RAPID OLFACTORY ADAPTATION INDUCED BY SUBTHRESHOLD STIMULATION IN HUMAN OBSERVERS

By

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Major: Psychology

Olfactory adaptation to peri-threshold odors has not been clearly characterized. To better understand perceptual adaptation to sub-threshold and near-threshold odors, we used a psychophysical method in which simultaneous adapting and target stimuli were presented. A custom-built olfactometer was used to determine the effect of an adapting odorant on the detection of a coincident target odorant. Twenty normosmic college-aged volunteers (ages 18-24; 14 females) served as subjects in this experiment. Subjects' detection thresholds were measured for a brief (600 ms) target of vanilla diluted in DH2O. Thresholds were measured as vol/vol liquid-phase concentration. To evaluate adaptation effects, detection thresholds for a brief (600 ms) vanilla target alone were compared with those for a 600-ms vanilla target presented 500 ms after onset of a 1500-ms adapting stimulus set to .25, .5, 1, or 2x subject's initial threshold. The 500-ms onset delay corresponds to a 500-ms exposure to the adapting stimulus. Significant increases in threshold were evident with exposure to all adapting odorant levels, suggesting subject sensitivity for the target was attenuated by exposure to near and below-threshold odorants.

CHAPTER 1
INTRODUCTION

In detecting and processing olfactory information, prolonged stimulation can obscure comparatively brief or novel odors. To compensate for sustained stimulation, the olfactory system loses sensitivity to a stimulus during prolonged exposure—a process termed sensory adaptation. By attenuating the olfactory system's responses to extraneous stimuli, adaptation facilitates the detection of novel odors (Dalton, 2000).

Psychophysical studies investigating how adaptation affects perceptual olfactory experiences have traditionally made use of serially presented stimuli that allowed time to pass between presentations of an adaptation-inducing odorant and a successive sensitivity test (Pierce, et al., 1996; Dalton, 2000; Linster, et al., 2001). These gaps in odorant delivery, however short, permit subjects to regain some level of olfactory sensitivity, yielding an inaccurate and diminished estimation of the adapting odorant's effect. Such methods fail to represent natural conditions, in which the olfactory system simultaneously encounters background adapting stimuli in combination with novel odors. Smith, and colleagues (2010), however, recently presented a novel psychophysical method that makes use of overlapping adaptation and test stimuli, with a brief delay in the onsets of the two odorants. This technique, known as the "simultaneous-presentation method," allows researchers to adjust the adaptation exposure period by varying the delay between odorant onset times, and reduces problematic stimulus discontinuities observed in previous serial-presentation approaches.

Smith and colleagues (2010) employed the simultaneous-presentation method in their examination of perceptual olfactory adaptation's time course. Each subject's detection threshold for a vanilla odor was measured—first in isolation, and then in the presence of a vanilla adapting odorant set to twice the initial detection threshold. The onset delay between the adapting and target odors was manipulated, and the resulting changes in subjects' thresholds revealed perceptual adaptation effects with a time constant of 319 ms. This time course for olfactory adaptation's onset is much more rapid than previously published estimates (c.f. Pryor, et al., 1970; Stone, et al., 1972; Wuttke and Tompkins, 2000), possibly due to the elimination of stimulus discontinuities and resulting perceptual effects.

In the investigation of olfactory adaptation's onset time course, the simultaneous-presentation method was employed to specifically address effects of supra-threshold odors (Smith, et al., 2010). Preliminary findings collected while demonstrating adaptation's level-dependence with this technique, however, suggested possible effects of near- and sub-threshold odors. Level dependence—where the degree of adaptation is related to the intensity of an adapting stimulus—is a consistently identified feature of olfactory adaptation studies (Dalton, 2000). Demonstrating this reliable quality reinforces the validity of a novel technique. To investigate level dependence with the simultaneous-stimulation method, fixed-concentration adapting odorants (1%, 10%, and 30% vanilla in DH2O) were used, regardless of individual subjects' detection thresholds for the vanilla target. In agreement with previous findings, the subjects exhibited greater adaptation to the highest-concentration stimuli and less adaptation in response to lower-concentration stimuli. Because odorants were chosen irrespective of the subjects' detection thresholds (mean = 6% vol/vol), many were exposed to sub-threshold adapting stimuli. Analyses of individual subjects' data suggested that some may have shown adaptation effects to these near- or sub-threshold odorants, though results were not conclusive.

The aim of the current study was to specifically investigate the possibility that olfactory sensitivity may be influenced by peri-threshold odors. The simultaneous-presentation method was adapted to specifically characterize the manner in which a peri-threshold background odor affects sensitivity for a brief, overlapping target odor. Gaining insight into how near- and sub-threshold stimuli influence perception will add to our knowledge of perceptual olfactory adaptation and expand our understanding beyond adaptation induced by readily detectible odors.

CHAPTER 2
METHODS

Subjects

Thirty-one subjects (13 Male, 18 Female), ages 18–24 were recruited for this study. To ensure the subjects' normal olfactory function, individuals completed a brief questionnaire prior to data collection that screened for the following exclusionary criteria: a current nasal infection or a history of upper respiratory infections, use of nasal sprays, or smoking. Two subjects reporting one or more of these criteria were excluded from the study. In addition, a total of nine subjects exhibited an unusually high baseline threshold for the vanilla target stimulus alone, greater than 20% volume/volume (v/v) in liquid phase, and were excluded from further study. Such a high threshold would not permit a sufficient dynamic range for threshold increases to indicate significant changes in sensitivity related to the presence of the adapting odorant. Experimental data were collected from a total of twenty individuals (6 Male, 14 Female), ages 18–24. All experiments were pre-approved by the Institutional Review Board of the University of Florida.

Olfactometer

This study employed a custom-designed, automated, liquid-dilution olfactometer to evaluate the subjects' olfactory function. A schematic of the apparatus is shown in Figure 2-1. A PC-based program with a graphic user interface controlled the olfactometer, and subjects used a hand-held response box to receive instructions and respond to the experimental manipulations.

Ambient room air was pumped through a charcoal filter and divided into two independent air streams controlled by solenoid pinch valves—a stimulus stream and carrier stream—regulated odorant delivery. The stimulus stream controlled release of gas-phase odorants, while the carrier stream directed these stimuli to the subject. Flow rates for these air streams (carrier: 0.27 L/min, stimulus: 4.1 L/min) were selected to optimize the odorant onset rapidity at the nose.

Connected upstream of all odorants, a third charcoal-filtered, high flow-rate air stream flushed residual odors out of the system and into evacuation tubing after each stimulus presentation. Saturation bottles for each stimulus (target, control, and adapting) occupied a fixed position within the system to maintain consistent relative travel times of odors through the system to the nose.

Odorants

We used pure vanilla extract as the base for all odorant dilutions in this study because vanilla is an easily recognizable, pleasant odor; pure vanilla extract was purchased in bulk (Gordon Food Service, Grand Rapids, MI). Vanilla extract was selected in favor of pure vanillin; human detection thresholds for vanillin in solution are too high to allow a sufficient dynamic range for threshold increases to indicate significant changes in sensitivity related to the presence of the adapting odorant (unpublished observations).

Odorants were stored in a refrigerator under inert gas (nitrogen) to prevent oxidation. Serial dilutions of the odorant, in deionized water (DH_2O) as a diluent, represented both target and adapting stimuli. Ten mL of a liquid-phase, vanilla-based dilution, added to a 500-mL glass saturation jar, served as a target stimulus. Ten mL of the diluent, alone, in a 500 ML glass saturation jar acted as the control stimulus. Because of the longer presentation time, adapting stimulus dilutions were of necessarily higher volume (100 mL), and were contained within a larger saturation bottle (5000 mL).

Target (S+; vanilla in DH_2O diluent) and control (S-; DH_2O) stimuli each consisted of a single, 600-ms presentation of volatilized odorant. Adapting stimuli were 1500-ms presentations of vanilla diluted in DH_2O. As illustrated in Figure 2-1, solenoid pinch valves briefly allowed air from the stimulus stream to pass into the stimulus jar and bubble through liquid-phase odorant, producing volatilized stimuli that the carrier stream transported to the subject.

Concentration here refers here to the volume/volume (v/v) concentration of the liquid phase odorant in the saturation bottle, rather than stimulus concentration at the subject's nose. Gas-phase odorant concentration at the nose is comparatively unimportant because relative changes in threshold, rather than absolute threshold, were of interest in this study.

Psychophysical Methods

During the experimental session, each subject held the response box in one hand, and secured the nasal mask over his or her nose with the other. The response box's LCD screen presented instructions indicating experimental conditions and subject-response requests. With the nasal mask secured, the subject initiated a trial sequence by depressing and holding a "ready" response key. Once depressed, the LCD screen instructed the subject to slowly exhale for 3s. Following the exhalation period, the response box instructed the subject to inhale slowly and continuously for 3s. The adapting stimulus, as well as the target or control, were presented during this inhalation period.

Individual trials required subjects to discriminate dilutions of S+ from S-. This discrimination task is similar to the two-bottle, forced choice paradigm employed in a number of psychophysical studies of olfaction (Bodyak and Slotnick 1999; Laska and

Seibt 2002; Hernandez-Salazar et al. 2003). Immediately following the 3-s sampling period described above, subjects reported detection of the S+ by pressing a green response key, or failure to detect the S+ (i.e., “detection” of the S-) by pressing a red response key. The response box provided immediate feedback to the subject for correct (message, ascending tones) and incorrect (message, buzzer sound) responses. Trials were grouped into "blocks" of twenty, in which participants were scored for accurate detection of a single vanilla concentration.

For each block of twenty quasi-randomly presented S+ and S- trials (10 S+ and 10 S-), the subject’s correct response percentage was calculated (for both correct detection and correct rejection). Subjects were considered to have discriminated a target dilution from the control stimulus when he or she could accurately discriminate this concentration for 85% of trials within a block, for two consecutive blocks. If a subject satisfied this criterion, he or she was required to perform the same task again in the following block, but with a more dilute concentration (i.e., more difficult). However, if the subject was unable to accurately discriminate the target vanilla order from DH_2O, the following block of trials would require detection of a more concentrated stimulus (i.e., less difficult). Subjects were allowed a maximum of three blocks (60 trials) for a given dilution.

Due to time constraints and individual variation in performance, the subjects were evaluated during two to five experimental phases. Figure 2-2 illustrates how phases progressed. In all phases, subjects were presented with a target or control odor, which the subject was required to identify, and a coincident adapting odorant. The first phase of the experiment, in which subjects discriminated S+ from S- in the presence of a null adapting stimulus (DH_2O), allowed for the evaluation of a baseline threshold. Successive phases of the experiment employed adapting-odorant concentrations relative to this baseline: 0.25, 0.5, 1.0, or 2.0 times baseline threshold concentration. To control for experience and ordering effects, the adapting-odorant presentation sequence was randomized for each participant.

As demonstrated in Figure 2-2, trials within all experimental conditions followed the same progression of stimulus presentation. Shortly after the beginning of a trial, subjects were presented with the 1500-ms adapting stimulus. The 600-ms target (S+ or S-) was presented during the 1500-ms adapting stimulus presentation, following a 500-ms delay from the adapting odorant's onset. A 500-ms onset delay is equivalent to a 500-ms exposure to the adapting stimulus and was selected for two reasons—500 ms is slightly longer than the 319-ms time constant established for the onset of perceptual adaptation, and this onset delay was previously demonstrated to produce consistent, near-complete adaptation across subjects when using a twice-threshold adapting stimulus (Smith, et al., 2010).

To ensure that changes in threshold were not due to long-term adaptation effects, subjects' baseline thresholds were retested throughout the experiment. Such effects would render estimations of acute adaptation processes inaccurate. Any subject who exhibited a change in discrimination threshold for the S+ alone would have been removed from the experiment. No subjects, however, exhibited such long-term effects. Due to time constraints, the attenuating effects of every adapting-stimulus concentration could not be tested on every subject. This limitation was addressed, however, through the quasi-random ordering of adapting stimuli and the selection of a Wilcoxon signed-rank test to examine differences between experimental conditions.

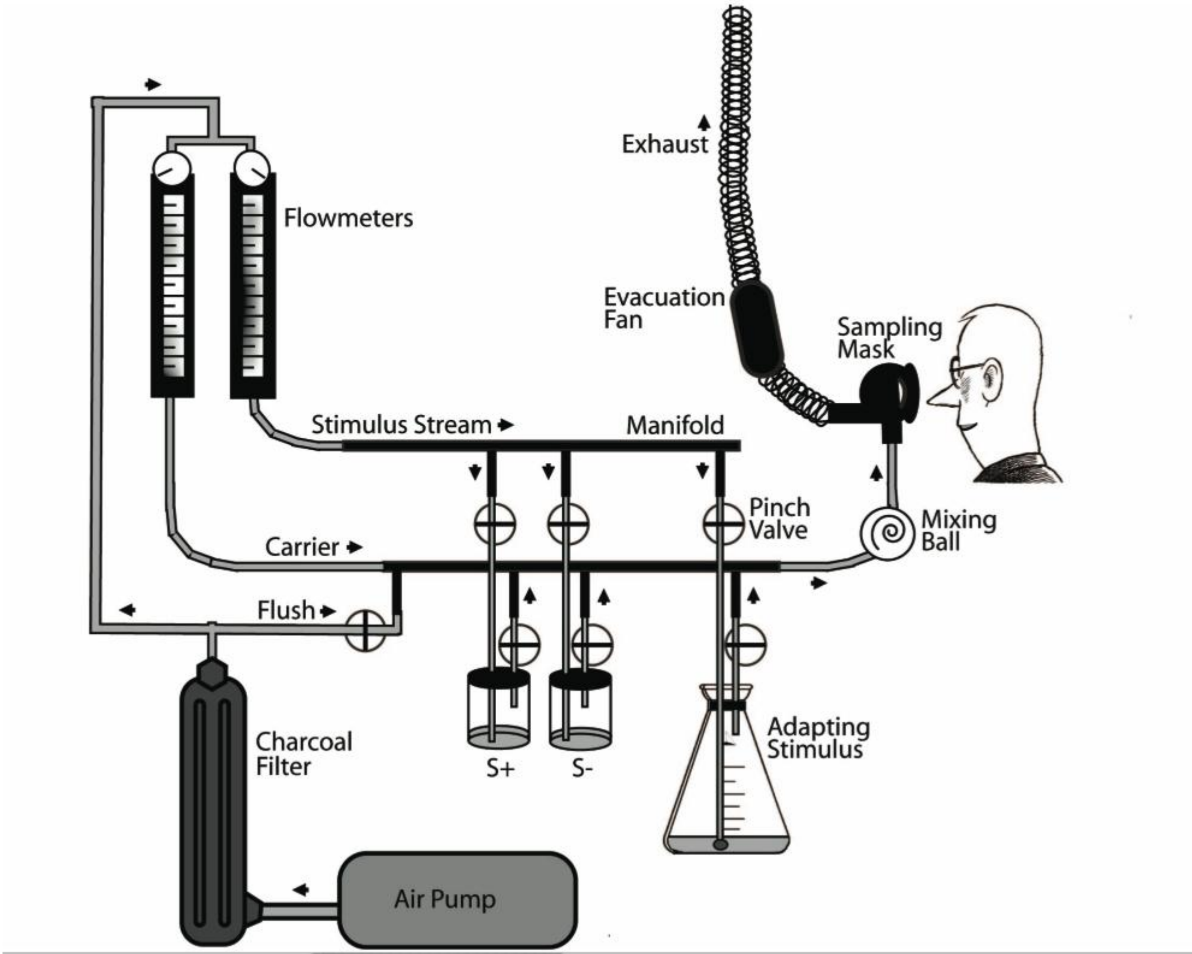

Figure 2-1. Schematic depiction of olfactometer. Ambient room air was pumped through a charcoal filter and divided into separately controlled stimulus and carrier air streams. Presentation and relative timing of adapting and target stimuli were controlled by a series of pinch valves which delivered the stimuli into the carrier stream, through a mixing ball and to the sampling mask. The odorants were flushed out of the sampling mask and into evacuation tubing by an inline fan. To ensure consistent, relative stimulus timing, the S+ (target + diluent) and S- (diluent alone) saturation bottles were fixed in position on the manifold upstream from the adapting odorant. (Reprinted with permission of Smith, David, Gamble Katherine, and Heil Tom. 2010. A novel psychophysical method for estimating olfactory rapid adaptation in humans. Chemical Senses. 35:8 717-725.)

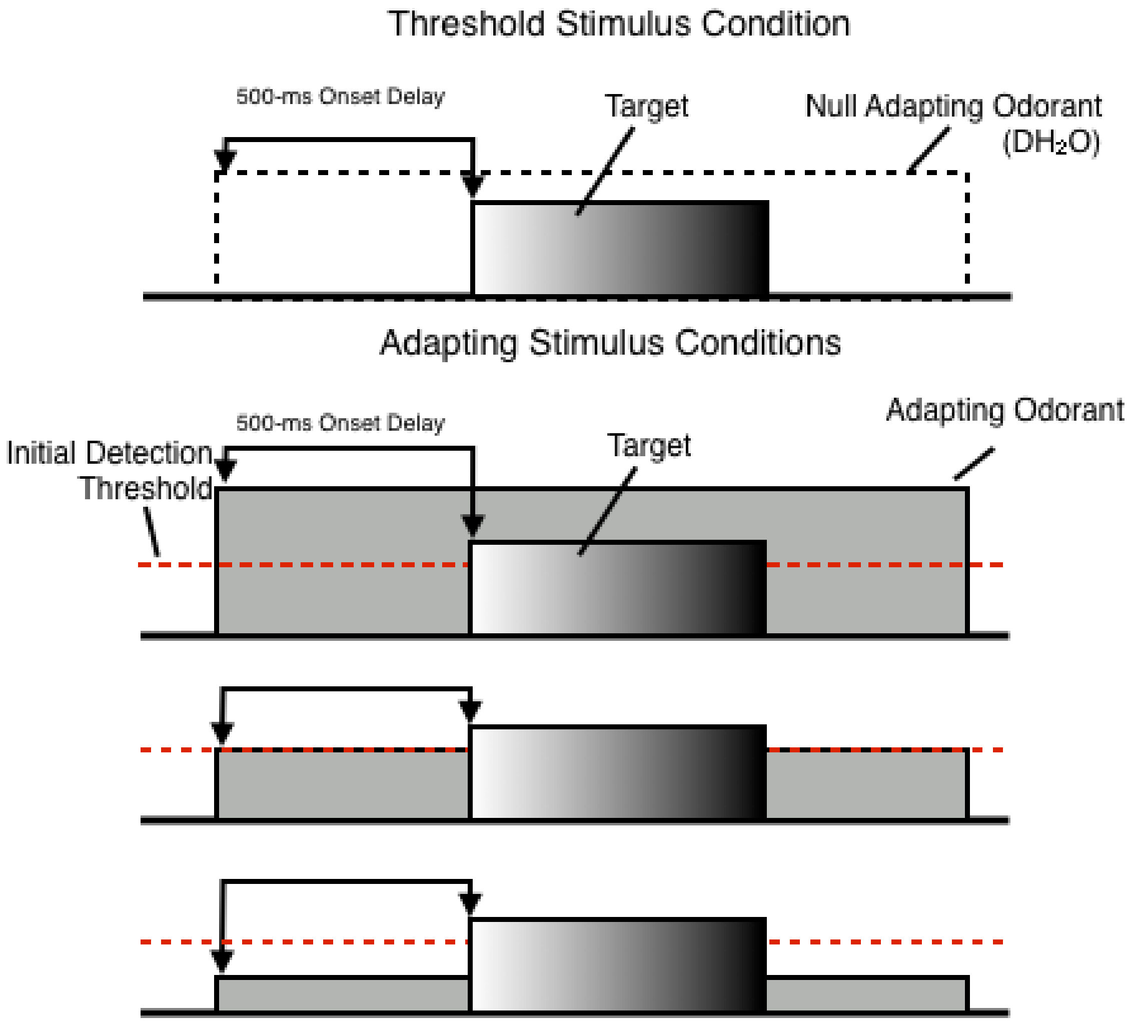

Figure 2-2. Schematic of stimulus conditions in the simultaneous-presentation paradigm. A subject's threshold was initially assessed for the target odor alone, in the presence of a null background (top line). In subsequent sessions (bottom three lines), subjects attempt to detect the target odor in the presence of a simultaneous adapting odorant that varied in concentration between experimental conditions. Time is represented on the horizontal axis; odorant concentration is represented on the ordinate axis.

CHAPTER 3
RESULTS

Initial baseline threshold measurements for the target odorant alone varied between subjects from 1% v/v to 10% v/v. Therefore, adapting stimulus concentrations across conditions varied from 0.25% v/v to 20% v/v, depending on a subject's baseline threshold and the relative adapting-odorant concentration. Figure 3-1 presents mean thresholds, averaged across subjects and plotted as a function of the adapting stimulus concentration.

A one-way analysis of variance (ANOVA) indicated that adapting-odorant concentration significantly influenced subjects' discrimination thresholds for the brief simultaneous target, $F(4, 51) = 9.579$, $p < .001$. Results from a post-hoc analysis, the Wilcoxon signed-rank test, indicated that threshold measurements for each adapting-odorant condition were significantly increased as compared to those for the target odorant alone (Table 3-1). Significant differences did not exist for subjects' mean detection thresholds between adapting-odorant conditions (0.25, 0.5, 1.0, and 2.0 times threshold).

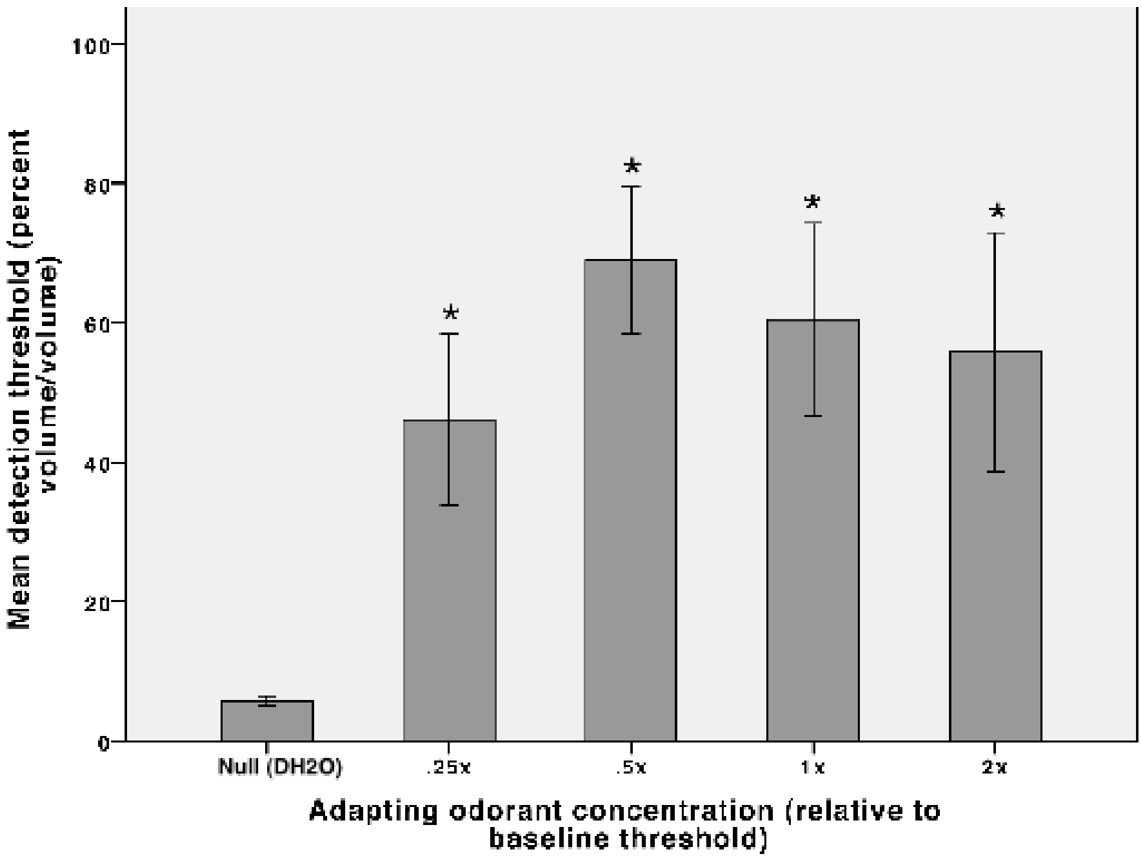

Figure 3-1. Mean detection thresholds for each adapting stimulus condition. A null stimulus (DH2O) served as the adapting odorant when determining subjects' baseline sensitivity for the target odor. Experimental conditions with mean thresholds differing significantly from the null condition are indicated with an asterisk (*). Mean threshold concentrations for all experimental conditions (0.25, 0.5, 1.0, and 2.0 times baseline threshold) differed significantly from the mean threshold concentration in the null condition. Error bars represent +/- 1 standard error of the mean.

Table 3-1. Comparison of mean detection thresholds for adapting-odorant conditions compared with the mean detection threshold for the null condition

Adapting Odorant Concentration	*Z* score	*P* value
1/4 Threshold	-2.67*	0.008
1/2 Threshold	-2.81*	0.005
Threshold Level	-2.68*	0.007
Twice Threshold	-2.21*	0.027

Pairwise Comparisons were performed with a Wilcoxon sign-rank test.
Significant comparisons indicated with *

CHAPTER 4
DISCUSSION

Given the problematic stimulus discontinuities present in serial-presentation approaches to evaluating adaptation, the effects of peri-threshold stimuli on subject detection of a target odor were investigated using the simultaneous-presentation method. Subjects exhibited threshold increases for detection of the target stimulus in the presence of adapting stimuli above, near, and below detection thresholds. Mean thresholds for the target odor alone and the 2.0 times threshold condition are consistent with those presented by Smith and colleagues (2010), who also employed the simultaneous-stimulation method and automated olfactometry. Many subjects in our study exhibited adaptation with exposure to odors ¼ of their original detection threshold for the target odor. Such threshold increases represent significant reductions in olfactory sensitivity to a stimulus following even brief exposure to peri-threshold levels of that odor.

Adaptation-inducing effects of sub-threshold odors were investigated previously in Amirov's comparison of perceptual olfactory adaptation in normosmics and patients with upper respiratory infections (Amirov, 1959). Subjects' thresholds for peppermint oil and camphor were evaluated using an ascending method of limits. Participants exhibited higher detection thresholds when the odorant's intensity was increased slowly from sub-threshold levels—corresponding to several minutes of exposure to the peri-threshold odor—than when odor intensity was increased rapidly. This effect, termed "subthreshold inhibition," was recorded, however, in only 10% of normosmic subjects and 50% of subjects with respiratory infections. Advantages conferred by the simultaneous-presentation method, as well as advances in olfactometry in the past 50 years, may have permitted our reliable identification of these effects, and after comparatively brief stimulation.

These psychophysical approaches can allow for observations of sub-threshold odors' perceptual effects, but the physiological mechanisms responsible may be revealed by observing transduction at the level of the olfactory sensory neuron (OSN). In the most widely accepted model of olfactory transduction, detection begins when odorant molecules become trapped in the olfactory mucosa. Acting as chemical ligands, these molecules bind to receptors located on OSN cilia embedded in the mucosa. OSN receptors are G protein-coupled receptors that, when activated, stimulate intracellular adenylyl cyclase to catalyze the conversion of ATP to cyclic adenosine monophosphate (cAMP). cAMP molecules bind to and open ion channels in the OSN membrane, leading to an influx of Ca^{2+} and OSN depolarization. (Zufall and Leinders-Zufall, 2000). Sustained, low-level stimulation modifies this intracellular cascade, operating as the mechanism responsible for adaptation to sub-threshold odors.

Odorant binding produces increases in intracellular Ca^{2+}. The increase in calcium-ion concentration, in turn, regulates OSN activity by modulating the transduction process in at least two key ways: adenylyl cyclase phosphorylation which leads to decreased cAMP production, and decreased binding affinity between cAMP and OSN-membrane ion channels (Zufall and Leinders-Zufall, 2000). While characterizing the former process in in vitro OSNs, Leinders-Zufall, and colleagues (1999) identified that this particular feedback process begins to affect OSN sensitivity prior to action potential generation. In addition, odorant signals too weak to activate an OSN were shown to induce adenylyl cyclase phosphorylation and decreased cAMP production. Together, these findings suggest that even at the olfactory periphery, within individual OSNs, olfactory stimuli can reduce sensitivity without giving rise to detection.

Threshold changes observed in the present study represent the perceptual effects of self-adaptation, where exposure to an odor decreases sensitivity for that odor, and much of the research examining perceptual olfactory adaptation has focused on this effect (c.f. Pryor, et al., 1970; Dalton, 2000; Kelliher, et al., 2003). Some evidence exists, however, for cross adaptation, in which exposure to one odor inhibits perception of dissimilar odorants (c.f. Cain and Polak 1992; Pierce, et al. 1996). Findings from these studies indicate that while cross adaptation may occur following exposure to specific odors, sensitivity suppression is normally limited to a small number of structurally and perceptually similar odorants, and cross-adaptation effects are less pronounced that those observed in self-adaptation.

Sub-threshold odors' potential to induce cross-adaptation has not yet been explored. Subtle stimuli's ability to facilitate detection of specific dissimilar odorants, however—an effect referred to as mixture agonism (Miyazawa, et al., 2009b)—has been demonstrated. Using a manually operated sniff-bottle procedure, Laska and Hudson (1991) demonstrated perceptual mixture agonism. Subjects exhibited lower thresholds for 3-, 6-, or 12-component odorant mixtures, than for their unmixed component odorants. More recently, Miyazawa and colleagues (2008b) provided further evidence of synergy in olfactory perception. Automated olfactometry similar to that described in the current study was used to present subjects with brief (2.5 seconds) pulses of maple lactone, an odorant, either alone or in a binary mixture with sub-threshold levels of dissimilar odorants, acetic or butyric acid. Subjects exhibited lower detection thresholds for the binary mixtures of maple lactone than for the odorant alone, extending Laska and Hudson's findings (1991) and demonstrating further that peri-threshold odors can facilitate olfactory sensitivity.

A growing literature on perithreshold odor interactions continues to demonstrate mixture agonism (c.f. Miyazawa, et al., 2009a; Miyazawa, et al., 2008a). Findings from studies of particular odorant combinations, however, suggest that the level of facilitation depends on the structural similarity of odorants (Wise, et al., 2007) and number of components in the odor mixture (Miyazawa, et al., 2009b).

The involvement of peri-threshold stimuli in shaping perception is not limited to olfaction. Sub-threshold olfactory stimuli, for example, have been demonstrated to enhance the dectectability of particular tastants (c.f. Dalton, et al., 2000; Labbe, et al., 2007; Labbe and Martin, 2009). In addition, studies of contrast-gain adaptation in vision (Kohn, 2007) and medial-efferent-mediated auditory adaptation (Winslow and Sachs, 1987) demonstrate that other sensory modalities possess the ability to adapt to subtle environmental elements. Such studies of the sensory periphery, as well as evidence of adaptation in the olfactory cortex (Kadohisa and Wilson, 2006) suggest that these processes facilitate figure-ground discrimination—suppressing detection of even weak redundant stimuli may facilitate the detection of novel signals.

Future studies of perceptual olfactory adaptation to peri-threshold stimuli could specifically investigate its function in enhancing figure-ground discrimination. Such a study could identify subjects' ability to detect a brief target odor in the presence of a dissimilar masking agent, with or without prior exposure to sub-threshold levels of the masking odor. Future research could also extend the present findings in two key ways—

by characterizing the time course for the loss and recovery of sensitivity with exposure to sub-threshold stimuli, and by examining the specific effects of a broader range of odorants. These examinations would provide an opportunity to directly compare these data with those characterizing supra-threshold stimuli.

REFERENCE LIST

Amirov RZ. 1959. Effect of sub-threshold olfactory stimuli on the sensitivity of the sense of smell in normal and pathological conditions. By Exp Biol Med-USSR. 47:562-565.

Bodyak N, Slotnick B. 1999. Performance of mice in an automated olfactometer: Odor detection, discrimination and odor memory. Chem Senses. 24:637-645.

Cain and Polak. 1992. Olfactory adaptation as an aspect of odor similarity. Chem Senses. 17: 481-491.

Dalton P. 2000. Psychophysical and behavioral characteristics of olfactory adaptation. Chem Senses. 25:487-492.

Dalton P, Doolittle H, Nagata, and Breslin P. 2000. Merging of the senses: Integration of subthreshold taste and smell. Nat Neurosci. 3:5 431-432.

Hernandez-Salazar L, Laska M, Rodriguez Luna E. 2003. Olfactory sensitivity for aliphatic esters in spider monkeys (Ateles geoffroyi). Behav Neurosci. 117:1142-1149.

Kadohisa M, Wilson D. 2006. Olfactory cortical adaptation facilitates detection of odors against background. J Neurophysiol. 95:1888-1896.

Kelliher K, Ziesmann J, Munger S, Reed R, Zufall F. 2003. Importance of the CNGA4 channel gene for odor discrimination and adaptation in behaving mice. P Natl Acad Sci USA. 100:4299-4304.

Kohn, A. 2007. Visual adaptation: physiology, mechanisms, and functional benefits. J Neurophysiol. 97:3155-3164.

Labbe D, Rytz A, Morgenegg C, Ali S, and Martin N. 2007. Subthreshold olfactory stimulation can enhance sweetness. Chem Senses

Labbe D, and Martin N. 2009. Impact of Novel Olfactory Stimuli at Supra and Subthreshold Concentrations on the Perceived Sweetness of Sucrose after Associative Learning. Chem Senses. 34:645-651.

Laska M, Hudson R. 1991. A comparison of the detection thresholds of odor mixtures and their components. Chem Senses. 16:6, 651-662.

Laska M, Seibt A. 2002. Olfactory sensitivity for aliphatic esters in squirrel monkeys and pigtail macaques. Behav Brain Res.134:165-174.

Leinders-Zufall T, Ma M, Zufall F. 1999. Impaired odor adaptation in olfactory receptor neurons after inhibition of Ca2+/calmodulin kinase II. J Neurosci. 19:1-6.

Linster C, Johnson B, Yue E, Morse A, Xu Z, Hingco E, Choi Y, Messiha A, Leon M. 2001. Perceptual correlates of neural representations evoked by odorant enantiomers. J Neurosci 21:24 9837-9843.

Miyazawa T, Gallagher M, Preti G, Wise P. 2008. The impact of subthreshold carboxylic acids on the odor intensity of suprathreshold flavor compounds. Chem Percept. 1:163-167.
Miyazawa T, Gallagher M, Preti G, Wise P. 2008. Synergistic Mixture Interactions in Detection of Perithreshold Odors by Humans. Chem Senses. 33:363–369.

Miyazawa T, Gallagher M, Preti G, Wise P. 2009. Odor detection of mixtures of homologous carboxylic acids and coffee aroma compounds by humans. J Agr Food Chem. 57:9895-9901.

Pierce JD, Wysocki CJ, Aronov EV, Webb JB, Boden RM. 1996. The role of perceptual and structural similarity in cross-adaptation. Chem Senses 21:2 223-37

Pryor G, Steinmetz G, Stone H. 1970. Changes in absolute detection threshold and in subjective intensity of suprathreshold stimuli during olfactory adaptation and recovery. Percept Psychophys. 8:5 331-333.

Smith D, Gamble K, Heil T. 2010. A novel psychophysical method for estimating olfactory rapid adaptation in humans. Chem Senses. 35:8 717-725.

Stone H, Pryor G, Steinmetz, G. 1972. Comparison of olfactory adaptation among 7 odorants and their relationship with several physiochemical properties. Percept Psychophys. 12:6 501-504.

Winslow R, Sachs M. 1987. Effect of electrical stimulation of the crossed olivocochlear bundle on auditory nerve response to tones in noise. J Neurophysiol. 57:1002-1021

Wise P, Miyazawa T, Gallagher M, and Preti G. 2007. Human odor detection of homologous carboxylic acids and their binary mixtures. Chem Senses. 32:475-482.

Wuttke M, Tompkins L. 2000. Olfactory adaptation is TRP-independent in Drosophila larvae. J Neurogen. 14:43-62.

Zufall F, Leinders-Zufall, T. 2000. The cellular and molecular basis of odor adaptation. Chem Senses. 25:473-481.

BIOGRAPHICAL SKETCH

Ryan R. Keith received his B.A. in psychology from the New College of Florida in 2007. For his undergraduate thesis project, supervised by Dr. Gordon Bauer, Keith investigated color constancy in honeybees. Under Dr. David Smith's direction, he continued his research in sensory processes, studying olfactory performance in humans and mice, which developed into the research for his M.S. thesis.