The Feasibility of Gelatin-Based Retronasal Stimuli to Assess Olfactory Perception

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Abstract

Links between some psychological disorders and olfactory deficits are well documented, and screening tests have been developed to exploit these associations. Odors can take one of two routes to the olfactory receptors in the nasal epithelium, the orthonasal or retronasal route. This article discusses the potential use of the retronasal route to assess olfaction using gelatin-based stimuli delivered orally. Using a relatively new psychophysical method, the Single-Interval Adjustment Matrix task, we estimated vanillin thresholds for five healthy participants sampling small vanillin flavored gels. Our data demonstrate the feasibility of using solid-state gustatory stimuli to assess retronasal perception.

Keywords

odor identification, retronasal, threshold, SIAM task, psychopathology

Introduction

Impairment of olfactory function, including odor identification, is implicated in numerous psychopathologies (Killgore, Killgore, Mcbride, Kamimori, & Balkin, 2008; Martzke, Kopala, & Good, 1997). For example, premorbid olfactory function is a strong predictor of Parkinson’s disease, and olfactory assessment is currently a major component of routine diagnostic tests, to the degree that normal olfactory function all but eliminates the likelihood of a Parkinson’s diagnosis (Landis et al., 2009). The perception of odorants is mediated by two independent sensory pathways (Heilmann & Hummel, 2004): the nasal route (i.e., orthonasal olfaction) and the oral/nasopharynx route (i.e., retronasal olfaction). The orthonasal route involves airborne aromatics being drawn through the nostrils upon inhalation, this being what we normally associate with nasal breathing. The retronasal route involves the migration of volatile chemicals to the olfactory receptors embedded in the olfactory mucosa by way of the nasopharynx cavity. The mechanical forces associated with mastication cause the breakdown of the food matrix and a subsequent increase in surface area that determines the transfer characteristics of volatile flavor compounds (i.e., odorants) from the mouth to the nose. Whereas orthonasal olfaction occurs through the inspiration of odorants through the external nares of the nose, retronasal olfaction is dependent upon exhalation or swallowing, which coincides with the migration of odorants through the posterior nares of the nasopharynx (Diaz, 2004; Masaoka, Satoh, Akai, & Homma, 2010).

Schizophrenia (Kasai et al., 2003), obsessive-compulsive disorder (Goldberg, Goldberg, & Vannoppen, 1991), depressive symptoms (Killgore et al., 2008), traumatic brain injury (Callahan & Hinkebein, 2002), and neurodegenerative disorders such as Alzheimer’s (Bahar-Fuchs, Moss, Rowe, & Savage, 2010) and idiopathic Parkinson’s disease (Heilmann, Strehle, Rosenheim, Damm, & Hummel, 2002; Landis et al., 2009) have all been linked to the central impairment of olfactory function. The concurrence between central olfactory impairment and some psychopathologies has led to the suggestion that psychological assessments probing olfactory ability be adopted in the clinical environment (Moberg et al., 1999). To date, these tests of olfactory dysfunction have focused on impairments of odor identification, with the dominant tests being the orthonasally administered University of Pennsylvania Smell Identification Test, the European Test of Olfactory Capabilities (Thomas-Danguin et al., 2003), and the Sniffin’ Sticks Test (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). This orthonasal bias may reflect the belief that the orthonasal route is more efficient than the retronasal route (Diaz, 2004), though arguably tests utilizing the retronasal pathway remain a viable alternative, and perceptual differences between the two routes appear overstated (Landis et al., 2009).
pathway, only Heilmann et al. (2002) and Landis et al. (2009) have applied retronasal assessment in a clinical context, assessing olfaction in Parkinson’s disease patients using common food items administered to the tongue in powdered form. In addition, Renner et al. (2009) administered aromatized sorbitol candies to children to assess olfactory function, and reported positive findings. Thus, the potential use of orally administered olfactory stimulants to assess central olfactory processes has yet to be sufficiently explored, possibly due to the challenge of stimulus generation and delivery methods.

Psychometric studies into the olfactory sense are comparatively few, with both the acuity of the system as well as general methodology being understudied relative to other sensory systems (Miyazawa, Gallagher, Preti, & Wise, 2009). One practical challenge is the laborious nature of estimating olfactory thresholds, at least relative to other sensory modalities. Typically, participants become rapidly satiated, and to control carry-over effects between trials, they may have to regularly pause, even though they see no reason to. Furthermore, detection is a probabilistic, as opposed to a deterministic, process and so large sets of trials are required around the “true” threshold value to obtain accurate and reliable estimates. Added to these are the inherent difficulties in producing and controlling olfactory stimuli. Developing techniques that maximize precision while minimizing the number of stimulus presentations is a central objective of the sensory sciences. A relatively new technique capable of estimating sensory thresholds using fewer trials than standard methods is the Single-Interval Adjustment Matrix (SIAM) task (Kaernbach, 1990). The SIAM task works by controlling the participant’s response criterion, and in the process produces a bias-free estimate of the detection threshold. A thorough description (Kaernbach, 1990) and validation (Hautus, Stocks, & Shepherd, 2010; Shepherd, Hautus, Stocks, & Quek, 2011) of the SIAM approach have appeared in the literature. Hitherto unreported in the olfactory literature, the SIAM approach offers the opportunity to robustly test the perception of orally administered olfactory stimulants while minimizing methodological barriers.

The aim of this feasibility study is to further develop orally administered stimuli that, by the utilization of the retronasal pathway, can be used to assess central olfactory function and potentially inform further research developing olfactory-based psychological assessments. We used an efficient sensory threshold-estimation procedure, the SIAM (Kaernbach, 1990) task, to estimate thresholds for a single olfaction-based flavorant, vanillin. The use of a threshold-estimation task presents a more severe test of the psychophysical properties of our retronasal stimuli, and was therefore chosen over a simple identification task. Gelatin-sucrose gels were selected as stimuli as their use has been validated elsewhere in the sensory sciences (e.g., Baek, Linforth, Blake, & Taylor, 1999; Mestres, Moran, Jordan, & Buettnner, 2005), while the role of sucrose was to act as a binding agent to bind water in the gel phase and act as a tastant, making the capsules more palatable. The human olfactory system lacks receptors responsive to sucrose, and therefore sucrose can be considered a neutral olfactory stimulus.

Method

Participants

Five non-smoking participants, screened for anosmia and health status, were recruited from a pool of university postgraduate science students. There were four females and one male between 21 and 30 years, none of whom reported a history of respiratory tract infection, hay fever, mental illness, or other potentially confounding health states (e.g., common cold or chronic sinusitis). Participants were instructed to consume only water in the hour leading up to their testing session. The study was approved by The University of Auckland Human Participants Ethics Committee, and written informed consent was provided by each participant.

Materials

Supermarket grade gelatin crystals (Davis), sucrose (Chelsea), and vanillin essence (Hansells) were used to manufacture retronasal stimuli. Stimuli consisted of a sweetened gelatin base, shaped into small circular gels, with vanillin essence added to one half of the gels, while the other half contained no further additives.

Gelatin gels were made by adding 20 g of gelatin and 5 g of sucrose to 500 mL distilled water, and the mix heated until the gelatin and sugar dissolved and the temperature reached 60°C. Next a calculated amount of cold water was added to overcome the loss of water by the process of vaporization. This mixture was allowed to stand for 2 min before transfer to custom-made disposable molds manufactured from food-grade polyvinyl chloride. Gel dimensions were 13 mm in length and 5 mm deep, ±1 mm, and between 0.48 g and 0.50 g. Separate batches were prepared for samples containing the vanillin, with 10 equally spaced concentrations ranging from 10 µL to 55 µL being added to the cooled gelatin–sucrose mix before gelation occurred. Once the samples cooled, they were maintained at room temperature. A steel plucker was used to remove the samples from the molds to prevent damage to the texture of the gels. Samples were produced on a daily basis and surplus samples were discarded within 24 hr of manufacture.

Procedure

The testing location was a purpose built food science laboratory fitted with professionally designed and installed sensory booths. A solid wall partition separated the tasting booths from the laboratory where the stimuli were prepared. The
tasting room had its own entrance and contained isolated tasting booths connected to the laboratory by “bread-bin” style receptacles. The pressure between the tasting room and the laboratory was equalized and both sides were illuminated by white fluorescent tubes. Participants were tested independently rather than in groups, meaning no two participants were tested at the same time.

The standard method of retronasal stimulus delivery as described by Pierce and Halpern (1996) was employed, as care has to be taken that odorants did not stimulate the olfactory epithelium via the orthonasal route. During retronasal testing, participants were warned of the imminent presentation of a stimulus and instructed to pinch their noses to impede airflow and thus avoid activation of the orthonasal route. Once the stimulus was in the mouth and the mouth firmly closed, participants released their grip on the nose and practiced normal breathing for 30 s. Participants were instructed not to make a judgment until they had swallowed at least once, and to avoid masticatory movement (Burdach & Doty, 1987). The intervals between successive trials were not timed, but were usually a minimum of 2 min, chosen on the basis of Baek et al.’s (1999) volatile release profiles for gestation epithelium via the orthonasal route. During retronasal testing, participants were warned of the imminent presentation of a stimulus and instructed to pinch their noses to impede airflow and thus avoid activation of the orthonasal route. Once the stimulus was in the mouth and the mouth firmly closed, participants released their grip on the nose and practiced normal breathing for 30 s. Participants were instructed not to make a judgment until they had swallowed at least once, and to avoid masticatory movement (Burdach & Doty, 1987). The intervals between successive trials were not timed, but were usually a minimum of 2 min, chosen on the basis of Baek et al.’s (1999) volatile release profiles for gelatin–sucrose gels. Each trial began with the participant rinsing with filtered water equilibrated to room temperature (≈21°C). Rinsing with water is standard practice and serves to eliminate residual volatile compounds and to minimize individual differences in salivation, which can impact the release of odorants (Heilmann et al., 2002).

The intensity of vanillin on any one presentation was determined by the SIAM (i.e., target performance of 50%) proposed by Kaernbach (1990). The blank (i.e., vanillin free) and vanillin gels were presented in a random order as calculated by a Microsoft Excel spread sheet, with a unique order across each block and participant, but with a constraint of 10 blank trials and 10 vanillin trials per block of 20 trials. Figure 1 depicts a single presentation of a stimulus, which either contained vanillin (or not) with equal probability (p = .5). Participants were required to respond “Yes vanillin present” or “No, vanillin not present,” with the outcome (i.e., hit, miss, false alarm, or correct rejection) determining the concentration of the next vanillin-containing stimulus, which could be between 55 µL and 10 µL in 5 µL steps. A hit is defined as detecting vanillin when it is present, and results in the subsequent vanillin concentration being decremented by one step (i.e., −5 µL). Making the same judgment when vanillin is not present yields a false alarm, which raises the subsequent vanillin concentration in two steps (i.e., +10 µL). A judgment of “No vanillin” leads to a correct rejection if no vanillin is present, resulting in no change in concentration; or if vanillin was in fact present, a miss, resulting in an increment of one step (+5 µL). The starting concentration was 50 µL, and was selected after each participant underwent seven practice sessions of 20 trials each, which familiarized them with the stimuli and the method to mitigate practice effects. Six sessions provided data for analysis, each consisting of a block of 20 trials lasting approximately 30 to 40 min, with no more than one block of trials conducted on a single day.

**Data Analysis**

Detection thresholds were calculated as the average concentration presented on all trials following the first reversal. Here a reversal is defined as the position in a series of trials in which the general trend in the concentration of stimuli presented on successive trials changes from a decrease in concentration to an increase in concentration (or vice versa).

All threshold estimates were based on a minimum of five trials, and for each individual a grand threshold (GT) estimate was obtained by averaging across their six blocks of trials.

**Results and Discussion**

Figure 2 shows a typical block of trials, with correct (filled symbols) and incorrect (unfilled symbols) responses plotted as a function of trial number. The dashed horizontal line indicates the threshold calculated from the 20 trials (here 19.6 µL). The rate of descent of the function clearly demonstrates the efficiency of the SIAM procedure to rapidly converge on the vanillin threshold, echoing previous research undertaken in the gustatory modality using this technique (Hautus et al., 2010). Although a greater number of trials would afford more robust estimates of threshold, it is not the threshold value that is of most interest in Figure 2. Rather, the series can be treated as a dose–response relationship of sorts, in which higher vanillin concentrations reliably elicit correct responses (solid symbols) whereas circa threshold concentrations do so less...
reliably. As applied, the threshold-based SIAM approach offers a method to determine suitable flavor concentrations for stimuli. It should be noted, however, that any clinical procedure involving the assessment of olfactory identification would not utilize methods such as the SIAM task due to time constraints. Instead, assessments would entail only a small number of presentations (i.e., one or two) of a suprathreshold stimulus, in which odor identification judgments are elicited. What can be concluded from the trend in Figure 2, however, is that vanillin odorant delivered by gelatin–sucrose gels is an effective means to stimulate olfactory receptors and, what is more, can be controlled in a proportional dose–response manner. Thus, for those with normosmia, odorant delivery via the retronasal pathway using gelatin-based solid-state stimuli offers a viable method with which to assess central olfactory function.

Figure 3 plots threshold estimates as a function of block number for all five participants and for aggregated data. Table 1 displays detection thresholds for each participant, organized by block, and their overall threshold. In terms of detection, it appears that concentrations of around 30 µL to 40 µL can be considered suprathreshold for those without any peripheral impairment of olfactory ability, and so may represent an optimal dose for use in identification tasks employing gelatin stimuli. One advantage of identification testing is that stimuli can be suprathreshold, that is, sufficiently amplified above the absolute threshold. Thus, for identification tasks, stimuli should not be too weak so as not to be detectable, and also not so intense that they are unpleasant or trigger other processes that may mask the vanillin. For example, when using vanillin (and other stimuli besides), care must be taken as higher concentrations can lead to a bitter taste resulting in the activation of the gustatory and trigeminal systems (Ashkenazi & Marks, 2004). The activation of these other systems is undesirable as they may also provide participants with additional cues with which to make their judgments. We noted that, during our stimulus development phase, vanillin could not be detected in doses between 5 µL and 100 µL when the taster’s nose was clamped, indicating that detection was not occurring as a result of gustatory or trigeminal receptor stimulation. However, in the development of any clinical assessment tools, it would be essential to determine the dose–response relationship between retronasal odorants and the activation of other pathways besides the retronasal route.

Table 1 displays vanillin thresholds for each participant, organized by block, and their overall threshold. At the group level (see also Figure 3, bottom right), there is little evidence of practice effects, though the participants had undergone an intensive training regime to establish the range of concentrations to be used in the procedure. Furthermore, irrespective of session number, upon arriving at the testing locality the participants were fully briefed on testing protocols to reduce warm-up effects (Jaeger, Nihal de Silva, & Lawless, 2014; Thieme & O’Mahony, 1990). The slender confidence intervals most likely reflect the homogeneous nature of the sample, though a more heterogeneous sample differing in age would likely have produced wider intervals (Koskinen & Tuorila, 2005). Thus, it appears that the SIAM task itself is quite stable, echoing previous gustatory research (Hautus et al., 2010; Shepherd et al., 2011), and supports the suitability of this method in future olfactory research.

**Limitations and Suggestions for Future Research**

These findings should be considered with reference to the study’s limitations. First, the sample size was small, though typical of threshold-estimation research which often utilizes
small subject pools exposed to a large number of experimental trials. Thus, although there are only five estimates of threshold, they can be considered quite robust. However, given the small sample size and homogeneity of the participants (i.e., mostly young females), the findings cannot be generalized to other populations with confidence. In terms of the stimuli, only vanillin was used, and thus other studies are required to broaden the range of flavorants. Last, a detection approach was taken to argue for the efficacy of stimuli to be used in identification tests. We believe that the approach permitted greater scrutiny of the stimuli while still remaining relevant. Notably, feedback from the participants indicated that, when they were not guessing at lower vanillin concentrations, the “taste of vanilla” was experienced and obviously lacking in the blank stimuli. Thus, although the SIAM task was measuring detection thresholds, to a degree these reflected the minimum amount of vanillin that
could be identified. All of these limitations can be practically addressed in future research validating stimuli of this kind.

Any future development of retronasal-based psychological tests should consider employing more rapidly disintegrating substances that dissolve in saliva to produce aromatic compounds that then travel along the retronasal pathway. The process of freeze-drying (Sugimoto et al., 2006) or the use of oil body suspensions (Fisk, Linforth, Taylor, & Gray, 2011) are potential candidates that may permit the production of stimuli that facilitate rapid dissolution and volatilization of flavor compounds. Furthermore, in gel systems, there is an inverse relationship between the rigidity of the gel and flavor intensity (Mestres et al., 2005), with softer gels (e.g., pectin or starch) generally associated with greater and faster volatile liberation than harder gels (e.g., gelatin). The rigidity of a gelatin-based gel is proportional to the concentration of gelatin, with concentrations of 2% releasing odorants that are perceived as four times as intense as 8% concentrations of gelatin (Baek et al., 1999).

The use of solid delivery agents such as gels also allows the multiple volatiles to be presented in a single sample, offering the potential to increase the complexity of identification tests and to examine how central processes such as attention mediate the relationship between stimulus and response, and how these relationships vary with psychopathology. In addition, it may be that stimuli could be developed capable of transporting pharmaceutical agents from the mouth space to the olfactory epithelium. Finally, given the smooth dose-response relationships evident in the participant data, these stimuli may also be adapted to estimate olfactory detection and discrimination thresholds.

### Conclusion

The olfactory sense can reflect functional processes occurring in higher brain regions. Odor identification tests are already being recommended as clinical screening tools for a variety of emotional and cognitive disorders. Although orthonasal testing dominates current clinical practice and research, the potential for, and the advantages of, retronasal testing has been recognized by some. In addition, the approach promises a potential increase in control over the concentration of odorants delivered, an ongoing challenge in olfactory research (Evans et al., 1993). These results support the viability of using solid-state gustatory stimuli to deliver odorants to the olfactory epithelium in an effective and pleasant manner. As olfactory tests become more routine in clinical practice, stimuli of this type can facilitate assessment and diagnosis of psychopathology through the detection of biomarkers, and confer specific advantages over contemporary assessment approaches. Research implications include suggestions for other potential substances and flavorants to be tested, and use of the potential use of the retronasal route in general olfactory research.

### Acknowledgment

The authors would like to thank Aditee Naik for her assistance in preparing the stimulus materials and with data collection.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: This research was funded by a grant from the Faculty Research Development Fund (3624433/9853) from the University of Auckland.

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