from a human perception point, gLMS demonstrated a trend in the Weber-Fechner law of differential sensitivity (Fechner, 1965; Weber, 1834). This was evidenced by perceived changes to small increments in UTC magnitude at sub-threshold or weak capsaicin stimuli (0, 10, 20, 30, 40 μM) and little or no perceived detection change UTC magnitude at higher thresholds or for stronger capsaicin stimuli (200 and 300 μM). Given that the object of the Weber-Fechner psychophysical law is the equal supra-threshold perception when the stimuli are equally above their corresponding thresholds, the magnitude estimation data of UTC derived from gLMS demonstrated a reasonable fit to this law (Patel, Bedell, Tsang, & Ukwade, 2009). In contrast, the magnitude estimation data derived from MBS did not demonstrate this relationship, although the possibility of scale clustering by the MBS and scale compression by gLMS could have influenced our results to some extent. We still cannot rule out if the dynamic range from our chosen set of 11 concentrations influenced the UTC sensory growth continuum and this effect was demonstrated differentially by the two scales. This question is open to debate and requires testing of the scales based on psychophysical testing models, with inclusion of a wider dynamic range (i.e., wider representations of concentrations in sub-threshold, threshold, and supra-threshold ranges) as well as a choice of neighboring concentrations based on proper inference of the Weber fraction.

Modern psychophysics postulates that there exists a deeper relationship between discrimination of stimuli detection that causes sensations, discrimination of the perceived magnitudes of those sensations, and the experience of the sensation magnitudes themselves (Teghstoonian, 2012; Ward, 2017). Given this postulate, cough psychophysical testing models should also incorporate human cognitive operations that include perceptual judgment and decision making to report sensory magnitudes. However, we are still primitive in our understanding of all of these concepts that it warrants extensive scientific investigations.

Taken together, the results of the present investigation confirmed that the UTC sensation can be measured with good reliability and reasonable validity using the two magnitude estimation tools, the MBS and the gLMS. The UTC measurements obtained from both tools are also valid predictors of the cough motor behavior. Although the choice of the tool depends on the context and goal of the psychophysical experiment and cough testing paradigms, based on our results alone we cannot determine if one tool is psychometrically superior than the other. Future psychophysical studies using both these tools are required to compare and develop valid protocols for absolute threshold estimation and discrimination testing for UTC sensations as well as comparisons of those cough sensory measures using signal detection methods. Given the established validity of the gLMS for group comparisons from the taste, temperature, and chemesthesis literature and the validity of MBS in differentiating healthy young, elderly, and patients with PD (Troche et al., 2016), it is projected that development of valid and reliable cough sensory measures through the gLMS and MBS tools have tremendous utilization for translational research on cough in clinical populations.

Limitations

The study findings must be noted in light of some limitations in the current methodology and research design. The instructions provided to our participants to rate the MBS in our study could be different from the conventionally provided instructions in the cough literature. This could have influenced our UTC sensitivity results inferred from the MBS. Variations in instructional cues and lack of consistency in methodologies make interpretation of results challenging and difficult to compare with previous literature. In addition, since our participants were HYA, we instructed them to hold the facemask during the cough testing procedure. This could have impacted our cough airflow data capture, which in turn might have influenced our PEFR measures. The capsaicin concentrations chosen were based on the experimenter's assumed logic of 10, 15, and 100 µM difference between a neighboring range of concentrations (0, 10, 20, 30, 40; 50, 65, 80; 100, 200, and 300µM). The differences were not necessarily chosen based on Weber ratio determination as this information is currently unknown for UTC. However, this study's use of chosen capsaicin concentrations could have influenced the results of UTC sensitivity slopes for both scales.

Directions for Future Research

The reliable and valid magnitude estimation tools (MBS and gLMS) have tremendous potential for future research in quantitative cough sensory testing using valid psychophysical models and designs. A few potential research possibilities are as follows. First and foremost, the magnitude estimation data used for comparisons across the scales (MBS and gLMS), though subject to logarithmic conversion, were still raw data and not necessarily cross-modally validated data. The field of taste science has attempted to control for this variability through cross-modality matching procedures, wherein stimulus magnitude from one sensory modality is matched with another (Bartoshuk et al., 2004; Kalva, Sims, Puentes, Snyder, & Bartoshuk, 2014; Lawless, 2013). Therefore, it will be interesting to see the potential differences in scale performances when the data are standardized to an actual cross-modal sensory reference such as loudness of pure tones (Bartoshuk et al., 2004).

Also, both of the scales represent a numerical range of 0-10 (as in the MBS) and 0-100 (as in the gLMS), which may be subject to bias by having 0 as the starting point as well as result in clustering effect. Although this effect was demonstrated more by the MBS than the gLMS in our data, technically, we do not know if there is a well-defined zero point for UTC. Use of 1-9 or 10-99 can be adopted in the future to prevent this bias. This has been reported in psychophysical studies by Poulton (1979). If all of these holds true, do we then need to use or create a scale without a well-defined zero point, and will this affect the ratio properties? If so, what cognitive operational strategies will then be used by humans to report sensory magnitude?

It is well known that UTC involves both discriminative and affective components (Davenport et al., 2002). However, we currently evaluated UTC from a unidimensional discriminative component of stimulus intensity only. Discriminative components pertaining to temporal duration and spatial aspects of stimulus should be explored. More importantly, there exists considerable speculation that the UTC can be associated with a negative emotional valence, or unpleasantness, but evaluations of this attribute have not been reported to date (Farrell et al., 2012). Literature has reported a variety of affective instruments to measure urge/urgency in adults (Das, Buckley, & Williams, 2011). Thus, it will be interesting to explore the affective attribute of UTC, potentially through development of a hybrid scale that is capable of evaluating both discriminative and affective attributes of UTC, and also has the ability to separate perceptual distances between stimuli. Notably, one such affective instrument called the Yale Craving Scale (YCS, Rojewski et al., 2015) developed based on gLMS properties has been recently validated to be a psychometrically sound scale to assess smoking and drinking urges in dependent populations.

Furthermore, with respect to instructions during cough inhalation challenge procedures, we did not specifically control for voluntary suppression and its influence on execution of cough response. There could thus exist a difference in UTC perception with respect to volitional control. Variations in instructional cues and lack of consistency in methodologies pose the risks of introducing bias in an individual's perception and elicitation of a cough response. This certainly warrants future investigation.

Currently, the Weber fraction is unknown for UTC. Future studies should be designed to determine the Weber ratio for UTC based on just-noticeable differences for a variety of cough-inducing stimuli (e.g., capsaicin, fog, citric acid, tartaric acid, ethyl butrate) and sensations with designs that include wider dynamic ranges. This will not only have potential utility in testing the dynamic ranges of scales, but also in developing standardized peripheral and central cough-processing tests with valid psychophysical models that can aid in differential diagnoses. More specifically, valid research on the development of peripheral cough sensory tests such as UTC threshold estimation, UTC discrimination testing through difference limen procedures, and validation of UTC measures through signal detection methods (controlling for human uncertainty and response bias) should be pursued.

Last but not the least, although our first-tier multivariate statistical analyses revealed a trend for the non-mediating effect of the cough motor response on UTC magnitude, advanced statistical designs through use of structural equation modeling (SEM) are advised for future analyses of the current data and probe into the latent components of cortically mediated UTC sensations more effectively.

Clinical Implications

Sensation is critical for the airway-protective behaviors of cough and swallowing. Recent evidence points to dysphagia (disordered swallowing) co-occurring with dystussia (disordered cough) in patients with neurogenic disorders (i.e., Parkinson's disease, stroke, amyotrophic lateral sclerosis [ALS]) and head and neck cancer (Hegland et al., 2014; Hutcheson et al., 2018; Pitts et al., 2010; Plowman et al., 2016; Troche et al., 2014). Specifically, a blunted perception of UTC sensitivity has been demonstrated in patients with Parkinson's disease (PD) and stroke as well as in older adults with a history of aspiration pneumonia (Hegland et al., 2016; Troche et al., 2014; Yamanda et al., 2008). The UTC has also been demonstrated to be an important predictor of swallowing safety in PD more than PD-specific factors (Troche et al., 2016). Furthermore, there is strong evidence to support that penetration and aspiration of not just large amounts but even small amounts of ingested material over time can result in pneumonia, owing to the absence of a cough response (Ebihara et al., 2008). Given this high clinical relevance, it has been suggested that improving airway-protective outcomes may be dependent on improving cognitive awareness and immediate response to cough-inducing stimuli (Hegland et al., 2016; Troche et al., 2014; Yamanda et al., 2008). Thus, it is important to understand and evaluate the sensory-motor aspects of cough with consideration of cough-inducing stimuli and its sensory-perceptual correlates. Such an understanding is crucial for developing valid early identification and intervention protocols for cough rehabilitation and improving clinical outcomes.

Conclusions

The present investigation is the first to systematically compare two magnitude estimation tools, the Modified Borg Scale (MBS) and the generalized Labeled Magnitude Scale (gLMS) to measure UTC sensations in humans. Both tools were reliable and valid in detecting UTC sensations and predicting cough motor response. The MBS tool was more sensitive and highly reliable in detecting differences in UTC sensations for stronger sensory stimuli at and above cough motor thresholds. The gLMS tool was more sensitive and moderately reliable in detecting differences in UTC sensations for weaker sensory stimuli at sub-thresholds of cough. The choice of the scale is contingent upon the goals of psychophysical cough evaluations. Future studies are required to develop valid cough sensory evaluation protocols that have tremendous utilization for translational research in clinical populations.

Disclosures

None

Ethics Statement

This study was carried out in accordance with the recommendations of the Institutional Review Board of Teachers College, Columbia University. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Teachers College, Columbia University.

Authors' Contributions

AR and MT conception and design of research; AR acquired data, performed experiments, and analyzed data; AR and MT interpreted results of the experiment; AR prepared figures and tables; AR drafted the manuscript; AR and MT edited and revised the manuscript.

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Abbreviations

UTC urge to cough; PD, Parkinson's disease; HYA, healthy young adults; GERD, gastro esophageal reflux disease; μM, micromolar; Cr2, two-cough motor response; ME, magnitude estimation; MBS, Modified Borg Scale; gLMS, generalized Labeled Magnitude Scale; log, logarithmic; MANOVA, multivariate analysis of variance;

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Chapter 4

OVERALL DISCUSSION

The overall purpose of this dissertation research was to improve the methods for sensory testing of cough for clinical research and practice. We identified two significant gaps pertaining to measurement of cough sensations from the existing literature. The first was about a valid descriptor for cough sensations (i.e., UTC) and the second was about a valid tool to measure it. We designed two specific studies to address these gaps. We extensively applied the principles of psychophysics in our methodological designs based on existing literature from the sensory sciences (Hayes, Allen, & Bennett, 2013; Lawless et al., 2010) as well as based on the literature from cough evaluations (Davenport et al., 2002; Hegland et al., 2016; Troche, Schumann, Brandimore, Okun, & Hegland, 2016).

The first study informed us that the conventionally used "UTC" descriptor, when paired with an equally predominant "warm/burn" sensory descriptor (related to the cough stimuli capsaicin), was more sensitive and a valid predictor of the cough motor function. This provided an answer to the predominant question that /has lingered in the clinical and research world of cough testing, ever since Paul Davenport introduced the UTC terminology (Davenport et al., 2002). The study confirmed that the "UTC" is indeed a very valid descriptor for cough testing. We also learned that differential cough sensations such as tickle also exist at sub-thresholds of capsaicin stimuli and these should not be overlooked, owing to their potential clinical implications. Our focus thus shifted to the original tool that was used to measure UTC (i.e., MBS, Davenport et al., 2002) and we critically evaluated its candidacy for UTC measurement.

Detailed study of the MBS tool revealed that it was revised and adapted from the modified Borg pain and dyspnea scale (Borg, 1998) as a category scale and has certain limitations. We learned that the category scales assume the adjective labels to mean the same thing to all participants within a specific sensory modality. However, Linda Bartoshuk's work from taste (Bartoshuk et al., 2004) informed us that this is not a valid assumption, as it does not tell us about the actual perceived intensity of the UTC experience. Individuals are prone to use the same number or label for a particular experience in its context, which makes it challenging to capture their actual magnitude of experience (i.e., absolute magnitude). The remediation of this problem through development of the gLMS (adapted from the Labeled Magnitude Scale; Green, Shaffer, & Gilmore, 1993) with its top anchor "maximum sensation of any kind" made us aware that such a scale structure can elicit a normalized sensory response and make our UTC group comparisons valid (Bartoshuk et al., 2004). Given this empirical validation of gLMS from taste, we became curious to see if we could use this tool to measure UTC reliably and if it can be compared with our existing MBS tool. Thus, we embarked on our second study in search of a reliable tool for UTC and compared the reliability and validity of the gLMS and MBS in measuring UTC.

The results from the second study informed us that the UTC can be effectively measured using two metrics, the Modified Borg Scale (CR-10, Borg, 1952) as well as the gLMS (Bartoshuk et al., 2004). Additionally, the methodological design and results from both studies provided extensive insights into the didactic interaction between the experimenter and the subjects that was critical for sensory science investigations, whether it was to describe a sensation or evaluate its strength.

The study findings from both of the studies also aligned in many ways with the existing literature from chemosensory sciences as well as from cough research. The descriptive quality of warm/burn reported in chemosensory sciences for capsaicin was further supported by the phase I results of our first study (Hayes et al., 2013; Lawless et al., 2010). The enhanced sensitivity of the UTC descriptor to varying effects of stimuli concentration as well as its predictive value of cough response aligned with the findings from the seminal work on UTC (Davenport, Sapienza & Bolser 2002; Davenport, et al., 2007). The similarities of warm/burn and UTC descriptor inferred from a human psychophysical perception view were also well supported by cognitive psychology models related to sensation and urge-to-act (Cameron, 2001; Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011). The similarities and differences in the scale performances also aligned with the existing body of literature. Both scales demonstrated good validity in measuring UTC sensitivity and also in predicting the cough motor behavior for the capsaicin stimuli. This stimulus-sensation-response relationship is well supported by the existing sensory cough research based on the use of modified Borg category scale (Davenport et al., 2002; Hegland et al., 2016; Troche et al., 2016). The differences in scale performance at low and high concentrations of capsaicin stimuli were attributed to the individual design of the scales and its susceptibility to compression and clustering, as widely reported in the chemosensory science literature (Bartoshuk et al., 2002; Hayes et al., 2012).

With respect to the use of gLMS, although it was reliable and valid in estimating UTC, we opine that the use of a generalized top anchor can be challenging at times if participants report their maximum sensation as a cough. This was encountered in our study, where three out of thirty-four participants had reported their maximum sensation ever experienced as "intense coughing followed by broncho-constriction." Since the gLMS scale usage requires that the top anchor should not match the sensation of interest, we redirected our participants to report any maximum sensation other than cough. We speculated whether this would have affected their sensory magnitude reporting. A scale that was originally created for one purpose may be challenging when it is translated to other measurements. This was potentially the problem with the MBS tool since it was originally created to evaluate strength of exertions and eventually found its way to measure UTC. Thus, we need more research to understand the scale structure and design of gLMS before we translate it to cough-specific evaluations.

The studies have some limitations and should be addressed in future research. Notably, the significant limitation in the second study was the use of the Modified Borg Scale ratings as a continuous measure and not based on ordinal measurement, as reported in the conventional cough literature (Davenport et al., 2002). This makes the comparisons challenging with the existing literature regarding scale usage as well as in making decisions about the right tool. The study design should thus be repeated using the MBS tool with UTC measurements obtained the way they have been traditionally used in the cough literature and then compared with the results of this study. This will provide a complete picture regarding the tool selection for cough sensory testing. Additionally, cross-modal data validation of the UTC measurements (with other sensations) should be done with a magnitude estimation tool to ensure whether individual differences in UTC sensations are exclusively because of the scale usage. The cross-modally validated UTC tool can then be used for developing peripheral and central cough sensory measures, based on the Weber fraction and dynamic range determination, absolute threshold estimation, and difference limen testing. Subsequently, these measures should be further validated using signal detection methods (i.e., sensitivity and specificity). This should be done for a variety of cough-inducing stimuli with variable parameters of stimuli intensity and temporal duration. Development of such quantitative cough sensory measures is crucial because they directly reflect the inner functioning of the sensory processing system. This is vital for translational research, and relevant basic science work should be thus pursued with utmost vigilance.

The study results have some potential implications for clinical practice. Both tools have demonstrated an excellent ability to capture a wide range of participants' UTC sensory experiences, detect subtle differences in UTC at neighboring concentrations, predict cough motor responses, and have good to excellent between-trial reliability. This is the first study to demonstrate valid and reliable UTC responses across a wide range of sensory continua. The data from the study can thus serve as a normative reference to differentiate between normal and impaired groups and aid in diagnosis and differential diagnosis as well as evaluate various therapeutic interventions. In addition, as recently reported in the literature (Troche et al., 2016), the UTC sensory measure can independently serve as an effective prognostic indicator to evaluate airway protective deficits in impaired population.

Conclusion

The two scientific investigations conducted as part of this dissertation thesis are novel and provide valid contributions to the cough literature. The studies have validated a descriptor for cough sensation that can be used for psychophysical testing and introduced an additional metric to measure the UTC sensation, the gLMS (Bartoshuk et al., 2004). The studies have also demonstrated that both psychometric tools (i.e., MBS and gLMS) are reliable and valid for cough sensory testing. More importantly, the studies have advanced our understanding of the psychophysics of cough testing and identified a programmatic line of basic science work to methodologically test and validate cough psychometrics for clinical translational purposes.

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Appendix A

Preliminary Screening Questionaire

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University
Capsaicin Descriptor Study
Preliminary Screening Form

Participant ID: **Age/Sex**:

Screening Questions- Part A	**Responses**	
1. Do you have a history of neurological disease?	Yes	No
2. Do you have a history of respiratory disease such as COPD, asthma, bronchitis and sleep apnea?	Yes	No
3. Do you currently have any respiratory illness such as common cold or any seasonal allergies within the last 4 weeks?	Yes	No
4. Do you have a history of head, neck or chest surgery?	Yes	No
5. Do you smoke? If so how many cigarettes per day? ____________ 6. Do you have a history of smoking (E-cigarettes, marijuana, use of tobacco, nicotine gum) in the last 5 years? a. When was the last time you smoked and how frequent was it? ________________________ 7. Do you have an exposure to passive smoking?	Yes Yes Yes	No No No
8. Do you have a history of gastro esophageal reflux disease (GERD) and paradoxical vocal fold movement (PVFM)?	Yes	No
9. Do you have a history of chronic cough or swallowing difficulty?	Yes	No
10. Are you currently using codeine, medications for cough suppression and high blood pressure?	Yes	No
Screening Questions- Part B	**Responses**	
1. Do you have allergy to capsaicin or hot peppers?	Yes	No
2. Are you sensitive to eating spicy food or hot peppers?	Yes	No

Appendix B

Data Collection Forms

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University
Capsaicin Descriptor Study

Data Collection Form-Visit 1 (Cough Sensation Descriptor Series)

Participant Instructions: "You will be given some stimulus to inhale and you are to breathe in and out normally and respond with a behavior that comes naturally upon its inhalation. After that, please describe your sensation for that stimulus by indicating your top choice from these 3 choices. It's okay if you don't respond to one or other".
Clinician Instructions: Please provide water to the patient right after they rate the sensation. Make sure to present the next stimuli only after the participant reports of no lingering residual sensation. Provide more water if necessary.

Capsaicin Stimuli (µM)	**Trials**	**Descriptor**		
		No Sensation	**Tickle**	**Irritation**
0	**Trial 1**			
	Trial 2			
	Trial 3			
25	**Trial 1**			
	Trial 2			
	Trial 3			
50	**Trial 1**			
	Trial 2			
	Trial 3			
100	**Trial 1**			
	Trial 2			
	Trial 3			
200	**Trial 1**			
	Trial 2			
	Trial 3			

Definitions of capsaicin sensations provided to participants (Bennett and Hayes, 2012)

	Sensation	Definition
1.	No Sensation	Feeling of no perception or sensation of any sort
2.	Tickle	Feeling of a sensation of mild itch or mild scratch at the back of throat
3.	Warm/Burn	Feeling of a sensation of burn, sting, warm or heat at the back of throat

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University
Capsaicin Descriptor Study

Data Collection Form- Visit I (Warm/Burn and Urge -to -Cough (UTC) series across varying capsaicin concentration)

<u>Participant Instructions:</u> You will be given some stimulus to inhale and you are to breathe in and out normally and respond with a behavior that comes naturally upon its inhalation. After that, please rate your magnitude of perception of the sensation you have on this modified Borg scale, with 0 being no sensation and 10 being the strongest sensation of all.
<u>Clinician Instructions</u>: Please provide water to the patient right after they rate the sensation. Make sure to present the next stimuli only after the participant reports of no lingering residual sensation. Provide more water if necessary. Also, mark participants ratings from the Borg scale based on the randomization presentation of the stimuli and the perception of warm/burn or UTC

Test Block

Capsaicin Stimuli (µM)	Trials	Modified Borg Ratings	
		Warm/Burn	Urge to Cough (UTC)
0	Trial 1		
	Trial 2		
	Trial 3		
	Trial 4		
25	Trial 1		
	Trial 2		
	Trial 3		
	Trial 4		
50	Trial 1		
	Trial 2		
	Trial 3		
	Trial 4		
75	Trial 1		
	Trial 2		
	Trial 3		
	Trial 4		
100	Trial 1		
	Trial 2		
	Trial 3		
	Trial 4		
200	Trial 1		
	Trial 2		
	Trial 3		
	Trial 4		

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University

Capsaicin Descriptor Study

Practice Trial Block – Visit II

Capsaicin Stimuli (µM)	Trials		
0	Trial 1		
50	Trial 1		
200	Trial 1		

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University

Capsaicin Descriptor Study

Modified Borg Scale Rating Form

Participant Instructions: Please rate your magnitude of perception of the sensation you have on this scale, with 0 being no sensation and 10 being the strongest sensation of all.	
0	None at all
0.5	Just noticeable
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very Very Severe
8	
9	
10	Very, Very, Very Severe (Almost Maximal)

(Reference: Borg et al., 1982; Davenport et al., 2002)

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University
Magnitude Estimation Study

<u>Magnitude Estimation Data Collection Form</u>

PARTICIPANT ID: ______________________ DATE: _____________ VISIT: □ 1 □ 2

VISIT 1: □ MBS □ gLMS

VISIT 2: □ MBS □ gLMS

<u>*Participant Instructions:*</u> *"You will be given a stimulus. You are to breathe in and out through your mouth and do whatever feels natural when given the stimulus. After that, please rate your magnitude perception of the UTC sensation using these two scales.*

a) Modified Borg scale, with 0 being no sensation and 10 being the strongest sensation of all".
b) gLMS scale, 0 being no sensation and 100 being the strongest imaginable sensation of all

<u>*Clinician Instructions*</u>*: Please provide water to the participant right after they rate UTC. Make sure to present the next stimuli only after the participant reports of no lingering residual sensation. Provide more water if necessary. Also, mark participants ratings from the Borg scale or the gLMS based on the randomization presentation of the stimuli and the perception of UTC*

TEST BLOCKS

Capsaicin Stimuli (µM)	Trials	Modified Borg Ratings	Cough Response	Recovery Time (secs)
		Urge to Cough (UTC)		
0	Trial 1			
	Trial 2			
	Trial 3			
10	Trial 1			
	Trial 2			
	Trial 3			
20	Trial 1			
	Trial 2			
	Trial 3			
30	Trial 1			
	Trial 2			
	Trial 3			
40	Trial 1			
	Trial 2			
	Trial 3			
50	Trial 1			
	Trial 2			
	Trial 3			
Capsaicin Stimuli	Trials	Modified Borg Ratings	Cough Response	Recovery Time

(μM)				**(secs)**
65	**Trial 1**			
	Trial 2			
	Trial 3			
80	**Trial 1**			
	Trial 2			
	Trial 3			
100	**Trial 1**			
	Trial 2			
	Trial 3			
200	**Trial 1**			
	Trial 2			
	Trial 3			
300	**Trial 1**			
	Trial 2			
	Trial 3			

Capsaicin Stimuli (μM)	**Trials**	**gLMS Ratings**	**Cough Response**	**Recovery Time (secs)**
		Urge-to-Cough (UTC)		
0	**Trial 1**			
	Trial 2			
	Trial 3			
10	**Trial 1**			
	Trial 2			
	Trial 3			
20	**Trial 1**			
	Trial 2			
	Trial 3			
30	**Trial 1**			
	Trial 2			
	Trial 3			
40	**Trial 1**			
	Trial 2			
	Trial 3			
50	**Trial 1**			
	Trial 2			
	Trial 3			
65	**Trial 1**			
	Trial 2			
	Trial 3			
80	**Trial 1**			
	Trial 2			
	Trial 3			
Capsaicin Stimuli (μM)	**Trials**	**gLMS Ratings**	**Cough Response**	**Recovery Time (secs)**
100	**Trial 1**			

	Trial 2			
	Trial 3			
200	**Trial 1**			
	Trial 2			
	Trial 3			
300	**Trial 1**			
	Trial 2			
	Trial 3			

Appendix C

Practice/Warm-up Trial Instructions

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University
Magnitude Estimation Study

PRACTICE/WARM-UP TRIAL INSTRUCTIONS

Cross Modal Orientation Protocol Instructions: Please rate the following imagined sensations using both the scales (MBS and gLMS). Follow the instructions below for rating scales.

□ **Loudness of whisper** □ **Sweetness of cotton candy** □ **Burn of cinnamon gum**
□ **Pain of tongue bite** □ **Loudest sound**

Instructions for Modified Borg Scale (MBS):
First determine which descriptor most appropriately describes the intensity of the sensation, then fine-tune your rating by placing a mark on the scale at the proper location between that descriptor and the next most appropriate one. Please rate the magnitude as 0 if there is no perception and 10, if there is maximal sensation.

Instructions for generalized labeled magnitude scale (gLMS):
Please write down at the top of the scale- the strongest imaginable sensation of any kind. Then, please rate the sensation of interest in comparison to your strongest imaginable sensation of any kind.

First determine which descriptor most appropriately describes the intensity of the sensation, then fine-tune your rating by placing a mark on the scale at the proper location between that descriptor and the next most appropriate one. Please rate the magnitude as 0 if there is no perception and 100, if it's the strongest imaginable sensation every experienced of any kind. Now, using the same method, please rate the magnitude of sensation for the cough stimulus.

TRIAL BLOCK- VISIT 1

Capsaicin Stimuli (µM)	**Trials**	**UTC**	
		gLMS	**Borg**
0	**Trial 1**		
50	**Trial 1**		
200	**Trial 1**		

TRIAL BLOCK- VISIT 2

Capsaicin Stimuli (µM)	**Trials**	**UTC**	
		gLMS	**Borg**
0	**Trial 1**		
50	**Trial 1**		
200	**Trial 1**		

Appendix D

Modified Borg Scale

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University
Magnitude Estimation Study

Modified Borg Scale Rating Form

Participant Instructions: Please rate your magnitude of urge-to- cough you have on this scale, with 0 being no sensation and 10 being the strongest sensation of all.	
0	**None at all**
0.5	**Just noticeable**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very Very Severe**
8	
9	
10	**Very, Very, Very Severe (Almost Maximal)**

(Reference: Borg et al., 1982; Davenport et al., 2002)

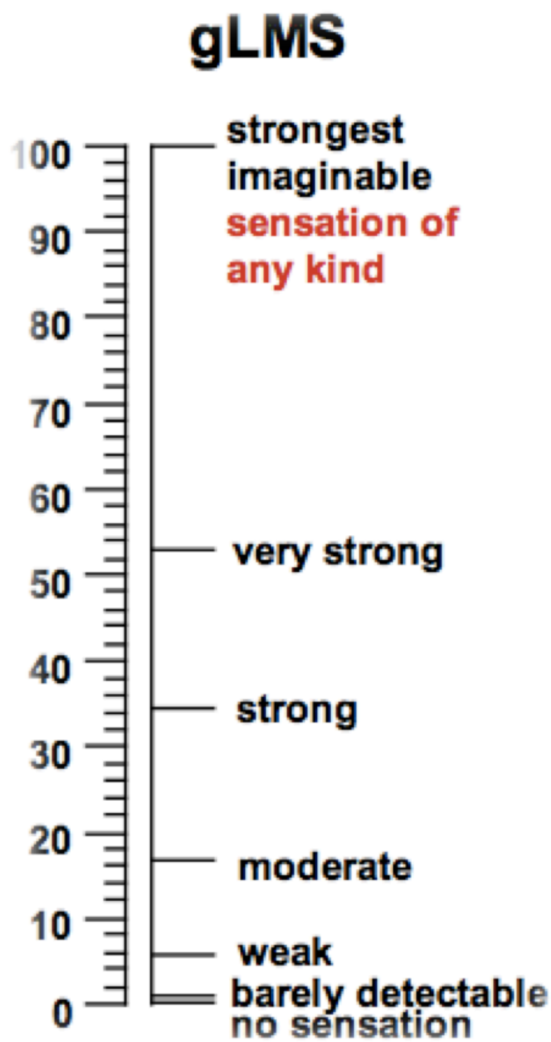
Appendix E

generalized Labeled Magnitude Scale

Laboratory for the Study of Upper Airway Dysfunction
Teachers College, Columbia University

<u>Magnitude Estimation Study</u>

<u>gLMS Rating Form</u>



(Reference: Bartoshuk et al., 2004)

Appendix F

Recruitment Flyers

RESEARCH PARTICIPANTS NEEDED

The *Upper Airway Dysfunction Lab* at Teachers College, Columbia University is looking for healthy individuals without neurological diseases/conditions to participate in a research study aimed at examining perceptual descriptors and sensitivity for cough inducing stimuli at varying concentration levels.

Many times, people with neurological conditions such as Parkinson's disease will develop difficulty with swallowing and coughing. Early identification of these impairments is important to prevent detrimental effects on health and quality of life. In order to develop and advance early identification process in disease population, it is important to study healthy population first.

Therefore, the purpose of this research study is to examine perceptual descriptors and sensitivity for cough inducing stimuli at varying concentration levels in healthy young adults. Your participation will enable development of evaluation protocols that can be used to compare healthy and impaired groups.

This study will require two visits. Each visit will require about 1 hour of participation

To participate in this study you must:

- Be between the ages of 18-35 years of age
- Not have a neurological and respiratory condition/disease
- No active smoking

If you are interested, please contact:

Akila Rajappa at (212) 678-3072

Email: atr2123@tc.columbia.edu; t4.tc.columbia.edu/uadlab

Participate in Cough Sensation Study

Are you a healthy 18-35-year-old?

Without a neurological or respiratory condition or disease

No Active Smoking

Come for Two Visits to UAD Lab 1-Hour Duration Each

Call: (212)-678-3072

Email: atr2123@tc.columbia.edu

t4.tc.columbia.edu/uadlab

Teachers College, Columbia University
Institutional Review Board
Protocol Number: 18-466
Consent Form Approved Until: 08/17/2019

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