AN ABSTRACT OF THE THESIS OF

Tyler J. Flaherty for the degree of Master of Science in Food Science and Technology presented on April 5, 2016.

Title: Individual Differences in Retronasal Odor Responsiveness: Effects of Aging and Concurrent Taste

Abstract approved:

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Taste sensitivity has been considered the primary chemosensory factor in studies of chemical senses and ingestive behavior. However, recent research has shown that retronasal olfaction is at least equally important in food preference and selection. Additionally, taste has been shown to modulate perceived intensity of retronasally perceived odors. The objectives of this study were (1) to measure individual differences in retronasal olfactory responsiveness to food odors in the presence and absence of a congruent taste; and (2) to determine the effect of aging and gender on retronasal olfactory responsiveness. We hypothesized that when measured independently, variations in responsiveness to retronasal odors are greater than those of tastes, but that these variations are effectively reduced by the presence of a congruent taste, particularly for older individuals. Additionally, as taste and retronasal odor were being evaluated separately, it provided us a unique opportunity to compare responsiveness within and across modality. Two groups of subjects (young cohort, n=54, and old cohort, n=48) were asked to sample 2 tastants, 4 food odorants, and the

congruent taste-odor pairs, and rate intensities for appropriate categories. Results showed that responsiveness to odors varied greatly among individuals compared to that of tastes and further that variations in odor responsiveness were greater for old compared to young cohort. In the presence of a congruent taste, however, the variations in responsiveness to the odors were significantly reduced, with greater effect in the old cohort. In addition, responsiveness to the tastes and odors were correlated. Furthermore, the degree of correlation was greater within taste or odor attributes than across modality. These findings imply that an individual's responsiveness to 1 or 2 prototypical tastants or food odors may be predictive of an individual's overall responsiveness for the given modality. The current data also suggest that older individuals, or those with low olfactory sensitivity in general may not recognize the reduced sensitivity when consuming foods.

Individual Differences in Retronasal Odor Responsiveness: Effects of Aging and Concurrent Taste

by
Tyler J. Flaherty

A THESIS

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Master of Science

Presented April 5, 2016
Commencement June 2016

Master of Science thesis of Tyler J. Flaherty presented on April 5, 2016

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I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

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ACKNOWLEDGEMENTS

The author expresses sincere appreciation to his major advisor, mentor, and principal investigator, Dr. Juyun Lim. Her expertise and guidance made this research possible, and positively influenced the authors' growth as a researcher, writer, and scientist. The author would like to thank committee members, Dr. Elizabeth Tomasino, Dr. Robert McGorrin, and Dr. James Males for their commitment of time, advice, and feedback on the present work. Also, the author would like to thank his lab mates for their great discussion on topics related to our research (or otherwise), and for the shared joy of watching one another grow professionally and personally. Finally, the author would like to thank his family for their continued support. The educational journey has been long and often not easy; their patience and support has always been greatly appreciated. Of particular recognition, the author wants to thank his wife, Erika, for being a constant source of inspiration and motivation to do the best possible in all of life's endeavors.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (CONTINUED)

Page

LIST OF FIGURES

LIST OF TABLES

1 General Introduction

1.1 The Role of Smell and Taste in Human Ingestive Behavior

The senses of smell and taste are the primary means by which foods are perceived by humans. Accordingly, these are also important for humans to make decisions about food selection and preference (i.e., ingestive behavior). Smelling and tasting are both important in ingestive behavior, yet each sense is represented by a physiologically separate sensory system. Olfaction, or the sense of smell, is unique in the fact that it has a dual nature, or two routes of reception (Rozin 1982). These two routes are orthonasal olfaction, or sniffing through the nostrils, and retronasal olfaction, or smelling through the mouth and exhaling through the nose. Both routes are mediated by the same set of receptors in the olfactory epithelium. Even so, orthonasal and retronasal odor perception activate different regions of the brain (Shepherd 2006). Taste perception, on the other hand, is mediated through an array of taste buds and taste cells throughout the mouth, with a high concentration of these cells on the anterior and posterior surface of the tongue (Breslin and Spector 2008).

Even though separated anatomically, smell and taste share functions within ingestive behavior, ranging from getting the first whiff of a potential food source and locating it, all the way to serving as the final checkpoint before a food item is ingested. The role of olfaction in human ingestive behavior is diverse and can be separated, mostly, by the route of olfaction involved. Beginning with orthonasal olfaction, distal location and tracking of a potential food source is commonplace for many mammals (Porter et al. 2007). However, for humans, distal location of suitable food is often not necessary given food security in a modern environment. When food

is much closer, further olfactory cues can be used to determine the valence, or suitability of the given food for consumption (Fallon and Rozin 1983; Cain et al. 1998; Boesveldt et al. 2010; Yamada et al. 2014). Pleasant and unpleasant orthonasally perceived odors can also modulate a person's appetite for, or satiety from, a specific food source (Yeomans 2006 for review). Once a food is placed into the mouth, odors are perceived retronasally. Specifically, odor volatiles are released during chewing and pumped from the back of the mouth up the nasopharynx, which are then delivered to the olfactory epithelium upon exhalation through the nose (Rozin 1982). Before a food is swallowed, retronasally perceived odors, along with taste, serve as a final check to evaluate the safety of the food. If the flavor of food deviates from the expected perception, the food may be rejected (e.g. rotting vs. fresh fruit). Sustained consumption of a safe food can lead to a satiation effect, where retronasally perceived odors are considered a key component, along with texture, taste, and temperature (Ruijschop et al. 2008).

In addition to olfaction, taste plays an important role in food preference and selection. Taste receptors can only be stimulated by several classes of stimuli, which are sweet, salty, sour, bitter, and umami (Breslin 2013). While there are arguably additional taste categories, including taste of starch hydrolysis product (Lapis et al. 2014), fatty acids (Running et al. 2015), and others (Liman et al. 2014 for review of non-canonical taste perception), discussion is beyond the scope of the present study. Within the 5 known tastes, each signals for a positive or negative response, although such response can be changed based on previous experience. Sweetness signals the presence of carbohydrates, or energy; saltiness signals for sodium; umami signals for

amino acids, specifically L-glutamate in humans; bitter signals for potential toxins; and sour signals for rancidity, or decay. Tastes that signal for beneficial nutrient content are often considered pleasant (i.e. sweet, salty, savory), and tastes that signal a toxin or rancid food are considered unpleasant (i.e. sour or bitter) (Breslin and Spector 2008). The signal from these taste qualities, in addition to the perceived intensity of each taste, modulates the overall pleasantness of taste stimuli, and therefore the likelihood of a food being consumed (e.g., Lucas et al. 2011). For instance, if a food has an extremely strong bitter quality, the food will likely be rejected very quickly. However, if the bitterness is weak, other factors such as concurrent positive tastes or pleasant retronasal odors may increase overall pleasantness of the food. Beyond determining nutritional value of foods and then accepting or rejecting a food, taste has been shown to modulate appetite and satiety as well (Yeomans 1998).

1.2 Individual Differences in Olfactory and Taste Responsiveness

1.2.1. Individual differences in Olfactory Responsiveness

Individuals can vary in their perception of odors. Differences in odor perception can relate to both quality and sensitivity. Individual differences in the perception of odor quality infer that the same odorant can be perceived differently between individuals. For example, perceived pleasantness of various herb odors (i.e. basil, cilantro), have been shown to have a very wide range of individual differences as well (Knaapila et al. 2012). These authors, as well as others, have also shown that individuals vary in odor perception as a result of differences at the genetic level. For instance, variation in perception of cis-3-hexen-1-ol, an odor molecule with a distinct

"green leaf" or "grassy" aroma has been linked to genetic variation in expression of the odorant receptor *OR2J3* (Jaeger et al. 2010). Accordingly, recent work has shown that liking and disliking of specific vegetables are related to how pleasant or unpleasant the retronasally perceived vegetable odor are to each individual (Lim and Padmanabhan 2013). In addition to differences in perception of odor quality, there have been numerous studies showing inter-individual differences in sensitivity and responsiveness to odors (Berglund et al. 1971; Burdach et al. 1985; Powers and Shinholser 1988; Wysocki and Gilbert 1989; Walker et al. 2003; Keller et al. 2012). Note that sensitivity is defined as threshold measurement, and responsiveness is defined as measurement of suprathreshold intensity. Among the large body of work looking at olfactory sensitivity, a common finding is that thresholds for a particular odor can vary widely across individuals. Peng et al. (2012) found orthonasal olfactory thresholds for 1,8-cineole (eucalyptus), isobutyraldehyde (straw-like), and β-damascenone (a rose-like odorant in bourbon) to vary by up to 5 orders of magnitude across individuals. Wide inter-individual variation in responsiveness to odors at supra-threshold concentrations has been noted as well. Berglund et al. (1971) found that individual exponents of the power function for eugenol (cinnamon or clove-like odor) varied between individuals more than 8 orders of magnitude. It should be noted that most, if not all, of the previous research on individual differences in olfaction have evaluated orthonasal sensitivity, despite the obvious role that retronasal olfaction plays during food consumption.

To explain wide individual differences in olfactory sensitivity, a number of factors have been linked to variations in sensitivity. These factors include

demographical and behavioral differences among individuals, such as gender and age, and differences in lifestyle, such as alcohol consumption and smoking. With advancement in laboratory capabilities and decrease in cost of genetic sequencing, individual genetic differences have also been evaluated in recent years as well (e.g., Jaeger et al. 2010, as mentioned previously).

Both age and gender have been classical means by which researchers ascribe individual differences in olfactory sensitivity. Age, in particular, has been given special attention, as it is often attributed with decrease in olfactory perception. Therefore, it impacts quality of life (Temmel et al. 2002; Philpott and Boak 2014), and loss of appetite may influence nutrient intake (e.g. Schiffman and Warwick 1993). Peak olfactory abilities are seen from humans in their 20's and 30's, with a steady decrease until their 60's (Doty et al. 1984). After that point, decrease in olfactory function is far more rapid, due to physiological changes such as cribriform plate ossification (Kalmey et al. 1998) as well as general degradation of cognitive ability (Murphy 1985).

Research on the effect of gender on olfaction has shown less consistent effect. Some researchers have noted women as having greater ability to detect, identify, and perceive odors than men (Wysocki and Gilbert 1989; Brand 2001 for review). Wysocki and Gilbert (1989) conducted a smell survey in conjunction with National Geographic and had up to 1.2 million respondents complete the test. In their study, women had a small, yet significant increase compared to men in odor detection, identification, and perceived intensity. Other research has shown mixed results, showing female olfactory superiority only in odor identification (Cowart 1989;

Michon et al. 2009). In addition, numerous studies, many of which were not specifically testing for gender effects, saw no difference at all (e.g. Stevens and Cain 1986; Cain and Gent 1991). The true nature of differences in olfactory responsiveness between men and women appear rather unclear based on previous literature.

Other factors that have been well established as having an effect on individual differences in olfaction include differences in lifestyle, such as alcohol use and smoking. Not surprisingly, smoking has been shown to have adverse effects on numerous psychophysical measurements of olfactory performance, with a dose-dependent increase in impairment from greater cigarette use (Katotomichelakis et al. 2007). Alcohol dependence has shown to decrease olfactory performance in several measures as well (i.e., threshold, discrimination, and identification) (Rupp et al. 2003). Given the general health concerns involved with tobacco use and alcohol dependence, it is not unusual then, that olfactory responsiveness suffers on average as well.

1.2.2. Individual Differences in Taste Responsiveness

Individual differences in taste responsiveness have been studied extensively, with the majority of research relating to the bitter taste of 6-*n*-propylthiouracil (PROP). The ability of an individual to taste PROP has been associated with heightened sensitivity to many other stimuli, including other bitter tastants (Bartoshuk 1979; Bartoshuk et al. 1988; Drewnowski et al. 1997b) and sweet tasting substances (Bartoshuk 1979; Drewnowski et al. 1998; see Bartoshuk 2000 for review). Also, PROP taster status has been linked to sensitivity within other modalities, such as chemesthetic stimulation (Tepper and Nurse 1997; Tepper and Nurse 1998; Prescott

and Swain-Campbell 2000) and sensitivity to orthonasal odors (Yackinous and Guinard 2001). Finally, by extension of heightened sensitivity to other tastes, chemical irritants, and odors, PROP tasting ability has also been considered as a factor that influences food preference and selection (Bartoshuk 1993; Drewnowski et al. 1997b; Dinehart et al. 2006; Tepper et al. 2009). However, another study evaluated responsiveness to PROP, as well as all prototypical tastes (i.e. sucrose, NaCl, quinine HCl, and citric acid), to see how strongly responsiveness correlated amongst PROP and the basic taste qualities (Lim et al. 2008). The authors found that responsiveness to PROP was only correlated to responsiveness of quinine HCl (another bitter taste), whereas responsiveness to other basic taste qualities significantly correlated with one another. This suggested that individual taste responsiveness may in fact be better predicted by evaluating individual responsiveness to prototypical tastes rather than PROP.

1.3 Comparing Independent Sensations to Multimodal Flavor Perception

While human sensory systems are made up of physiologically separate sets of receptors, neurons, and pathways, consumption of food does not involve just one sense. Most often, overall perception of a food is referred to a "flavor" of the food . In fact, it is well known that flavor is a multi-modal percept, primarily attributed to sensations of taste, retronasally perceived odor, and somesthetic stimulation (see Delwiche 2004; Auvray and Spence 2008 for reviews). Therefore, in order to evaluate individual differences in relation to ingestive behavior, both taste and retronasally perceived odor must be evaluated together as well as separately.

1.4 Research on Taste-Odor Interactions

Because taste, retronasally perceived odor, and somatosensation occur so frequently together during food consumption, it makes sense that these senses may interact or integrate with one another. Indeed, much research has been done to show that there are numerous interactions within and across modalities (Delwiche 2004; Verhagen and Engelen 2006; Stevenson 2009). In connection to human ingestive behavior, the relationship between individual differences in taste and retronasal olfaction can be further investigated by looking at taste-odor interactions. Of particular interest would be taste enhancement by retronasal odor and retronasal odor enhancement by taste. In both types of enhancement, there are specific conditions under which the effects are observed. While there is still disagreement among researchers as to which of these are these are perceptual phenomena (see Green et al. 2012; Linscott and Lim 2016 for discussion), some of the underlying conditions are the same. It is well documented that both taste and retronasal odor enhancement require the taste-odor pairs to be congruent in nature (Frank and Byram 1988; Kuo et al. 1993; Schifferstein and Verlegh 1996; Lim et al. 2014; Linscott and Lim 2016). Also, enhancement seems to only occur at relatively low concentrations of odor, and only if the taste signals the presence of a "beneficial" substance (i.e. sweet, salty, umami) (Green et al. 2012; Fujimaru and Lim 2013; Lim et al. 2014; Linscott and Lim 2016). These conditions support the proposed function of retronasal odor enhancement, which is to increase the perceived intensity of a nutritionally beneficial substance when the odor alone is not strong enough to bring attention to the fact that a

food with nutritional value is present (Green et al. 2012; Linscott and Lim 2016). Perceived intensity is not only a function of physical concentration, but can vary based on individual differences in olfactory responsiveness as well. Therefore, it is likely that individual differences in retronasal olfactory responsiveness may modulate the degree to which food odors can be enhanced by a congruent, nutritive taste.

Although retronasal olfaction plays an integral role in flavor perception and human ingestive behavior, no research has evaluated individual differences in retronasal olfaction. Furthermore, nearly all previous studies have evaluated threshold sensitivity, whereas odors and tastes in foods are most often found at supra-threshold concentrations. In addition, food consumption is never comprised of just odor or taste, and known interactions between modalities suggest an additional source of individual variation. Thus, both modalities should be evaluated within the same study to see direct effects of taste on retronasal odor. Therefore, this study aims to evaluate the effects of aging, gender, and concurrent taste on retronasal olfactory responsiveness, with an emphasis on how this translates to food consumption and human ingestive behavior.

Individual Differences in Retronasal Odor Responsiveness: Effects of Aging and Concurrent Taste

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Key words: Aging; Flavor; Individual Differences; Retronasal odor; Responsiveness; Taste-odor interaction

2.1 Abstract

Individual differences in taste sensitivity have been considered the primary chemosensory factor in studies of chemical senses/ingestive behavior. Recent findings suggest, however, that retronasal odor perception is equally important in food preference and selection and, furthermore, the presence of a congruent taste can modulate responsiveness to retronasally perceived odors. The primary objective of this study was to measure individual differences in responsiveness to food odors in the presence and absence of a congruent taste. In order to achieve this goal, we experimentally manipulated the way taste and odor stimuli are presented. We hypothesized that when measured independently, variations across subjects in responsiveness to retronasal odors are greater than those of tastes, but that these variations are effectively reduced by the presence of a congruent taste, especially for the older cohort. Two groups of subjects (young vs. old cohorts) were asked to sample 2 tastants, 4 food odorants, and the congruent taste-odor pairs, and rate intensities for appropriate categories. Results showed that responsiveness to odors varied greatly across individuals compared to that of tastes and further that variations in odor responsiveness were greater for old compared to young cohort. In the presence of a congruent taste, however, the variations in responsiveness to the odors were significantly reduced, in particular for the old cohort. The current data suggest that older individuals and those with low olfactory sensitivity may not recognize the reduced sensitivity when consuming foods.

2.2. Introduction

Olfaction is one of the primal senses for many animals, including humans. The sense of smell, just like any other senses, allows us to gather information regarding our environment and respond to it. Accordingly, the human olfactory system has its distinctive functions relating to social communication, avoidance of environmental hazards, and ingestive behavior (see Stevenson 2010 for review on human olfactory function). The olfactory function within ingestive behavior is particularly of great interest given its significant impact on the quality of life (Miwa et al. 2001; Temmel et al. 2002; Hummel 2005; Philpott and Boak 2014) and its unique aspect as a dual sensory process (Rozin 1982) for perceiving odors orthonasally through the nostrils and retronasally through the mouth. In particular, orthonasally perceived odors can be used to locate the source of a potential food from far distance (Porter et al. 2007) and also to determine the suitability as a food by sniffing from near distance (Fallon and Rozin 1983; Cain et al. 1998; Boesveldt et al. 2010; Yamada et al. 2014). Additionally, appetite and satiety can be affected by orthonasally perceived odors (see Yeomans 2006 for review). Once a potential food is placed in the mouth, volatiles are released during mastication. Retronasally perceived odors, in conjunction with taste and oral somatosensation, are then used to screen for potential deviation from the concept of a safe, known flavor (e.g., fresh milk). Retronasally perceived odors can also play a significant role in the acceptance and rejection of a food, by modulating the overall valence of the food as well as its perceived odor strength (i.e., too bland or too intense). Additional evidence shows that retronasal olfaction also can influence appetite and satiety (Ruijschop et al. 2008).

It is widely known that individuals differ greatly in terms of olfactory perception. For example, some individuals perceive the smell of certain vegetables and herbs being pleasant, while others find it unpleasant (Jaeger et al. 2010; Knaapila et al. 2012; Lim and Padmanabhan 2013). Accordingly, the valence of a food odor modulates the acceptance and rejection of the food. Beyond individual differences in the perception of odor quality, sensitivity to odors can vary across individuals as well (Berglund et al. 1971; Burdach et al. 1985; Powers and Shinholser 1988; Wysocki and Gilbert 1989; Walker et al. 2003; Keller et al. 2012). For example, sensitivity to vanillin, a common food odor, varies as much as 5 orders of magnitude across individuals (Powers and Shinholser 1988). Such large individual differences in olfactory sensitivity have often been linked to factors such as age and gender. Study findings suggest that a decline in olfactory sensitivity is common in the older population (Stevens and Cain 1987; Cain and Gent 1991; Doty and Kamath 2014) and that such change begins in healthy persons before old age (Stevens and Cain 1987). Observed sex differences have been less prominent, with cases showing females having generally greater sensitivity (see Brand 2001 for review). It should be noted that the vast majority, if not all, of previous studies tested individual differences in orthonasal olfactory perception in the form of threshold measurement. Exceptions we found are the studies that investigated the impact of aging on sensitivity or responsiveness to retronasally perceived food odors (Stevens and Cain 1986; Cain et al. 1990; Duffy et al. 1999) and the ability to identify foods (Murphy 1985). Note that the terms sensitivity and responsiveness are used to distinguish threshold and suprathreshold measures of perceived intensity.

Although individual differences in retronasal odor sensitivity/responsiveness have received little consideration, taste --another flavor component-- has been studied extensively in relation to how gustatory responsiveness influences human ingestive behavior. Historically, research on this topic has focused almost exclusively on the responsiveness to the bitter tastant 6-*n*-propylthiouracil (PROP) reporting that the ability to taste PROP is associated with higher responsiveness to other stimuli, including bitter substances (Bartoshuk 1979; Bartoshuk et al. 1988; Drewnowski et al. 1997a), sweet compounds (Bartoshuk 1979; Drewnowski et al. 1998; Bartoshuk 2000 for review), chemical irritants (Tepper and Nurse 1997; Tepper and Nurse 1998; Prescott and Swain-Campbell 2000), and also with food preference and selection (Bartoshuk 1993; Drewnowski et al. 1997b; Dinehart et al. 2006; Tepper et al. 2009). Recent study findings have shown, however, that prototypical tastants (i.e., sucrose, sodium chloride, citric acid, and quinine hydrochloride) may serve as a better predictor for an individuals' overall taste responsiveness than PROP does (Lim et al. 2008). Furthermore, the use of a single marker, whether it is PROP or a prototypical tastant, may not be sufficient to fully characterize individuals' orosensory responses and further to relate them to ingestive behavior (Hayes and Keast 2011).

Flavor components, taste, retronasal odor, and somatosensation, are rarely perceived independently during normal food consumption. In fact, there has been mounting evidence showing that sensations of taste, retronasal odor, and somatosensation integrate and interact with one another (see Delwiche 2004; Verhagen and Engelen 2006; Stevenson 2009 for reviews). In particular, the phenomenon of taste enhancement by retronasal odor and retronasal odor

enhancement by taste would be of great relevance in the studies of individual differences in taste and retronasal odor responsiveness in the context of ingestive behavior. While there are some contradictions and disagreement in the conditions under which taste and odor enhancement occur (reviewed in Green et al. 2012; Linscott and Lim 2016), it is generally agreed that one of the prerequisites of taste and retronasal odor enhancement is the congruency between taste and odor pairs (Frank and Byram 1988; Kuo et al. 1993; Schifferstein and Verlegh 1996; Lim et al. 2014; Linscott and Lim 2016). Study findings so far also suggest that retronasal odor enhancement occurs only for tastes that signal the presence of "nutritive" or "beneficial" substances (i.e., sweet, salty and umami) (Green et al. 2012; Fujimaru and Lim 2013; Lim et al. 2014; Linscott and Lim 2016). In addition, both enhancement effects seem to occur, if at all, only at relatively low concentration ranges (see Linscott and Lim 2016 for discussion, also see Fujimaru and Lim 2013). The proposed biological function of retronasal odor enhancement is to "boost" responsiveness to a nutritionally beneficial substance when the odor signal alone is not strong enough to indicate the presence of said substance (Green et al. 2012; Linscott and Lim 2016). If that is true, it seems likely that not only physical concentration of an odor stimulus, but also variation in individual perception of odor intensity would affect the potential for a retronasally perceived odor to be enhanced.

The primary objective of this study was thus to investigate inter-individual differences in responsiveness to retronasally perceived odors and tastes, independently and together. We hypothesized that when measured independently, the difference in responsiveness to retronasal odors is greater than to tastes across

individuals. However, when measured together, there would be less inter-individual difference in retronasal odor responsiveness in the presence of a nutritive, congruent taste. Given the known effects of age and gender on olfactory sensitivity, both factors were considered in the present study. Since responsiveness to both retronasal odors and tastes were measured independently, we had a unique opportunity to compare individual differences in responsiveness within and across modalities as well.

2.3 Materials and Methods

2.3.1. Subjects

A total of 102 subjects (68 female, 34 male) between the ages of 18 and 70 years old were recruited for this study. Two separate age groups were recruited: 54 young adults (35 females, 19 males; mean age = 23 years, ranging from 18 to 35 years) and 48 older adults (33 females, 15 males; mean = 63 years, ranging from 53 to 70). Subjects were recruited from the Oregon State University campus and surrounding community in Corvallis, OR. Individuals interested in participating in the study were asked to fill out a screening questionnaire. Subject inclusion criteria were individuals who 1) are non-smokers; 2) are not pregnant or lactating; 3) are not taking prescription pain medication; 4) do not have tongue, lip, or cheek piercings; 5) have no history of known food allergies; 6) do not have known deficit in taste or oral disorder; 7) are fluent English speakers; and 8) are familiar with strawberry, vanilla, chicken, and soy sauce. College-level educational attainment was also a prerequisite for participation to reduce any potential confounding effects associated with cognitive abilities. Subjects were asked to refrain from eating or drinking beverages other than water, and also not to use products containing menthol (e.g. mouthwash, toothpaste, chewing gum) at least 1 hr prior to their scheduled sessions. Additionally, subjects

were asked not to consume any spicy foods or use and strong-scented personal care products on the day of the test. The experimental protocol was approved by the Institutional Research Board at Oregon State University. Subjects gave written, informed consent prior to participation and were compensated at the end of the testing session.

2.3.2. Stimuli

A total of 10 test stimuli were used in this study: 2 taste stimuli [0.32 M sucrose (Macron Chemicals), and 0.18 M sodium chloride (NaCl, Macron Chemicals)], 4 odor stimuli [0.001% strawberry (v/v) (Abelei Flavors), 0.03% (v/v) vanilla (Abelei Flavors), 0.0009% (v/v) chicken (MANE Inc.), and 0.003% (v/v) soy sauce (MANE Inc.) odors], and 4 congruent taste-odor pairs (i.e., strawberry and vanilla odors with sucrose, chicken and soy sauce odors with NaCl) using the same concentrations as above. Odor cocktails (e.g., vanilla), instead of a single odor chemical (e.g., vanillin), were used in order to closely simulate heterogeneous mixtures of odors found in foods (Tranchida et al. 2009) and also to reduce the chance of a subject having a specific anosmia for an odor compound (Triller et al. 2008). The concentrations of test stimuli were chosen to ensure that both taste and odor stimuli concentrations elicited distinct, equi-intense sensations at least within each modality. Taste stimuli were prepared weekly using deionized water and kept in airtight glass jars at 4-6 °C. Odor stimuli used were lipid soluble and thus were diluted down from the stock odorant using United States Pharmacopeia grade mineral oil, to an intermediate concentration, at a factor of 151 times higher than the final test concentrations stated above. The diluted samples were poured into multiple 4-mL vials (National Scientific

Company) and each vial was used for the preparation of samples for up to 5 subjects, within the same day testing. Final concentrations of test odors were prepared immediately before individual sessions to ensure no loss of volatiles. All test stimuli were allowed to come to room temperature (20-22 °C) before presenting to subjects.

2.3.3. Odor Delivery

All odor stimuli were delivered retronasally using a specialized odor delivery device developed in our lab (Lim and Johnson 2011), which allowed for vapor phase delivery of odor compounds with no associated taste and/or tactile sensation. A 30 mL sample of odorants was held in 130mL glass jars (VWR environmental sample container) sealed with a plastic lid in which 1 – 7mm and 2 – 2mm diameter holes were made. The holes were sealed using laboratory masking tape to eliminate loss of volatiles. The exterior of the odor delivery device was covered with aluminum foil to mask any visual cues. To ensure consistent delivery of odor, each sample was stirred for 1 min at 600 rpm on a stir plate, prior to each trial. Immediately before presentation to subjects the tape was removed and the short side of a bent flexible straw was inserted into the 7 mm hole. The straw was secured in place with the aid of laboratory parafilm (see Lim and Johnson 2011 for details and picture of device).

2.3.4. Procedure

Each subject participated in 1 experimental session, of which included two parts: training/practice and data collection. Sessions lasted about 75 minutes on average.

2.3.4.1. Training and Practice

Prior to the data collection began, all subjects were verbally instructed on how to use the generalized version of the Labeled Magnitude Scale (gLMS) (Green et al. 1993;

Green et al. 1996; Bartoshuk et al. 2002). The scale was displayed on a computer screen, and subjects were shown how to use a mouse to make their ratings. The experimenter described unique features of the scale to subjects, and then gave practice by having them make intensity ratings for 15 remembered or imagined sensations (e.g., the sourness of a lemon, the pain from biting your tongue, the weight of a feather in your hand). This gave subject practice using the scale in the context of sensations that they may have experienced in everyday life.

Subjects were then given a practice run, to familiarize them with the testing procedures and also taste and odor qualities that they would experience during data collection. For taste stimuli, each subject was asked to open his/her mouth and the experimenter placed a disposable pipette filled with 2-mL of stimulus (0.32 M sucrose or 0.18 M NaCl) on the top of the tongue. As the subject closed his/her mouth around the pipette, the experimenter delivered the stimulus onto the surface of the tongue. The subject was asked to hold the liquid sample on the surface of the tongue for three seconds, expectorate it into the sink, and identify the sensation. For odor stimuli, the experimenter placed an odor delivery device containing one of four odor qualities (i.e., strawberry, vanilla, chicken, or soy sauce) in front of the subject. The subject was instructed to place his/her lips around the straw, inhale through the mouth, and exhale through the nose while taking two full breaths. Emphasis was given that the subject should take the same size breaths throughout the sampling period. After completing the second breath, the subject was asked to describe qualities of the sensation experienced for each of the four practice stimuli. The experimenter used this time to relate the subject's descriptions to the terminology that

would be used during the test (e.g., vanilla, chicken). When subject's descriptions were not synonymous with the odor name, statements were made to try and relate the two terms (i.e., "You mentioned that you would describe this sample as broth-like or savory. Would you agree that these qualities could also be described as chicken-like?"). Only in a few instances (fewer than 5), subjects could not agree to the identity of the odor. In those cases, they were told to replace, in their mind, their own descriptors with the actual odor quality (i.e., "When you receive a sample that you perceive as having a smoky odor to it, I will ask that you make an intensity rating for soy sauce odor"). Subjects were told that during the data collection part they could receive any combination of the sensations they experienced during the practice and that they may perceive one sensation, multiple sensations, or no sensation at all for each trial.

2.3.4.2. Data Collection

During the data collection, a total of 10 trials (2 taste alone, 4 odor alone, and 4 taste-odor pairs) were given in a randomized, counter-balanced scheme. For each trial, both a pipette and straw in the odor delivery device were presented simultaneously (see Lim et al. 2014 Fig. 4 for an example). In the cases of odor alone condition, deionized water was presented in a pipette. In the cases of taste alone condition, deionized water was placed in an odor jar. Before the data collection began, subjects were given a chance to practice using water in a pipette and an empty jar. On each trial, as subjects began breathing through the mouth, the experimenter pipetted the taste solution on the tongue. After the second breath, subjects discontinued inhaling and expectorated the liquid into the sink. Immediately after expectoration, subjects made intensity

ratings for all six attributes (i.e., sweetness, saltiness, strawberry, vanilla, chicken, and soy sauce) on the gLMS displayed on 6 separate screens. During a 1-min inter-trial interval, subjects were asked to rinse vigorously with 37 ±0.5° C deionized water. After the 10^{th} trial, a 3-minute break was given followed by another set of 10 replicate measurements using a different presenting order. Note that this experimental procedure was employed to deconstruct taste from retronasal odor although it is not how a food flavor is perceived during eating.

2.3.5. Data Analysis

All data collected were log transformed before any statistical analysis, as gLMS responses tend to be log-normally distributed (Green et al. 1993; Green et al. 1996). In order to investigate a potential replicate effect, repeated-measures analyses of variance (ANOVA) were first performed on the intensity ratings of all relevant attributes for single and binary stimuli (e.g., sweetness of sucrose, vanilla for vanilla odor, sweetness and vanilla for sucrose-vanilla pairs) using stimulus and replicate as factors. Replicate effect was not significant ($F_{1,101}$= 3.37, p=0.07), although there was a trend of lower responsiveness for the second replicate. When age group and sex were added as categorical predictors to the model, there was a significant main effect for replicate ($F_{1,98}$= 4.37, p=0.04). However, there was no significant main effects of cohort ($F_{1,98}$= 1.52, p=0.22) and sex ($F_{1,98}$= 0.02, p=0.88), and further no significant interaction effects of replicate on cohort ($F_{1,98}$= 0.27, p=0.60) or sex ($F_{1,98}$= 1.20, p=0.28). In other words, a slight replicate effect was observed across all subjects, which is not uncommon with naïve subjects using gLMS (Green et al. 2012). Thus, all results are reported as averaged intensity ratings across replicates.

In order to investigate individual differences in taste and odor responsiveness, two statistical methods were employed. First, coefficients of variation (CV) were calculated across individual intensity ratings of the relevant attribute to quantify variability of responsiveness for each stimulus. Second, the independent sample t-tests were performed to examine the difference between the means of taste and odor responsiveness of age and gender groups. Given the known age (Schiffman 1997 for review) and gender effects (e.g., Wysocki and Gilbert 1989; Michon et al. 2009), 1-sided p-values were used.

To determine whether the presence of a congruent taste has an effect on odor responsiveness, data were analyzed in two ways. The paired t-tests were performed on odor ratings of each odor stimulus presented with and without a congruent taste. Linear regressions were also performed on odor intensity ratings for odor alone and binary taste-odor mixtures to investigate the effect of a congruent nutritive taste on odor responsiveness.

Finally, Pearson product-moment correlations were performed across all individual intensity ratings for relevant attributes to test the relationship between intensity ratings within and between modalities. Bonferroni correction was used to reduce type-I errors. Statistical significance was set at $\alpha = 0.05$ for all analyses. All statistical analyses were performed using Statistica 12 (StatSoft, Inc.).

2.4. Results

2.4.1. Individual Differences in Taste and Retronasal odor Responsiveness

2.4.1.1. Ranges of Taste and Retronasal odor Responsiveness

Distributions of individual responsiveness for the primary attributes of the 2 taste and 4 odor stimuli (e.g., sweetness of sucrose, saltiness of NaCl, vanilla for vanilla odor) are shown in Figure 1. Visual inspection indicated that, in general, the dispersion of individuals' responsiveness were greater for odors (Fig. 1 C-F) than for tastes (Fig 1 A-B). The coefficients of variation (CV) confirmed that the responsiveness to odors had greater variances (C-F; 76.5 ~ 95.7%) compared to the responsiveness to tastes (A-B; 32.1 ~ 37.4%). The greater variances for odor responsiveness can be explained by the observation that a significant number of subjects were insensitive to the test odors; for example, about 14 ~ 23% of the subjects rated specific odor attributes (i.e., vanilla, strawberry, chicken, and soy sauce) below 'barely detectable'. In contrast, only 2 ~ 3% the same group of subjects rated sweetness of sucrose and saltiness of NaCl below 'barely detectable'.

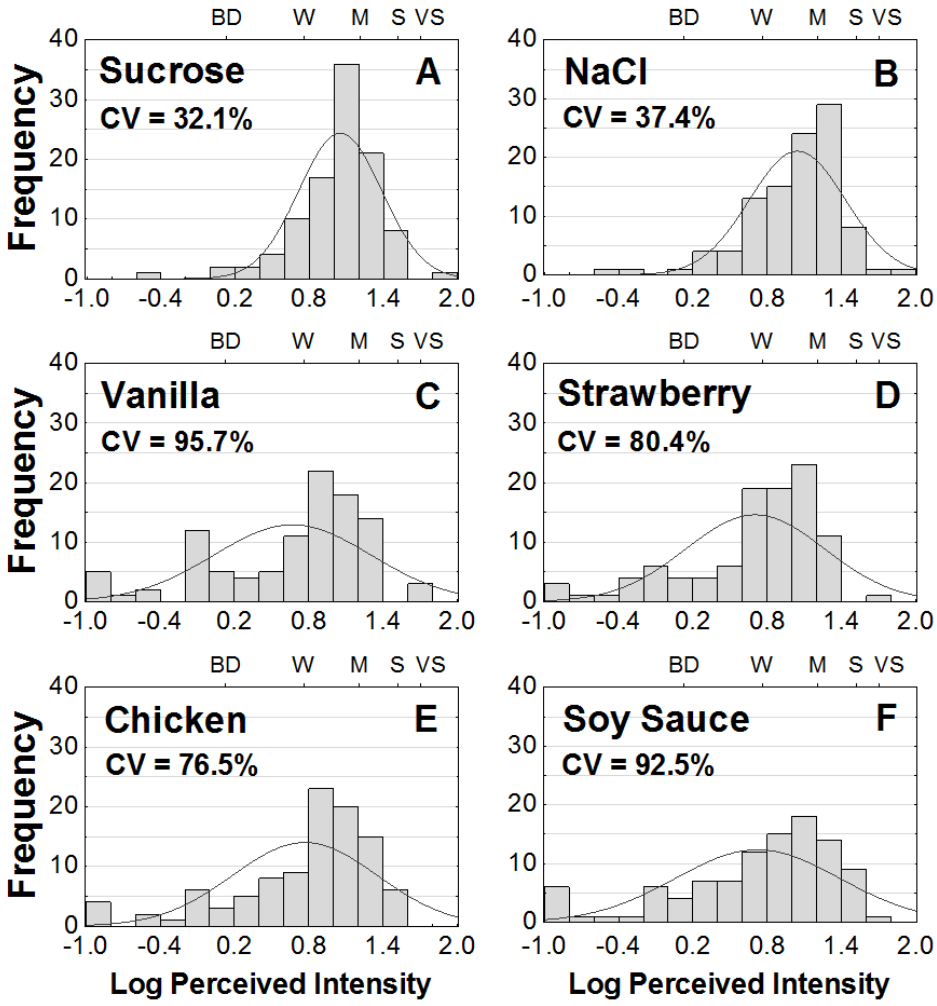

Fig. 1 Frequency counts of log perceived intensity ratings of primary attributes for taste (A and B) and odor (C-F) stimuli. Coefficient of variation (CV) represents the amount of variability across subjects in responsiveness. Fitted normal distribution curves are overlaid to show spread of data. Top x-axis shows semantic word labels on the gLMS: BD = barely detectable, W = Weak, M = moderate, S = strong, VS = very strong.

2.4.1.2. Effect of Age and Sex on Taste and Retronasal Odor Responsiveness

To investigate whether age and sex have an impact on taste and retronasal odor responsiveness, the mean taste and odor responsiveness and variation in responsiveness between the groups were compared. Table 1 shows the mean ratings grouped by young and old cohorts, along with CVs for each group. While mean ratings were generally lower for the older cohort, independent sample t-tests showed no significant differences between the groups, except vanilla and soy sauce ratings approaching a significance (p-value = 0.07 and 0.05, respectively). In terms of variance, the CVs for odors showed a larger variance for the older cohort compared to young cohort (e.g., 130.4% vs. 69.2% for vanilla), while the CVs for tastes were rather equivalent between the age groups. When the effect of sex was considered, no significant differences in taste and odor responsiveness were found between the groups ($p > 0.05$, Table 2). In addition, the CV values were generally similar between groups for all taste and odor responses.

Table 1 The mean intensity ratings, t values between the means, and coefficient of variance (CV) for young (Y) and old (O) cohorts[1]

	Mean (Y)	Mean (O)	t-value (p-value[2])	CV (Y)	CV (O)
Sucrose	1.08	0.99	1.35 (0.09)	24.5%	39.7%
NaCl	1.04	1.03	0.19 (0.20)	37.7%	37.4%
Vanilla	0.75	0.56	1.49 (0.07)	69.2%	130.4%
Strawberry	0.73	0.65	0.70 (0.24)	66.2%	97.2%
Chicken	0.81	0.71	0.85 (0.20)	69.9%	85.1%
Soy Sauce	0.81	0.60	1.63 (0.05)	71.0%	121.8%

[1]Young: n =54; 35 F, 19 M; mean age = 23 years; ranging from 18 to 35 years vs. old: n = 48; 33 F, 15 M; mean = 63 years, ranging from 53 to 70 years

[2]1-sided p-values are reported.

Table 2 The mean intensity ratings, t values between the means, and coefficient of variances (CV) for the groups of female (F) and male (M) [1]

	Mean (F)	Mean (M)	t-value (p value[2])	CV (F)	CV (M)
Sucrose	1.02	1.09	-1.11 (0.19)	37.4%	19.1%
NaCl	1.01	1.09	-1.01 (0.16)	43.1%	24.5%
Vanilla	0.66	0.66	0.02 (0.50)	92.1%	104.1%
Strawberry	0.74	0.60	1.18 (0.12)	70.4%	103.5%
Chicken	0.73	0.83	-0.83 (0.21)	76.2%	77.1%
Soy Sauce	0.72	0.70	0.10 (0.46)	83.0%	111.1%

[1] Female: n = 68; mean = 41 years, ranging from 18 to 69 years vs. male: n = 34; mean = 41 years, ranging from 18 to 70 years.

[2]1-sided p-values are reported.

2.4.1.3. Correlations Within and Across Modalities

To evaluate the relationships between the individual ratings within and across modalities, Pearson product-moment correlations were performed. As shown in Table 3, correlations among all taste and odor responsiveness were significant ($p \leq 0.001$), even after the Bonferroni correction was made ($\alpha = 0.003$), with the correlation between saltiness and soy sauce odor nearing a significance ($p = 0.009$). In particular, the 2 taste ratings were highly correlated ($r = 0.76$), while the 4 odor ratings were moderately correlated ($0.36 \leq r \leq 0.54$). Correlations across modalities were also significant, but the degree of correlations were somewhat lower ($0.26 \leq r \leq 0.43$) compared to the correlations within modalities.

Table 3 Correlation coefficients (*R*) between the intensity ratings of stimuli across all subjects.

	Sucrose	NaCl	Vanilla	Strawberry	Chicken
NaCl	0.76, $p < 0.001$				
Vanilla	0.35, $p < 0.001$	0.33, $p = 0.001$			
Strawberry	0.36, $p < 0.001$	0.43, $p < 0.001$	0.54, $p < 0.001$		
Chicken	0.42, $p < 0.001$	0.35, $p < 0.001$	0.43, $p < 0.001$	0.41, $p < 0.001$	
Soy Sauce	0.32, $p = 0.001$	0.26, $p = 0.009$	0.44, $p < 0.001$	0.36, $p < 0.001$	0.44, $p < 0.001$

The light gray regions of the matrix represent within modality correlations, whereas dark gray region represents cross-modal correlations Coefficients are significant at an adjusted alpha level of 0.05 after Bonferroni correction ($\alpha = 0.003$).

2.4.2. Effect of Taste on Retronasal Odor Responsiveness

2.4.2.1. Role of a congruent taste in retronasal odor responsiveness

Fig. 2 displays the log mean ratings of all 4 odors in the absence and presence of a congruent taste. To investigate the effect of a congruent taste on retronasal odor responsiveness, paired t-tests were performed. Results showed that odor responsiveness was significantly higher when a congruent taste was presented concurrently ($p<0.05$). When taste ratings were compared in the absence and presence of a congruent odor (e.g., sweetness of sucrose vs. sucrose + vanilla), no significant enhancement was observed (data not shown). These results are in support of previous findings that a congruent, nutritive taste can enhance retronasally perceived odors (Green et al. 2012; Fujimaru and Lim 2013; Linscott and Lim 2016).

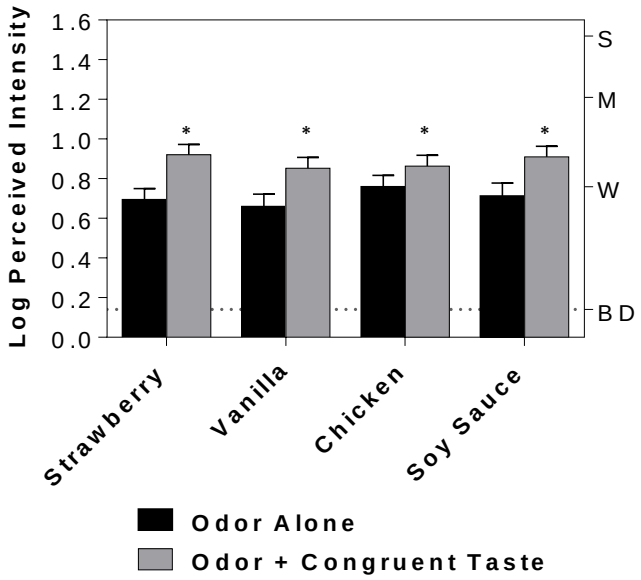

Fig. 2 Mean log perceived intensity ratings of specific odor for the odor stimuli in the absence and presence of a congruent taste (i.e., sucrose for strawberry and vanilla odors; NaCl for chicken and soy sauce odors). Letters on the right y-axis represent word labels on the gLMS: BD = barely detectable, W = weak, M = moderate, S = strong. Vertical error bars = SEMs. *, $p < 0.05$, one-tailed paired t-test.

2.4.2.2. Differences in the degree of Retronasal Odor Enhancement across subjects

Fig. 3 shows scatterplots of the odor intensity ratings in the absence (x-axis) and presence (y-axis) of a congruent taste for each individuals. 45-degree reference lines were added to the scatterplots of each odor quality to aid visual inspection of the data. Individual points appearing above the reference lines indicate that odor responsiveness was higher in the presence of a congruent taste compared to odor alone. For all 4 odor qualities, more than half of the individual points fall above this line (i.e., 73% for vanilla, 73% for strawberry, 63% for chicken, and 71% for soy sauce). More interestingly, greater enhancement effects were seen for the subjects who were somewhat insensitive to the odors alone (i.e., top left). To test this observation, simple linear regressions were performed. The results confirmed that the slopes of the regression line for each test stimuli were all less than 1 (Fig. 3), suggesting that odor responsiveness was shifted at a greater degree for those individuals who had a lower responsiveness compared to those who had a higher responsiveness. For example, based on the model equation, if an individual rated the intensity of chicken odor alone as 0.2, their perceived intensity of chicken odor in the presence of NaCl would be 0.59 (195% increase). However, if the initial perceived intensity of chicken alone were 0.8, the perceived intensity of chicken odor for the congruent pair would be 0.88 (10% increase).

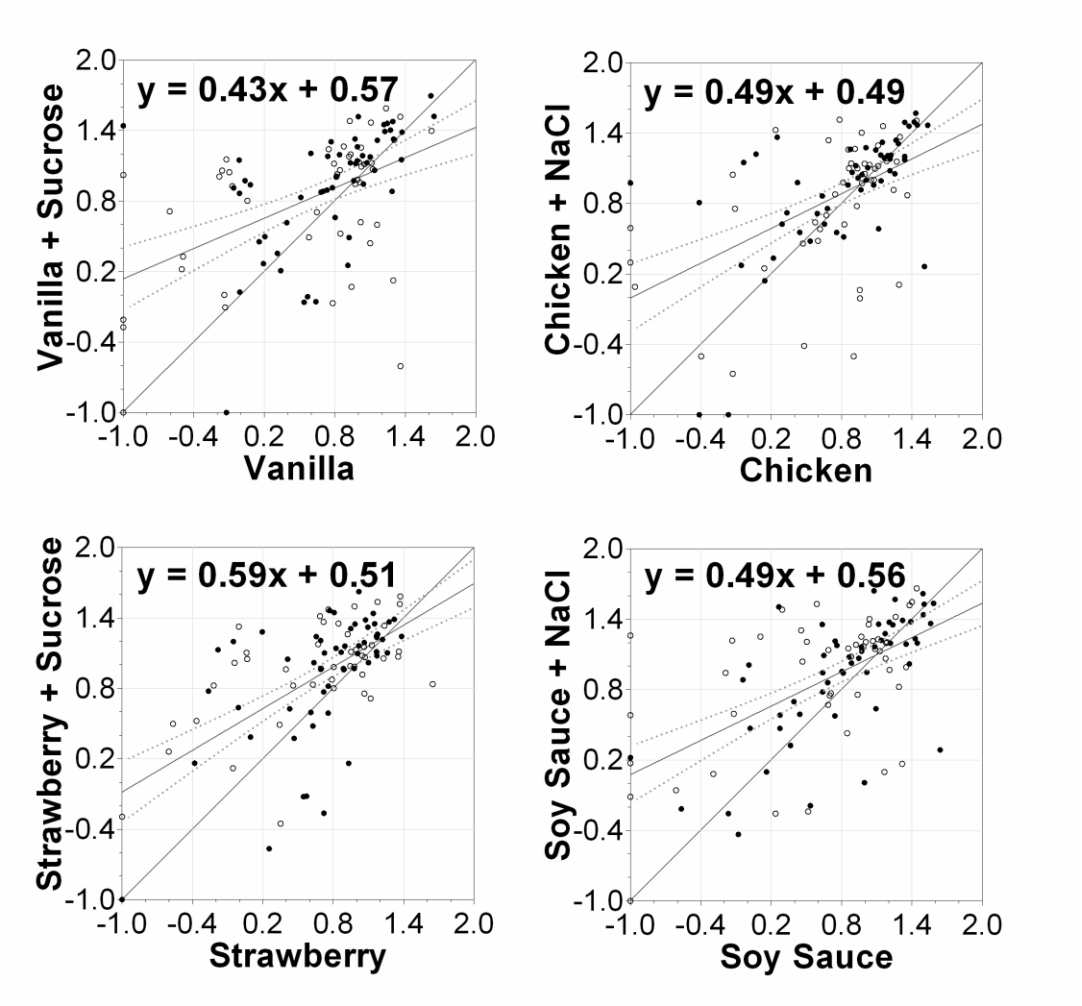

Fig. 3 Scatterplots of individual log perceived intensity ratings for each odor in the absence (x-axis) and presence (y-axis) of a congruent taste, with young (● closed circles), and old (○ open circles) cohorts. 45° reference line, regression line, and 95% CI band shown in gray. Equations for the regression line are also shown.

To further investigate the differences in the degree of odor enhancement across subjects, the ranges of responsiveness to odors in the absence and presence of a congruent taste were also compared (Table 4). Recall that odor stimuli generally showed wider ranges of responsiveness (Fig. 1), and that variation in odor responsiveness was greater for the older cohort than for the young (e.g., vanilla CV = 130.4% and 69.2%, respectively) (Table 2). In the presence of a congruent taste, variation in odor responsiveness was effectively reduced (e.g., vanilla, CV = 95.7%; vanilla + sucrose, CV = 65.2%; ΔCV = -30.5%; Table 4). Furthermore, the older cohort observed a greater decrease in variation of odor responsiveness compared to the young cohort (e.g., strawberry ΔCV = -43.2% and -6.0%, respectively) (Table 4). These results show that individual differences in retronasal odor responsiveness can be effectively reduced when an odor is perceived in the presence of a congruent taste, especially in the case of the older cohort.

Table 4 Coefficient of Variation (CV) for responsiveness of odor alone and odor in the presence of a congruent nutritive taste

	Without a taste	With a congruent taste	Change (Δ)[b] in CV
	CV % Combined (Y, O [a])	CV% Combined (Y, O)	CV% Combined (Y, O)
Vanilla	95.7 (69.2, 130.4)	65.2 (56.5, 76.0)	-30.5 (-12.7, -54.4)
Strawberry	80.4 (66.2, 97.2)	57.0 (60.2, 54.0)	-23.4 (-6.0, -43.2)
Chicken	76.5 (69.9, 85.1)	62.5 (55.8, 70.9)	-14.0 (-14.1, -14.2)
Soy Sauce	92.5 (71.0, 121.8)	60.1 (56.5, 64.8)	-32.4 (-14.5, -57.0)

[a] Values in parentheses are CV values for young (Y) and older (O) cohorts. [b] Change in CV is shown to display the percent change in responsiveness between the two conditions.

2.5. Discussion

The present study had two primary objectives: first, to investigate inter-individual differences in responsiveness to retronasally perceived odors, in the absence and presence of a congruent taste; second, to compare individual differences in responsiveness within and across modalities.

2.5.1 Individual Differences in Retronasal Odor Responsiveness

2.5.1.1 Variation in Retronasal Odor Responsiveness among Individuals

Results from the current study suggest that variations in retronasal odor responsiveness (Fig. 1 C-F; CV 76.5 ~ 95.7%) are much greater than variations in taste responsiveness (Fig. 1 A-B; CV 32.1 ~ 37.4%). The greater variations in responsiveness to odors can be explained by the fact that a significant number of subjects were insensitive to the test odors (i.e., 14-23% of subjects rated the odor intensity as below 'barely detectable'), while only 2-3% of the same group of subjects were insensitive to the taste stimuli. While not many studies have directly compared individual differences in taste and odor responsiveness, the idea that a range of odor responsiveness is generally larger than that of taste responsiveness is well accepted. One exception is the well-known large individual differences in responsiveness to the bitter tasting compound PROP, which is directly linked to genetic variation in expression of the T2R38 bitterness receptor (Kim et al. 2003; Duffy et al. 2004). In contrast, numerous studies have shown previously that individuals differ greatly in olfactory sensitivity (Berglund et al. 1971; Powers and Shinholser 1988; Buttery et al. 1995; Lehrner et al. 1999; Walker et al. 2003; Czerny et al. 2008). For instance, Berglund and colleagues (1971) measured psychophysical functions of 28 odorants for individual subjects and compared both intra- and inter-individual differences in

the exponents for different odorants. They reported that the exponents of the functions varied greatly among individuals, while those were more consistent within individuals. Individual differences in olfactory sensitivity have been established at the threshold level as well. For example, individual thresholds for t,t-2,4-decadinenal (an odor compound in lean ground beef) ranged from 0.013 ppm to 3.08 ppm across only 10 experienced panelists (Brewer and Vega 1995). It should be noted, however, that most of the previous studies investigating olfactory sensitivity have focused almost exclusively on orthonasal olfaction. Nevertheless, it has been shown that psychophysical functions for both orthonasally and retronasally perceived odors are almost identical, suggesting that the wide range of orthonasal responsiveness may provide a good indication of similar ranges for retronasal odor responsiveness (Voirol and Daget 1986).

The present results showed that aging has impact on responsiveness to retronasally perceived odors, but not necessarily on responsiveness to tastes. The CV values (i.e., the ratio of the standard deviation to the mean) for the odor responsiveness were much greater for the old cohort than the young in all cases (e.g., vanilla CV 130.4% vs. 69.2%, respectively), while those for the taste responsiveness were relatively similar across the two cohorts (Table 1). This observation suggests that the generally large individual differences in odor responsiveness become even greater when aging is considered as a factor. Recall that the relative insensitivity of individuals to odors (i.e., subjects who rated odor intensity as below ‘barely detectable’) ranged between 14% and 23% of the whole group. Further investigation revealed that more than a half of these insensitive individuals belong to the old cohort

(31% vs. 17% for vanilla, 22% vs. 13% for strawberry, %17 vs. 15% for chicken, 23% vs. 15% for soy sauce, percent of old and young cohort that was insensitive, respectively). Direct support for the impact of aging on retronasal odor responsiveness comes from the study of Stevens and Cain (1986). The authors obtained magnitude estimation of NaCl and ethyl butyrate solutions, both orally sampled, with and without the nose pinched from two age groups. They reported that the young cohort perceived the overall intensity of ethyl butyrate solutions to be much stronger with the nose unpinched, while for the elderly it made little difference whether the nose was pinched or unpinched, suggesting that aging impacts the responsiveness to retronasally perceived odor. Large variations in older cohorts to identify odors have also been reported by Doty and colleagues (1984).

Given the large differences in the CV values for odor responsiveness between the two age groups, it is interesting to notice that the mean intensity ratings were not statistically different between the groups although reaching for significance in some cases. Literature on the effect of aging on suprathreshold measures of odors is somewhat mixed in results. Some studies showed diminished intensity ratings with age (Stevens et al. 1982; Stevens and Cain 1985; Wysocki and Gilbert 1989), while others did not see the effect (Rovee et al. 1975; Cowart 1989). Discrepancies between the current and other studies can be explained by differences in study population, odorants tested, and experimental procedures. First, the sample population of the old cohort tested in the current study is healthy individuals, whose age range (53-70, mean = 63 yrs) is somewhat lower than that of others (e.g., 65-83; Stevens et al. 1982). Previous work has shown that olfactory function reaches its peak around 30

years of age and declines steadily until the late 60's and early 70's, at which point there is a sharper decline in function (Doty et al. 1984). These well documented decreases in olfactory responsiveness come primarily from the changes in cognitive ability (Murphy 1985), chronic environmental assault (Doty and Kamath 2014), physiological changes (e.g., cribriform ossification, Kalmey et al. 1998), and medication use (Schiffman 1997). Additional decrease in retronasal olfactory function, but not necessarily orthonasal olfactory function, can arise from oral conditions associated with aging (e.g., dentures) (Duffy et al. 1999). Accordingly, research has shown lesser impairment of olfactory function for relatively healthy older individuals (Ship and Weiffenbach 1993). Second, the current study used odor cocktails instead of a single compound. When perceived together, the various odor compounds may have additive or synergistic effects on overall detectability and/or perceived intensity (Guadagni et al. 1963; Miyazawa et al. 2008). In addition, the use of a mixture of odors can lower the chance of subjects having a specific anosmia compared to the use of a single compound (Triller et al. 2008). Finally, procedural differences may have influenced results of previous studies. For instance, various scales (e.g., magnitude estimation, magnitude matching, category scale) have been used in the previous studies and the use of certain scales (e.g., magnitude matching) tended to find significant differences between age groups (see Doty and Kamath 2014 for excellent review). Had we evaluated an older group of individuals and/or used a single odor compound, more defined differences in olfactory responsiveness between young and old cohorts would likely have emerged. Combined together, the current study support the previous findings that aging may adversely affect taste (Baker et al.

1983; Weiffenbach et al. 1986) and orthonasal olfaction (Stevens and Cain 1985; Cain and Stevens 1989), but that the degree of decline is much greater for olfaction than for taste (Stevens et al. 1982; Stevens et al. 1984; Murphy 1985; Stevens and Cain 1985; Stevens and Cain 1986; Cowart 1989). In addition, current findings also suggest that while some older individuals may lose their olfactory sensitivities, others may maintain their sensitivities fairly well.

Results from the current study showed no significant differences in taste and odor responsiveness between men and women (Table 2). These findings were not consistent with our expectation that women might have greater responsiveness to retronasally perceived odors than men do. While this statistical insignificance may be due to a limited sample size of male subjects (males = 34 vs. females = 68), previous research related to sex differences in olfactory sensitivity is, in fact, inconclusive. Some research suggest that women have superior olfactory abilities (e.g., Wysocki and Gilbert 1989; Brand 2001; Michon et al. 2009), while others found mixed results or no effect at all (e.g., Cowart 1989; Cain and Gent 1991). This does not include the innumerable studies that did not study sex *per se*, but found no differences between men and women (e.g., "The groups were balanced for sex although no sex differences emerged", Stevens and Cain 1986). In cases where an effect of sex was significant, female's superiority in odor identification appears to be more prevalent than thresholds or suprathreshold measurement. This is true in the case of Cowart (1989), where sex was an insignificant factor for olfactory threshold and suprathreshold intensity, but significant for odor identification. Similarly, Michon et al. (2009) saw differences in odor identification, but not simple odor detection. Wysocki and Gilbert

(1989) also found small, yet significant differences between men and women for some odor identification, detection, and intensity tests based on up to 1.2 million individuals. Studies specifically evaluating retronasal olfactory responsiveness did not see a sex effect (Stevens and Cain 1986; Duffy et al. 1999). While women may have better ability to identify odors, their heightened responsiveness to odor intensity may be arguable.

2.5.1.2 Effect of Congruent Taste on Retronasal Odor Responsiveness

Current study findings confirmed our hypothesis that when measured separately among healthy individuals, variations in responsiveness to retronasal odors are great, but that theses variations are effectively reduced by the presence of a congruent taste (i.e., sucrose for vanilla and strawberry odors and sodium chloride for chicken and soy sauce odors). As shown in Table 4, the CV values for the perceived odors alone (Table 4, CV = 76.5 ~ 95.7%) became somewhat smaller in the presence of a congruent taste (Table 4, CV = 57.0 ~ 65.2%). More interestingly, the old cohort seems to be the driving force behind the observed reduction, as evidenced by the greater reduction in CV values for the old (ΔCV -14.2 ~ -54.4) compared to the young (ΔCV -6.0 ~ -14.5). Investigating scatterplots of individual intensity ratings for each odor in the absence and presence of a congruent taste (Fig. 3) provides further insights on the source of reduction in variations of the odor responsiveness. Looking at each scatterplot, individuals who had low responsiveness to an odor alone tended to have a greater responsiveness to the same odor when a congruent taste was accompanied. This observation is supported by simple linear regression, which shows

a shift toward greater increase in individual response at the low end of the range of responsiveness (s < 1 for all odors, Fig 3). Such a shift in the responsiveness resulted in the increase in the mean responsiveness to odors (see Fig. 2) and further effectively reducing the CV values (see Table 4). Additionally, individuals who rated odor alone as zero, yet saw enhancement in the taste-odor pair are of interest. It stands to reason that while the odor alone may have been below their individual odor threshold, they were able to perceive the odor at suprathreshold intensity when paired together with taste. Similar observation has been reported previously by Dalton et al. (2000).

No work to this point has evaluated the effect of congruent taste on retronasal odor responsiveness at individual level. However, literature on taste-odor interactions can provide insights to understand the current findings. Numerous studies have investigated the phenomena of taste enhancement (Frank and Byram 1988; Schifferstein and Verlegh 1996; Stevenson et al. 1999; Djordjevic et al. 2004; Labbe et al. 2006) and retronasal odor enhancement (Kuo et al. 1993; Green et al. 2012; Fujimaru and Lim 2013; Lim et al. 2014; Linscott and Lim 2016). The general consensus has been that both forms of enhancement occur only for congruent taste-odor pairs (Frank and Byram 1988; Kuo et al. 1993; Schifferstein and Verlegh 1996; Lim et al. 2014; Linscott and Lim 2016). More recent studies have shown that when tastes and retronasal odors are presented together and subjects are invited to rate the full range of sensations they perceived, the phenomenon of retronasal odor enhancement is more pronounced and reliable effect than that of taste enhancement (Green et al. 2012; Fujimaru and Lim 2013; Lim et al. 2014; Linscott and Lim 2016). More interestingly, it has been reported that retronasal odors can be enhanced by

sweet, salty, and umami tastes (i.e., tastes that signal beneficial substances), but not by sour or bitter tastes (Green et al. 2012; Lim et al. 2014; Linscott and Lim 2016). Based on the latter findings, the biological function of retronasal odor enhancement was explained; that is to reinforce the association between the unique odor of a food and its metabolic consequences by "boosting" the intensity of (weak) food odors (Green et al. 2012; Linscott and Lim 2016). Further work established that this function might be adaptive, as foods inherently possess various intensities of tastants and odor volatiles. In the cases where the odor was already of sufficient intensity, the signal no longer requires a boost to be cognitively salient. Previous data confirmed this argument by showing that the degree of odor enhancement is greater when retronasally perceived odors are weak (Fujimaru and Lim 2013). This explains potentially why the relatively insensitive individuals showed a greater improvement in odor responsiveness compared to others who were already quite responsive to odors alone. While the phenomenon of odor enhancement by taste cannot explain every data point of the current study, the current study offers insights on why those individuals who are relatively insensitive to food odors alone may not notice potential deficit during actual food consumption. Importantly, as much as our experimental set-up does not represent a normal eating condition, previous work has shown that similar conclusion can be drawn whether stimuli are presented together in solutions or experimentally manipulated similar to the current study (Fujimaru and Lim 2013).

2.5.2 Individual Variation in Responsiveness Within and Across Modality

While the primary objective of the current study was to investigate individual differences in responsiveness to retronasally perceived odors in the absence and

presence of tastes, the current experimental design provided us a unique opportunity to compare individual differences in responsiveness within and across modality. Results from the current study showed that individuals' responsiveness within each modality were all significantly correlated ($p \leq 0.001$, Table 3). More specifically, individuals' responsiveness to sucrose and NaCl were highly correlated ($r = 0.76$, Table 3), while their responsiveness to the 4 odorants were moderately correlated ($r = 0.36 - 0.54$, Table 3). These findings are in general agreement with Lundström et al. (2012), who showed a higher, significant correlation within taste threshold measures ($r = 0.45$), as opposed to lower correlation within odor threshold measures ($r = 0.09 – 0.22$). Other work evaluating a single modality has shown significant correlations within orthonasally perceived thresholds for single compounds (Croy et al. 2009, $r = 0.60 - 0.64$; Cain and Gent 1991; $r = 0.66 - 0.86$) and food odor cocktails (Burdach et al. 1985, $r = 0.80 - 0.87$), as well as suprathreshold prototypical taste responsiveness (Lim et al. 2008; $r = 0.33 - 0.43$). As such, current findings suggest that responsiveness to as few as one or two retronasally perceived food odors or prototypical tastants might provide indication of an individuals' overall responsiveness within that modality.

The present findings also showed that an individuals' responsiveness to tastes and retronasally perceived odors were also significantly correlated (Table 1, $p \leq 0.009$), although the degree of correlations were somewhat low ($r = 0.26 – 0.43$). While not specifically hypothesized, based on previous literature we expected that individual responsiveness across modality might be correlated as well. While reporting that individuals who perceived taste from thermal stimulation alone gave

significantly higher taste ratings to all tastes (sucrose, saccharin, sodium chloride, citric acid, quinine sulfate, MSG and PROP) and an olfactory stimuli (vanillin), Green and George (2004) suggested that ‘gain’ of CNS processes are involved in perception of both taste and retronasal odor. This ‘central gain’ is thought to boost central nervous responsiveness where gustatory and retronasal olfactory inputs converge, which would potentially explain why the present study shows moderate, yet significant correlation across these two modalities.

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3 General Discussion

One of the objectives of the current study was to compare ranges of responsiveness for both taste and retronasal olfactory responsiveness within the same set of individuals. Additionally, the effect of a concurrent taste on retronasal olfactory responsiveness was evaluated. Individuals were separated into cohorts of young and older adults, as well as females and males, to see the effects of aging and gender on retronasal olfactory responsiveness. Overall, results from this study show that the range of responsiveness across all individuals varied to a greater extent for retronasally perceived odor than taste, especially for the older cohort. Also, retronasally perceived odors can be enhanced by concurrent taste, with those who are relatively insensitive to odors receiving the greatest degree of enhancement. Finally, the wide range of responsiveness to retronasally perceived odors was reduced in the presence of a congruent, nutritive taste, and again, most notably in the older cohort.

Results from this study have shown that taste responsiveness varies to a lesser degree than retronasal olfactory responsiveness between individuals. This was in part due to the fact that a large proportion of individuals were relatively insensitive to the odor alone (i.e. rated ‘below barely detectable’ on gLMS). While this result was not unexpected, very little previous work has evaluated responsiveness to both modalities within the same subjects. The only notable studies looking at differences in taste responsiveness have been studies of sensitivity to PROP, a bitter tasting compound that is only detected by the T2R38 bitterness receptor (Kim et al. 2003; Duffy et al. 2004). Beyond genetic variation in this single receptor, however, there is far less variation in prototypical taste (e.g. sucrose, sodium chloride, citric acid)

responsiveness across individuals (Lim et al. 2008). This is certainly not the case with olfactory responsiveness though, as numerous studies have noted a wide range of responsiveness to odor volatiles (e.g. Berglund et al. 1971; Stevens et al. 1988; Walker et al. 2003; Keller et al. 2012).

When individuals in the current study were grouped by age (i.e. 18-35 yrs for young, and 53-70 yrs for old) , it was observed that the older cohort had a much greater range of retronasal olfactory responsiveness compared to younger individuals, but both showed similar ranges for taste. Even so, the mean olfactory responsiveness between the young and old cohorts yielded minor statistical differences. These results are not incongruent with literature. Pointed research efforts have identified aging as a primary factor that influences olfactory responsiveness, with general desensitizing as humans age (Doty et al. 1984). While it is well known that advanced aging causes decrements in olfactory sensitivity (Schiffman 1997; Doty and Kamath 2014 for reviews), most research has evaluated olfactory sensitivity in much older adults than the current study (e.g. 53 – 70 yrs in current work, 78 – 90 yrs in Schiffman et al. 1976). Additionally, researchers have noted that older individuals may experience less impairment if they are relatively healthy and do not take medications (Ship and Weiffenbach 1993). Taste has shown less of a decrease in responsiveness with age compared to olfaction, in many cases showing relatively little decrease (Stevens et al. 1982; Stevens et al. 1984; Murphy 1985; Stevens and Cain 1986; Cowart 1989). Therefore, if the present study tested older age individuals and did not screen for good general health, statistical differences in responsiveness to retronasally perceived odors across age groups may have emerged.

Results from the present study on effect of gender showed no differences between men and women for taste or retronasally perceived odor responsiveness. Although this finding did not align with our original expectation, it is not surprising given the inconclusive nature of previous gender-related research on olfactory sensitivity. Research has often shown conflicting results within the same study (e.g., women have better odor identification, but no difference in sensitivity, Cowart 1989; Michon et al. 2009). At best, women may have a slight advantage in tasks involving odor identification, but differences in responsiveness appear negligible.

The present study results show that when a congruent, nutritive taste is paired with a retronasally perceived odor, the range of responsiveness to the odor is reduced compared to odor alone. Investigation of individual data points show that those who were relatively insensitive to the odor alone saw a greater boost in retronasal odor responsiveness, on average. This was especially true for the older cohort, who exhibited an extremely broad range of responsiveness to odors alone. These results can be explained by the taste-odor interaction, retronasal odor enhancement by a congruent, nutritive taste. Previous research has shown that on average, when a retronasally perceived odor is presented with a congruent, nutritive taste, the perceived intensity is greater than when the odor is perceived alone (Kuo et al. 1993; Green et al. 2012; Fujimaru and Lim 2013; Linscott and Lim 2016). The proposed biological function of this phenomenon has also been explored. If a food odor is perceived at a low intensity alone, it may be insufficient to signal that the potential food has any beneficial or nutritional value. However, when the relatively weak food odor is paired with a nutritive taste quality (i.e. sweet, salty, or umami), the perceived

intensity of the odor is 'boosted' to become more recognizable. This boost reinforces the association of said food odor with the beneficial taste quality (Green et al. 2012). This theory was further expanded to show that the physical concentration of food odor modulated the degree to which the odor was enhanced (Fujimaru and Lim 2013). This proposed function would then also explain why individuals in the present study who are relatively insensitive to odors alone saw a greater 'boost' in retronasal responsiveness than those who perceived the intensity of odor alone at sufficient levels.

In summary, the current research found that retronasal olfactory responsiveness to food odors varies greatly among individuals to a larger extent than taste. Older age exaggerated these inter-individual differences in retronasal olfactory responsiveness. When retronasal olfactory responsiveness was measured in the presence of a congruent, nutritive taste, inter-individual variations in responsiveness decreased, especially for the older cohort. Odor responsiveness for those who perceived odors alone relatively weak was enhanced to a larger degree than those with higher initial responsiveness. These findings imply that although there are some individuals, older or not, that are relatively insensitive to odors, they may not notice while consuming food. These effects were particularly notable in the healthy, older subjects tested. This does not imply, however, that effects of retronasal odor enhancement will negate the natural decrease in olfactory function associated with aging (Doty et al. 1984), simply that this decline may not be as apparent when consuming food. The present study showed that, on average, there was only a small decrement in olfactory responsiveness among the relatively healthy older group.

Certainly however, Duffy and colleagues (1999) have shown that at an older age, thresholds for food flavors significantly increase. Further studies may reveal at what age retronasal responsiveness declines to the point where taste can no longer boost odor responsiveness above a detectable level. From another perspective, it would be of interest to know at what point the effects of olfactory loss due to aging overcome the ability of retronasal odor enhancement aid in creation of a salient “flavor” percept.

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