HUMAN OLFACTORY PERCEPTION

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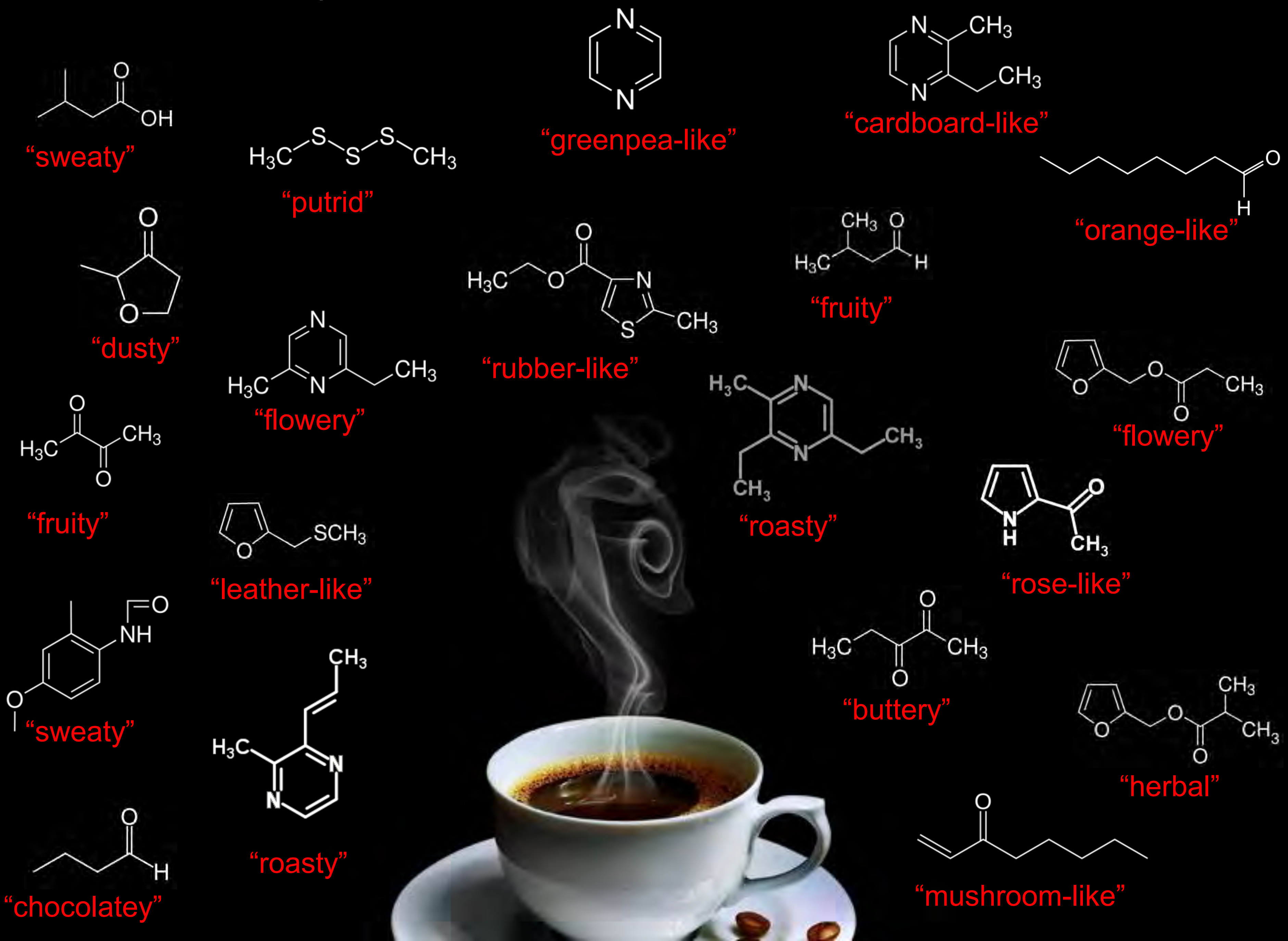
Natural odors are complex combinations of chemicals



STIMULUS
Natural source
Molecule(s) [single vs mixtures]

Chemistry

DETECTION
Sniffing
Olfactory mucus
Odorant receptor(s)
Signal transduction

Biology

CIRCUIT
Olfactory epithelium
Olfactory bulb / pre-processing
Olfactory cortex
Memory and association cortex

PERCEPTION
Experience
Memory
Emotion
Nasal health
Mental health / neurodegeneration

Psychology

1 2 3

STIMULUS

Natural source

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PERCEPTION

Experience

Memory

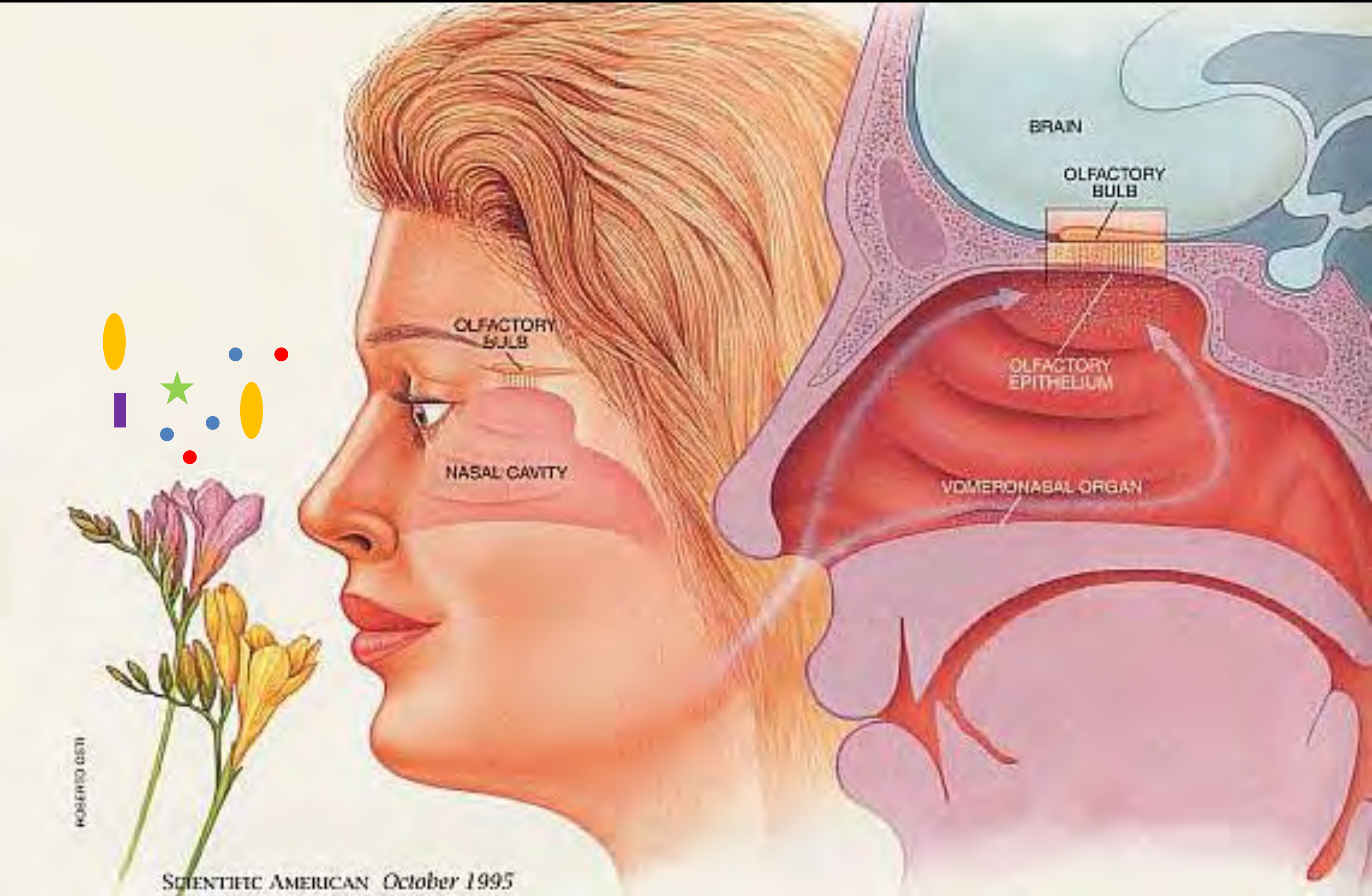
Emotion

Nasal health

Mental health / neurodegeneration

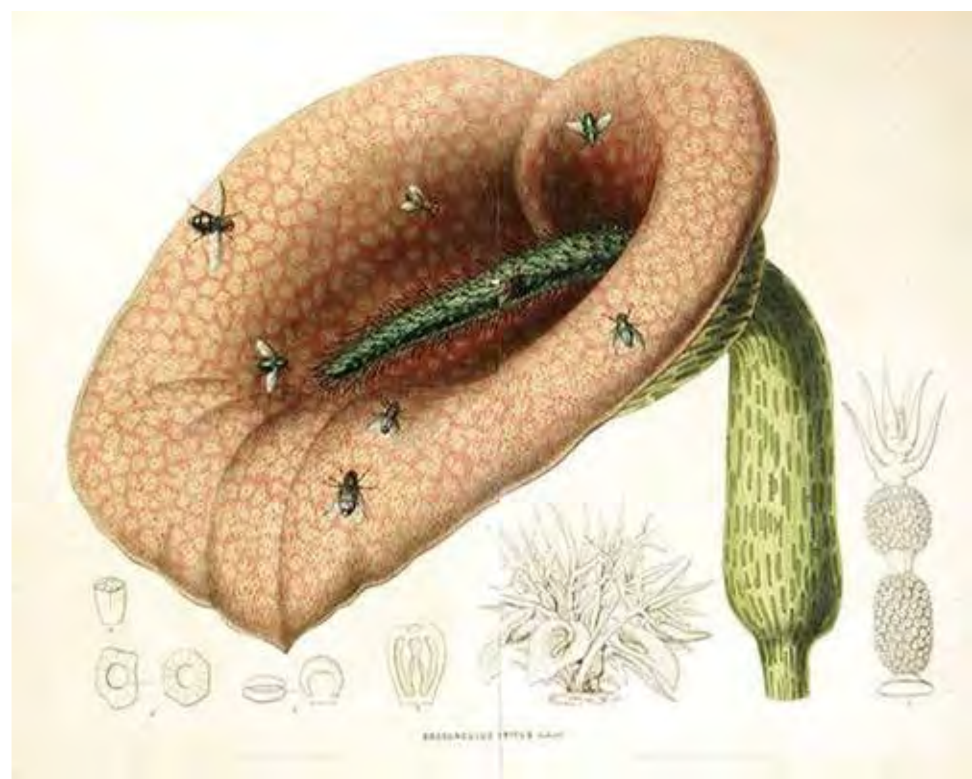
“Very Unpleasant”

SMELLING=SNIFFING

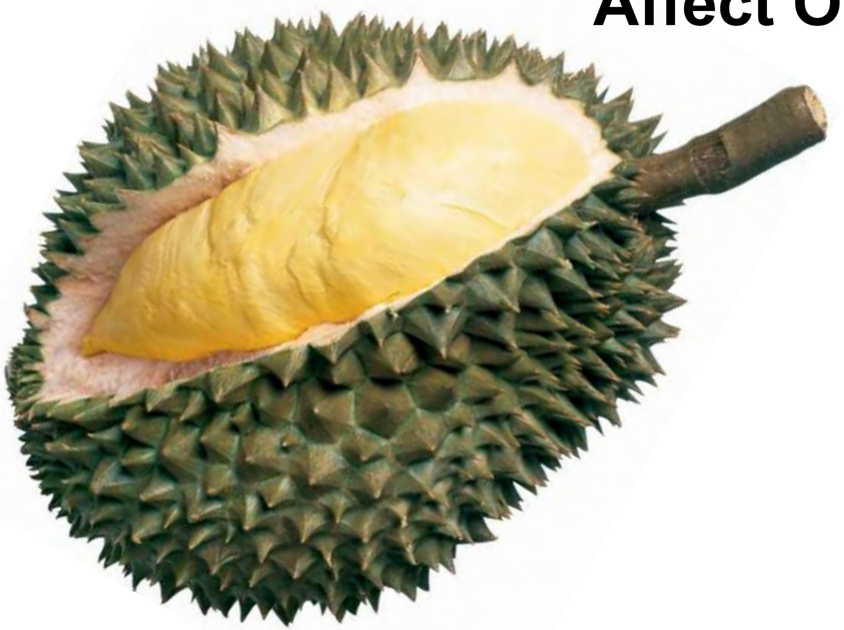



INTENSITY
Strong/Weak

VALENCE
Pleasant/Unpleasant



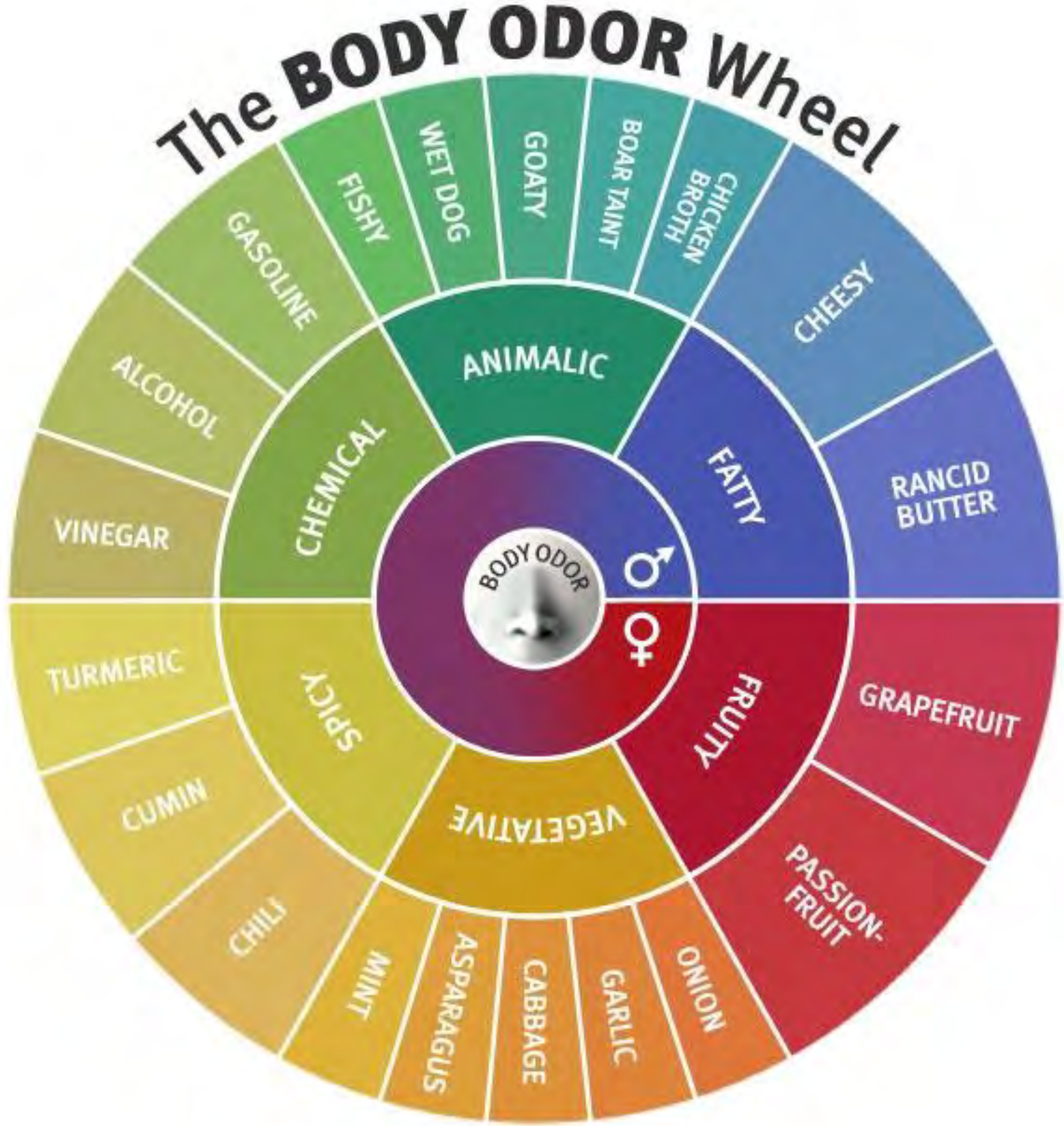
Culture & Experience Affect Odor Perception



CATEGORIZATION

CATEGORIZATION

ODOR CATEGORIES BY SEMANTIC DESCRIPTORS



Dravnieks 1985: a standard list of olfactory perceptual descriptors

Table 1. Semantic odor quality descriptors.

Materials	Chemicals	Outdoors	Fruits	Foods	Spices
dry, powdery	sharp, pungent, acid	hay	cherry, berry	buttery, fresh	almond
chalky	sour, acid, vinegar	grainy	strawberry	caramel	cinnamon
cork	ammonia	herbal, cut grass	peach	chocolate	vanilla
cardboard	camphor	crushed weed	pear	molasses	anise, licorice
wet paper	gasoline, solvent	crushed grass	pineapple	honey	clove
wet wool, wet dog	alcohol	woody, resinous	grapefruit	peanut butter	maple syrup
rubbery, new	kerosene	bark, birch	grape juice	soupy	dill
tar	househol				caraway
leather	chemi				minty, peppermint
rope	turpe				nut, walnut
metallic	varnis				eucalyptus
burnt, smoky	paint				malt
burnt paper	sulphi				yeast
burnt candle	soapy			bread	black pepper
burnt rubber	medic				tea leaves
burnt milk	disinfe				spicy
creosote	ether,				
sooty	cleani				
fresh tobacco smoke	mothbal				
stale tobacco smoke	nail polish remover				

Foul	Common	Common	Meats	Vegetables	Body
fermented, rotten fruit	sweet	sweaty	meat seasoning	fresh vegetables	dirty linen
sickening	fragrant	cool, cooling	animal	garlic, onion	sour milk
rancid	perfumery	light	fish	mushroom	sewer
putrid, foul, decayed	floral	heavy	kippery, smoked fish	raw cucumber	fecal, manure
dead animal	cologne	warm	blood, raw meat	raw potato	urine
mouse-like	aromatic		meat, cooked good	bean	cat urine
	musky		oily, fatty	green pepper	seminal, like sperm
	incense		sauerkraut		
	bitter		celery		
	stale		cooked vegetables		

Dated, obsolete: “carbonic” “kippery”

American vernacular: “root beer” “gingerbread” “cheddar cheese” “dill pickle” “wintergreen”


DISCRIMINATION

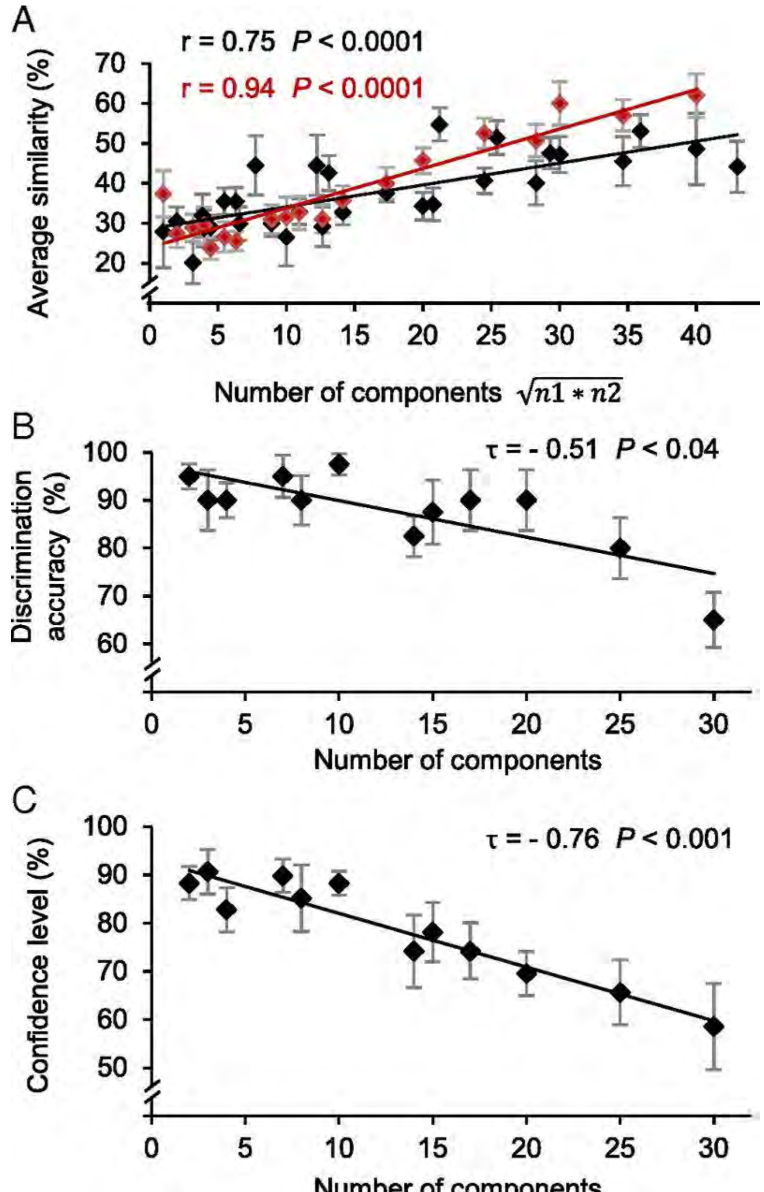
NOAM SOBEL'S OLFACTORY WHITE: Increasing the number of non-overlapping spanned components in two mixtures renders them more similar and less discernible

Although these mixtures converge upon a single semantic category,

"LORAX"

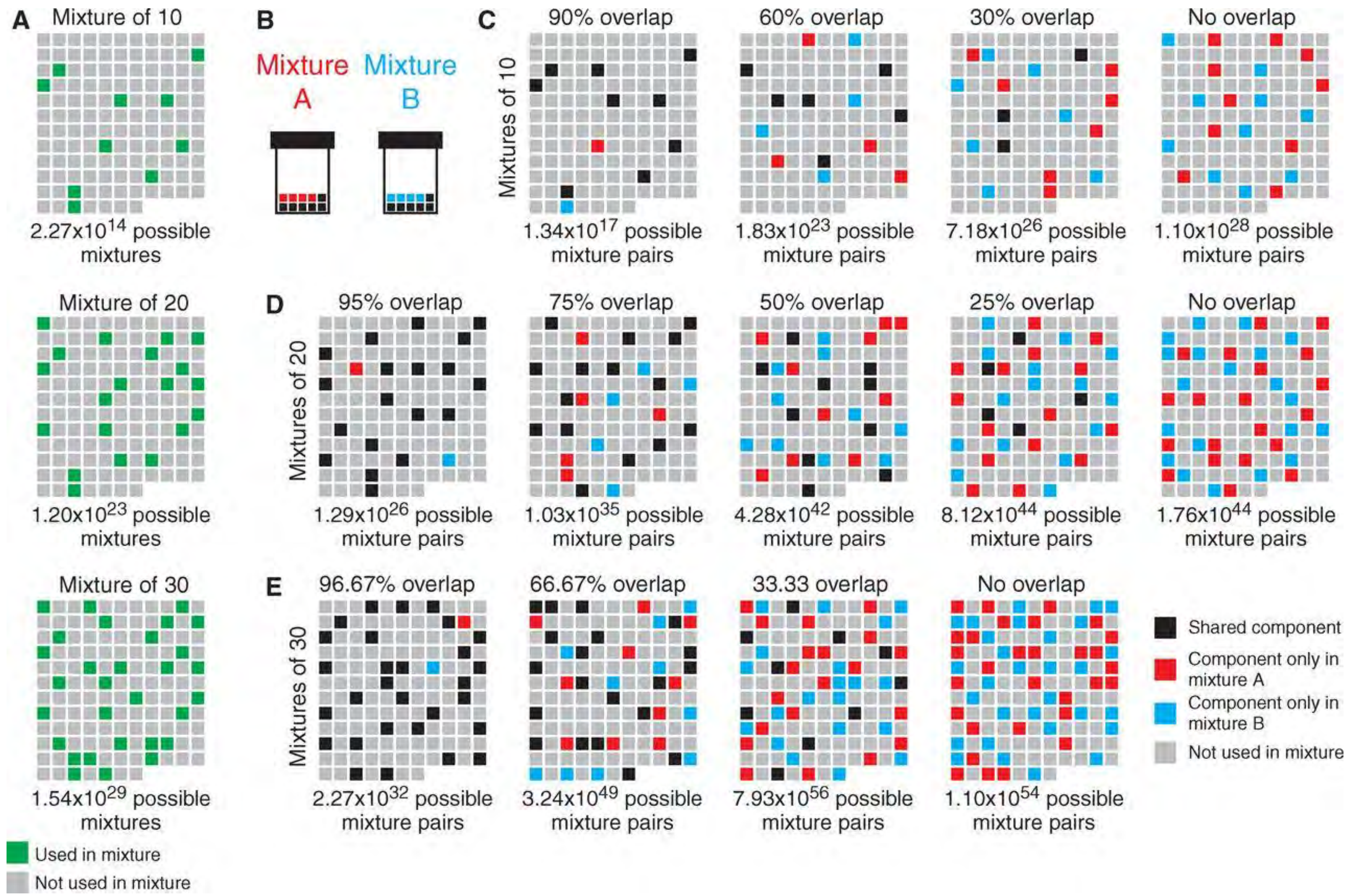
all are readily discriminable

"OLFACTORY WHITE"



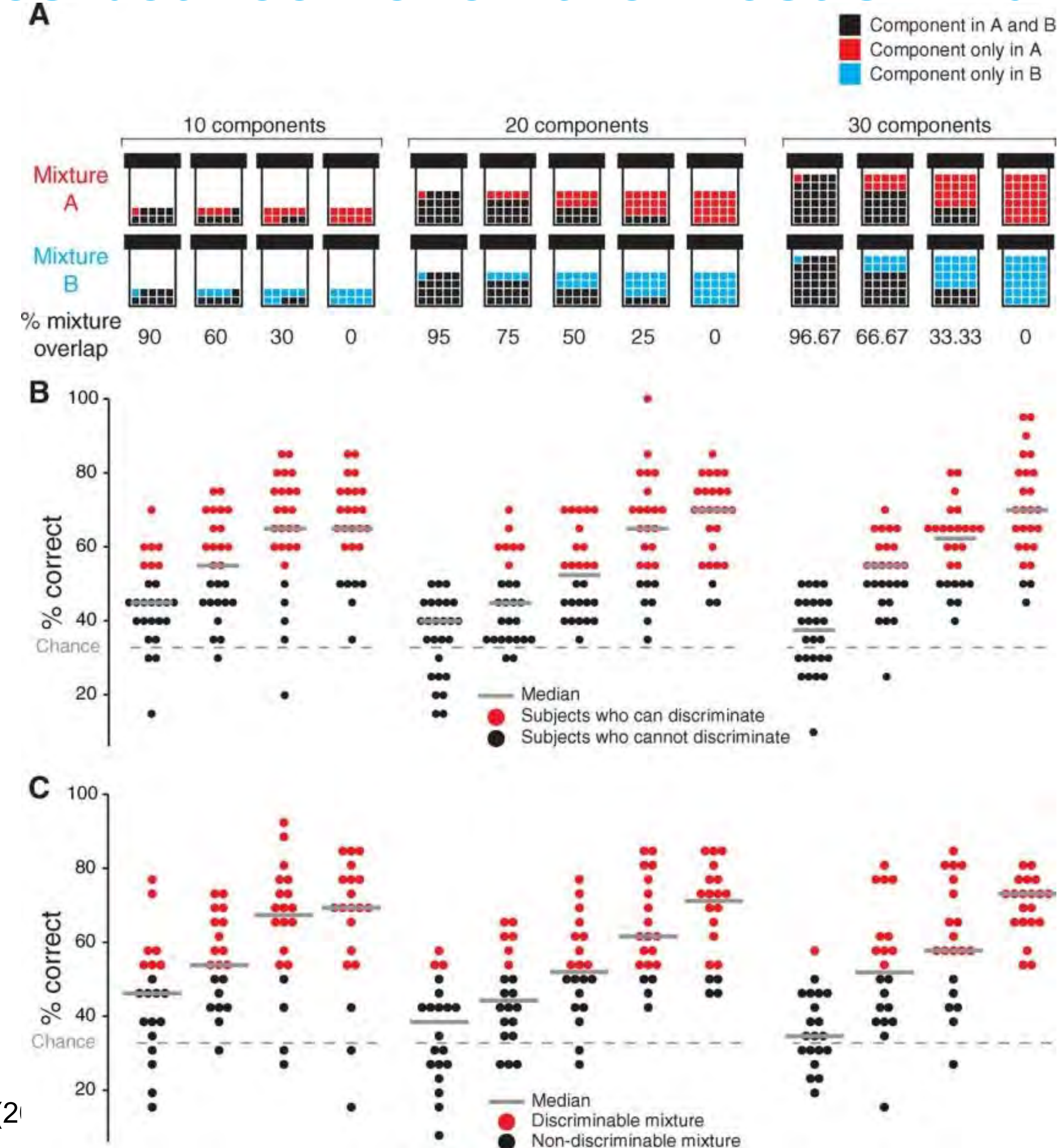
Tali Weiss et al. PNAS (2012)

A large number of complex "olfactory white" mixtures can be formulated with 128 starting components



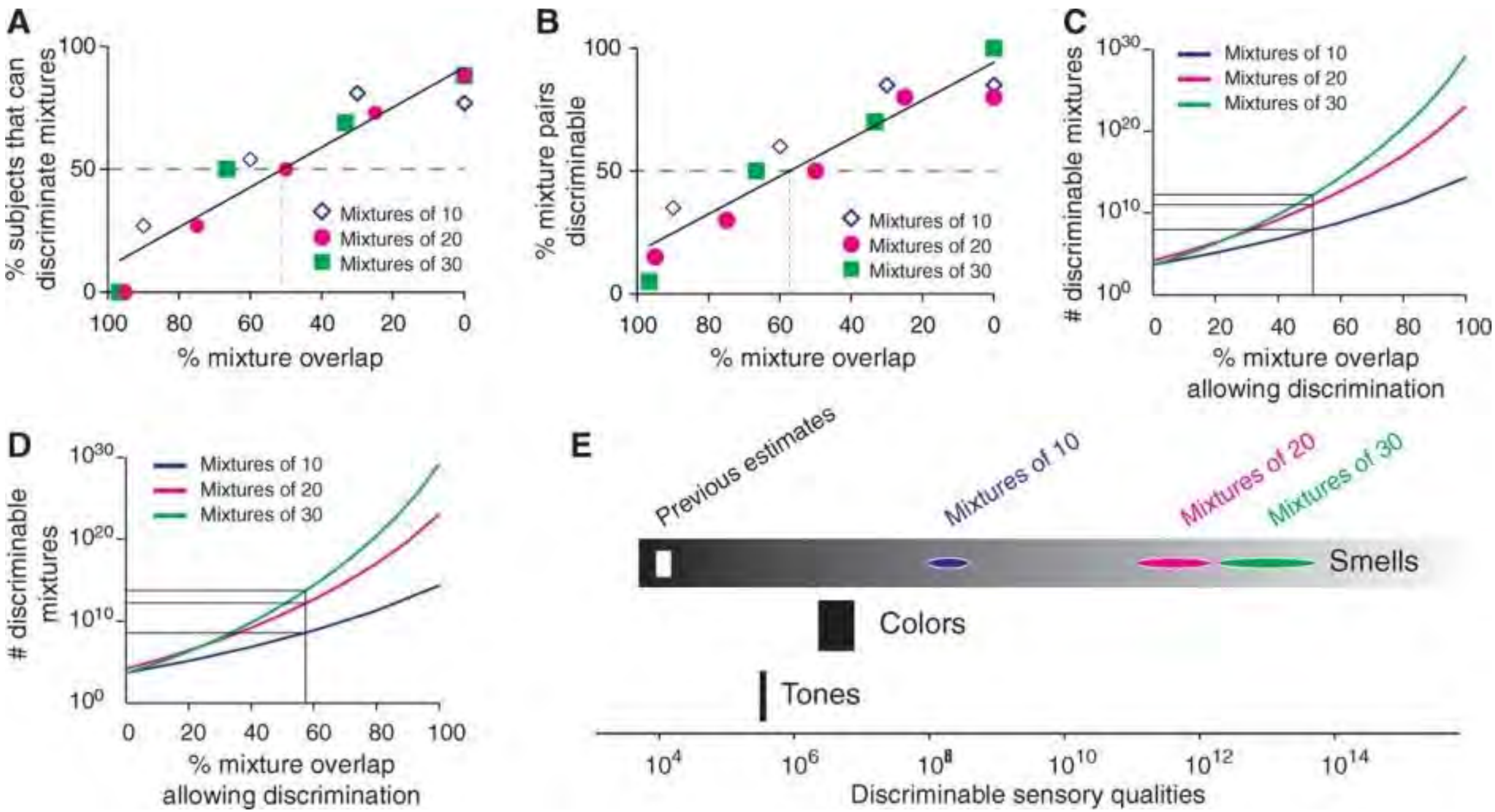
Bushdid et al., Science (2014)

Most subjects performed above chance to detect differences between even the most similar mixtures



Bushdid et al., Science (2

An *attempt* to extrapolate from these data to the discriminative capacity of human olfaction



Bushdid et al., Science (2014)

Humans can discriminate more than one trillion odors
Bushdid et al. Science 2014

Correction (18 August 2016): "Humans can discriminate more than 1 trillion olfactory stimuli" by C. Bushdid et al. (21 March 2014, p. 1370). The mathematical model used to extrapolate the number of olfactory stimuli that humans can discriminate was based on a number of assumptions. The authors inadvertently failed to state four of them:

First, the model assumed that odor stimulus space is isotropic, so that changing any component in any mixture in any direction is the same as any other direction.

Second, the authors assumed that olfactory perceptual space is high-dimensional. The authors agree that their extrapolation fails in regimes of low dimensionality (1), and subsequent analysis indicates that the results hold if the dimensionality of olfactory representations is $D \geq 25$ (2).

Third, the model used a simplified approximation to obtain the total number of spheres that can be packed in a space by dividing the overall volume of the space by the volume of a single sphere. The actual calculation of the number of packable spheres using the “spherical code” problem establishes a rigorous lower bound that is a factor of 10 smaller than our estimate.

Fourth, the authors considered any pair of statistically significantly discriminable stimuli as discriminable regardless of effect size. Their estimates hold if a conventional effect size of 20% is imposed.

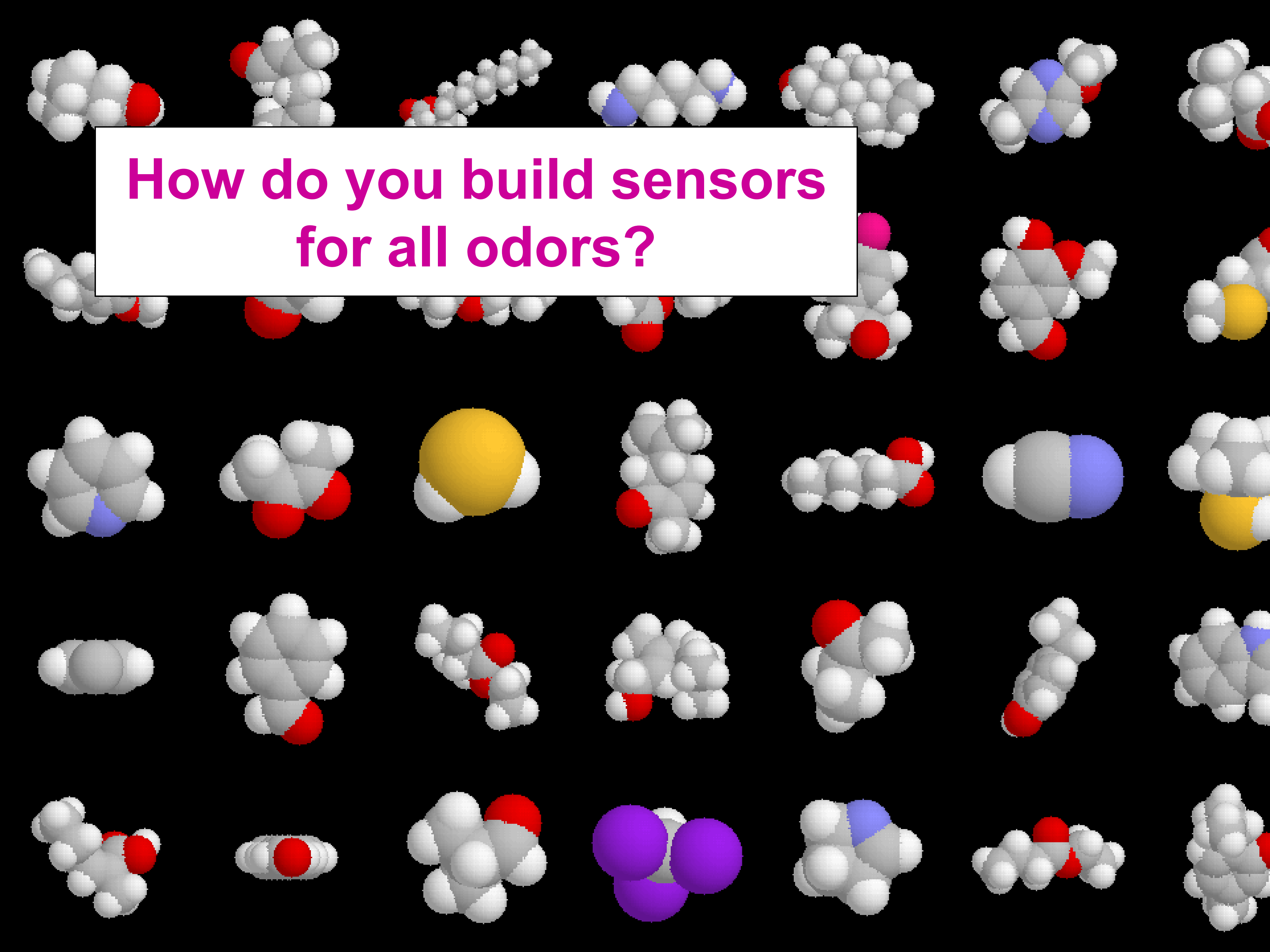
It has been pointed out that a model not constrained by these assumptions causes the number of discriminable stimuli to become arbitrarily small or large (1, 3). Any exponential function will be sensitive in this way, and the goal of the model was not to identify the exact number of discriminable olfactory stimuli but an estimate of the order of magnitude of human discriminatory power across a population of human subjects. The authors thank their colleagues for bringing these unstated assumptions to their attention.

1. M. Meister, On the dimensionality of odor space. eLife 4, e07865 (2015).

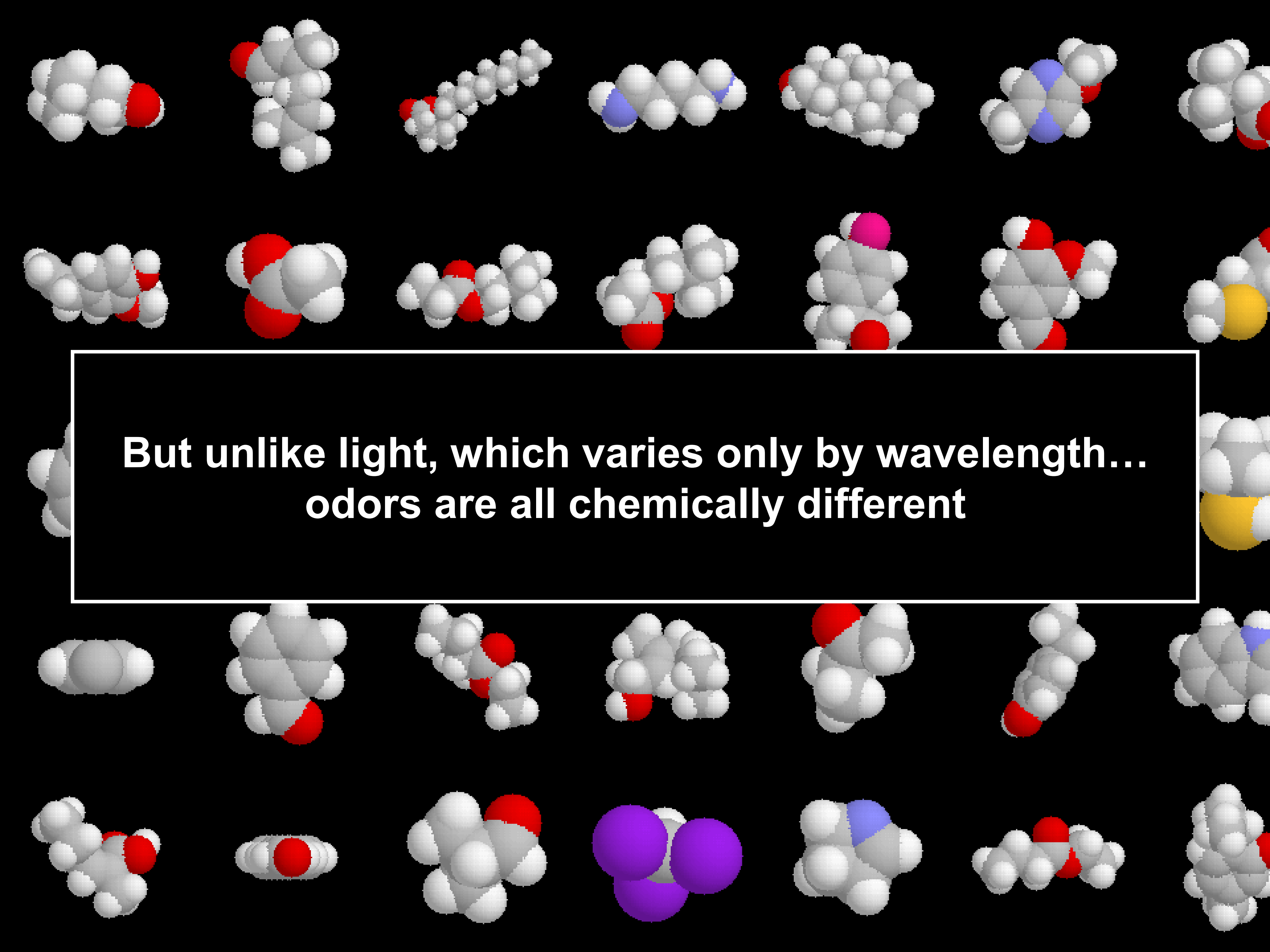
2. M. O. Magnasco, A. Keller, L. B. Vosshall, On the dimensionality of olfactory space. bioRxiv 10.1101/022103 (2015).

3. R. C. Gerkin, J. B. Castro, The number of olfactory stimuli that humans can discriminate is still unknown. eLife 4, e08127 (2015).

How do you build sensors for all odors?

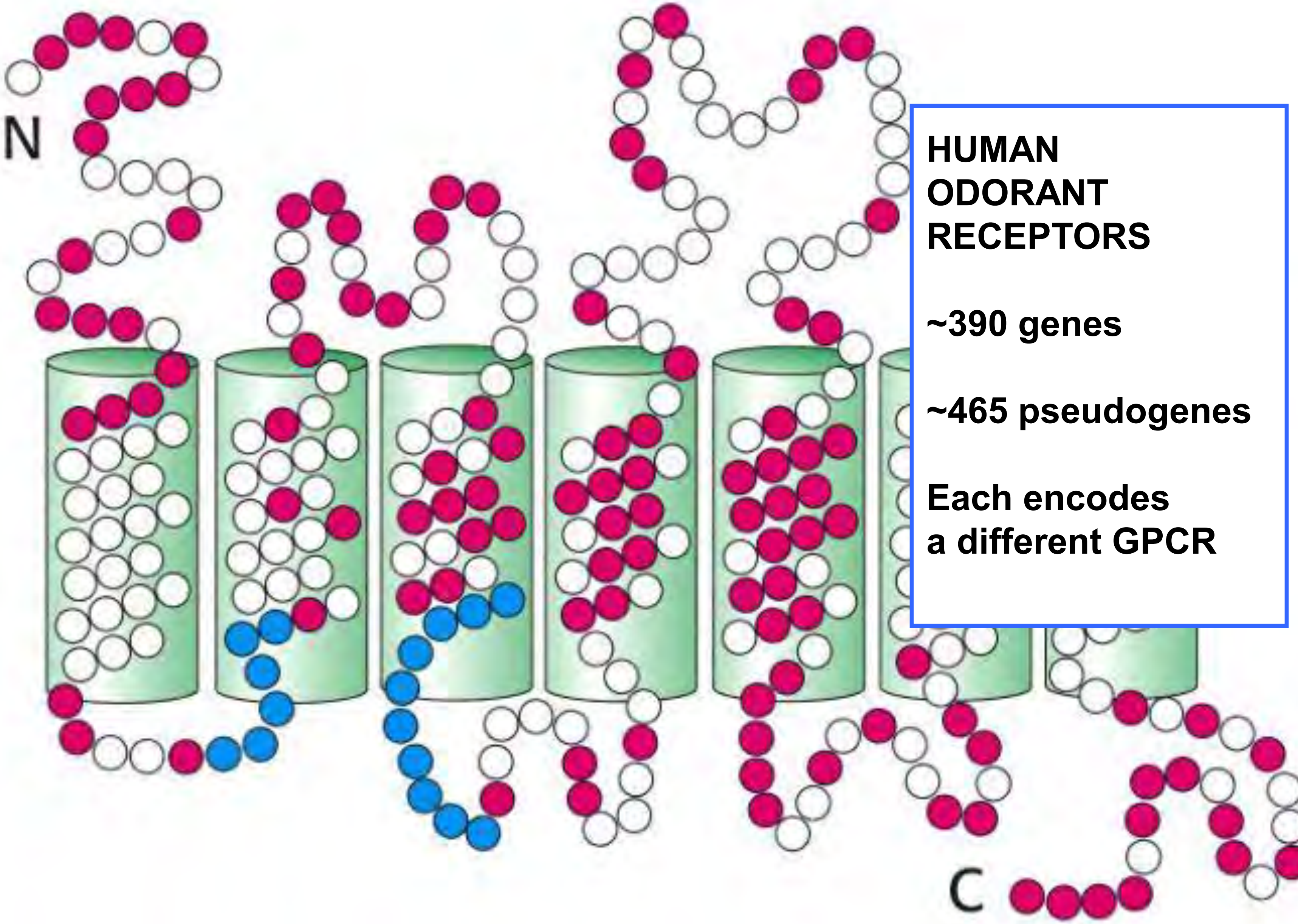



We detect all visible colors
with only 3 receptors



But unlike light, which varies only by wavelength…
odors are all chemically different

Vertebrate Odorant Receptors (ORs)



HUMAN ODORANT RECEPTORS

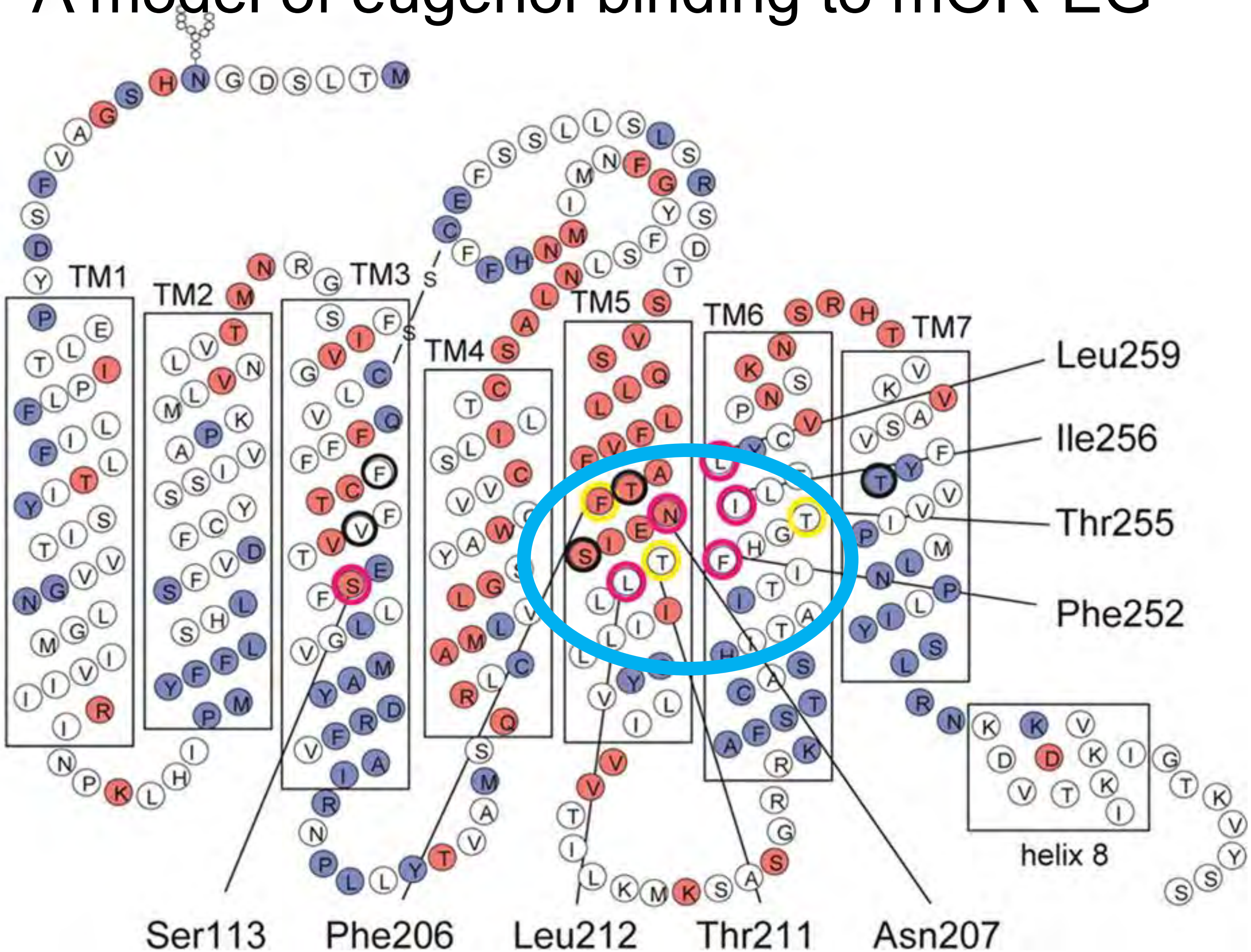
~390 genes

~465 pseudogenes

Each encodes a different GPCR

Buck and Axel, 1991

HOW DO ORs RECOGNIZE MOLECULES?
A model of eugenol binding to mOR-EG



Katada et al. J. Neurosci. 2005;25:1806-1815

Stuart Firestein (2000):

ARTICLE **FIRST ODORANT – ODORANT RECEPTOR MATCH**

Nature Neuroscience 3, 1248 - 1255 (2000)
doi:10.1038/81774

The molecular receptive range of an odorant receptor

Ricardo C. Araneda, Abhay D. Kini & Stuart Firestein

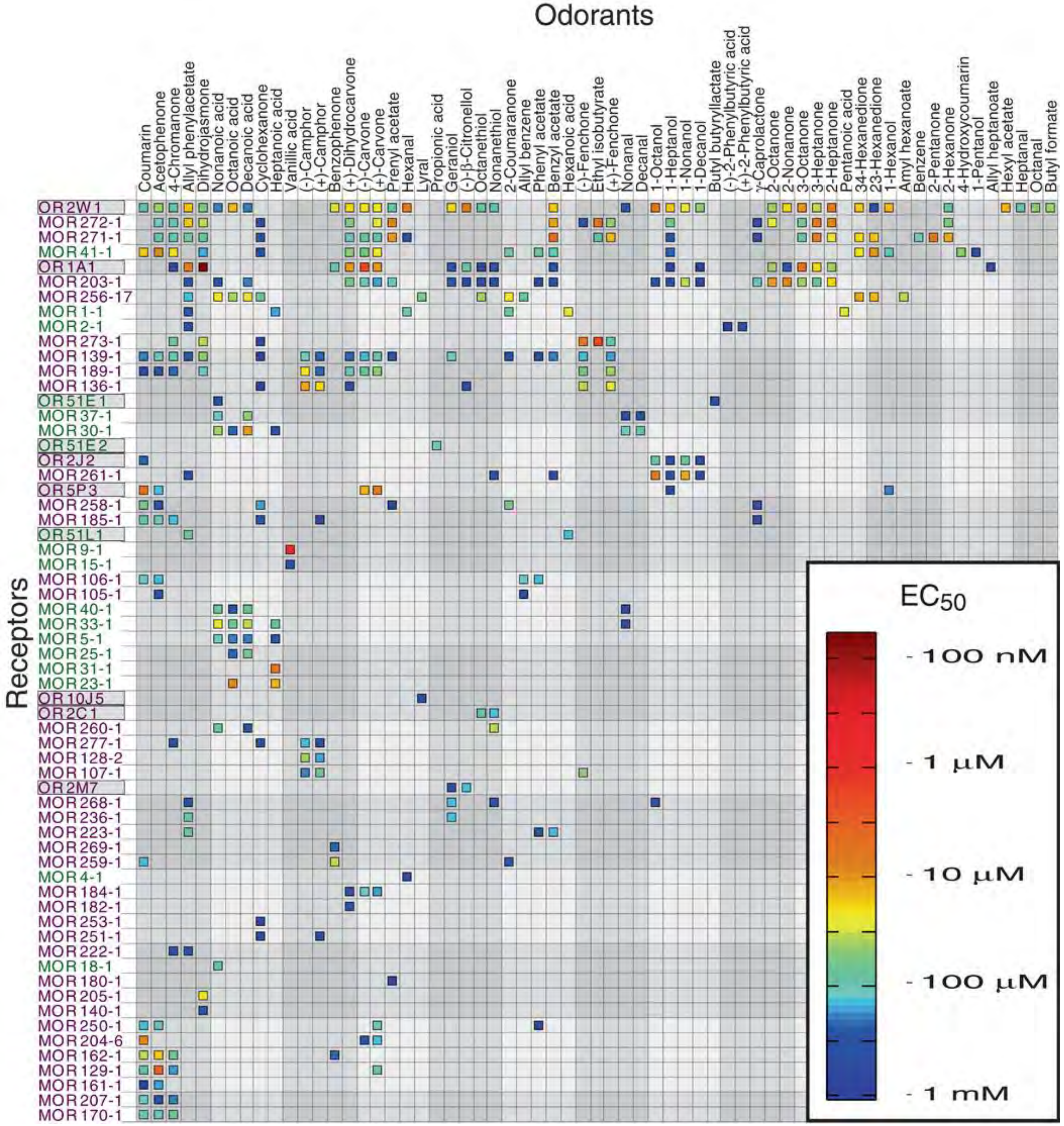
Department of Biological Sciences, Columbia University, New York, New York 10027, USA

Correspondence should be addressed to Stuart Firestein sif24@columbia.edu

An odor perception is the brain's interpretation of the activation pattern of many peripheral sensory neurons that are differentially sensitive to a wide variety of odors. The sensitivity of these neurons is determined by which of the thousand or so odor receptor proteins they express on their surface. Understanding the odor code thus requires mapping the receptive range of odorant receptors. We have adopted a pharmacological approach that uses a large and diverse pool of odorous compounds to characterize the molecular receptive field of an odor receptor. We found a high specificity for certain molecular features, but high tolerance for others—a strategy that enables the olfactory apparatus to be both highly discriminating, and able to recognize several thousand odorous compounds.

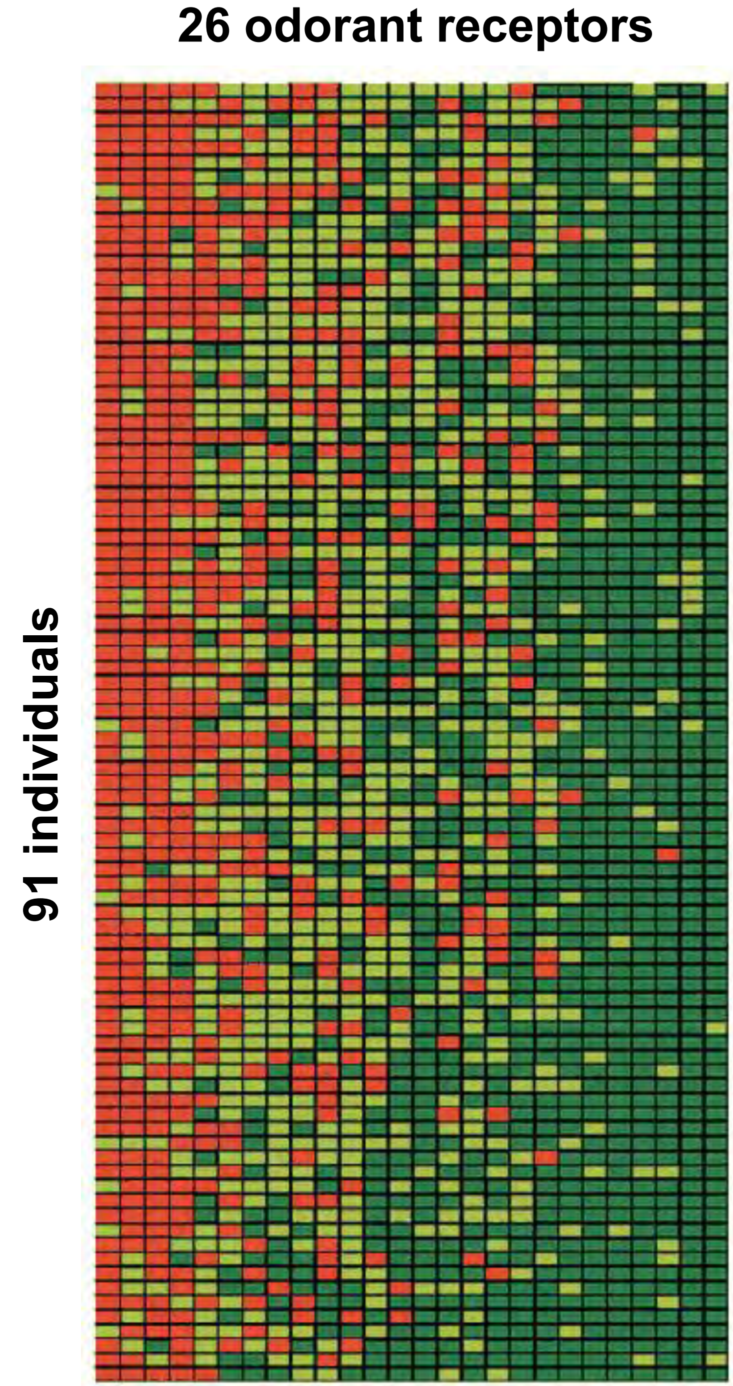
nsory system description and analysis have traditionally used the notion of a 'receptive ld,' which is defined as the stimulus range that can be detected at any particular stage of

COMBINATORIAL CODING OF ODORS: a potentially vast sensory coding space



Harumi Saito et al., Sci. Signal. 2009;2:ra9

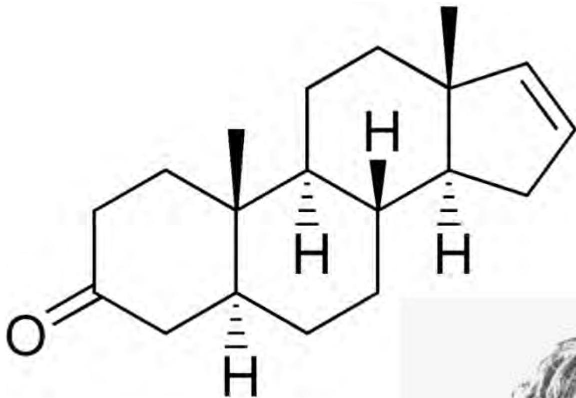
Every Human Has a Unique Nose



- Non-functional
- Non-functional (1 copy)
- Functional

Menashe, Nat. Genet. 34:143, 2003

These sex steroid-derived molecules smell different to different people



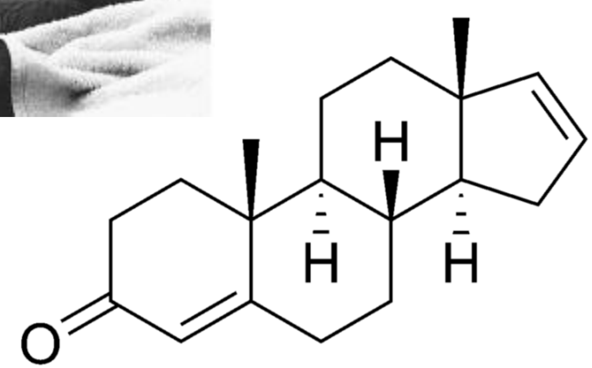
androstenone

"Sweaty, urinous"

"Sweet, floral"

"Odorless"

androstadienone



Variation in androstenenone perception

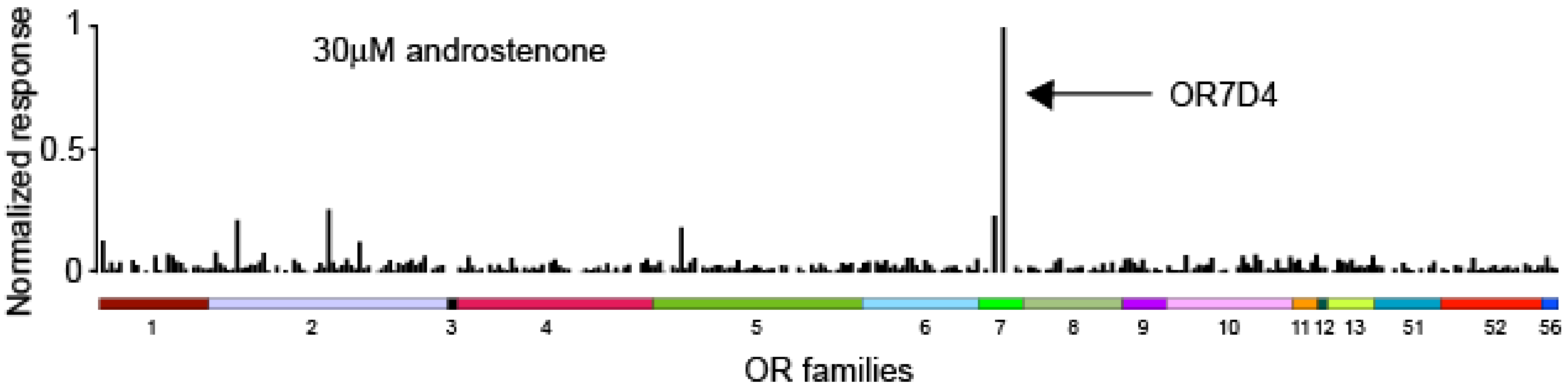
Vanillin descriptors

57	vanilla
17	sweet
6	fragrant
4	perfumery
3	aromatic
1	warm
1	peppermint
1	musky
1	maple syrup
1	floral
1	cologne
1	caramel
1	buttery fresh

Androstenone descriptors

8	chemical
8	musky
7	light
6	heavy
6	stale
5	fragrant
5	musty
5	sweaty
4	putrid
3	alcohol
3	ammonia
3	aromatic
3	cedarwood
2	bitter
2	buttery/fresh
2	cleaning fluid
2	disinfectant
2	floral
2	gasoline
2	nail polish remover
2	rancid
2	sharp
2	sweet
2	urine
1	animal
1	bark/birch
1	celery
1	clove
2	dead animal

OR7D4 responds to androstenone

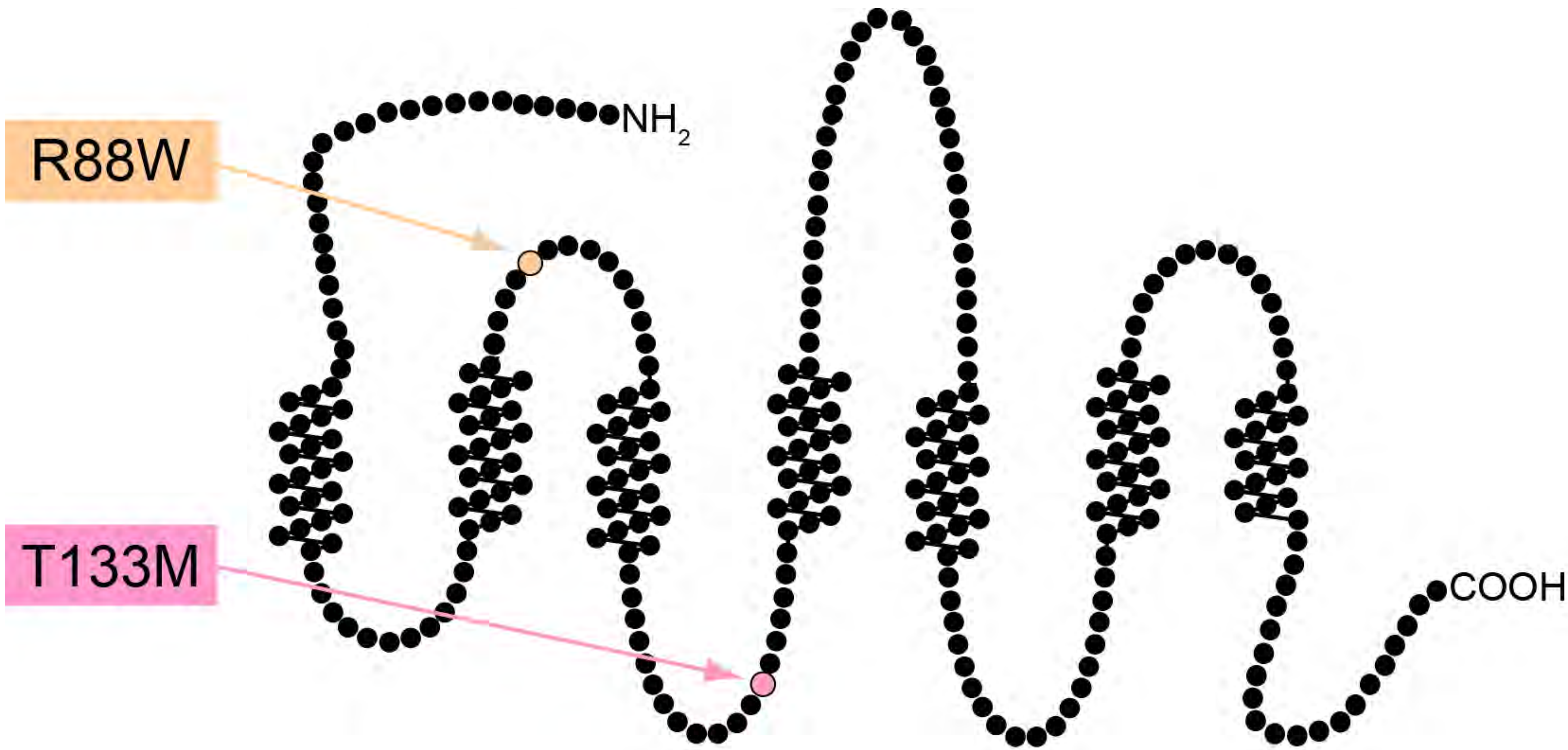


Keller, Zhuang, Chi, Vosshall, & Matsunami Nature 2007

OR7D4 responds selectively to androstenone & androstadienone

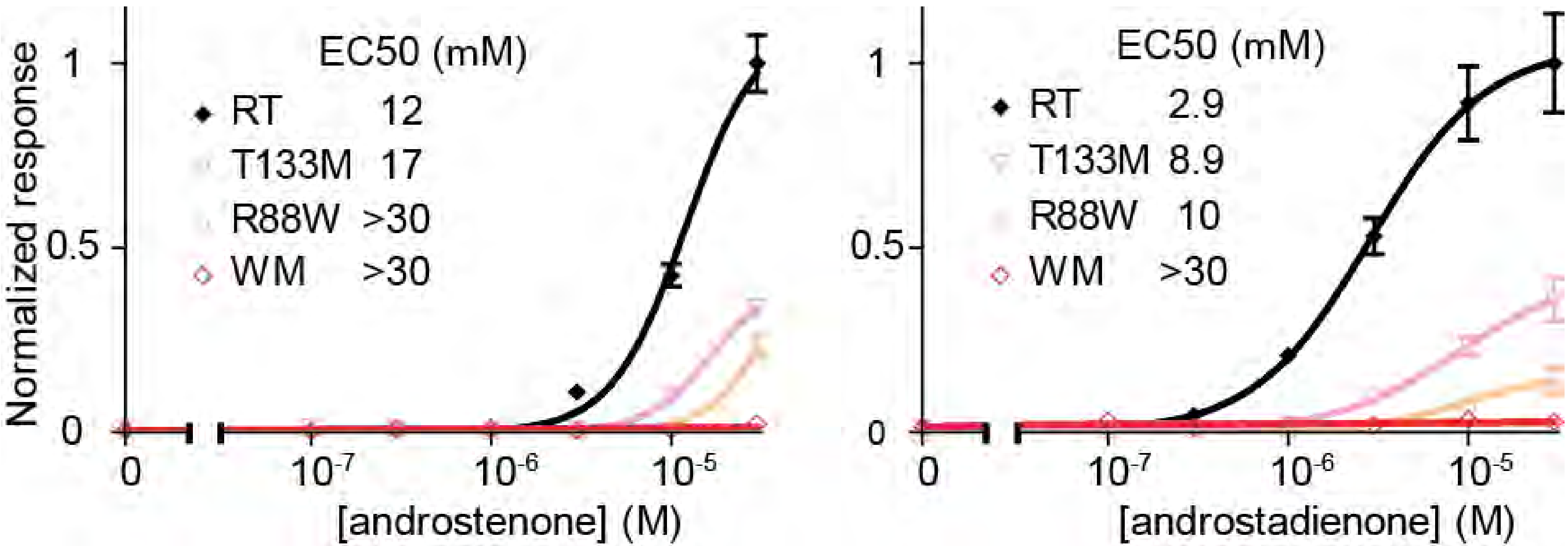
Keller, Zhuang, Chi, Vosshall, & Matsunami Nature 2007

2 amino acid changes in OR7D4 correlate with alterations in androstenone perception



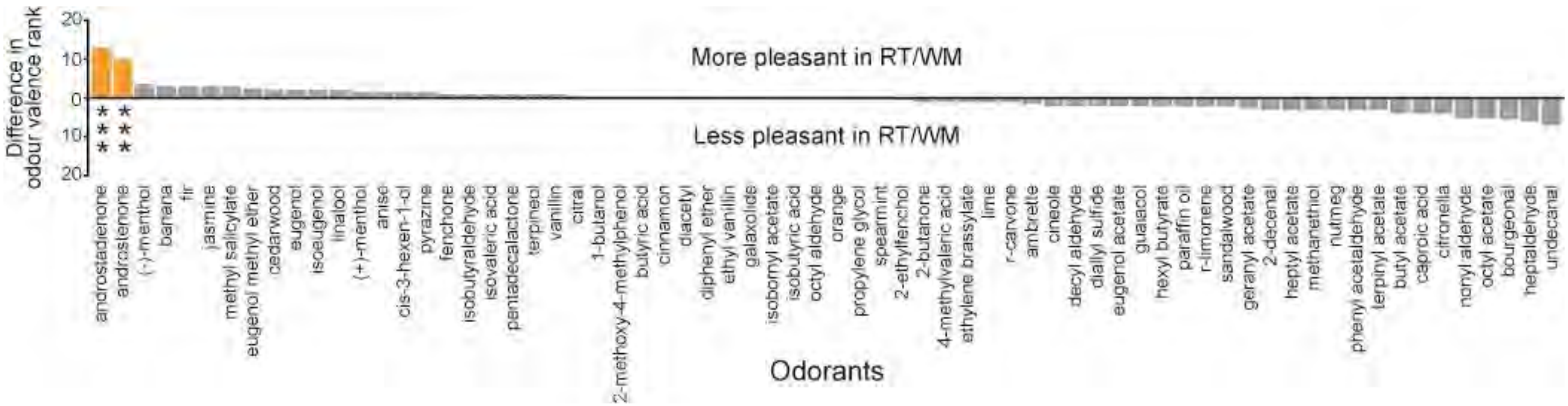
Keller, Zhuang, Chi, Vosshall, & Matsunami Nature 2007

OR7D4 T133M/R88W shows severe reductions in odor responsivity



Keller, Zhuang, Chi, Vosshall, and Matsunami, **Nature**, 2007

Subjects with non-functional OR7D4 perceive steroids as less unpleasant



Keller, Zhuang, Chi, Vosshall, & Matsunami Nature 2007

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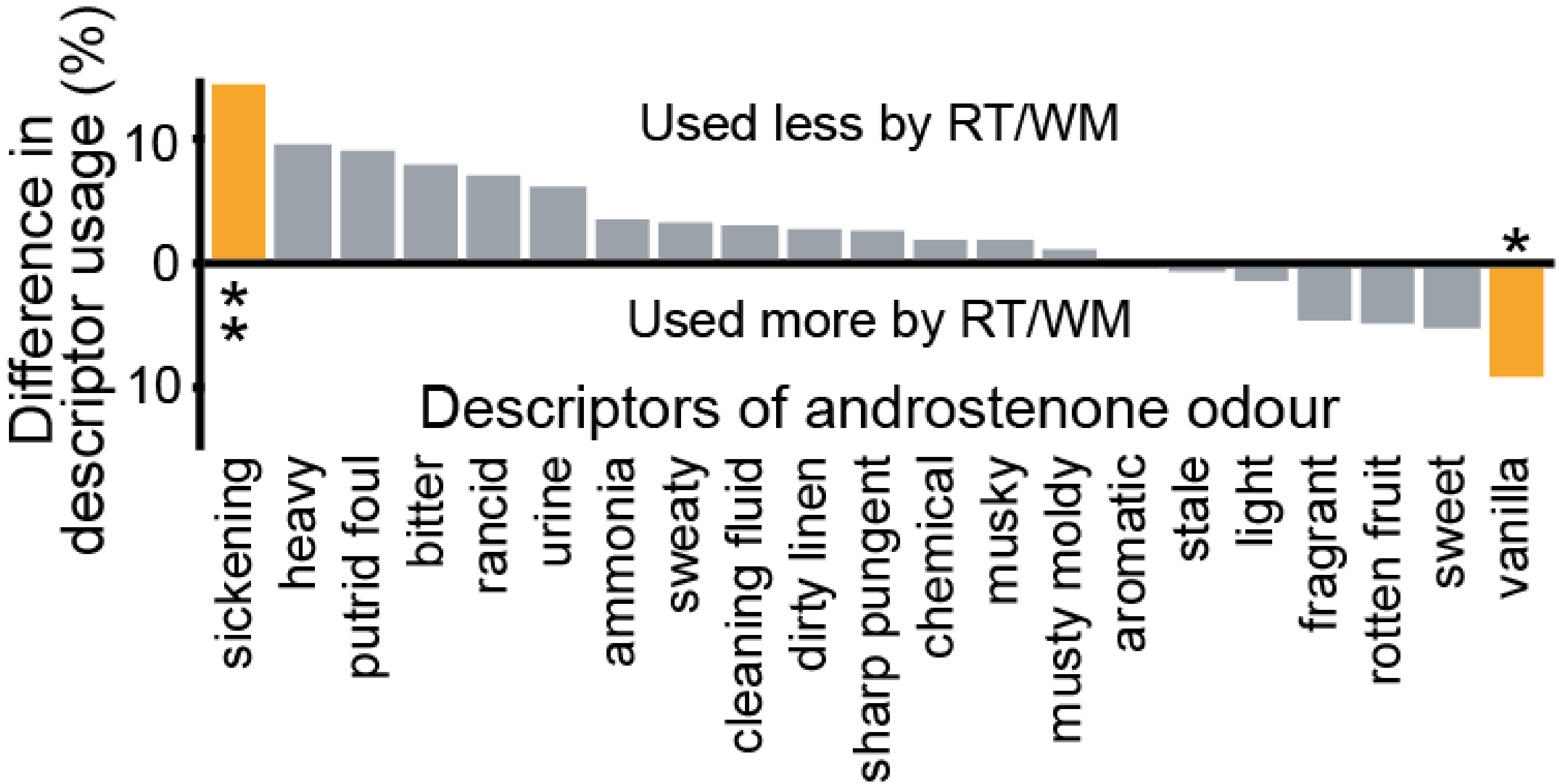
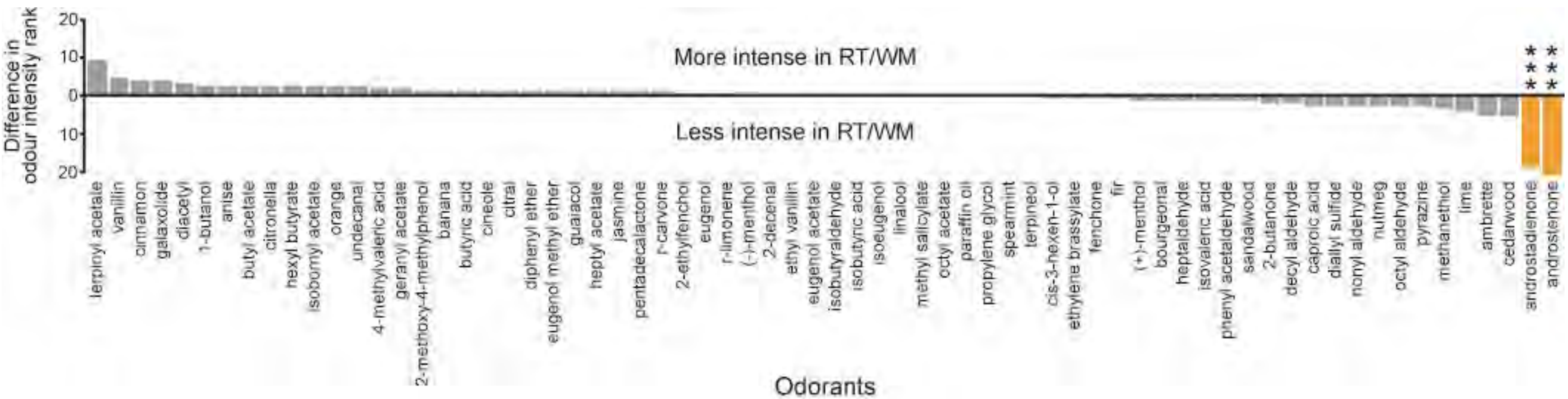
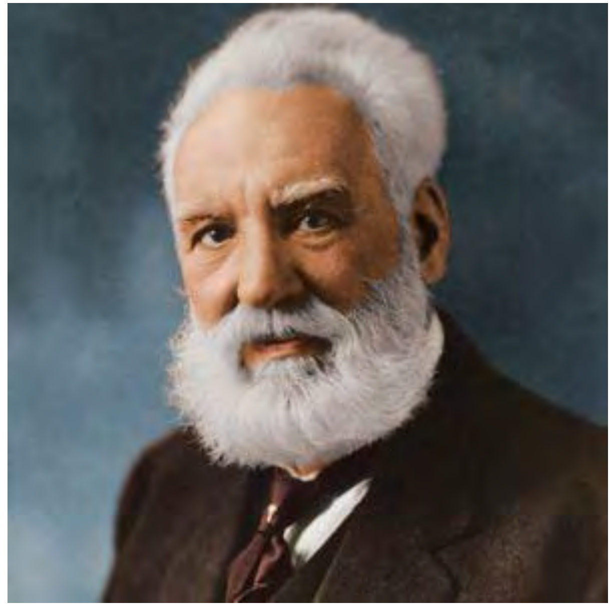


Keller, Zhuang, Chi, Vosshall, & Matsunami Nature 2007

Subjects with non-functional OR7D4 perceive steroids as less intense



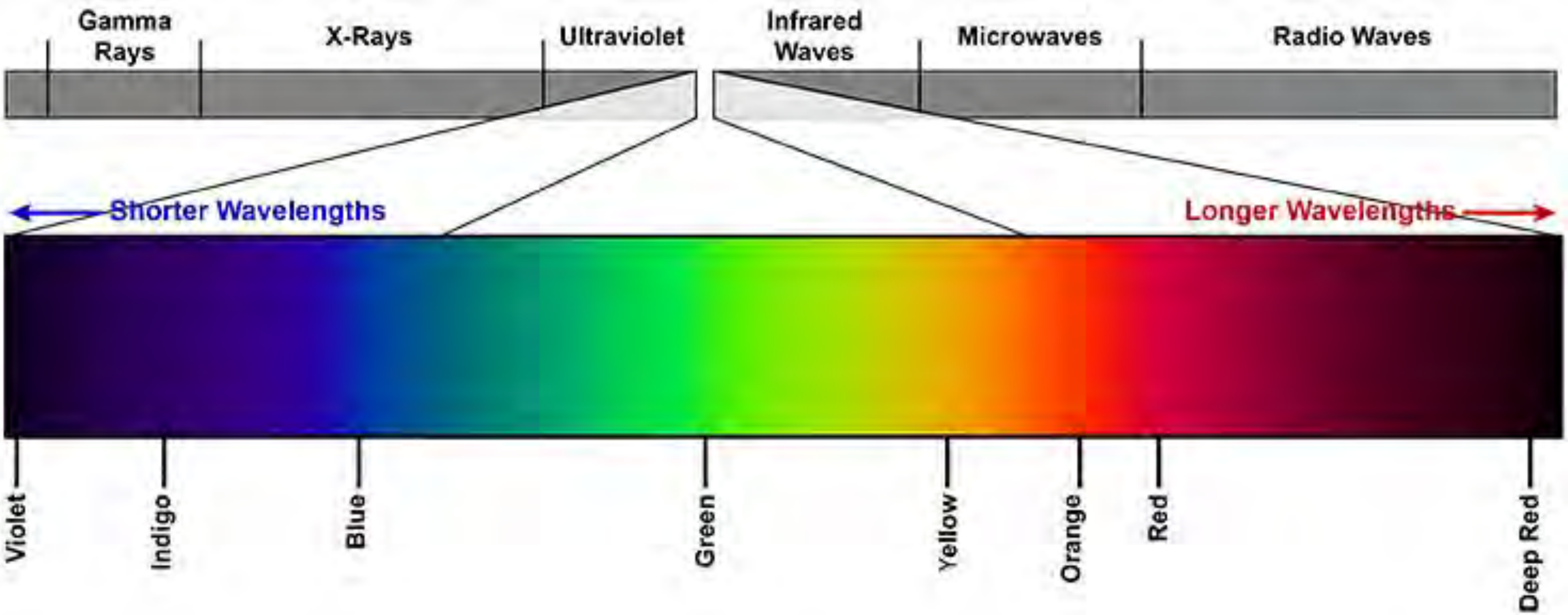
Keller, Zhuang, Chi, Vosshall, & Matsunami Nature 2007



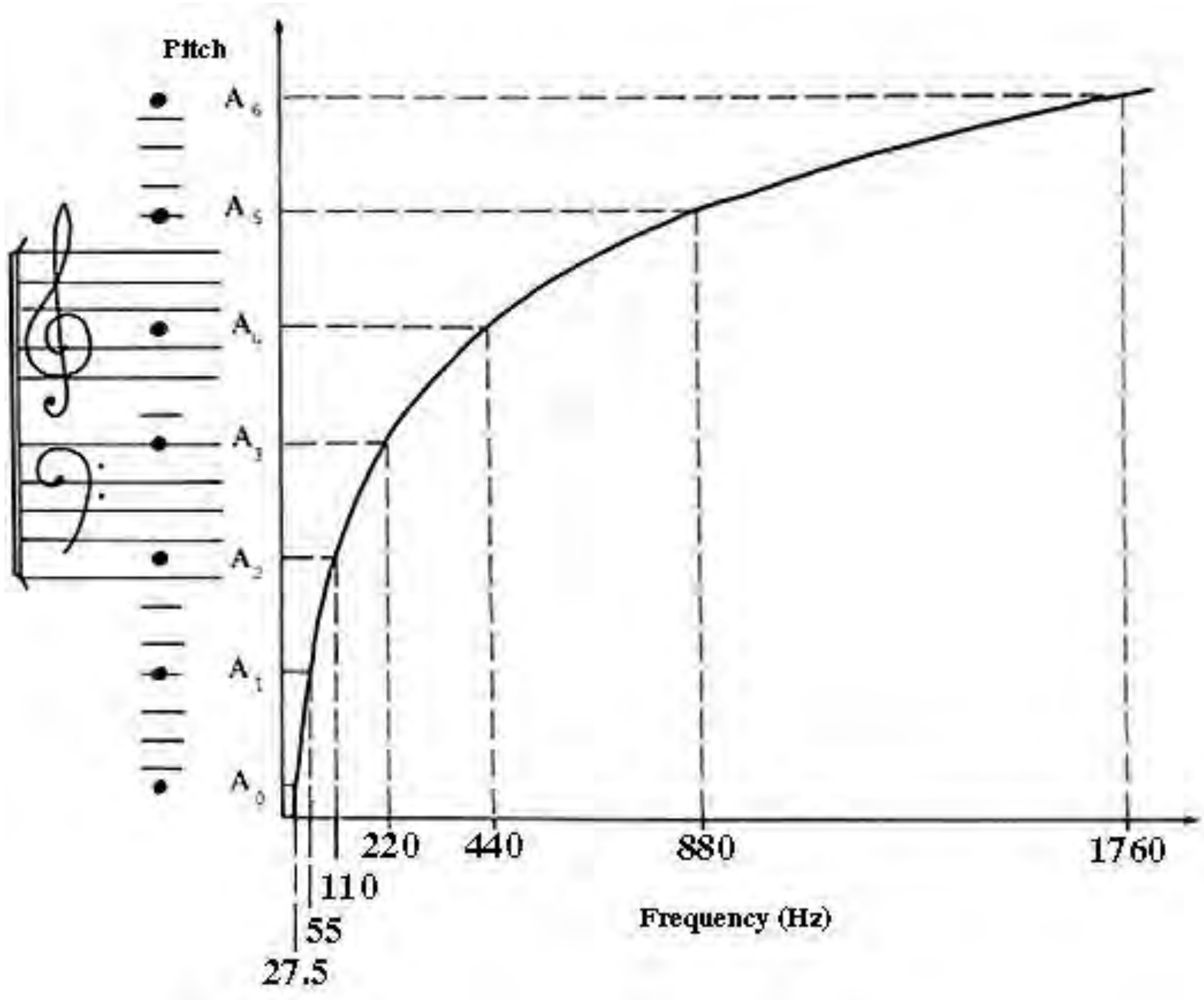
“Can you measure the difference between one kind of smell and another? It is very obvious that we have very many different kinds of smells, all the way from the odour of violets and roses up to asafetida. But until you can measure their likeness and differences, you can have no science of odour. If you are ambitious to find a new science, measure a smell.”

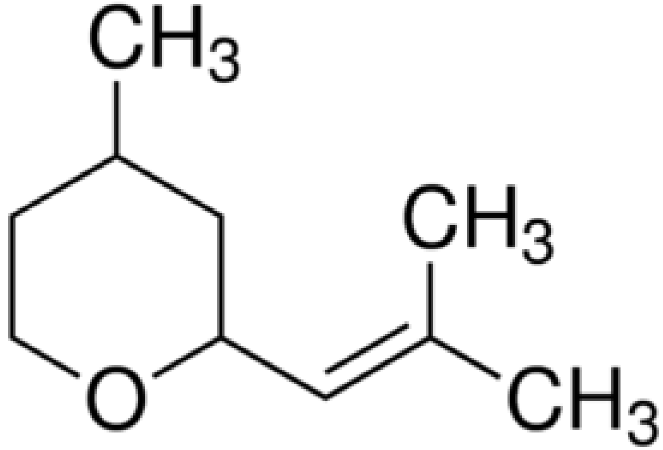
—Alexander Graham Bell, *1914*

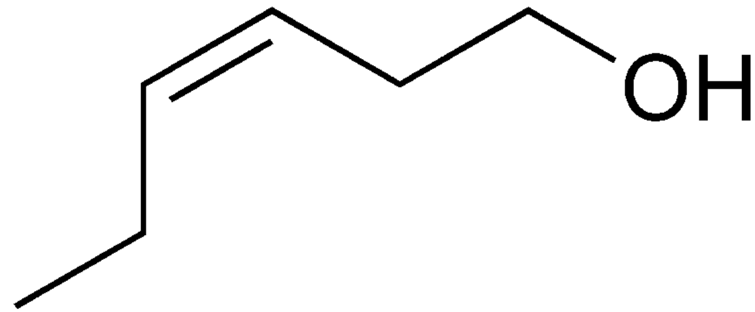
a predictable relationship between (color) **stimulus** and (visual) **percept**

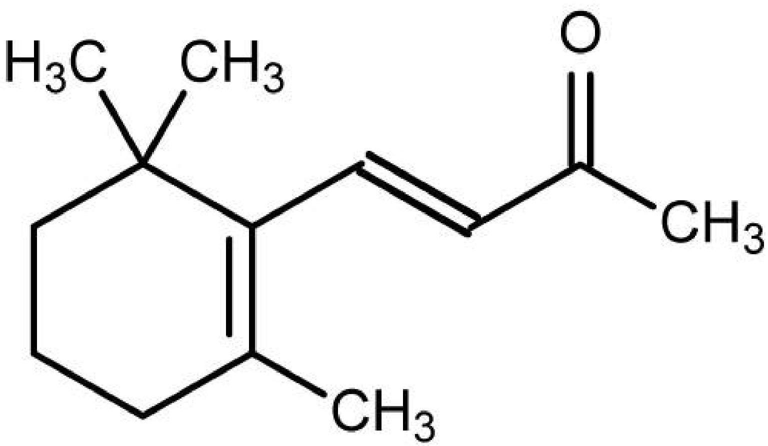


a predictable relationship between (sound) **stimulus** and (auditory) **percept**





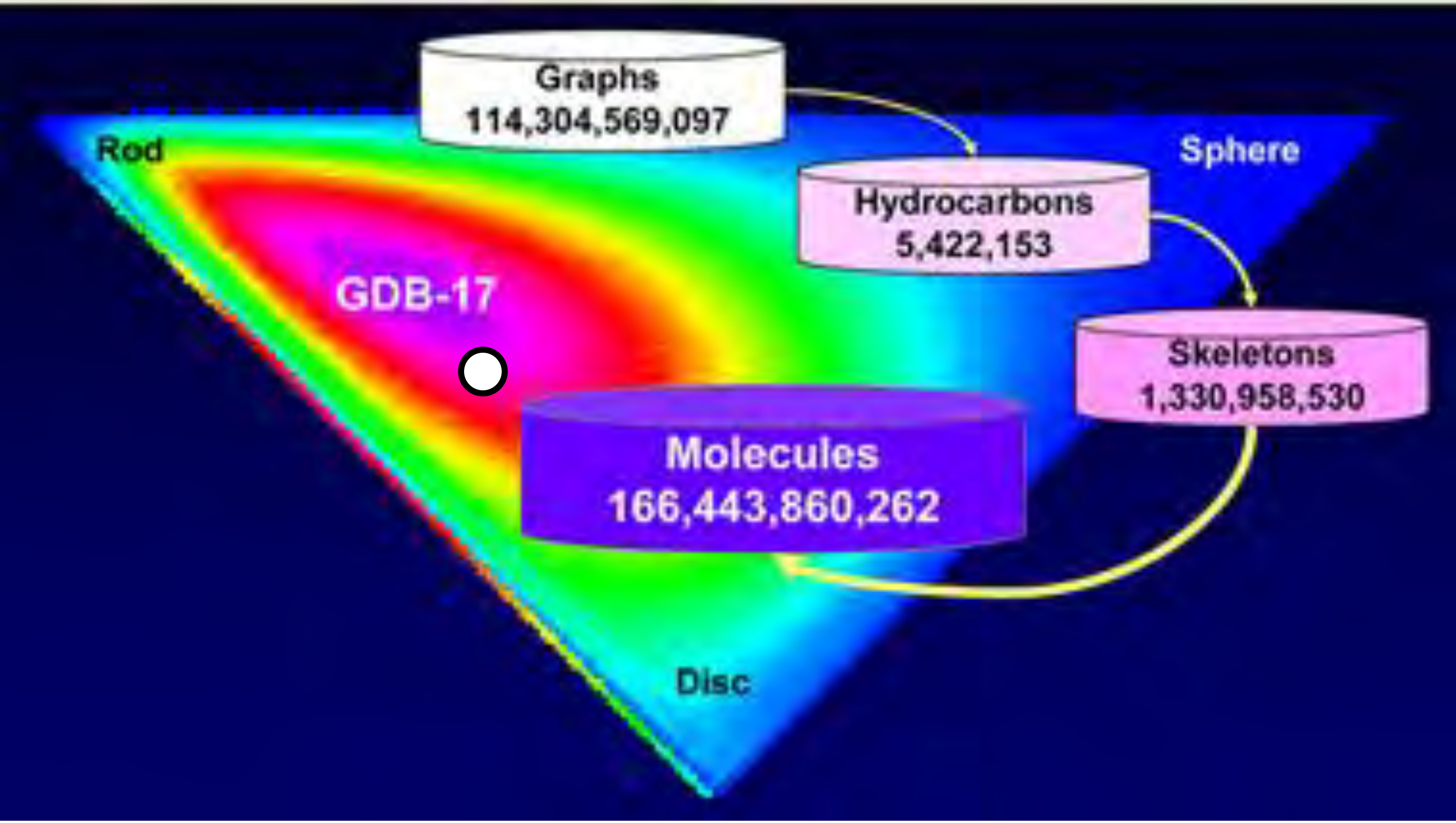




STIMULUS TO PERCEPT

STIMULUS TO PERCEPT

How many olfactory stimuli exist?

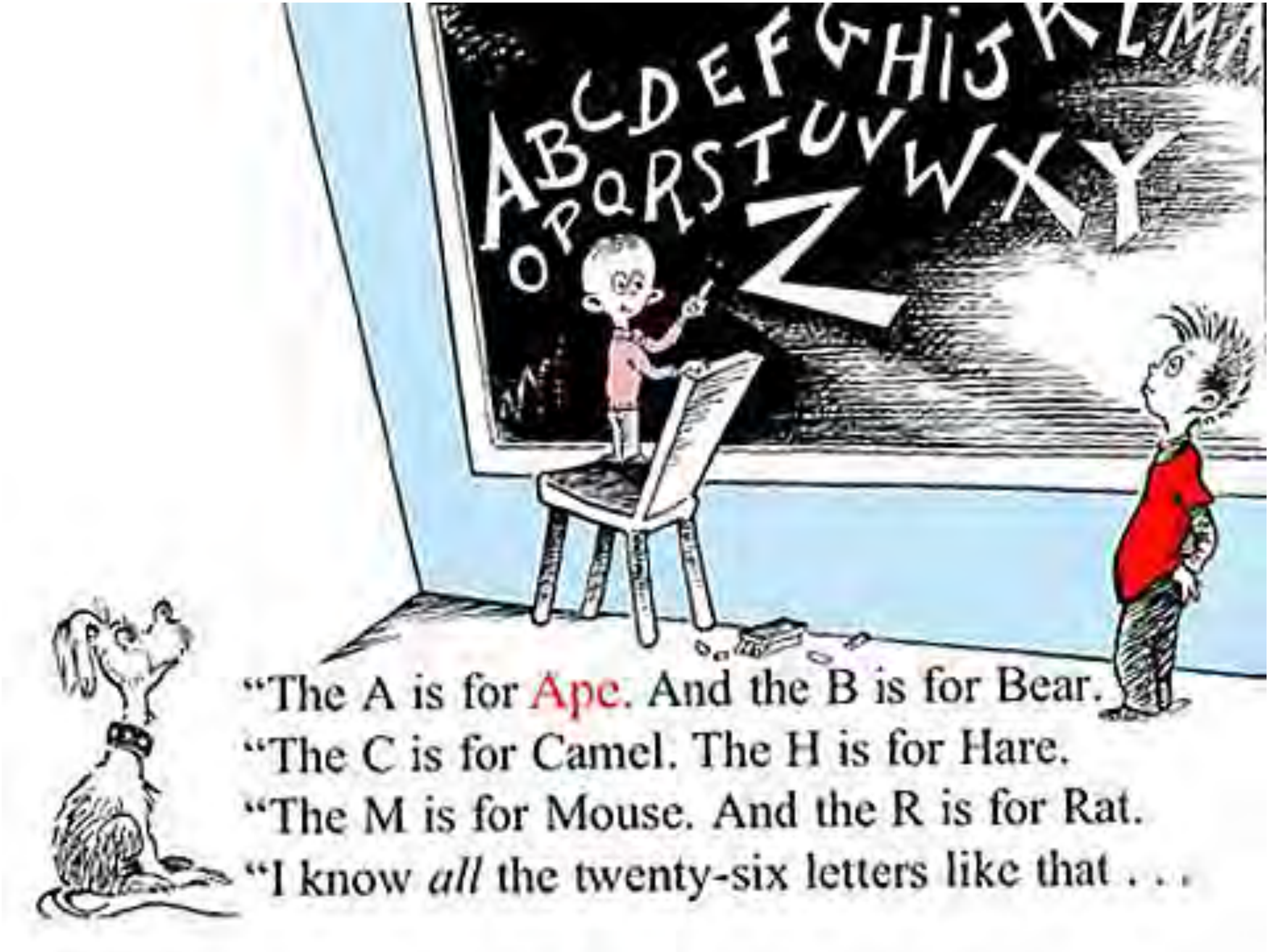


Enumeration of 166 Billion Organic Small Molecules in the Chemical Universe Database GDB-17

Ruddigkeit et al. J. Chem. Inf. Model (2012) 52:2864–2875

Most existing psychophysical data are from familiar food and fragrance odors

We need to go beyond this to solve the problem




Yuzz
Wum
Um
Humpf
Fuddle
Glikk
Nuh
Snee
Quan
Thnad
Spazz
Floob
Zatz
Jogg
Flunn
Itch
Yekk
Vroo
Hi!
-

Diverse odors, many never previously tested in human smell studies

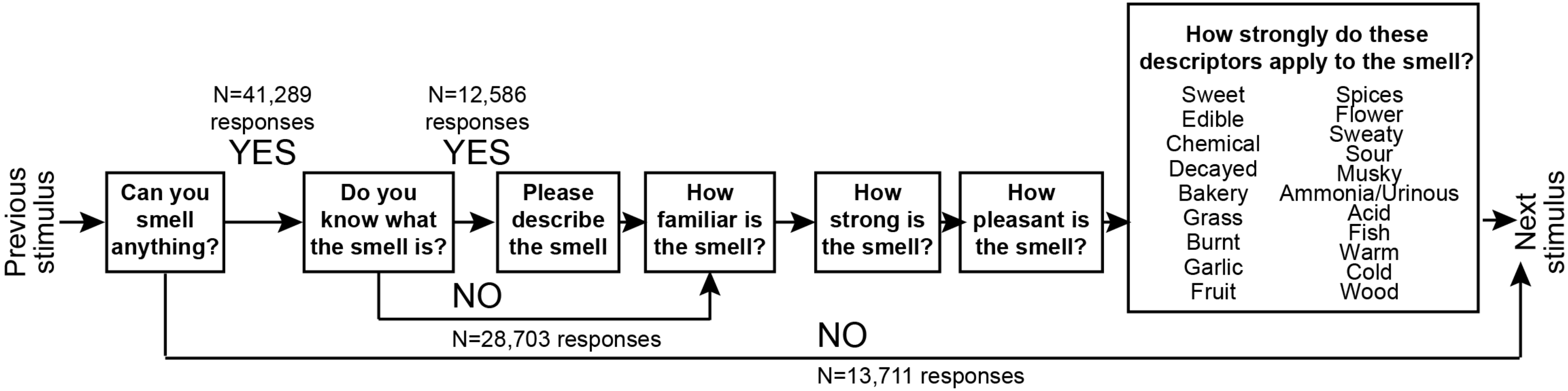
"we are creating a science of olfaction based on cinnamon and coffee“ (Gilbert and Greenberg 1992)

Study	Odor molecules	Atoms (excluding H)		Number of molecules containing:					
		Range	Average	O	N	S	Halogen	Acid	Amine
Wright and Michels (1964)	45	1 to 15	8.4	30	4	4	2	5	0
Harper et al. (1968)	51	1 to 21	8.2	35	9	4	1	2	3
Moncrieff (1956)	61	2 to 19	9.2	46	9	5	4	3	5
Amoore and Venstrom (1968)	107	3 to 21	10.3	79	7	1	14	1	0
Dravnieks (1985)	143	4 to 29	10.7	112	22	13	1	8	5
Boelens and Haring (1981)	309	3 to 22	13.0	287	14	0	1	4	0
This paper	***480***	***1 to 28***	***10.3***	***420***	***73***	***53***	***2***	***45***	***29***

Keller & Vosshall, BMC Neurosci (2016)

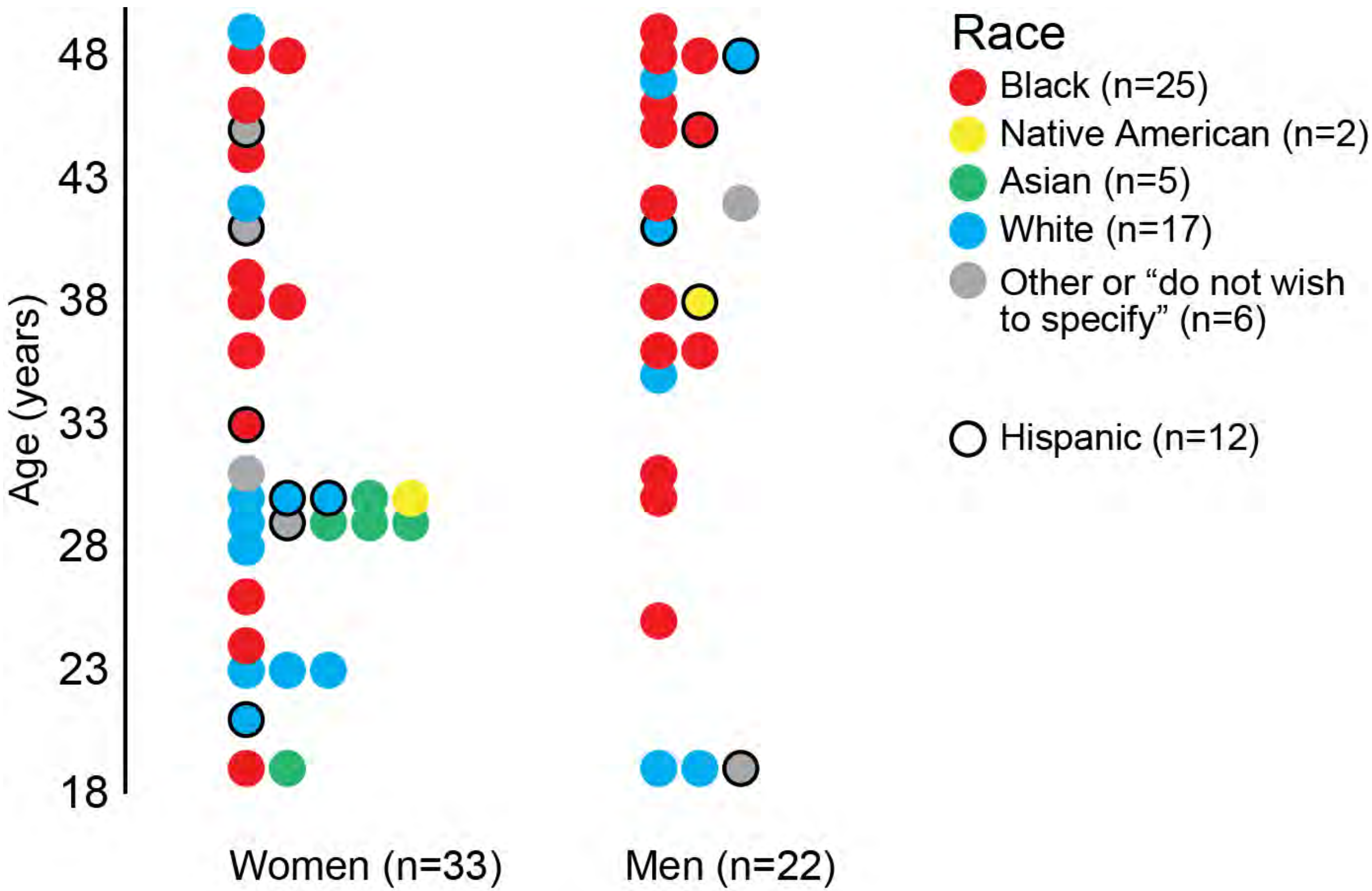
Study Design:
55 subjects x 1000 stimuli

INTENSITY PLEASANTNESS 19 DESCRIPTORS



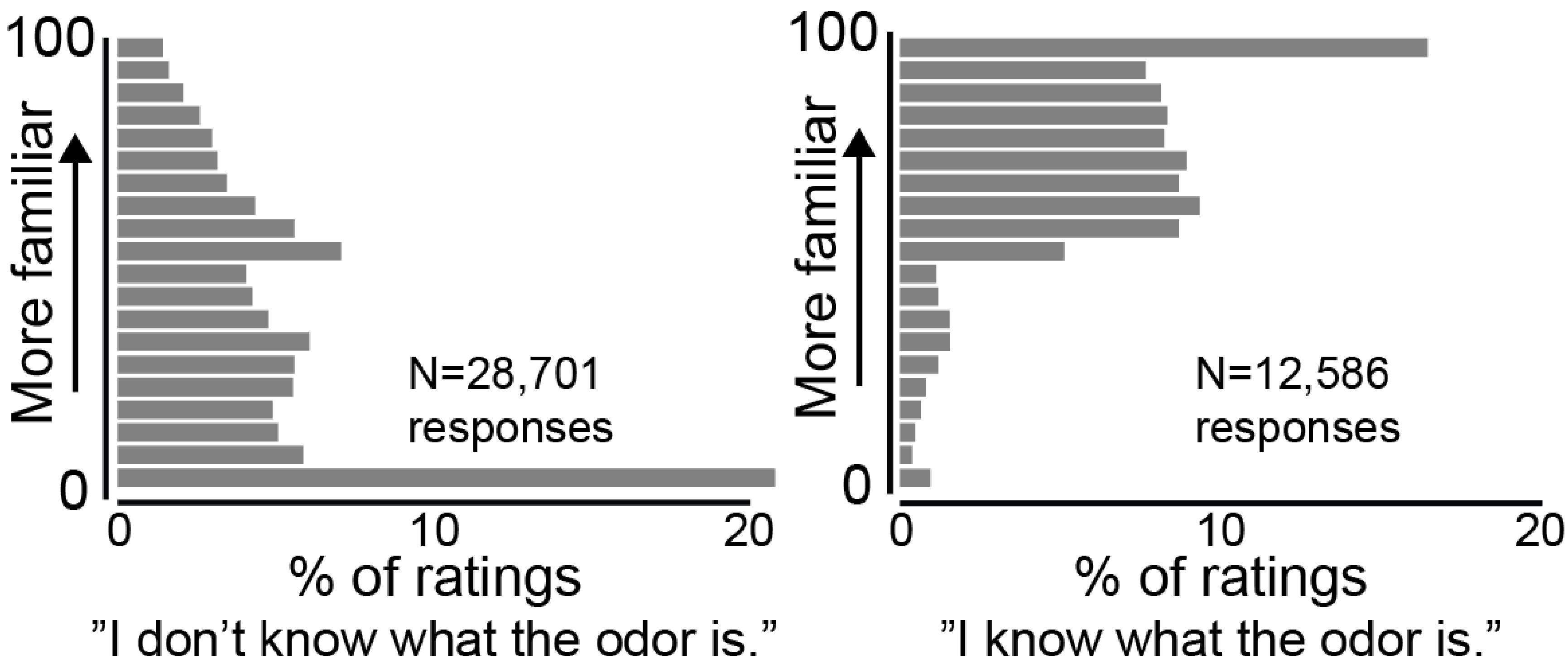
Keller & Vosshall, BMC Neurosci (2016)

Our diverse panel of 55 untrained subjects from metro New York City



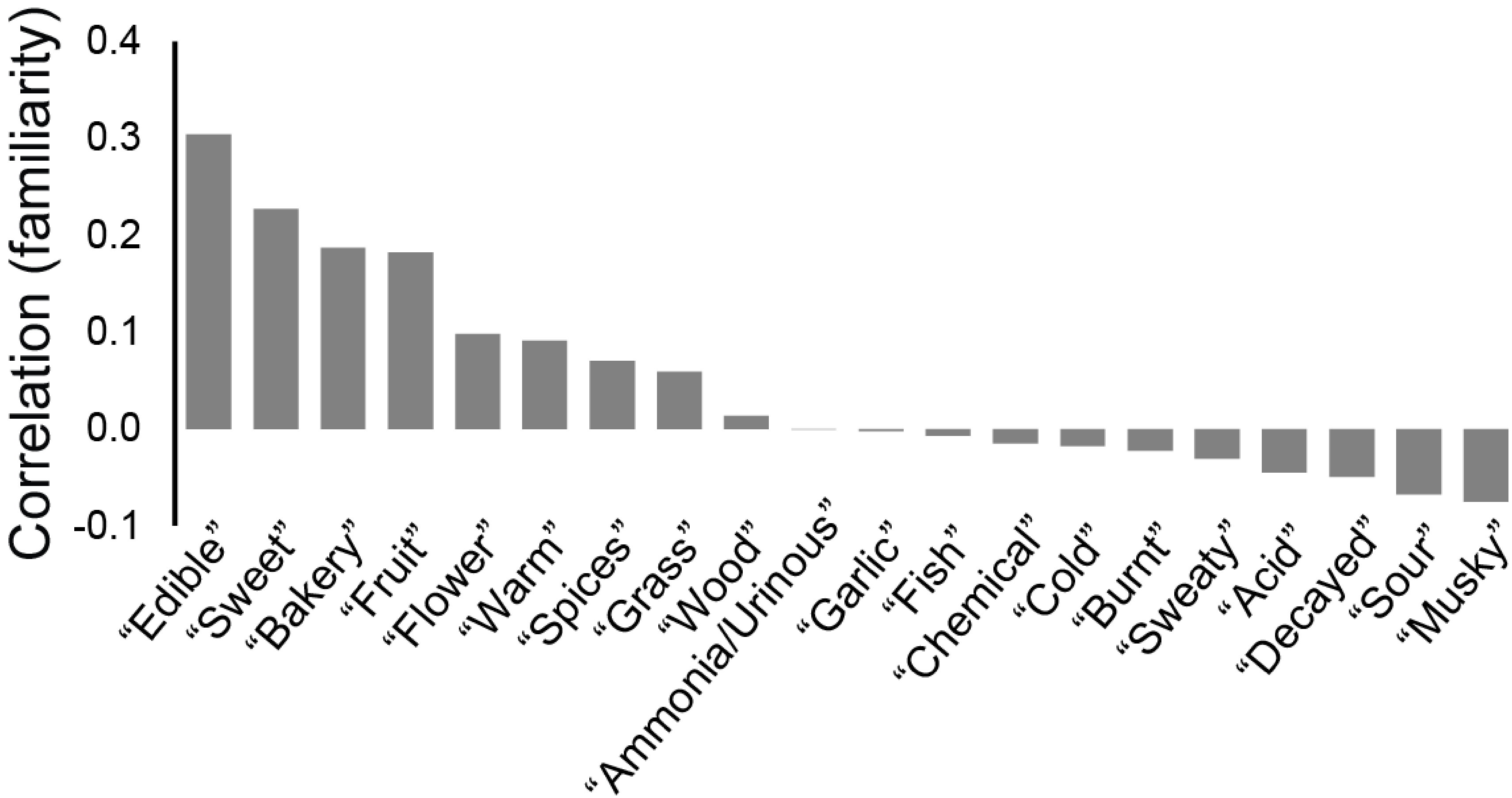
Keller & Vosshall, BMC Neurosci (2016)

Influence of familiarity on perception:
Unfamiliar odors receive fewer ratings



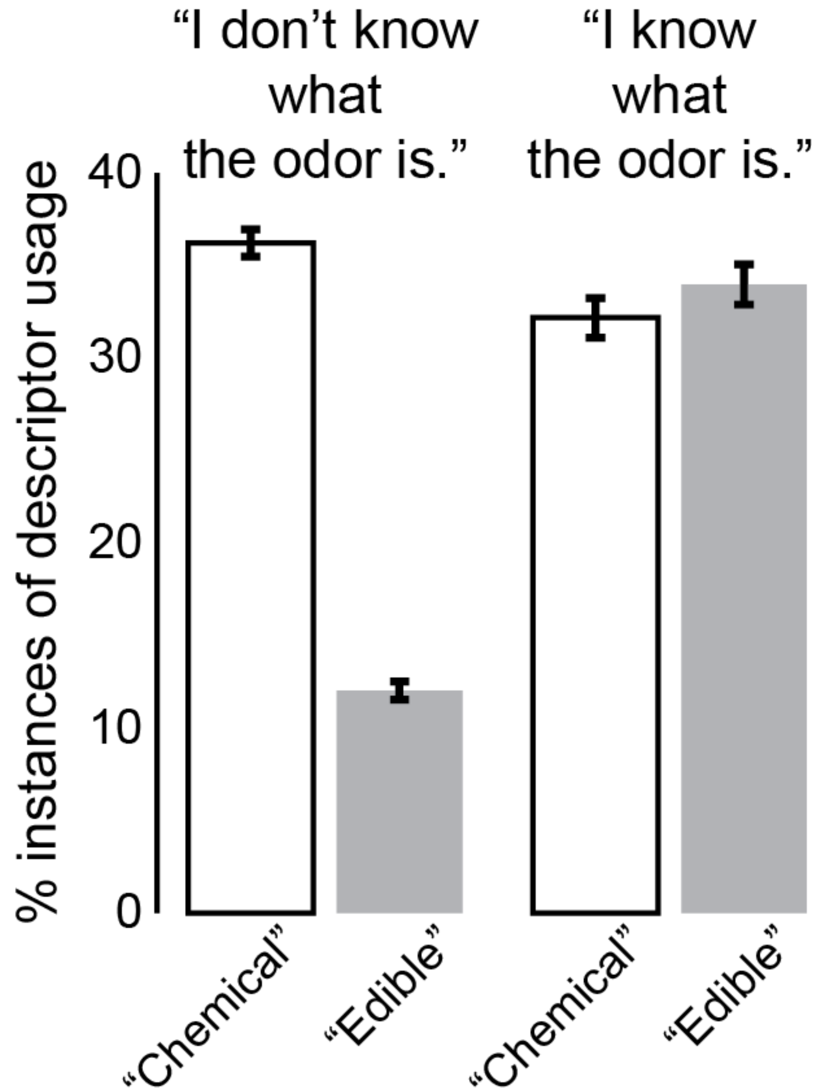
Keller & Vosshall, BMC Neurosci (2016)

Influence of familiarity on perception: pleasant ratings dominate



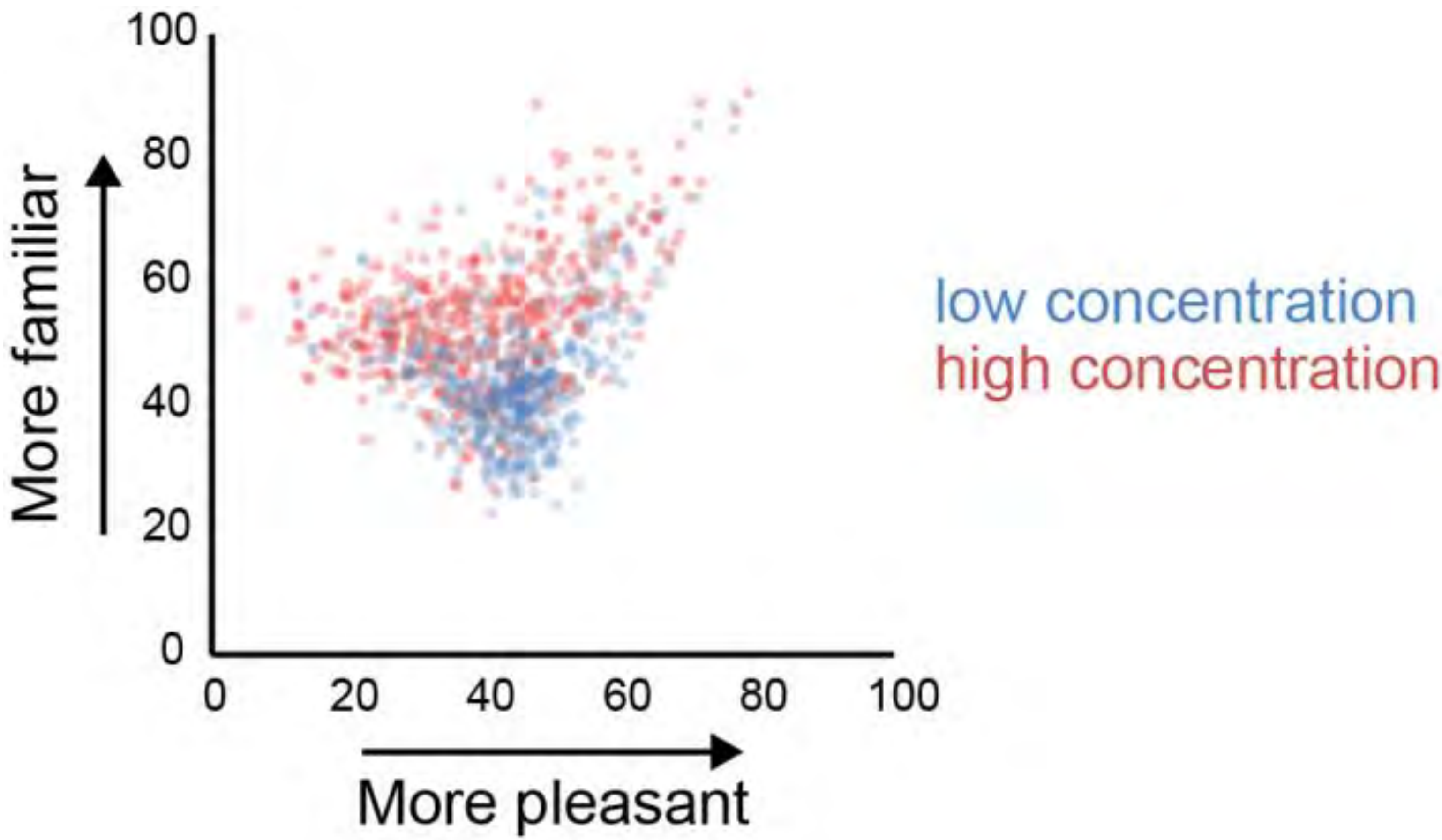
Keller & Vosshall, BMC Neurosci (2016)

Unfamiliar odors frequently described as "chemical"



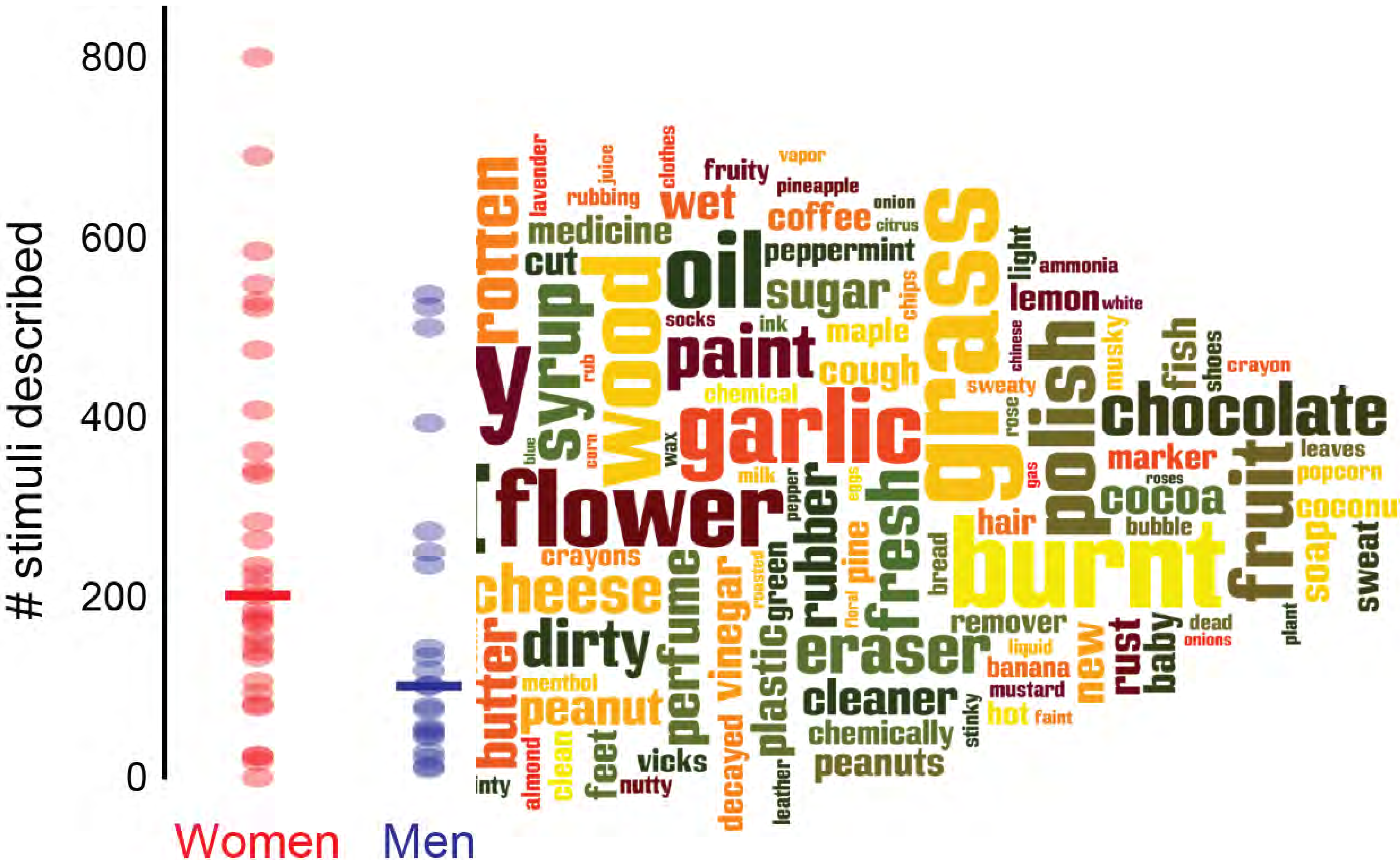
Keller & Vosshall, BMC Neurosci (2016)

Unfamiliar odors typically rated as neither pleasant nor unpleasant



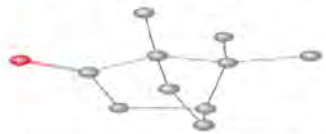
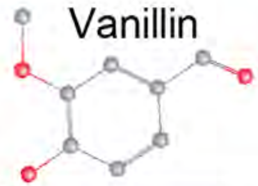
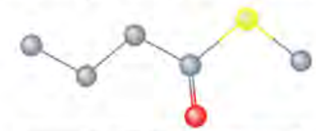
Keller & Vosshall, BMC Neurosci (2016)

Subjects’ Own Descriptors



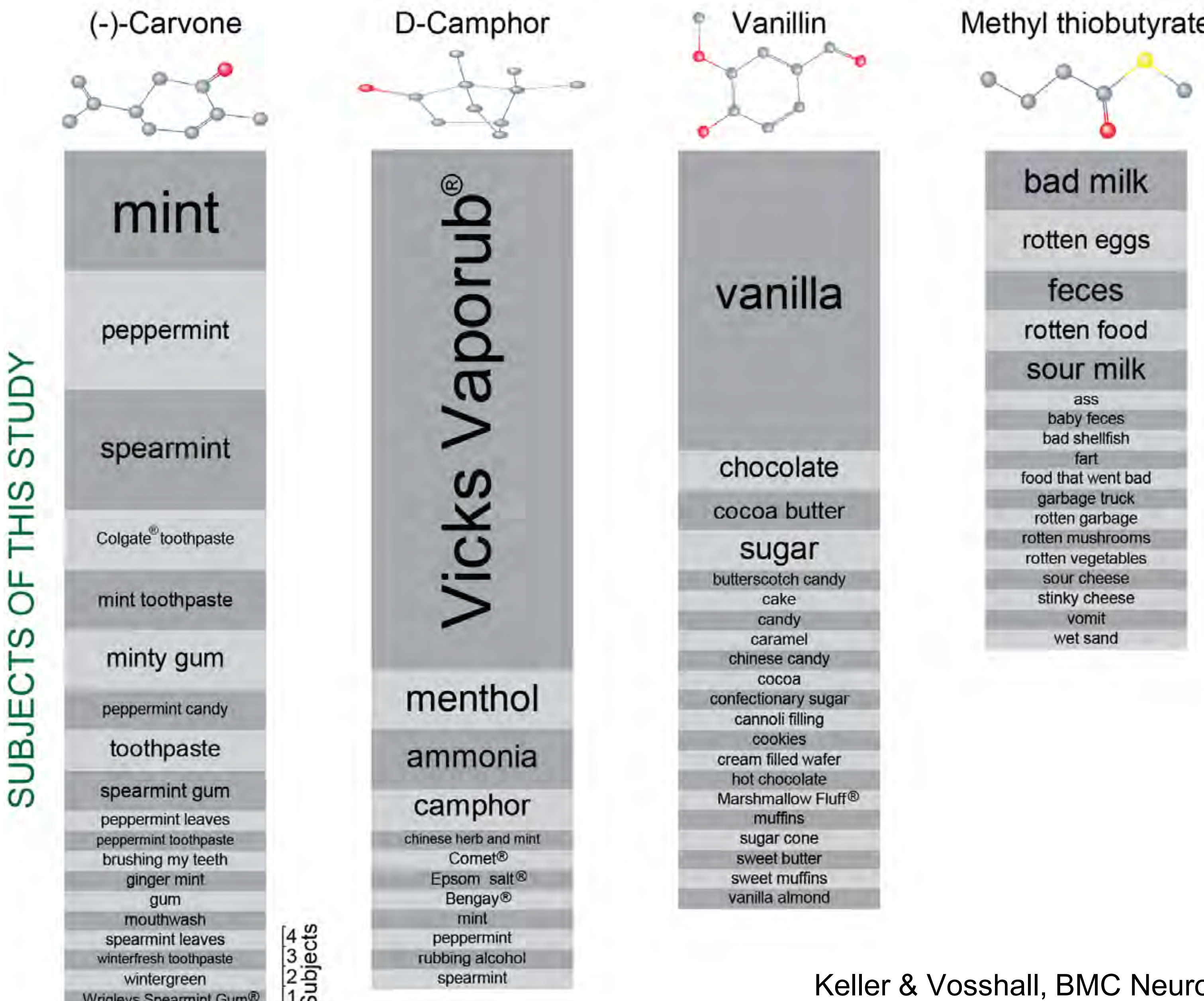
Keller & Vosshall, BMC Neurosci (2016)

Expert Descriptor usage

	(-)-Carvone	D-Camphor	Vanillin	Methyl thiobutyrate
				
SIGMA-ALDRICH	minty herbaceous	medicinal woody, vanilla	caramel, chocolate sweet, vanilla	cheese, musty vegetable, animal alliaceous (onion/garlic)
WIKIPEDIA	spearmint	fragrant penetrating	vanilla, sweet balsamic, pleasant	(no entry)
ATLAS OF ODOR CHARACTER PROFILES	minty/peppermint fragrant, cool/cooling aromatic, sweet	camphor, medicinal cool/cooling, aromatic woody/resinous	vanilla, sweet chocolate, fragrant aromatic	sickening putrid/foul/decayed rancid, sour milk sour/vinegar

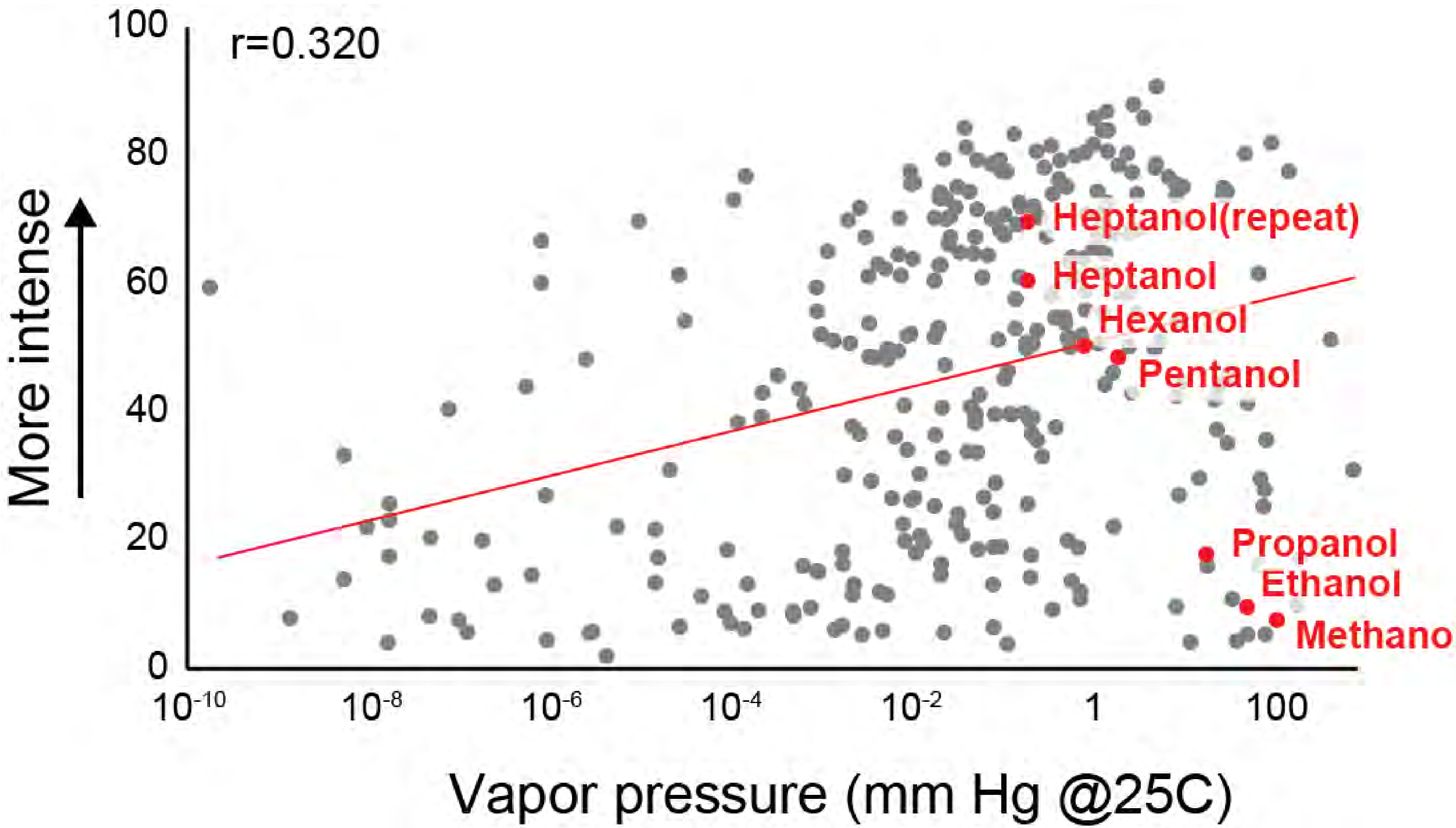
Keller & Vosshall, bioRxiv 049999 (2016)

Subjects' Own Descriptors



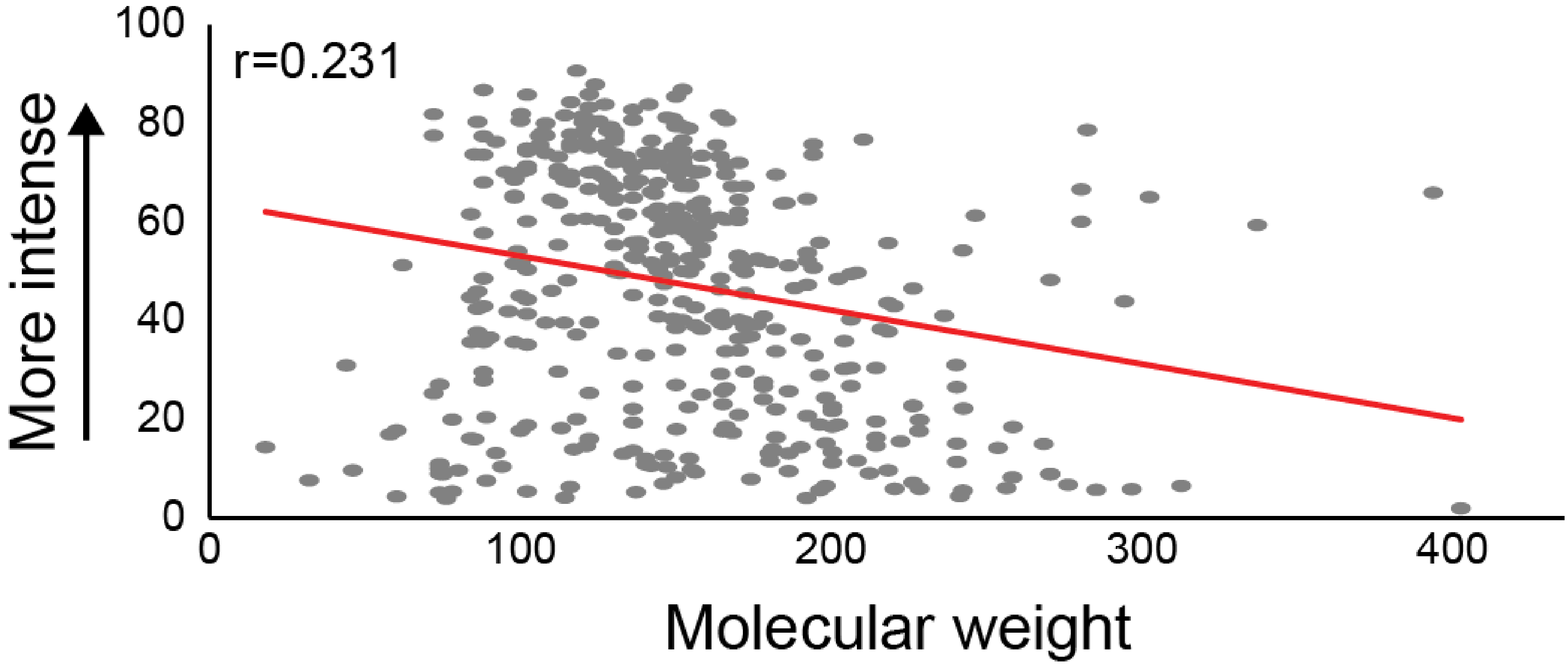
Keller & Vosshall, BMC Neurosci (2016)

Correlation between intensity and vapor pressure



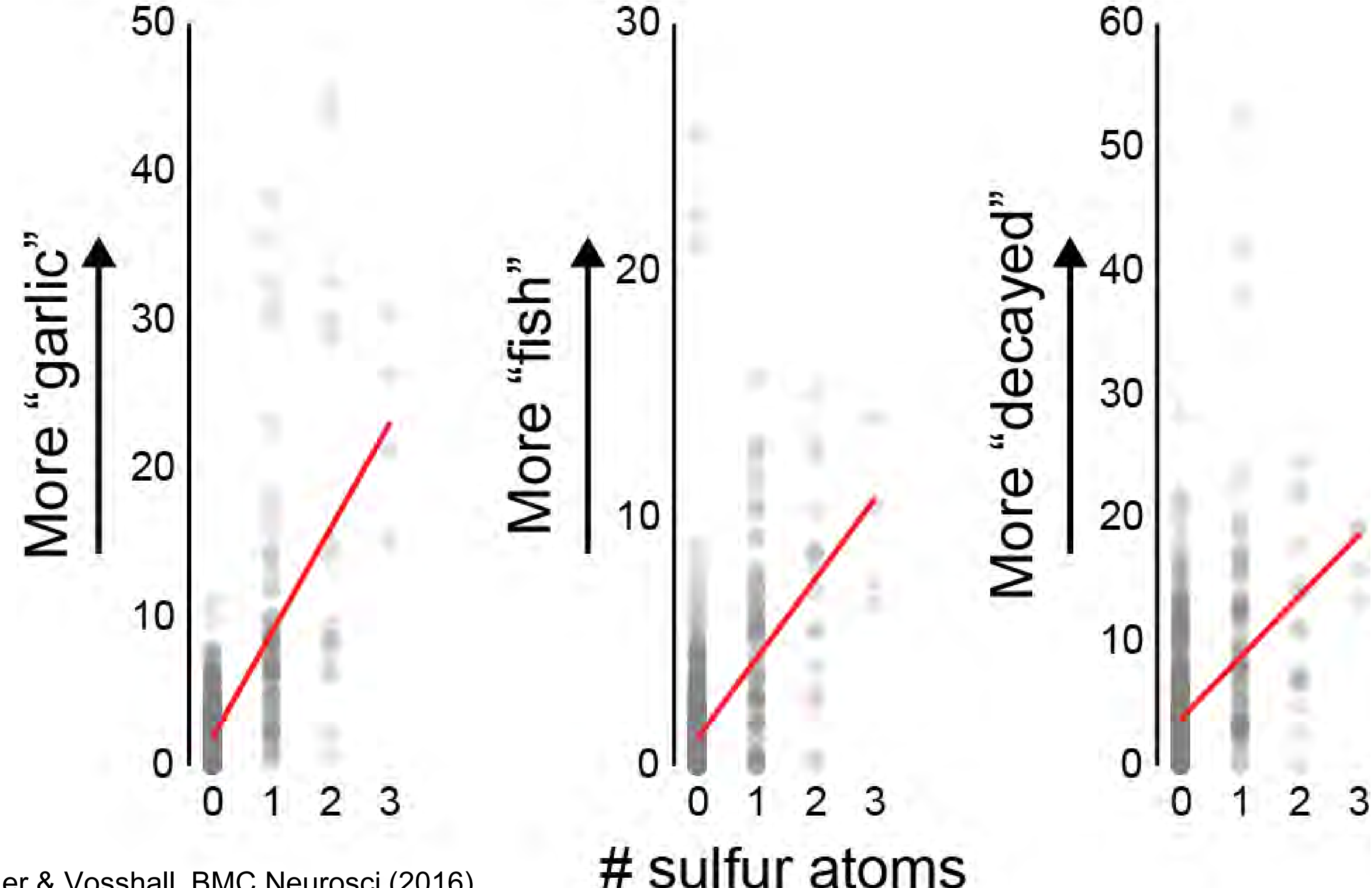
Keller & Vosshall, BMC Neurosci (2016)

Intensity and molecular weight are inversely correlated



Keller & Vosshall, BMC Neurosci (2016)

Correlation between # sulfur atoms and percept



Keller & Vosshall, BMC Neurosci (2016)

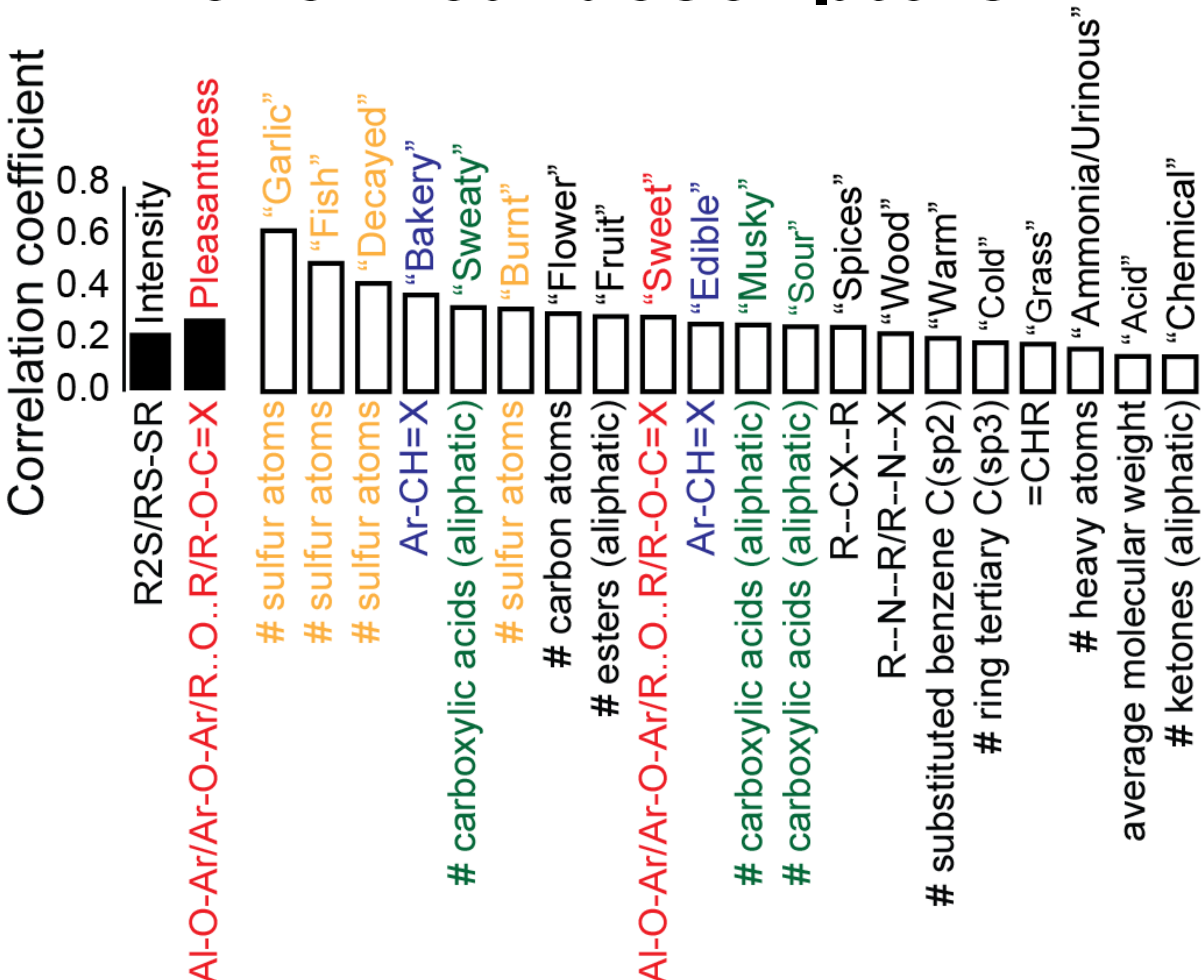
Dragon® chemical descriptors

Table 1. List of 21 descriptors for optimized mixture similarity prediction.

No.	Index out of 1433 descriptors	Abbreviation	Description
1	19	nCIR	Number of circuits (constitutional descriptors).
2	44	ZM1	First Zagreb index M1 (topological descriptors).
3	51	GNar	Narumi geometric topological index (topological descriptors).
4	96	S1K	1-path Kier alpha-modified shape index (topological descriptors).
5	175	piPC08	Molecular multiple path count of order 08 (walk and path counts).
6	289	MATS1v	Moran autocorrelation – lag 1/weighted by atomic van der Waals volumes (2D autocorrelations).
7	295	MATS7v	Moran autocorrelation – lag 7/weighted by atomic van der Waals volumes (2D autocorrelations).
8	321	GATS1v	Geary autocorrelation – lag 1/weighted by atomic van der Waals volumes (2D autocorrelations).
9	351	EEig05x	Eigenvalue 05 from edge adj. matrix weighted by edge degrees (edge adjacency indices).
10	407	ESpm02x	Spectral moment 02 from edge adj. matrix weighted by edge degrees (edge adjacency indices).
11	423	ESpm03d	Spectral moment 03 from edge adj. matrix weighted by dipole moments (edge adjacency indices).
12	430	ESpm10d	Spectral moment 10 from edge adj. matrix weighted by dipole moments (edge adjacency indices).
13	433	ESpm13d	Spectral moment 13 from edge adj. matrix weighted by dipole moments (edge adjacency indices).
14	477	BELv3	Lowest eigenvalue n. 3 of Burden matrix/weighted by atomic van der Waals volumes (Burden eigenvalues).
15	733	RDF035v	Radial Distribution Function – 3.5/weighted by atomic van der Waals volumes (RDF descriptors).
16	994	G1m	1st component symmetry directional WHIM index/weighted by atomic masses (WHIM descriptors).
17	1005	G1v	1st component symmetry directional WHIM index/weighted by atomic van der Waals volumes (WHIM descriptors)
18	1016	G1e	1st component symmetry directional WHIM index/weighted by Sanderson electronegativities (WHIM descriptors)
19	1040	G3s	3rd component symmetry directional WHIM index/weighted by atomic electropological states (WHIM descriptors)
20	1200	R8u+	R maximal autocorrelation of lag 8/unweighted (GETAWAY descriptors)
21	1295	nRCOSR	Number of thioesters (aliphatic) (Functional group counts)

Listed are the names, indices and a brief definition of the 21 descriptors selected as the optimized set in our angle distance model for odorant mixture similarity prediction.
doi:10.1371/journal.pcbi.1003184.t001

Correlation between semantic and chemical descriptors



Keller & Vosshall, BMC Neurosci (2016)

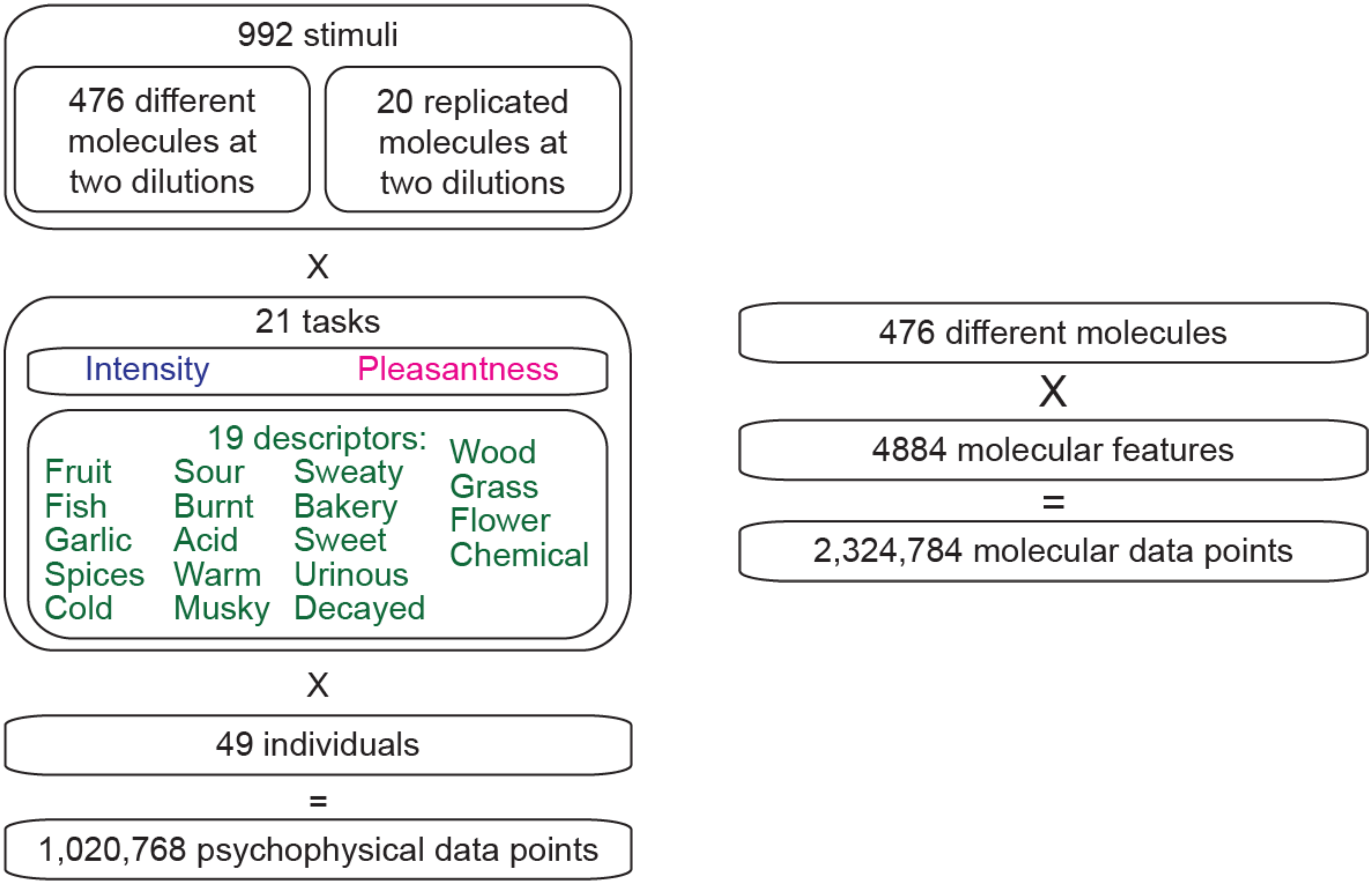
DREAM Olfaction Prediction Challenge

DREAM CHALLENGES powered by Sage Bionetworks | Sage BIONETWORKS | IBM Research

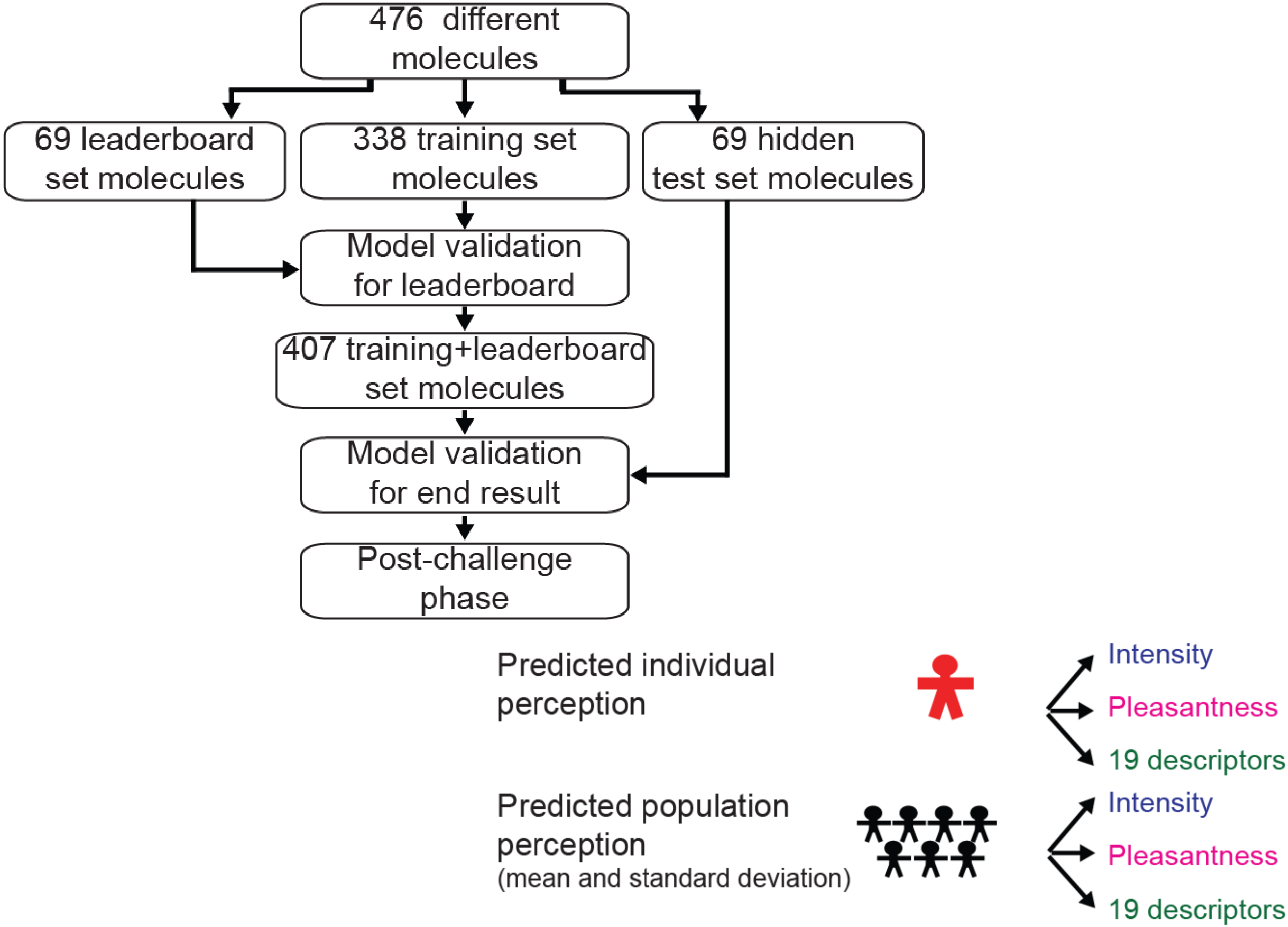
Predicting human olfactory perception from chemical features of odor molecules

Keller A, Gerkin RC, Guan Y, Dhurandhar A, Turu G, Szalai B, Mainland JD, Ihara Y, Yu CW, Wolfinger R, Vens C, Schietgat L, De Grave K, Norel R; DREAM Olfaction Prediction Consortium, Stolovitzky G, Cecchi GA, Vosshall LB, Meyer P.

Science 355:820-826 (2017)

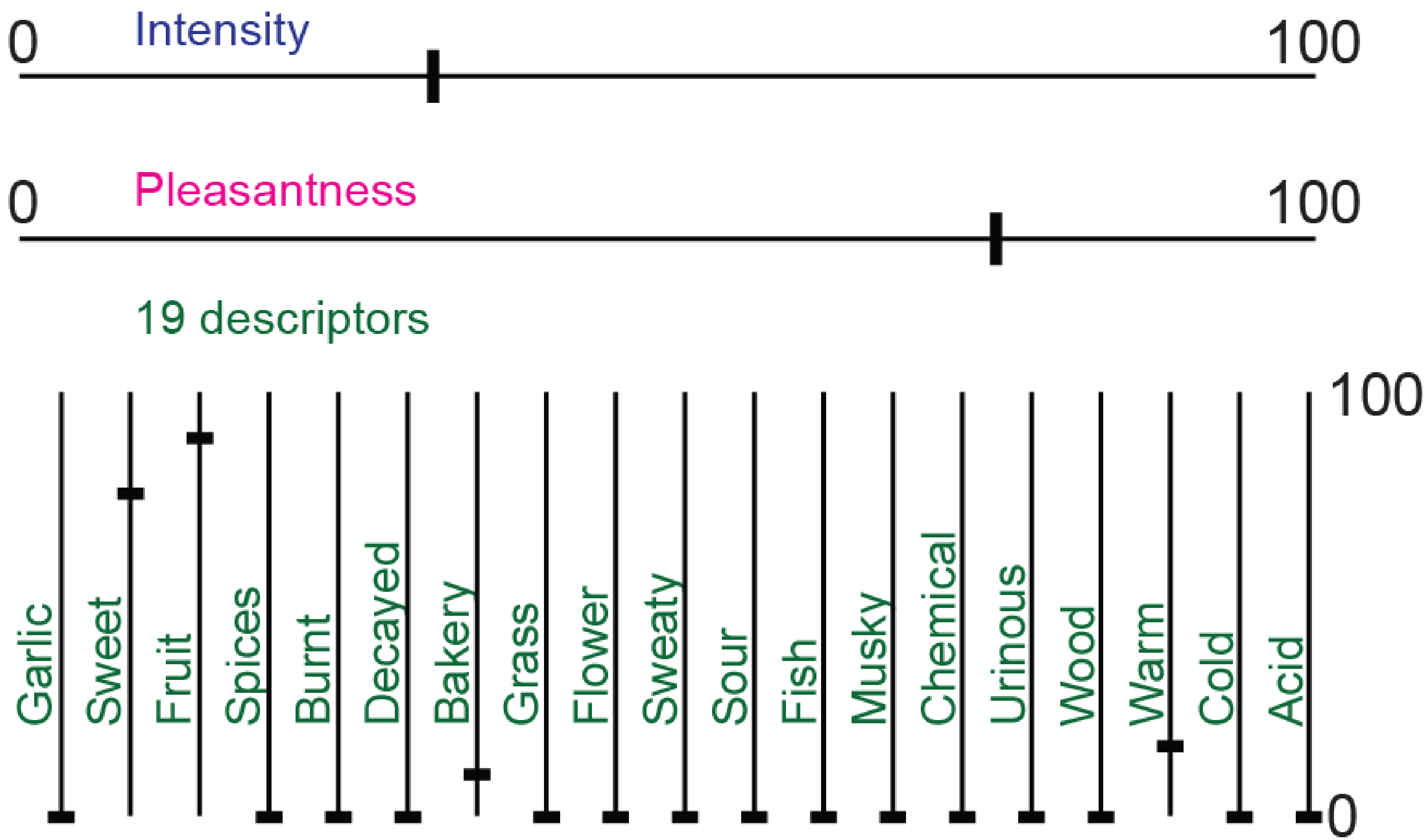


Keller, Gerkin, Guan et al. Science (2017)



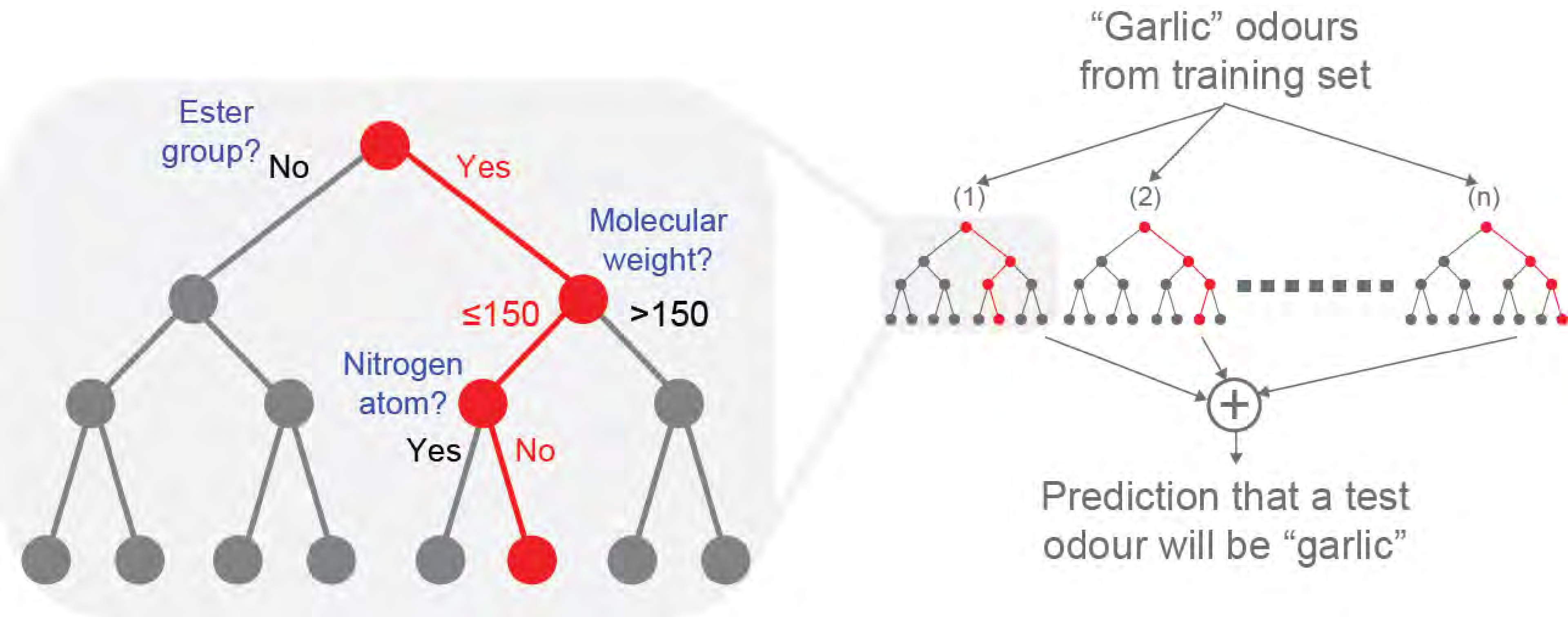
Keller, Gerkin, Guan et al. Science (2017)

Psychophysical tasks: labeled magnitude scale



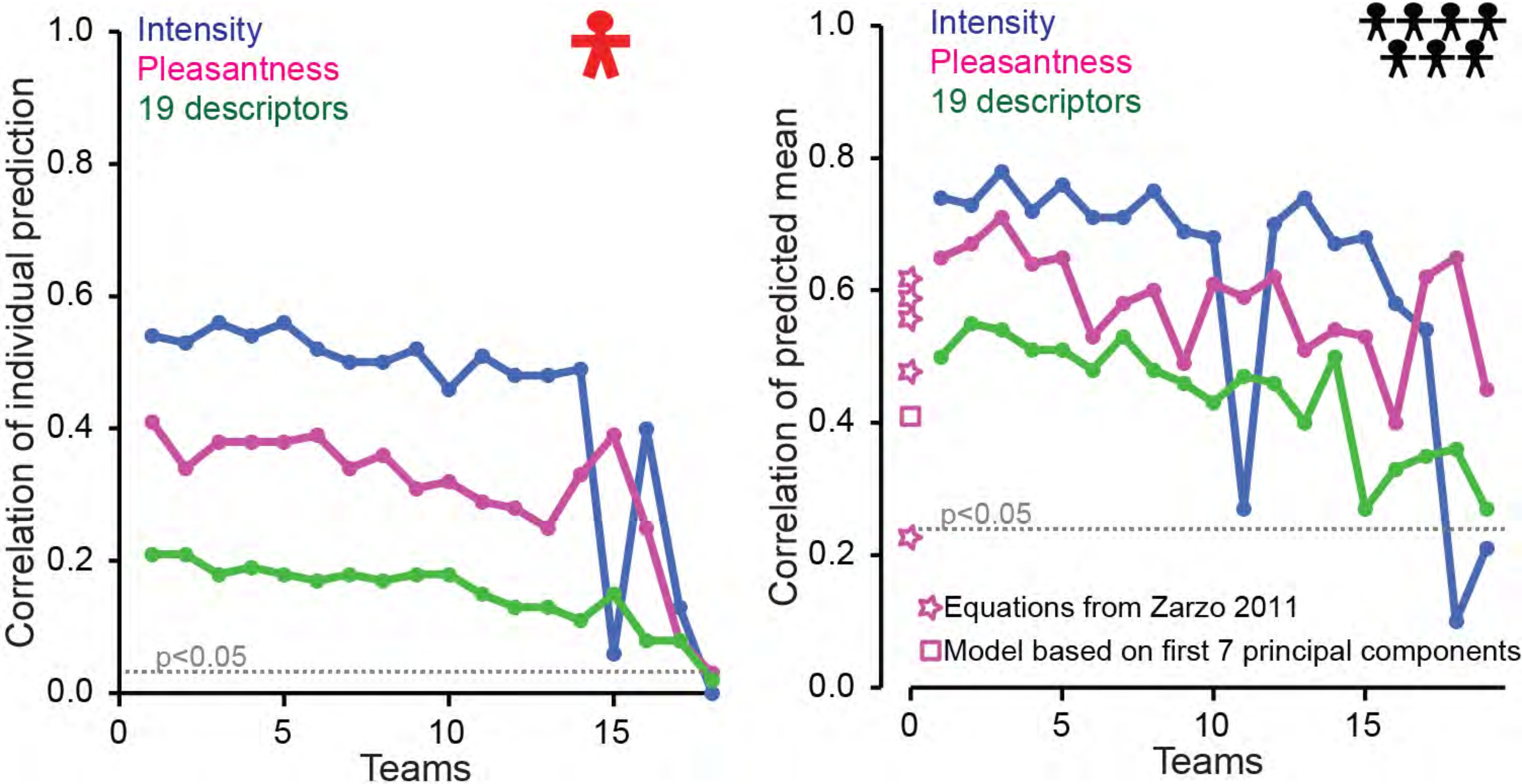
Keller, Gerkin, Guan et al. Science (2017)

Machine learning: random forest model



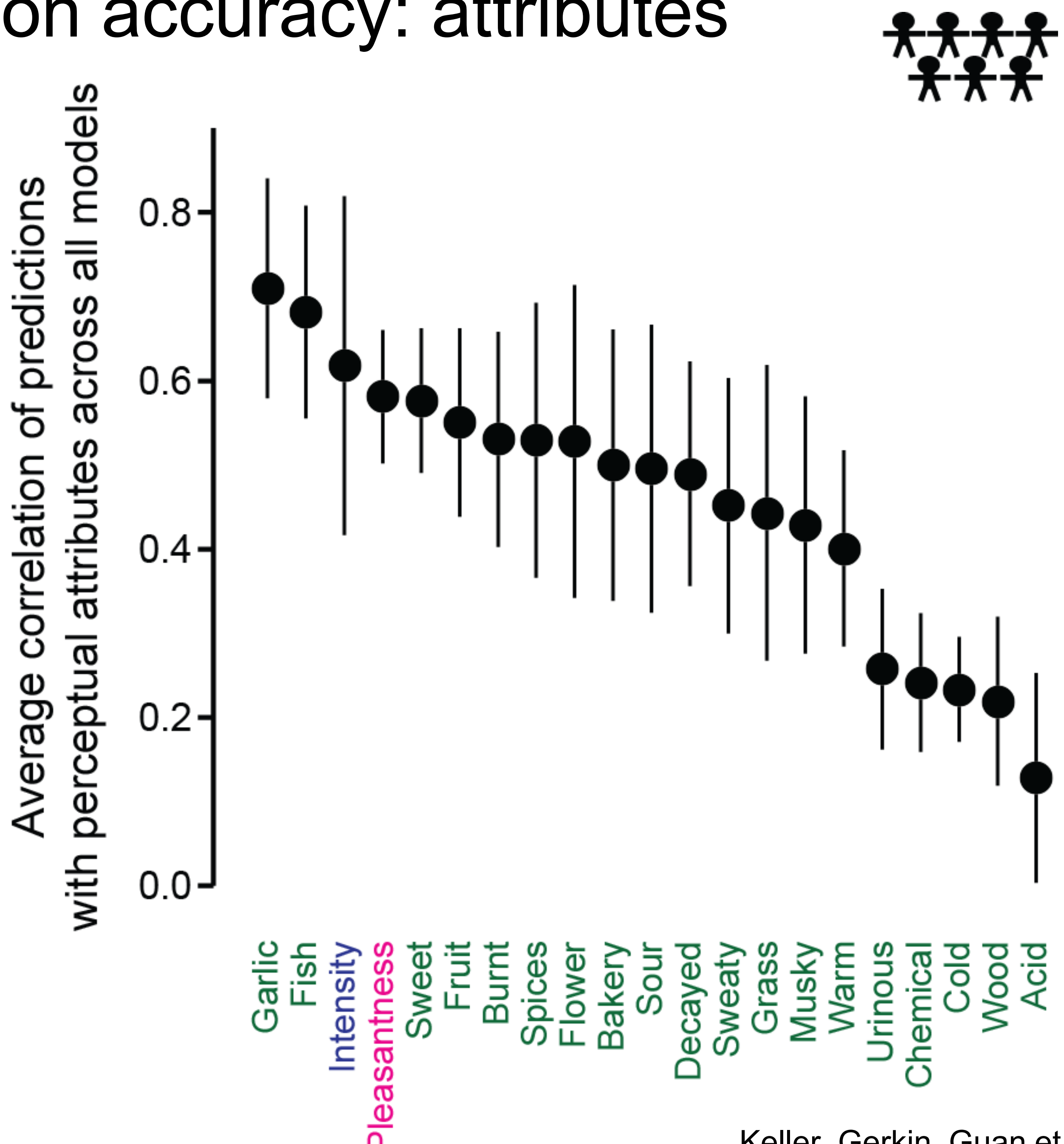
Keller, Gerkin, Guan et al. Science (2017)

Performance of ~20 DREAM Challenge Teams



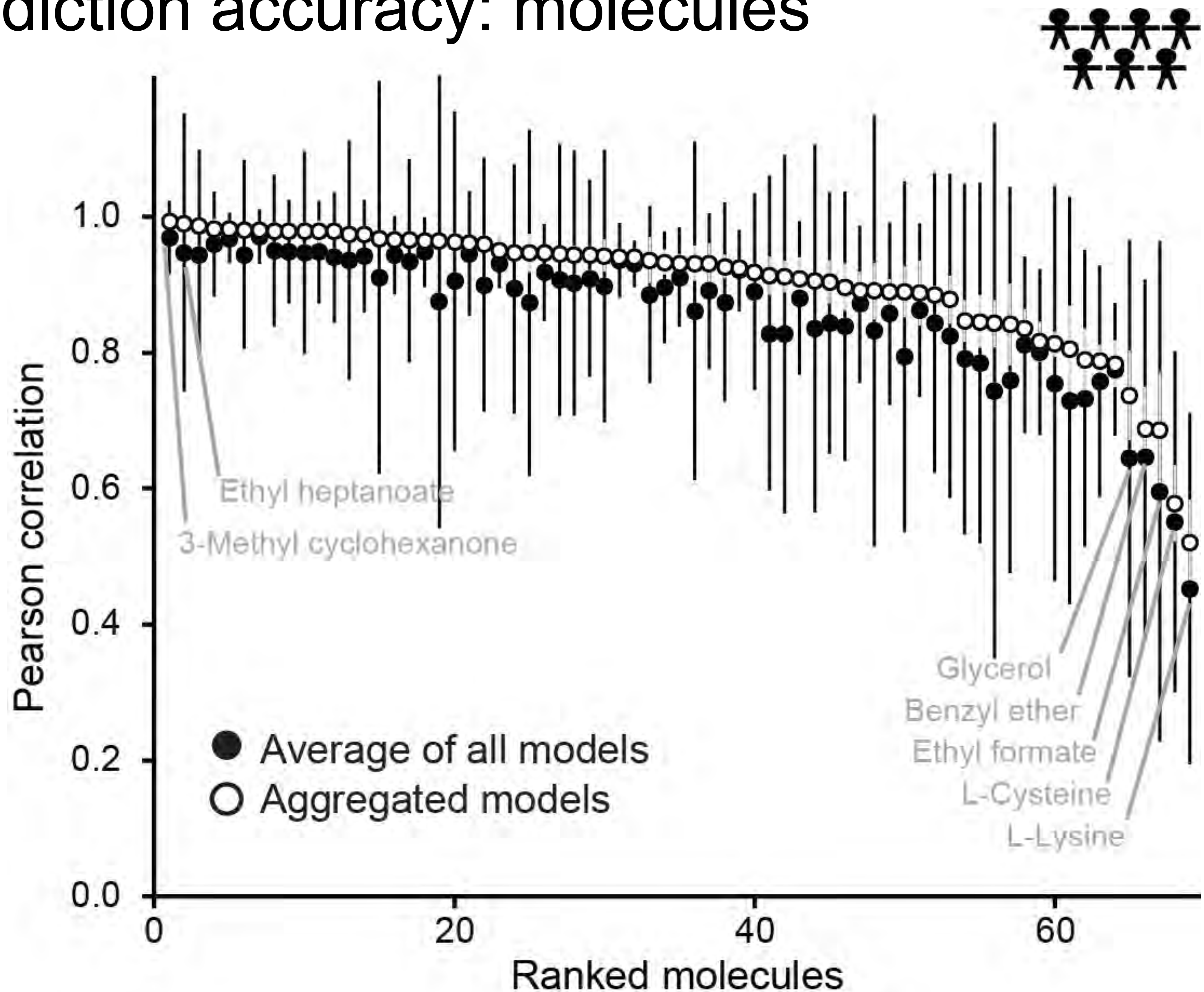
Keller, Gerkin, Guan et al. Science (2017)

Prediction accuracy: attributes



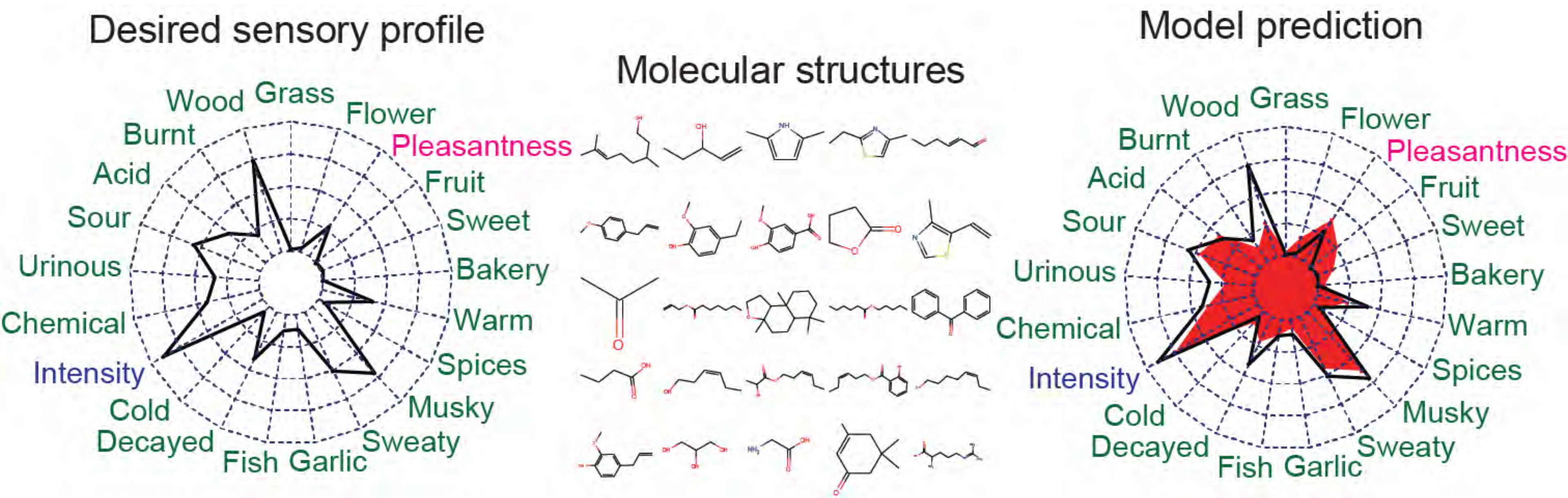
Keller, Gerkin, Guan et al. Science (2017)

Prediction accuracy: molecules



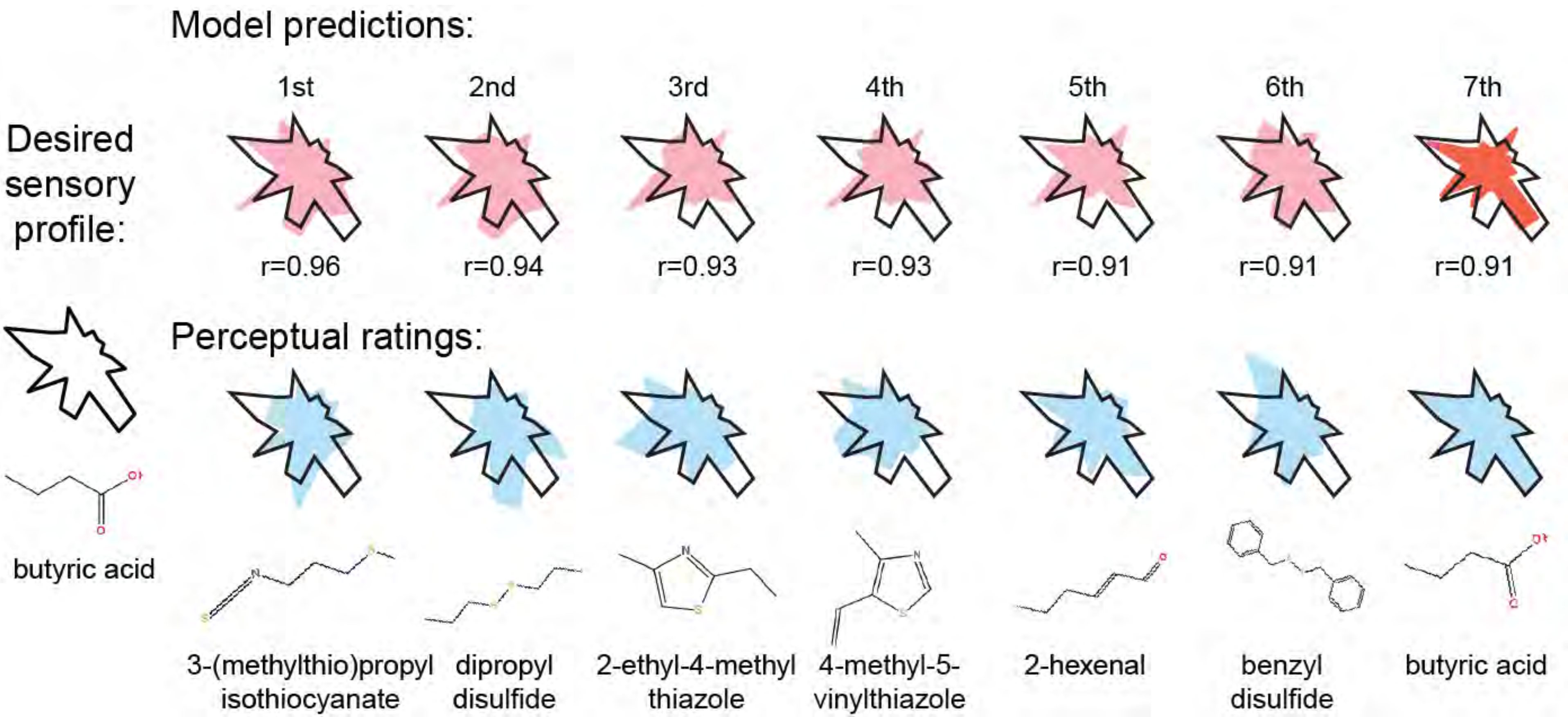
Keller, Gerkin, Guan et al. Science (2017)

What can the model "do"?



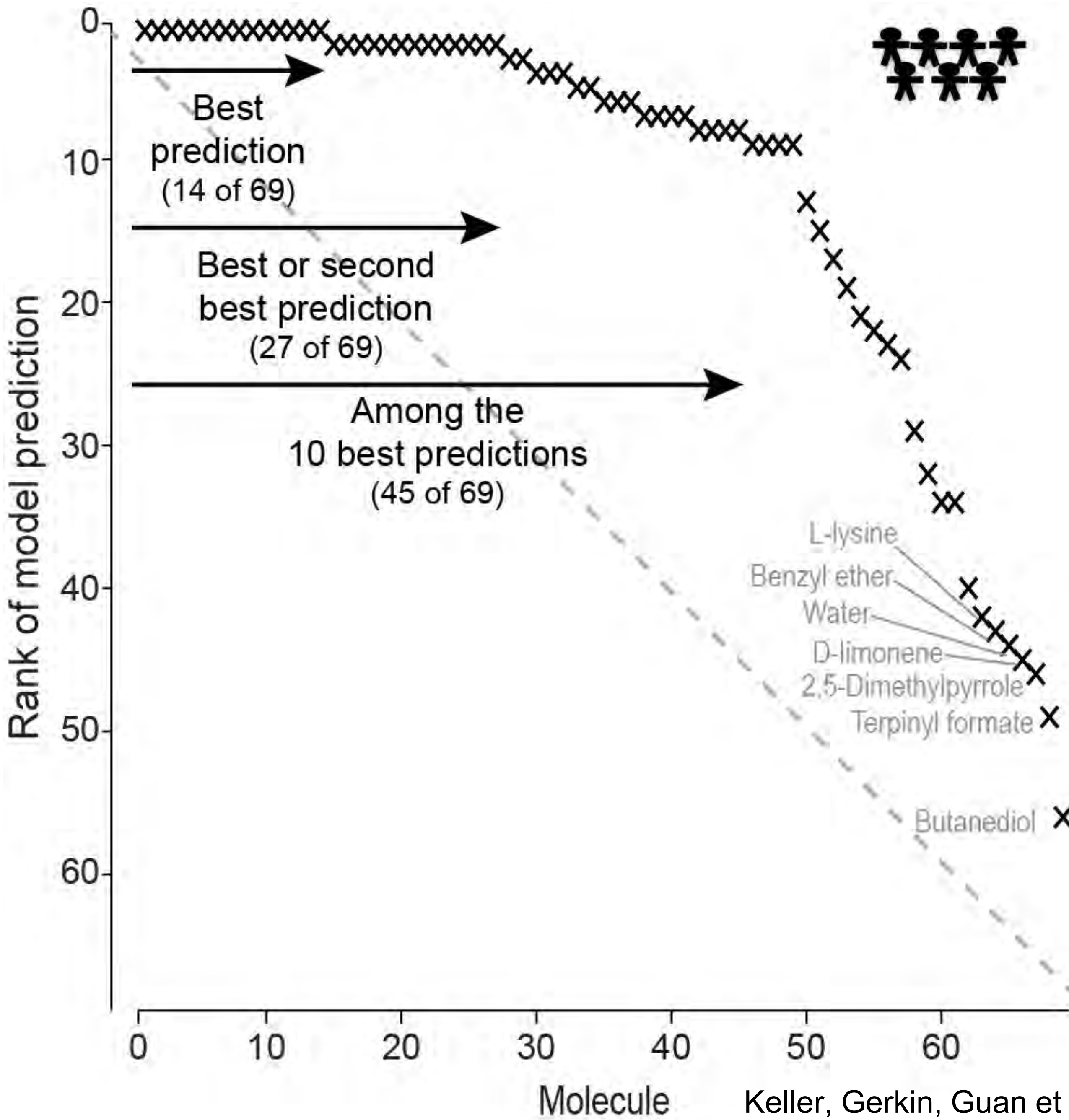
Keller, Gerkin, Guan et al. Science (2017)

Using the model to constrain the search for molecule to percept matches



Keller, Gerkin, Guan et al. Science (2017)

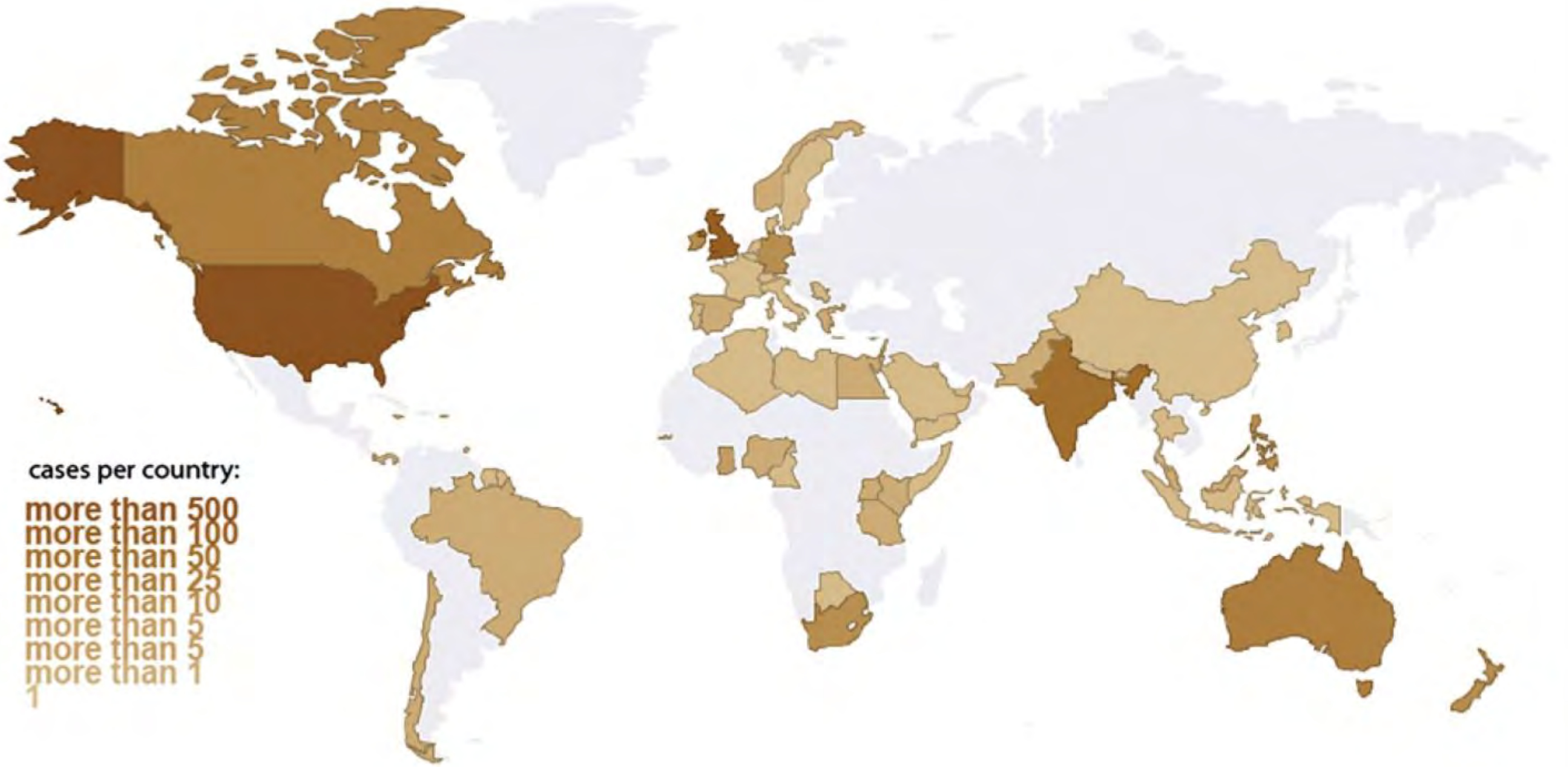
Using the model to constrain the search for molecule to percept matches



Keller, Gerkin, Guan et al. Science (2017)

Why does smell matter, anyway?

1000 people around the world with smell disorders told us about their condition



Keller & Malaspina BMC Ear, Nose and Throat Disorders 13:8 (2013)

Why does smell matter, anyway?

EATING

Food tastes like sawdust (subject 0632), cardboard (subject 0114), or paper with glue (subject 0804)

I frequently each spoiled food without knowing it (subject 0285)

I ended up gaining almost twenty pounds before realizing I was consuming more of every food in an effort to taste it (subject 0004)

Keller & Malaspina BMC Ear, Nose and Throat Disorders 13:8 (2013)

Why does smell matter, anyway?

HYGIENE AND SAFETY

I lost my sense of smell for no apparent reason five years ago at age 72. I never noticed it until my daughter said my house had a terrible odor and we then discovered a dead rodent that caused the odor (subject 0449)

My poor kids sat in dirty diapers longer than they should have because I couldn’t smell the soiled diaper (subject 0354)

Keller & Malaspina BMC Ear, Nose and Throat Disorders 13:8 (2013)

Why does smell matter, anyway?

MENTAL HEALTH

It is very difficult for me now to make plans, feel desire, feel good and happy. I live in a permanent present, I have lost the sensations linked to memories, I have no particular desire for the future (subject 0999)

I have a two year old daughter and I've never been able to smell her. I miss the smell of pickles, early September mornings, the ocean, gasoline, matches and garlic (subject 0008)

Keller & Malaspina BMC Ear, Nose and Throat Disorders 13:8 (2013)

19. This odor smells most like:

a. lemon

b. chocolate

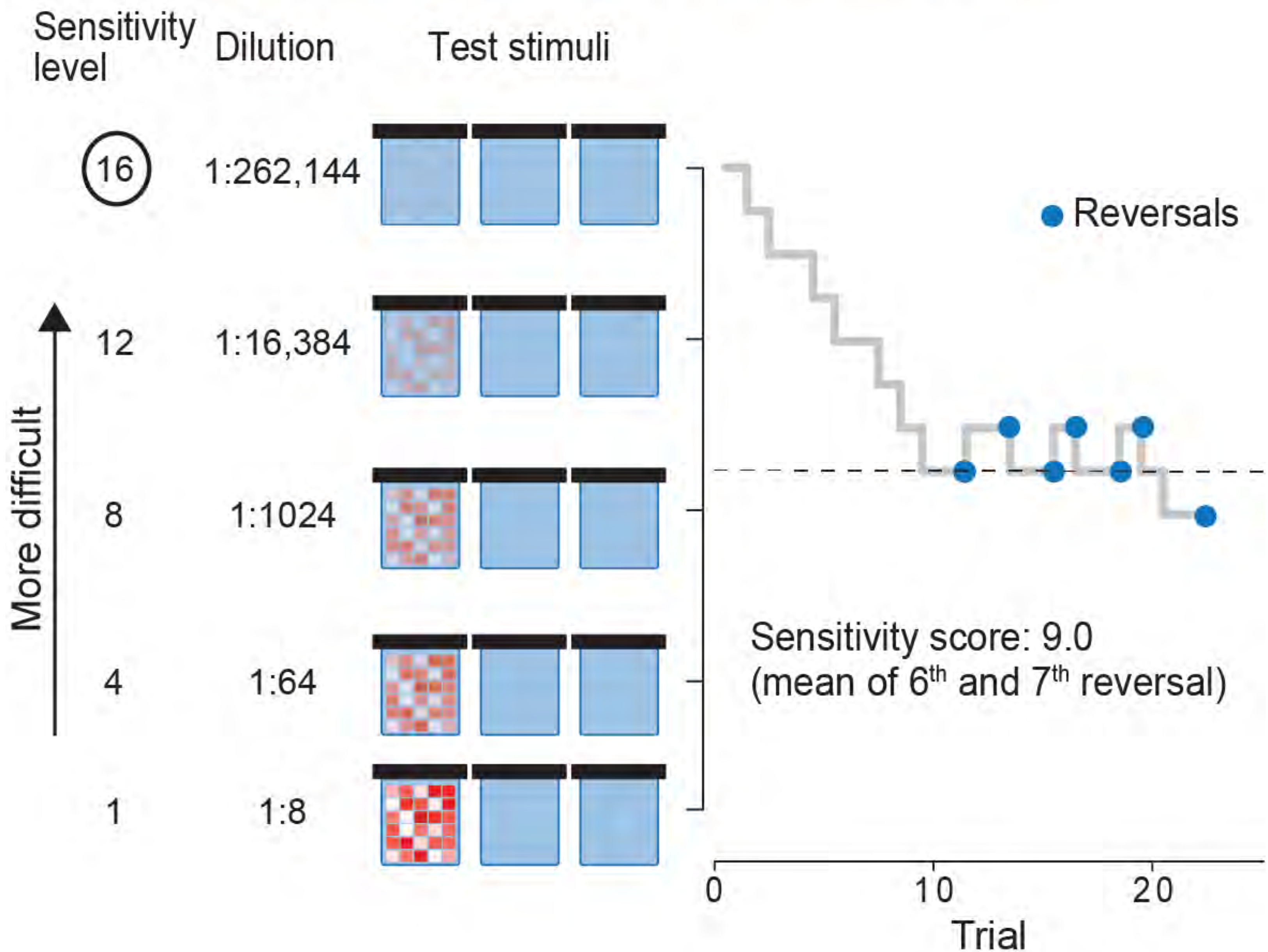
c. root beer

d. black pepper

UPSIT items with poor international performance

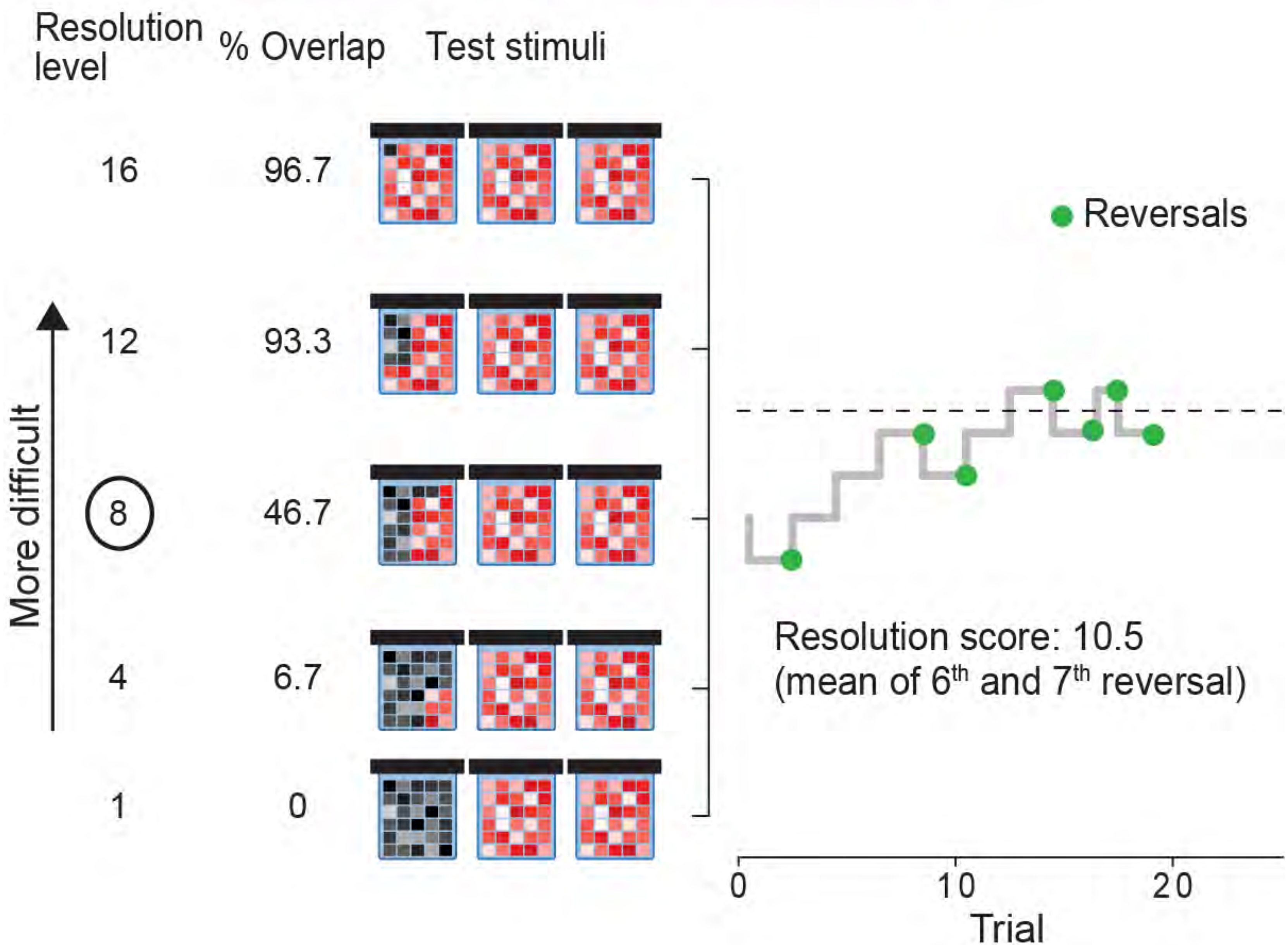
GERMANY	CHINA	ITALY	RUSSIA	FRANCE	COLOMBIA
cedar	cedar	cheedar cheese	bubble gum	cheddar cheese	cheddar cheese
cheddar cheese	cinnamon	dill pickle	cheddar cheese	dill pickle	dill pickle
cherry	clove	fruit punch	clove coconut	gingerbread	gingerbread
dill pickle	dill pickle	lilac	dill pickle	peanut	licorice
fruit punch	gingerbread	lime	fruit punch	root beer	peanut
gingerbread	mint	pumpkin pie	gingerbread	wintergreen	root beer
grape	pizza	root beer	licorice		wintergreen
natural gas	pumpkin pie	wintergreen	lime mint		
root beer	root beer		peanuts		
wintergreen	wintergreen		pizza		
			pumpkin pie		
			root beer		
			wintergreen		

Olfactory sensitivity test: SMELL-S



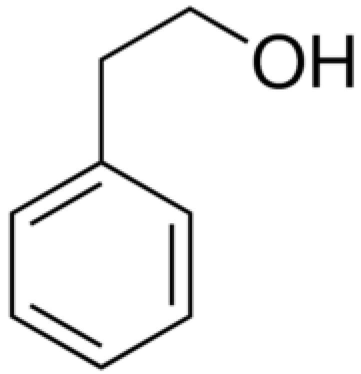
Hsieh et al. bioRxiv (2017)

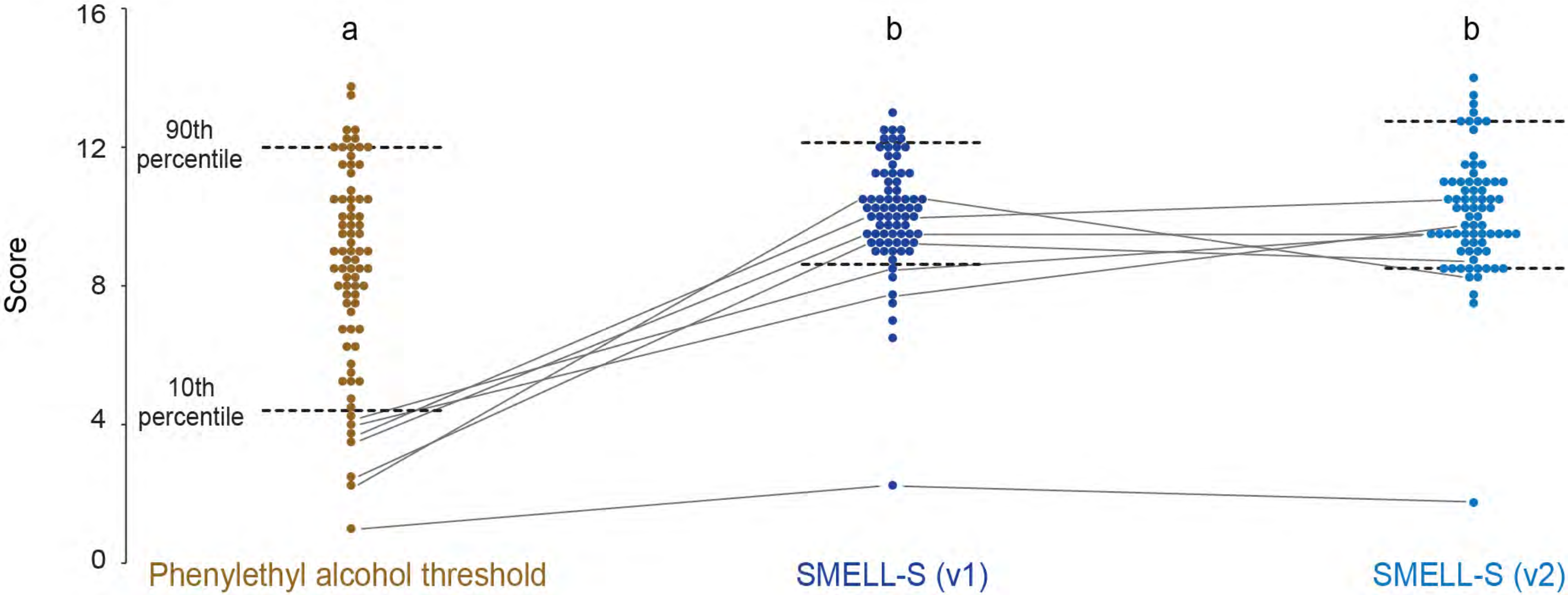
Olfactory resolution test: SMELL-R



Hsieh et al. bioRxiv (2017)

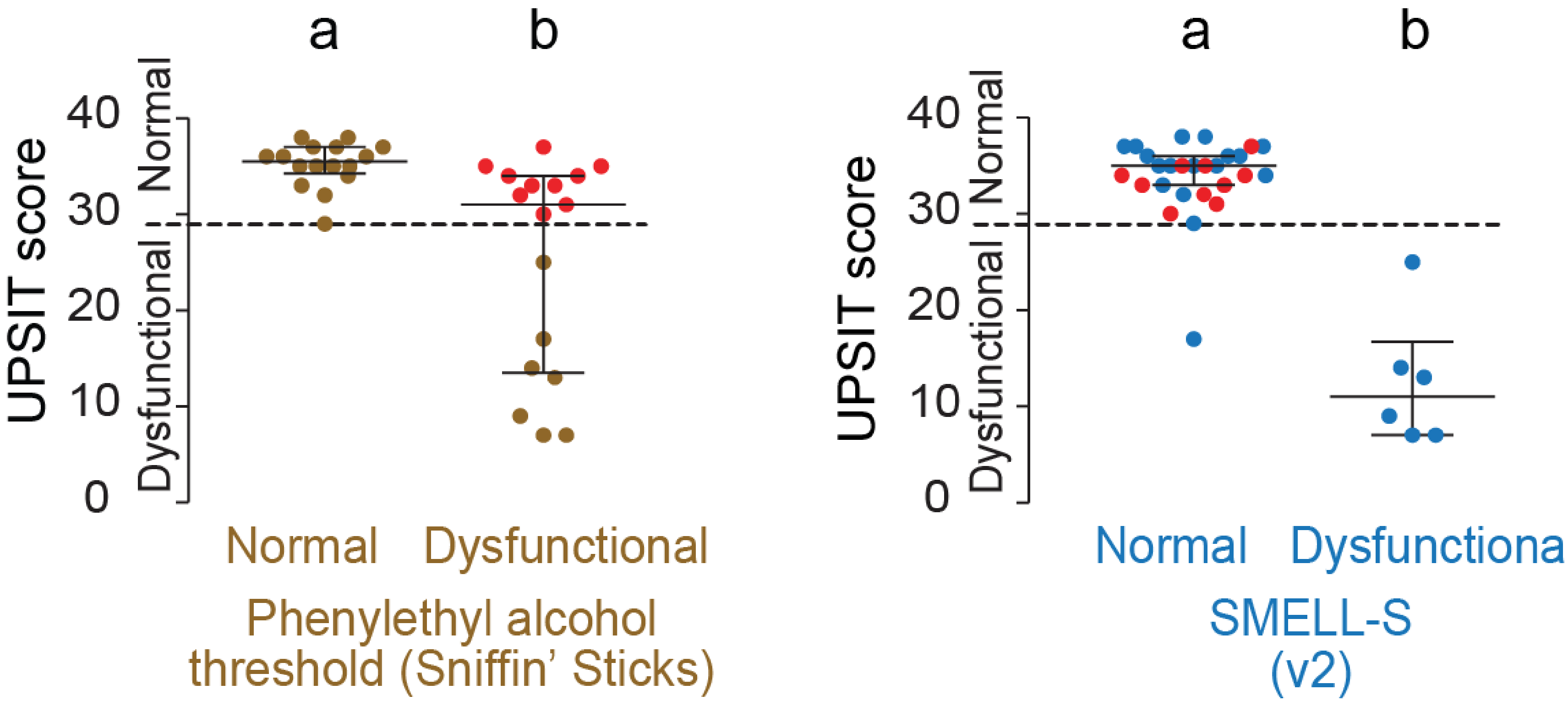
Addressing the problem of odorant-specific insensitivity



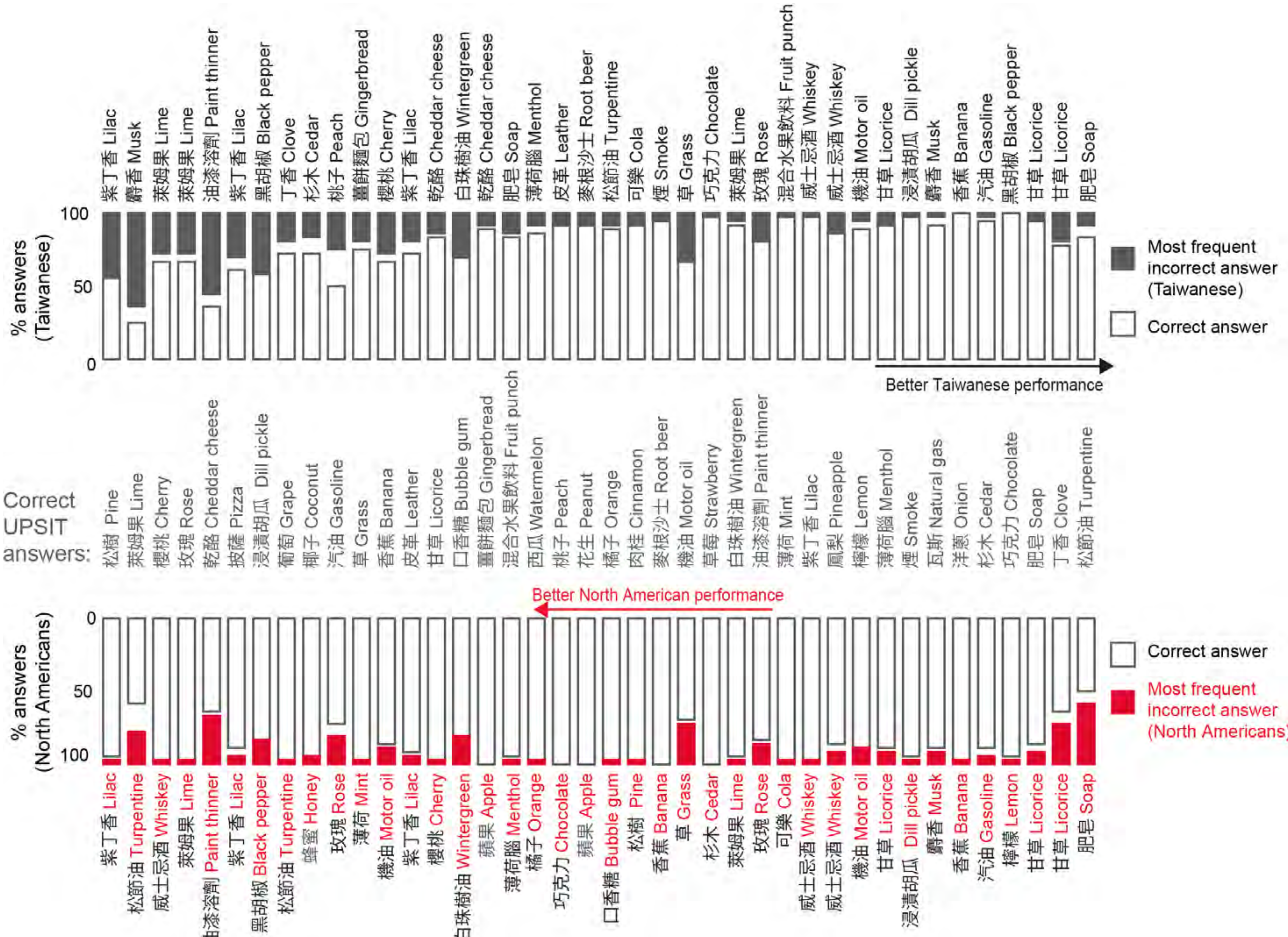


Hsieh et al. bioRxiv (2017)

Addressing the problem of odorant-specific insensitivity

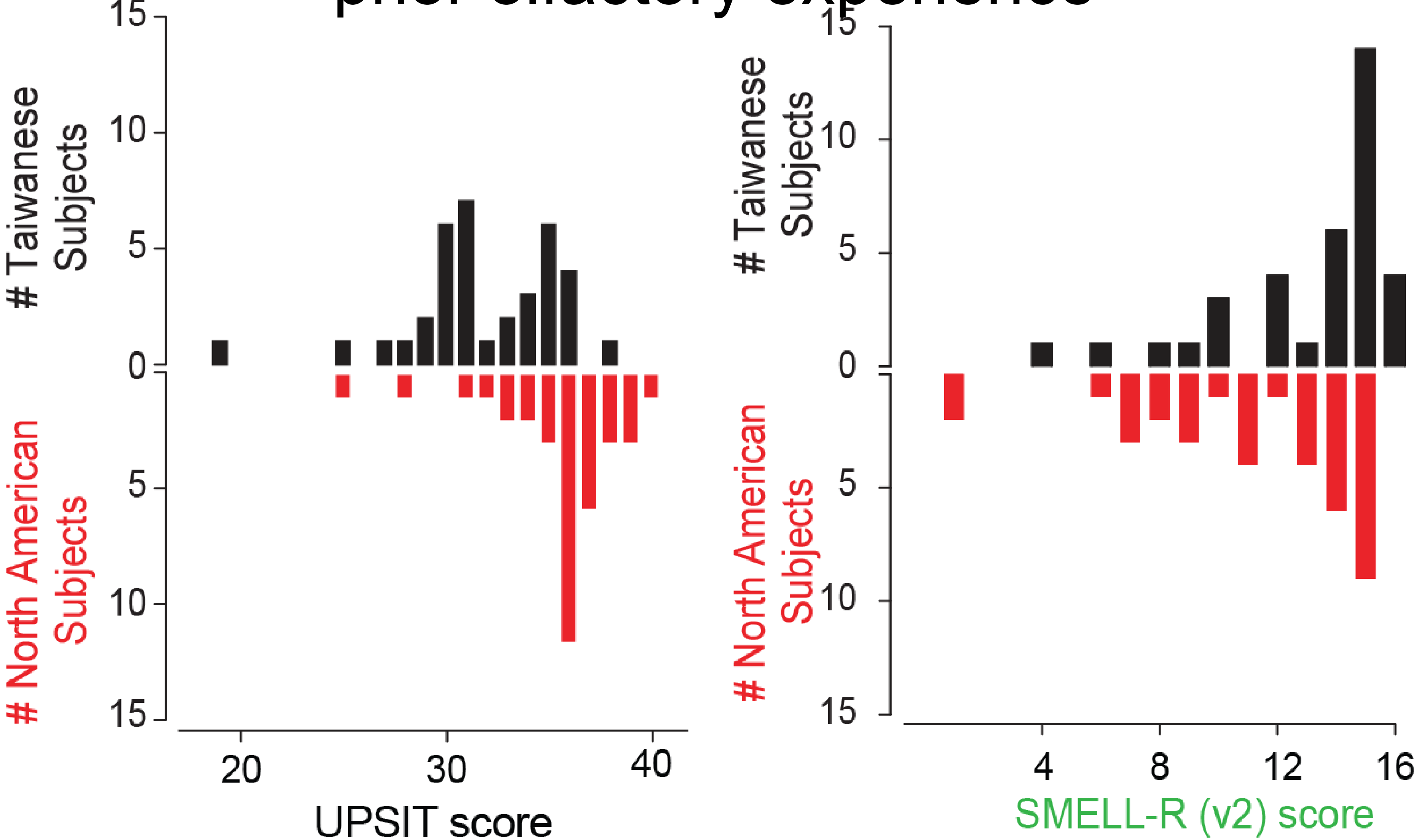


Hsieh et al. bioRxiv (2017)

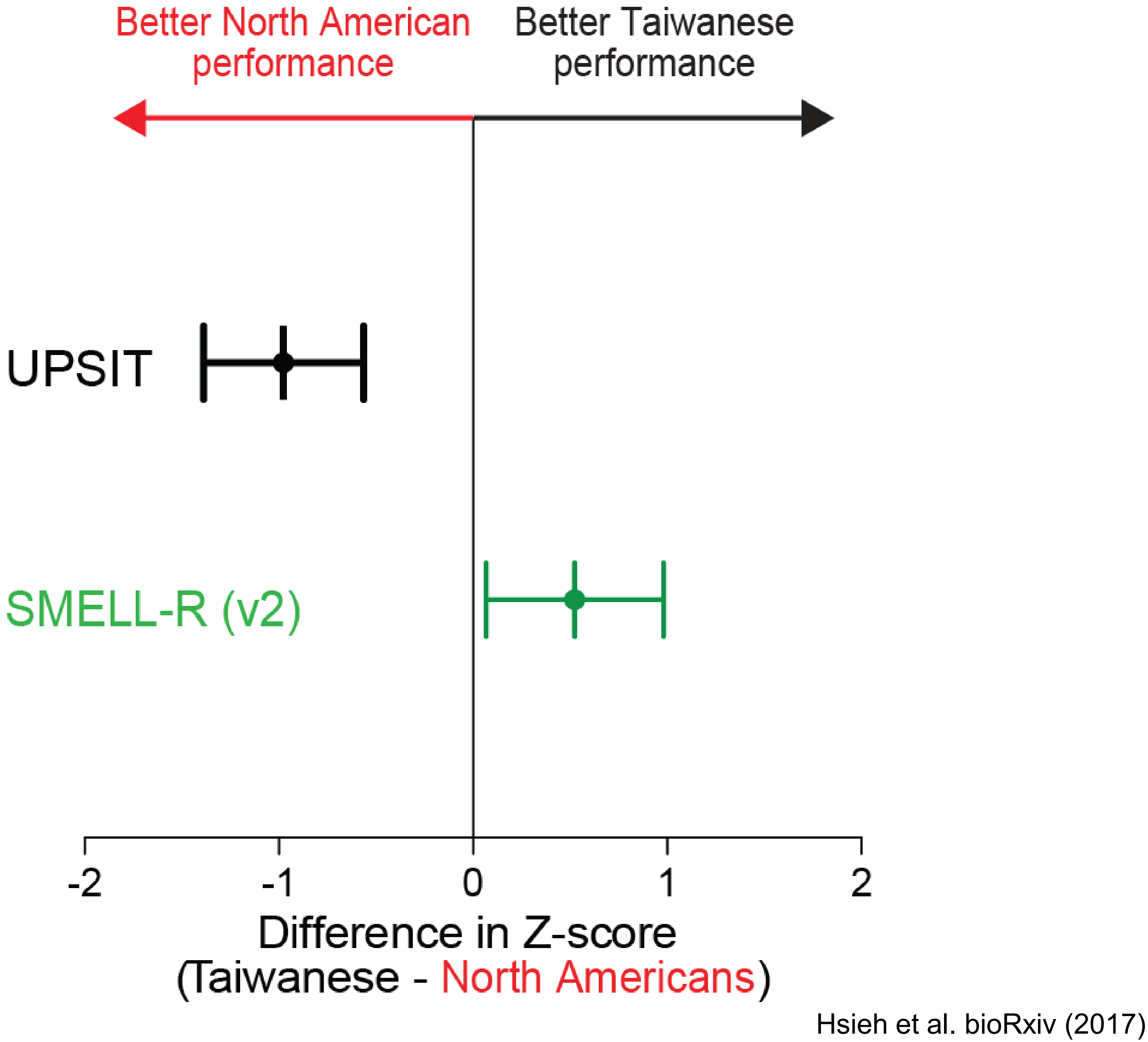


Hsieh et al. bioRxiv (2017)

Addressing the problem of prior olfactory experience



Hsieh et al. bioRxiv (2017)


Better North American performance
Better Taiwanese performance
UPSIT
SMELL-R (v2)
-2
-1
0
1
2
Difference in Z-score
(Taiwanese - North Americans)
Hsieh et al. bioRxiv (2017)

The Rockefeller University Smell Study
2004 – 2016
2942 subjects, 5907 clinic visits

Julien Hsieh
Michele Wong

Rong-San Jiang
(Taichung)

Duke University
Hiroaki Matsunami
Hanyi Zhuang
Joel Mainland

IBM Watson
Pablo Meyer
and colleagues
DREAM Challenge

NATIONAL INSTITUTES OF HEALTH

hhmi