Available online at www.sciencedirect.com

ScienceDirect

Review Article

Tracking traumatic head injuries with the chemical senses

Marion E. Frank*, Thomas P. Hettinger

Oral Health & Diagnostic Sciences, School of Dental Medicine, UCONN Health, Farmington, CT 06030, USA

Abstract   Chemosensory disorders, primarily olfactory, have diagnostic significance for prevalent human illnesses, but the multitude of smells makes measuring function appear daunting. The olfactory system operates under dynamic natural sensing conditions in which many individual odor chemicals are waxing and waning. Yet, in experimentally controlled simulations, mixture-component selective adaptation shows individual or shared prominent characteristic odors are detected but molecular stimulus features are not. As in other biological chemical signaling systems, including taste, odors activate dedicated receptors (OR). Given rapid OR adaptation with the passage of time, individual odor recognition is momentary. Receptive dendrites of the nearly 400 genetically variable human-OR in the olfactory epithelium critically project axons to the olfactory bulb through perforations in the cribriform plate of the skull. Analytic chemical-quality codes detect single odor-mixture components. However, identities of no more than 3 or 4 most salient odors are perceived due to central mixture-suppression, the mutual inhibition among diverse olfactory-bulb or cortical neurons. The componental codes allow olfaction to readily discern odor quality and valence of a wide range of unrelated chemicals, a few at a time. Head trauma may result in a partial or complete loss of smell and facial trauma a loss of taste-nerve function. Testing smell could plot the course of recovery from chronic traumatic encephalopathies that prevail in contact sports. Measuring brain function with olfaction would provide simpler and more direct monitoring of prognosis than biochemical sensors.
Copyright © 2018 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author. Oral Health & Diagnostic Sciences, School of Dental Medicine, UCONN Health, MC 1715, 263 Farmington Avenue, Farmington, CT 06030, USA.
  E-mail address: mfrank@uchc.edu (M.E. Frank).

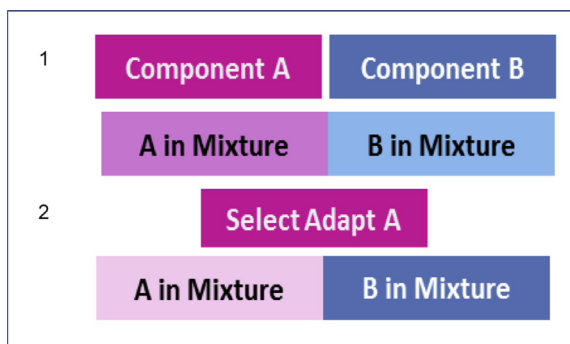**Production and Hosting by Elsevier on behalf of KeAi**

Introduction

Chemosensory disorders have diagnostic significance for prevalent human illnesses. Primarily olfactory, they are frequently considered gustatory due to the oral retro-nasal origin of some odorous volatiles.[1] However, the multitude of possible smells, recently exaggerated from thousands to more than a trillion,[2] makes measuring individual odor sensing appear daunting.[3,4] Furthermore, this conundrum has led to attempts to segregate roles of relevant functional groups,[5] or use of crowd-sourcing methods,[6] to count the number of recognizable multi-component odor objects that an individual can recognize.[7]

Odor component recognition

As in other biological chemical signaling systems, including taste-sensing[8–10]; distinct odors likely activate dedicated receptors (OR).[11,12] However, given the rapid odor adaptation with the passage of time, odor recognition is momentary.[4] The ortho-nasal odor-stimulus is limited to the inhalation phase by the act of sniffing,[13] and on the same time scale as sniffing, the odor rapidly adapts. To further complicate the stimulus situation, odor sensing occurs in dynamic natural sensing settings in which odors of many individual odor chemicals are simultaneously either waxing or waning. The olfactory system needs to be able to identify chemicals of harm or value under these conditions. Surprisingly, this may be accomplished by a combination of 'mixture suppression and selective adaptation.'

In experimentally controlled simulations, mixture-component selective adaptation shows individual or shared prominent characteristic odors ('odor notes') are detected by humans.[4] However, individual molecular stimulus features are not. The perceptual saliencies of two individually presented components, A and B 'odor notes', are represented by bright colors in Fig. 1. The saliencies are reduced when both components are within a mixture (below), the feature known as 'mixture suppression' in olfaction,[14–16] and taste.[17] However, when component A alone is adapted for 10 s (center), its ambient salience in

the following mixture (below) is further weakened but un-adapted component B is 'released' from mixture inhibition. This startling outcome resulting by combining 'mixture suppression' and 'selective adaptation' of independent stimuli (defined as those that do not cross-adapt) explains how the olfactory system is able to identify individual mixture components in few-component mixtures.[3,18,4] Thus, the odor mixtures are analyzed; they are not synthesized by a combinatorial process into a distinctly different quality. Gustatory mixtures of independent taste stimuli are also analyzed via the combination of 'mixture suppression' and 'selective adaptation'.[19]

An easy way to demonstrate selective adaptation is to use pieces of two kinds of chewing gum with independent odors (for example, juicy fruit and spearmint (®Wrigley's)). Three jars are set up with two having one or the other gum, and the third having both. Sniff for 10 s with a 10-sec inter-trial interval sniffing air. Test each type alone and mixed together. Then, test the mixture immediately after sniffing one kind of gum for 10 s. Repeat with the other kind. An efficient 'candy test' that uses retro-nasal smell,[20] has been described earlier.[21]

Limits to odor component detection

Although odor mixtures can have many more than a few components, identities of no more than 3 or 4 of the most salient odors are perceived simultaneously.[16,22,23] The biological basis for this limitation resides in the olfactory pathway: (1) 400 human OR with dedicated olfactory sensory neurons (OSN) in the nasal epithelium, (2) inhibitory neuropil in the olfactory bulb, and (3) a predominantly inhibitory olfactory cortex.[21] An odor stimulus activates OR located on OSN 'cilia' which excite neural action potentials in OSN axons. The axons must travel to the olfactory bulb on the under surface of the brain through perforations in the cribriform plate of the ethmoid bone of the skull, a site of OR vulnerability to head trauma shearing effects.[24] Bulbar glomeruli each process specific input from the many OSN carrying one OR type.[5,12,25,26] When activated simultaneously, glomerular inhibitory interneurons dedicated to different OR types shut each other down,[27–32] thus limiting the excitatory lateral olfactory tract input to the olfactory cortex to the most activated. Feedback inhibition from the cortex descends to the bulb.[33–35] Consequently, although componental odor codes readily discern odor quality of a wide range of unrelated chemicals, only a few are perceived at one time in a mixture.

Head trauma and olfaction

Head trauma may result in partial or complete loss of smell,[36,37] whereas, facial trauma may also reduce taste-nerve function.[24,38] Post-traumatic smell loss is associated with structural damage to olfactory bulbs and tracts.[39]

Testing smell could plot the course of recovery from chronic traumatic encephalopathies (CTE) that prevail in contact sports.[39,40] The measuring of brain function with olfaction, an early indication of neurodegeneration, would provide simpler and more direct CTE monitoring of prognosis than biochemical sensors,[41] and mouse models,[42] that

Fig. 1 **(1) Mixture-component suppression is influenced by (2) selectively adapting a component odor.** Odor intensity (color saturation) of a binary mixture component (rectangle) is either lowered (**ambient A**) or heightened (**extra B**) by 10-sec selective adaptation. Components may either be individual 'odor notes' or 'odor objects' having several notes.[4]

use post-mortem tissues. Phosphorylated tau protein pathology, the favored biomarker, has unfortunately not been measured simultaneously with olfactory perception.

A description of the concept and design of odor testing is given in section B above. Coordination with comparable taste testing would provide a convenient control for concurrent facial damage.

Conclusions

Simpler and more direct measurement of living brain function may be achieved with olfactory testing during football games and in other sports where players experience 'repetitive head impacts''. To date, the U.S. National Football League concussion protocol involves observation and evaluations of cognitive function from onset to recovery. Surprisingly, a test of olfactory function is not currently a part of the concussion protocol even though smell loss has been a common occurrence following head injuries. A test of olfactory function and CTE in real time would be a "game-changer" in our understanding of repetitive head injuries. A 5-min smell test given by a single technician could objectively track CTE over time.

Conflict of interest/Financial disclosures

References

1. Doty RL. Olfactory dysfunction and its measurement in the clinic. *World J Otorhinolaryngol Head Neck Surg*. 2015;1: 28—33.
2. Bushdid C, Magnasco MO, Vosshall LB, Keller A. Humans can discriminate more than 1 trillion olfactory stimuli. *Science*. 2014;343:1370—1372.
3. Goyert HF, Frank ME, Gent JF, Hettinger TP. Characteristic component odors emerge from mixtures after selective adaptation. *Brain Res Bull*. 2007;72:1—9.
4. Frank ME, Fletcher DB, Hettinger TP. Recognition of the component odors in mixtures. *Chem Senses*. 2017;42:537—546.
5. Nara K, Saraiva LR, Ye X, Buck LB. A large-scale analysis of odor coding in the olfactory epithelium. *J Neurosci*. 2011;31: 9179—9191.
6. Keller A, Gerkin RC, Guan Y, et al. Predicting human olfactory perception from chemical features of odor molecules. *Science*. 2017;355:820—826.
7. Hsieh JW, Keller A, Wong M, Jiang RS, Vosshall LB. SMELL-S and SMELL-R: olfactory tests not influenced by odor-specific insensitivity or prior olfactory experience. *Proc Natl Acad Sci U S A*. 2017;114:11275—11284.
8. Chandrashekar J, Kuhn C, Oka Y, et al. The cells and peripheral representation of sodium taste in mice. *Nature*. 2010;464: 297—301.
9. Zhao GQ, Zhang Y, Hoon MA, et al. The receptors for mammalian sweet and umami taste. *Cell*. 2003;115:255—266.
10. Yarmolinsky DA, Zuker CS, Ryba NJ. Common sense about taste: from mammals to insects. *Cell*. 2009;139:234—244.
11. Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell*. 1991; 65:175—187.
12. Buck LB. Unraveling the sense of smell (Nobel lecture). *Angew Chem Int Ed*. 2005;44:6128—6140.
13. Laing DG. Natural sniffing gives optimum odour perception for humans. *Perception*. 1983;12:99—117.
14. Laing DG, Willcox ME. Perception of components in binary odour mixtures. *Chem Senses*. 1983;7:249—264.
15. Laing DG, Panhuber H, Willcox ME, Pittman EA. Quality and intensity of binary odor mixtures. *Physiol Behav*. 1984;33: 309—319.
16. Livermore A, Laing DG. Influence of training and experience on the perception of multicomponent odor mixtures. *J Exp Psychol Hum Percept Perform*. 1996;22:267—277.
17. Bartoshuk LM. Taste mixtures: is mixture suppression related to compression. *Physiol Behav*. 1975;14:643—649.
18. Frank ME, Goyert HF, Hettinger TP. Time and intensity factors in identification of components of odor mixtures. *Chem Senses*. 2010;35:777—787.
19. Frank ME, Goyert HF, Formaker BK, Hettinger TP. Effects of selective adaptation on coding sugar and salt tastes in mixtures. *Chem Senses*. 2012;37:701—709.
20. Renner B, Mueller CA, Dreier J, Faulhaber S, Rascher W, Kobal G. The candy smell test: a new test for retronasal olfactory performance. *Laryngoscope*. 2009;119:487—495.
21. Frank ME. Chemoreception and perception. In: Hand AR, Frank ME, eds. *Fundamentals of Oral Histology and Physiology*. Wiley; 2014:191—220.
22. Laing DG. Identification of single dissimilar odors is achieved by humans with a single sniff. *Physiol Behav*. 1986;37: 163—170.
23. Laing DG, Link C, Jinks AL, Hutchinson I. The limited capacity of humans to identify the components of taste mixtures and taste-odour mixtures. *Perception*. 2002;31:617—635.
24. Reiter ER, Costanzo RM. Chemosensory impairment after traumatic brain injury: assessment and management. *Int Neurotrauma Lett*. 2014;23:3—5.
25. Ressler KJ, Sullivan SL, Buck LB. Information coding in the olfactory system: evidence for a stereotyped and highly organized epitope map in the olfactory bulb. *Cell*. 1994;79: 1245—1255.
26. Mombaerts P, Wang F, Dulac C, et al. Visualizing an olfactory sensory map. *Cell*. 1996;87:675—686.
27. Shepherd GM. The olfactory bulb: a simple system in the mammalian brain. In: Kandel ER, ed. *Handbook of Physiology, Section 1: The Nervous System*. Bethesda: MD: American Physiological Society; 1977:945—968.
28. Yokoi M, Mori K, Nakanishi S. Refinement of odor molecule tuning by dendrodendritic synaptic inhibition in the olfactory bulb. *Proc Natl Acad Sci U S A*. 1995;92:3371—3375.
29. Mori K, Nagao H, Yoshihara Y. The olfactory bulb: coding and processing of odor molecule information. *Science*. 1999;286: 711—715.
30. Yu Y, McTavish TS, Hines ML, Shepherd GM, Valenti C, Migliore M. Sparse distributed representation of odors in a large-scale olfactory bulb circuit. *PLos Comput Biol*. 2013;9, e1003014.
31. Maresh A, Rodriguez GD, Whitman MC, Greer CA. Principles of glomerular organization in the human olfactory bulb—implications for odor processing. *PLoS One*. 2008;3: e2640.
32. Moriya-Ito K, Tanaka I, Umitsu Y, Ichikawa M, Tokuno H. The olfactory bulb and the number of its glomeruli in the common marmoset (*Callithrix jacchus*). *Neurosci Res*. 2015;93: 158—163.
33. Isaacson JS. Odor representations in mammalian cortical circuits. *Curr Opin Neurobiol*. 2010;20:328—331.
34. Poo C, Isaacson JS. Odor representations in olfactory cortex: "sparse" coding, global inhibition, and oscillations. *Neuron*. 2009;62:850—861.

35. Boyd AM, Sturgill JF, Poo C, Isaacson JS. Cortical feedback control of olfactory bulb circuits. *Neuron*. 2012;76:1161—1174.

36. Schofield PW, Moore TM, Gardner A. Traumatic brain injury and olfaction: a systematic review. *Front Neurol*. 2014;5:5.

37. Ciofalo A, Zambetti G, Fusconi M, et al. Olfactory dysfunction after minor head trauma. *J Head Trauma Rehabil*. 2011;26, 418—418.

38. Bonardi JP, da Costa FH, Stabile GA, Pereira-Stabile CL. Traumatic dysgeusia, an unusual complication of facial trauma: a case report. *J Oral Maxillofac Surg*. 2016;74:1416—1419.

39. Yousem DM, Geckle RJ, Bilker WB, McKeown DA, Doty RL. Posttraumatic olfactory dysfunction: MR and clinical evaluation. *AJNR Am J Neuroradiol*. 1996;17:1171—1179.

40. Alosco ML, Jarnagin J, Tripodis Y, et al. Olfactory function and associated clinical correlates in former National Football League players. *J Neurotrauma*. 2017;34:772—780.

41. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68:709—735.

42. Tagge CA, Fisher AM, Minaeva OV, et al. Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model. *Brain*. 2018;141:422—458.

Edited by Yu-Xin Fang