Review article

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Information about space from time: how mammals navigate the odour landscape

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Abstract: Sensory input across modalities is highly dynamic, continuously confronting the brain with the task of making sense of the external world. Olfaction is a key sense that many species depend on for survival, for example to locate food sources and mating partners or to avoid encountering predators. In the absence of visual cues, olfactory cues are especially useful, as they provide information over a large range of distances. Natural odours form temporally complex plumes that show rapid fluctuations in odour concentration carrying information about the location of an odour source. This review focuses on how primarily mammals use this spatial information from olfactory cues to navigate their environment. I highlight progress made on the physical description of dynamically fluctuating odours, behavioural paradigms to investigate odour-guided navigation and review initial findings on the underlying neural mechanisms that allow mammals to extract spatial information from the dynamic odour landscape.

Keywords: active sampling; navigation; odour plume; olfaction; temporally complex structure.

Zusammenfassung: Sensorische Eindrücke aller Sinnesmodalitäten sind hoch dynamisch und stellen das Gehirn ununterbrochen vor die Aufgabe, die Außenwelt in ihrer Gesamtheit zu erfassen. Der Geruchssinn spielt für viele Spezies eine überlebenswichtige Rolle, zum Beispiel um Nahrungsquellen und Artgenossen zu finden, oder Begegnungen mit Raubtieren zu vermeiden. Olfaktorische Signale liefern sensorische Information über kurze und lange Entfernungen, auch wenn optische Eindrücke fehlen. Natürliche Gerüche bilden komplexe Duftwolken mit rapide fluktuierender Konzentration, die Informationen über den Ort einer Geruchsquelle tragen. Dieser Artikel gibt einen Überblick darüber wie vor allem Säugetiere räumliche Information aus Geruchssignalen ziehen können, um ihre Umwelt zu navigieren. Beleuchtet werden Fortschritte in der physikalischen Beschreibung dynamischer Gerüche, Verhaltensparadigmen zur Untersuchung olfaktorischer Navigation, sowie erste Erkenntisse über potentielle zu Grunde liegende neuronale Mechanismen, die es Säugern erlauben, räumliche Information aus der dynamischen Geruchswelt zu erlangen.

Schlüsselwörter: aktives Samplen; Duftwolke; Geruchssinn; Navigation; zeitlich komplexe Struktur.

Introduction and objectives

Organisms across phyla use olfactory information to orient themselves within their environment, for example to find food sources and mating partners. Odours carry information over a large range of distances, thus allowing behaviours that range from simple object detection and recognition, to trail tracking and navigation using odour plumes from afar. Recently, the temporal dynamics of odours have come into focus, introducing a shift from viewing olfaction as a static and slow modality. While the significance of temporal dynamics for invertebrates has been recognised some time ago (reviewed in Baker et al., 2018; Cardé and Willis, 2008; Reddy et al., 2022a; Vickers, 2000), it only recently started to gain interest in mammalian olfaction research (Ackels et al., 2021; Crimaldi et al., 2022; Marin et al., 2021; Reddy et al., 2022a), with the latter being the focus of this review.

Here, I first introduce what spatiotemporal information is inherent to odour signals, how to measure it, and which physical features can be used to characterise the complex distribution of olfactory cues in the odour environment. I next describe active sampling strategies that mammals, in particular laboratory rodents, use to gather olfactory information. I then give an overview of the computational capabilities of the olfactory system, with a focus on the olfactory bulb (OB), to process fine temporal information from dynamic odours. I next set out various experimental paradigms that have been designed to

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investigate olfactory-guided spatial behaviours, specifically the tracking of odour trails and navigation using airborne olfactory cues. This review aims to highlight how recent advances in understanding odour plume dynamics and the design of more naturalistic behavioural paradigms provide a promising gateway to gain mechanistic understanding of mammalian odour-guided navigation.

Spatiotemporal information in dynamic odour signals

Odour-guided animals are faced with two vital challenges: (1) separating out relevant odour sources from a complex olfactory landscape and (2) deducing the location of such odour sources, for example food sources or mating partners, when navigating their environment.

A prerequisite to investigate odour-dependent behaviours is a clear description of the sensory stimulus space. The perceptual space of colour vision is low-dimensional and is fundamentally defined by the wavelength spectrum of the light source. Such a clear-cut definition does not exist in olfaction as thousands of volatile odorous chemicals exist in nature. A quantitative understanding of odour space therefore remains a major point of discussion in olfaction research (Meister, 2015). In addition to the plethora of different chemicals, in a natural olfactory scene, odours rarely occur in isolation. Instead they most often compose complex mixtures consisting of many different molecules that vary in their composition and the concentration of their components (Mori et al., 1999). Moreover, environmental conditions generate complex air movements that lead to the formation of turbulent plumes that consist of odour filaments often fluctuating at high frequencies interrupted by odourless space (Figure 1). Odours in a natural environment are thus dynamic in both space and time (Celani et al., 2014; Moore and Crimaldi, 2004; Murlis et al., 1992; Mylne and Mason, 1991; Shraiman et al., 2000).

There are ways to faithfully measure spatial and temporal information of odour signals in order to characterise their physical features. A widespread method to detect odours at a single location is using a photoionisation detector (Justus et al., 2002) that ionises odour molecules with high temporal resolution with ultraviolet light and generates a concentration dependent voltage signal. It is furthermore feasible, albeit technically more challenging, to visualize odour plumes using planar laser-induced fluorescence (PLIF) and thereby perform measurements of plume dynamics with high temporal and spatial precision

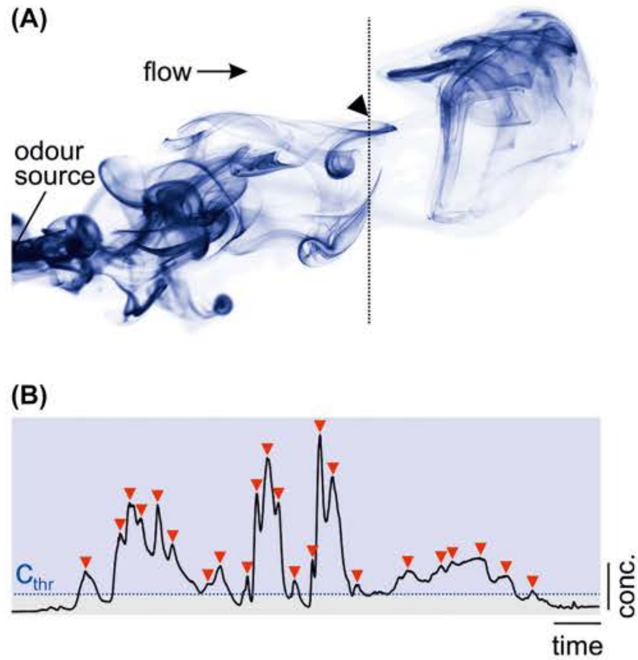

Figure 1: Structure and time course of a complex odour plume. (A) Two-dimensional section of a turbulent smoke plume highlighting its chaotic distribution in airflow direction. (B) Example recording of an odour plume reproduced using a high-speed odour delivery device (Ackels et al., 2021). Red triangles: odour concentration peaks above threshold (C_{thr}, dotted blue line). Plume in (A) adapted from (http://creativity103.com/collections/Smoke/smoke_plume.jpg).

(Connor et al., 2018; Crimaldi and Koseff, 2001). To predict how odours are transported in a turbulent environment is a computationally challenging problem. Computational fluid dynamics simulations (Celani et al., 2014) and information-theoretic approaches (Boie et al., 2018), however, can shed light onto odour plume statistics and the spatial information they carry.

As a plume emanates from its source, it widens in space, resulting in a change of the statistics of concentration fluctuations (Ackels et al., 2021; Moore and Atema, 1991; Murlis et al., 1992; Weissburg et al., 2002). Several features have been identified to vary reliably with distance to the source. These include the height and onset slope of a peak (Moore and Atema, 1991), intermittency, which is defined as the fraction of time the local concentration is above a certain threshold (Riffell et al., 2014) and average bout count, defined as events of large, consistent changes in the measured signal (Schmuker et al., 2016) (Figure 1B). Importantly, it has been suggested that the spatiotemporal patterns of odour plumes hold information about the location, distance and composition of odour sources (Celani et al., 2014; Hopfield, 1991; Murlis et al., 2000): Odours from the same or close by sources show a high degree of correlation in their concentration fluctuations, whereas odours from distant sources fluctuate in an uncorrelated manner, allowing mice to perform source separation (Ackels et al., 2021).

Understanding how odour signal features and animal sampling strategies are linked to neural correlates and behaviour has attracted considerable interest over the past years and has become an active field of research in mammalian neuroscience (Ackels et al., 2021; Findley et al., 2021; Gumaste et al., 2020; Jordan et al., 2018; Lewis et al., 2021; Tariq et al., 2021).

Active sampling of odour information

Animals continuously gather olfactory sensory information – a crucial precondition to successfully localize and identify an odour source. Additionally, odour-guided animals are usually not stationary but instead continuously sample olfactory cues while navigating the environment. Active exploration thus changes the odour signal dynamics and reformats it to ultimately allow for more efficient search strategies. Examples of active sensing in invertebrates manifest as movement of the entire body or its appendages, including wing flapping (Chapman et al., 2018; Li et al., 2018) or antennae flicking (Devine and Atema, 1982; Reeder and Ache, 1980), imposing additional intermittency onto the odour stimulus (Huston et al., 2015).

These behaviours can be considered as the functional equivalent of vertebrate sniffing – active sampling of olfactory information through the intermittent inhalation of odour molecules into the nasal cavity. The frequency of sniffing in rodents covers a wide range of 2–12 Hz (Welker, 1964) and changes with both stimulus and contextual features such as odour novelty (Esquivelzeta Rabell et al., 2017; Verhagen et al., 2007), and attentiveness of the animal (Jordan et al., 2018; Kepecs et al., 2006; Wachowiak, 2011; Wesson et al., 2008). Importantly, active sensing strongly impacts on how a stimulus is represented in the brain, for example by modulating the frequency content of the signal even before its initial transduction by olfactory sensory neurons (OSNs) in the nasal epithelium.

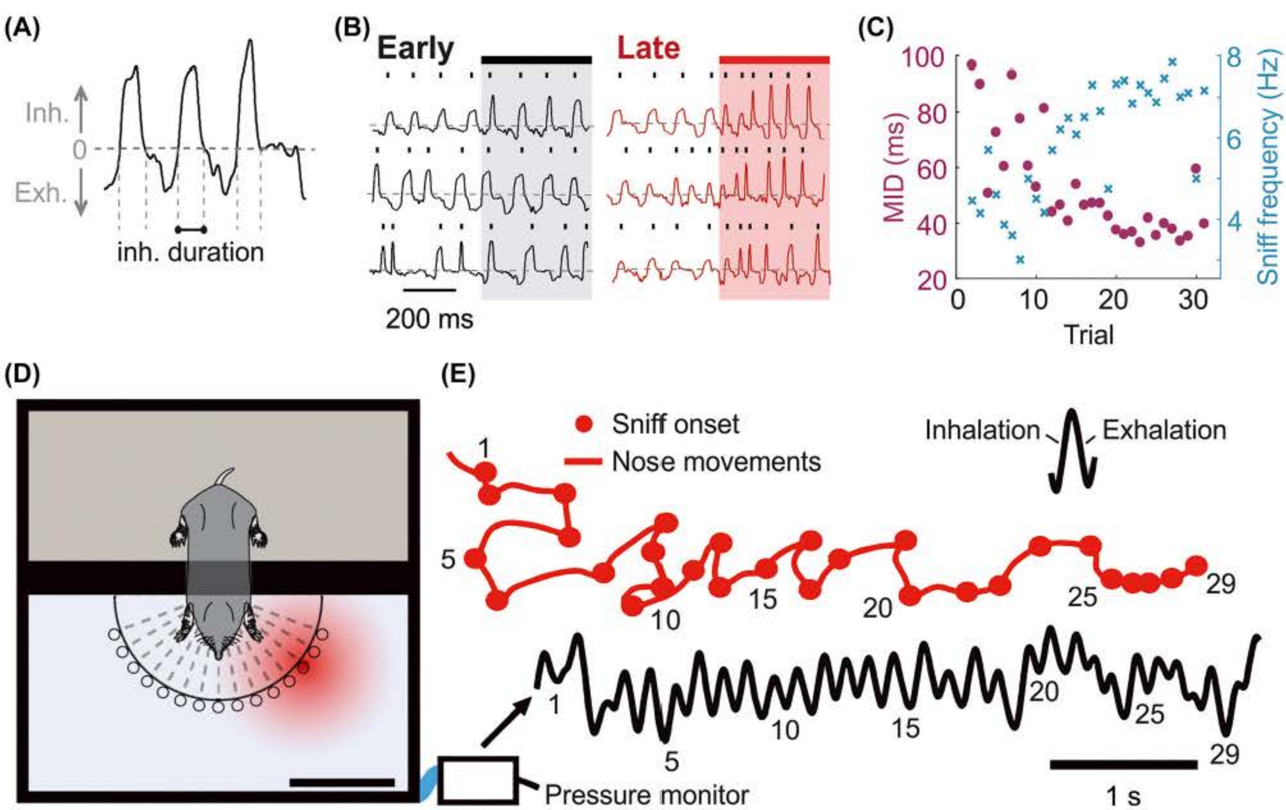

Figure 2: Active sampling behaviour.
(A) Diagram to show the extraction of inhalation duration from an example nasal flow trace. (B) Example nasal flow traces showing the emergence of rapid sniffing between early and late trials. (C) Mean inhalation duration (MID) for the example in (B) calculated for each trial (first 500 ms of stimulus) in purple dots. Blue crosses show corresponding sniff frequency for each trial (from Jordan et al., 2018).
(D) Experimental chamber to investigate serial and stereo olfactory sampling using an Eastern mole. (E) An air-pressure monitor recorded respiration. Sniffs (red dots) were correlated to nose movements (red lines) acquired by high-speed videorecordings (from Catania, 2013).

Modulation of sniff frequency and intensity affects odour representation in the brain (Parabucki et al., 2019; Verhagen et al., 2007; Wachowiak, 2011). Acceleration of sniff frequency and shorter inhalation duration, for example, evolve over the course of learning an odour discrimination task (Figure 2A–C) and enhance odour representation during learning (Jordan et al., 2018).

So far, an individual sniff has generally been considered to be the unit of information for olfactory processing, forming a 'snapshot' of the olfactory surroundings (Kepecs et al., 2006). According to this view, fast fluctuations in odour concentration at sub-sniff resolution would be rendered inaccessible to the mammalian olfactory system. An increasing number of studies, however, indicate that fine temporal information – faster than the respiration frequency – is accessible to mammals (Ackels et al., 2021; Cury and Uchida, 2010; Shusterman et al., 2011; Smear et al., 2011, 2013).

In addition to the active modulation of serial sniffing, the bilateral organization of the mammalian olfactory system allows for signal comparison across nostrils, analogous to depth perception and sound localization in the visual and auditory system, respectively. Mice and rats use binaral cues for inter-naris odour information comparison (Esquivelzeta Rabell et al., 2017; Rajan et al., 2006) and stereo-smelling has been shown to be used for navigation across species including snakes (Schwenk, 1994) and even humans (Bekesy, 1964; Porter et al., 2007; Wu et al., 2020). Eastern moles can readily locate a food source in a radial search paradigm, relying on information sampled through both nostrils (Catania, 2013) (Figure 2D, E). In accordance with this, occluding one naris reduced odour trail-tracking ability in rats (Khan et al., 2012) and mice (Jones and Urban, 2018) and impaired odour direction sensitivity in moles (Catania, 2013). The utility of stereo-olfaction is likely highest when sampling occurs in close proximity to an odour source, as with increasing distance the difference in signal across the two nares might become indistinguishable from fluctuations in turbulent mixing (Reddy et al., 2022). Another form of active sampling observed during trail tracking in rats, moles, dogs and humans is head-scanning (Catania, 2013; Khan et al., 2012; Porter et al., 2007) which often goes together with changes in sniff frequency.

Sniffing behaviour governs the way odour information reaches the olfactory system, making respiration activity a crucial parameter that needs to be monitored when studying olfactory physiology and behaviour. Based on the experimental conditions, a number of methods with varying precision, reliability and invasiveness have been developed over the past decades. These are reviewed in detail by Grimaud and Murthy (2018) and I will introduce only the most common techniques here.

An established way to measure respiration is using air movement through the nose, which provides a more direct readout compared to neural or muscular activity (Feldman et al., 2013). In stationary, head-restrained animals, a face mask combined with a flow meter can be positioned in front of the animal's snout to establish precise, non-invasive respiration recordings that can directly be paired with the delivery of odour stimuli (Bolding and Franks, 2017). Another method that has been extended to freely moving animals is to detect changes in pressure (Li et al., 2014; Reisert et al., 2014; Verhagen et al., 2007) or temperature (Jones and Urban, 2018; Khan et al., 2012; McAfee et al., 2016; Uchida and Mainen, 2003) using an intranasally implanted sensor. While intranasal sensors open up the possibility to study social or navigation behaviour, these implants can potentially disrupt airflow through the nasal cavity and thus affect odour perception. A less disruptive surgical procedure was established in recent studies, however, where a temperature probe is implanted between the nasal bone and inner epithelium of mice, and is thereby not protruding into the nasal cavity, leaving the nasal epithelium intact (Findley et al., 2021; McAfee et al., 2016).

Active sampling behaviour plays a major role in odour processing. To understand, how animals extract spatial information from natural odour plumes, therefore requires reliable, non-disruptive and precise recording of sniffing behaviour across experimental paradigms.

Temporal precision of olfactory signal processing

Natural odours often get transported via turbulent air flow which creates spatiotemporally complex plumes. Under these conditions, fluctuations in odour concentration can reach frequencies that far exceed the respiration rate of mammals. The mammalian sense of smell is generally considered to be a 'slow sense', with its temporal bandwidth governed by the respiration rate (Kepecs et al., 2006; Wachowiak, 2011). A number of recent studies, however, show that mammals can access sub-sniff odour information, providing them with the ability to encode temporal information from dynamic odour signals with astonishing precision.

It has been demonstrated that insects use the temporal structure of odour plumes to deduce information about the location (Demir et al., 2020; Mafra-Neto and Cardé, 1994;

Murlis et al., 1992; Vergassola et al., 2007; Vickers, 2000) and composition (Riffell et al., 2014; Szyszka et al., 2012, 2014) of an odour source. Insects can follow fast odour concentration changes (Brown et al., 2005; Geffen et al., 2009; Kim et al., 2011) due to their extremely fast olfactory signal transduction cascade that results in a response latency of approximately 2 ms as recorded from OSNs (Szyszka et al., 2014). Odour asynchronies as short as 6 ms suffice to segregate learned odour components within a mixture and are encoded differently from their synchronous counterparts in the antennal lobe (Stierle et al., 2013). The sensitivity to temporal odour dynamics therefore enables insects to perform odour-background segregation and source separation.

Much less is known for the mammalian olfactory system when it comes to sensitivity towards spatial and temporal patterns of odours. Mice can detect and discriminate odours within a few 100 ms (Abraham et al., 2004; Uchida and Mainen, 2003) and the olfactory bulb (OB) neural circuitry is, in principle, equipped to resolve fine odour dynamics on a millisecond timescale (Cury and Uchida, 2010; Shusterman et al., 2011). Light-evoked 'virtual odour' signals coupled to the respiration cycle can be discriminated by mice at the sub-sniff level when OSNs are stimulated optogenetically at only 10–20 ms intervals (Li et al., 2014; Smear et al., 2011, 2013). Patterned optogenetic stimulation of OB projection neurons, so called mitral/tufted cells (MTCs), revealed that stimulus delays of as little as 13 ms are distinguishable by mice (Rebello et al., 2014). Shifting stimulus timing of optogenetically targeted MTCs within the sniff cycle, in particular towards the beginning of the cycle, changes behavioural performance in mice when discriminating neuronal activation patterns (Chong et al., 2020). Synthetic odours created via optogenetic stimulation can thus be represented with high temporal precision at frequencies far exceeding that of the animal's respiration.

Artificial stimulation using optogenetics provides a well-controlled and precise way to probe the olfactory system. It should, however, not be seen as a substitute that is equivalent to presenting actual odours. A long-standing challenge in olfaction research is the precise control of the odour stimulus, owing to the high volatility of many odorous chemicals. Recent developmental advances in high-speed odour delivery devices (Ackels et al., 2021; Raiser et al., 2017) now allow to reproduce the complex temporal structure of natural odours with minimal stimulus onset delay. Presenting odours fluctuating at frequencies exceeding the respiration rate allows to test experimentally whether these dynamics are accessible to the mammalian olfactory system at the sub-sniff level. Recent work shows that mice can extract spatial information from high-frequency temporal odour dynamics carried by natural plumes. The correlation structure of odours fluctuating at 20 Hz is encoded in MTCs and thus, in principle, provides a neural correlate to perform odour-source separation (Ackels et al., 2021; Dasgupta et al., 2022). Presenting natural plumes from within a wind tunnel to head-fixed mice reveals that rapid odour concentration fluctuations structure the activity of glomerular MTC populations (Lewis et al., 2021).

Taken together, there is substantial evidence that the OB neural circuitry harbours the computational bandwidth to encode temporal information from dynamic sensory input at fast time scales – both created artificially using light pulses and from actual odour stimuli. This introduces the exciting prospect to further investigate the mechanisms underlying natural odour processing to better understand olfactory-guided behaviours.

Spatial behaviours based on olfaction

Some mammals are well-known to exploit their sense of smell for navigation. The complexity of natural odour landscapes and the difficulty to recreate these conditions in a laboratory setting, however, have constrained our understanding of how spatial information carried by natural odours aids navigation through complex environments. Assessing behavioural performance is further complicated by the fact that animals, for example trained to follow an odour track or to localise an odour source, will revert to a variety of strategies to solve this particular task, depending on a number of behavioural parameters such as experimental conditions and training level.

Promising new developments now allow to perform neurophysiological recordings, monitor respiration (Findley et al., 2021; Liu et al., 2020) and record odour information using head-mounted odour sensors (Tariq et al., 2021) in freely moving animals. This created the opportunity to directly link the sampling strategy and odour concentration profile to neural activity patterns during complex behaviours. New odour delivery devices that are capable of reliably reproducing the temporal dynamics of natural odour plumes (Ackels et al., 2021) give precise control over the odour stimulus and create the possibility to probe the olfactory system systematically using dynamic stimuli in a controlled laboratory setting, in particular during head-fixed physiology and/or behaviour experiments.

In the following sections, I will highlight what is currently known about how mammals can extract spatial information for navigation from surface-borne odour cues during trail tracking and from airborne olfactory cues.

Tracking surface-borne odours

Animals deposit and follow surface-borne scent trails in the context of several different behaviours. Tracking the trail of a specific odour and distinguishing it from the plethora of olfactory cues in a natural landscape can become vital to either find an odour source, in the case of food or mating partners, or to avoid approaching it, for example in the case of a predator animal. A prominent behaviour found in many species is placing urine scent marks within the home territory (Arakawa et al., 2008). This can serve multiple purposes: for example, to guide the depositor through its habitat by establishing navigation routes (Benhamou, 1989) but also to alert other animals about crossing into foreign territory (Hurst and Beynon, 2004).

Several experimental paradigms have been established to study odour trail tracking in the laboratory, including trails printed on paper spools in a treadmill (Khan et al., 2012; Mathis et al., 2018) or drawn on a surface in an open field (Jones and Urban, 2018; Porter et al., 2007). Rats (Khan et al., 2012; Wallace et al., 2002), mice (Jones and Urban, 2018) and even humans (Porter et al., 2007) can track odours using the concentration gradient formed around the trail. When tracking an odour trial, rats scan their nose across the trail and widen the scan path when the nose diverges too far from it (Figure 3A), reminiscent of casting movements seen in insects. Mice trained to follow an odour trail, and to ignore a distractor trail (Figure 3B), show increased cumulative distance from the trail when left with only one nostril available to sample information (Figure 3C). Both an increased sniff rate to compare sensory information between sniffs, and stereo-olfaction to gather directional information by comparing sensory input between both nares (Catania, 2013; Jones and Urban, 2018; Khan et al., 2012; Porter et al., 2007) maximise the sampling efficiency and result in improved odour trail tracking.

Tracking odour trails in the wild adds an additional layer of complexity: The animal needs to detect the direction from which an odour originates, for example when hunting for prey or avoiding to become preyed upon. To locate an odour source, tracking dogs follow a 3-step strategy: a searching phase, a deciding phase and a tracking phase (Thesen et al., 1993). It has been proposed that dogs base their decision on the direction of an odour trail by comparing the concentration of odour cues

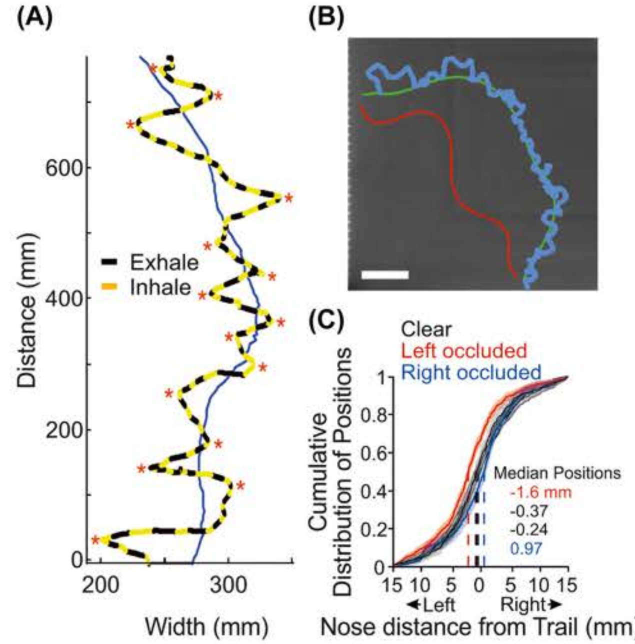

Figure 3: Surface-borne odour tracking.
(A) An example stretch of odour trail tracking showing each sniff overlaid on the nose trajectory. Black indicates inhalation and yellow exhalation. Multiple sniffs are taken during each nose oscillation (from Khan et al., 2012). (B) Nose positions (blue) of a trained mouse, tracking the rewarded (green) trail. Distractor trail is shown in red. (C) Cumulative distribution of nose position relative to the trail for one animal during clear/un-occluded (black), left nostril occluded (red), and right nostril occluded (blue), conditions. Dashed lines indicate position of the median of each distribution (B and C from Jones and Urban, 2018).

between a small number of footsteps (Hepper and Wells, 2005). Recent theoretical work shows that animals form an estimate of where the trail is headed by performing a sector search strategy and using past contacts with the help of an intrinsic, geometric notion of trail continuity (Reddy et al., 2022b).

The ability to follow surface-borne scent marks or food trails can be vital for the survival of an animal. When orienting in relation to more distant odour sources, however, the animal has to rely on tracking airborne odours that travel in the form of odour plumes.

Tracking airborne odours

Airborne odours show higher spatiotemporal complexity compared to surface-borne odours in several respects: Concentration gradients between the inside and the outside of an odour plume are less steep and the concentration profile of an odour plume often fluctuates at high-frequencies imposed by air turbulence (Figure 1). Wind speed and direction are additional parameters that the animal needs to factor in when localising the source of a plume. Navigating through airborne odours, therefore, likely imposes a significantly greater challenge than localising the source of an odour trail.

To investigate what spatial information animals are able to extract from odour plumes in a laboratory setting requires reproducing key features of a complex olfactory environment under controlled conditions. In recent years, significant advances have been made in the experimental design of tasks that reflect, at least in part, natural conditions. Examples include behavioural arenas in which mice are tasked to localise the source of odour plumes under turbulent airflow conditions (Findley et al., 2021; Gire et al., 2016; Gumaste et al., 2020; Liu et al., 2020) or probing mice with temporally complex odour stimuli and reproduced odour plumes in an automated behavioural setup (Ackels et al., 2021). Further, olfactory virtual realities (VR) have been proven to serve as a promising framework to investigate airborne odour tracking under turbulent conditions in stationary animals (Baker et al., 2018; Fischler-Ruiz et al., 2021; Radvansky and Dombeck, 2018; Radvansky et al., 2021).

To date, only a few studies have investigated mammalian plume-tracking navigation (Bhattacharyya and Singh Bhalla, 2015; Findley et al., 2021; Gire et al., 2016; Gumaste et al., 2020; Jackson et al., 2020; Liu et al., 2020). Mice efficiently locate the source of an airborne odour plume in a behavioural arena using a gradient-based algorithm (Gire et al., 2016). After memorising the port locations, however, the limited number of possible rewarded spots leads to a systematic serial-sampling foraging strategy. Consistent with this, rats move straight to one target port in a multichoice olfactory arena under near-laminar flow conditions and sample through potential targets until they reach the rewarded port (Bhattacharyya and Singh Bhalla, 2015). A serial-sampling strategy does not necessarily argue for navigation entirely based on olfactory information. It suggests, however, that animals make direct associations between the odour stimulus and target locations. Olfactory information is thereby integrated into their cognitive spatial map that they use to navigate. Even humans are capable of returning to a defined location in space using odours alone, corroborating the use of odour-informed spatial maps of the environment (Jacobs et al., 2015).

In an odour source localization task mice shift their search strategy with increasingly complex environmental conditions caused by turbulent airflow (Gumaste et al., 2020; Jackson et al., 2020) and with distance to the source, as measured by speed and orientation towards the source (Liu et al., 2020). To ensure that animals rely solely on odour information and to discourage serial sampling, trials were terminated when the animal reached an unrewarded port (Gumaste et al., 2020). In a study where mice were tasked to navigate towards an odour source, sniffing and head movements were highly synchronized (Findley et al., 2021). Here, task performance was not impacted by naris occlusion, suggesting that mice rely primarily on temporal comparisons across sniffs and not stereo-olfaction during airborne odour navigation.

Olfactory VR setups provide an experimental tool that allows for controlled stimulus presentation and recording neural activity in behaving, albeit head-fixed, animals. It has been shown that odour cues serve as landmarks to guide virtual navigation in the absence of visual stimuli and promote place cell representation in the hippocampus, thereby improving navigation performance over time (Fischler-Ruiz et al., 2021). This finding was supported by another study where different proportions of hippocampal CA1 neurons were activated during navigation, depending on whether mice were pursuing a visual landmark or tracking an odour gradient (Radvansky et al., 2021).

Where is the neural information underlying odour-guided navigation generated and processed? Mechanistic understanding of these behaviours remains sparse. Van Rijzingen et al. have shown that removal of the OBs in rats severely impairs spatial orientation in the Morris water maze, despite the presence of visual cues, thus illustrating the olfactory system's significance for navigation (van Rijzingen et al., 1995). Olfactory bulb cell populations recorded in head-fixed mice can follow the temporal patterns of odour plumes that were recorded in real-time with a head-mounted odour sensor (Lewis et al., 2021). Piriform cortex neurons recorded in freely moving rats performing an odour-cued navigation task form a spatial map of the environment by associating spatial and olfactory information (Poo et al., 2021).

In summary, progress made in recent years in terms of behavioural task designs and recording methods offers great opportunities to gain deeper understanding of how spatial information carried by odour plumes aides navigation.

Conclusions

The temporal dynamics of odours carry spatial information about an odour landscape. This can be of vital importance when navigating an environment, in particular for nocturnal animals such as mice or rats. In a recent paradigm shift, the sense of smell is increasingly acknowledged to be a high-bandwidth modality. In this review, I highlighted how this has led to major advances in describing dynamic odour statistics, designing behavioural tasks and presenting spatiotemporally complex odours. While this research has just started to gain traction in mammals, it has the potential to promote our understanding of how dynamic odours allow to infer information about space from time.

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References

Abraham, N.M., Spors, H., Carleton, A., Margrie, T.W., Kuner, T., and Schaefer, A.T. (2004). Maintaining accuracy at the expense of speed: stimulus similarity defines odor discrimination time in mice. Neuron *44*, 865–876.

Ackels, T., Erskine, A., Dasgupta, D., Marin, A.C., Warner, T.P.A., Tootoonian, S., Fukunaga, I., Harris, J.J., and Schaefer, A.T. (2021). Fast odour dynamics are encoded in the olfactory system and guide behaviour. Nature *593*, 558–563.

Arakawa, H., Arakawa, K., Blanchard, D.C., and Blanchard, R.J. (2008). A new test paradigm for social recognition evidenced by urinary scent marking behavior in C57BL/6J mice. Behav. Brain Res. *190*, 97–104.

Baker, K.L., Dickinson, M., Findley, T.M., Gire, D.H., Louis, M., Suver, M.P., Verhagen, J.V., Nagel, K.I., and Smear, M.C. (2018). Algorithms for olfactory search across species. J. Neurosci. *38*, 9383–9389.

Bekesy, G.von (1964). Olfactory analogue to directional hearing. J. Appl. Physiol. *19*, 369–373.

Benhamou, S. (1989). An olfactory orientation model for mammals' movements in their home ranges. J. Theor. Biol. *139*, 379–388.

Bhattacharyya, U. and Singh Bhalla, U. (2015). Robust and rapid air borne odor tracking without casting. ENeuro *2*, https://doi.org/10.1523/eneuro.0102-15.2015.

Boie, S.D., Connor, E.G., McHugh, M., Nagel, K.I., Ermentrout, G.B., Crimaldi, J.P., and Victor, J.D. (2018). Information-theoretic analysis of realistic odor plumes: what cues are useful for determining location? PLoS Comput. Biol. *14*, 1–19.

Bolding, K.A., and Franks, K.M. (2017). Complementary codes for odor identity and intensity in olfactory cortex. Elife *6*, 1–26.

Brown, S.L., Joseph, J., and Stopfer, M. (2005). Encoding a temporally structured stimulus with a temporally structured neural representation. Nat. Neurosci. *8*, 1568–1576.

Cardé, R.T., and Willis, M.A. (2008). Navigational strategies used by insects to find distant, wind-borne sources of odor. J. Chem. Ecol. *34*, 854–866.

Catania, K.C. (2013). Stereo and serial sniffing guide navigation to an odour source in a mammal. Nat. Commun. *4*, 1441.

Celani, A., Villermaux, E., and Vergassola, M. (2014). Odor landscapes in turbulent environments. Phys. Rev. X *4*, 041015.

Chapman, P.D., Burkland, R., Bradley, S.P., Houot, B., Bullman, V., Dacks, A.M., and Daly, K.C. (2018). Flight motor networks modulate primary olfactory processing in the moth Manduca sexta. Proc. Natl. Acad. Sci. U. S. A. *115*, 5588–5593.

Chong, E., Moroni, M., Wilson, C., Shoham, S., Panzeri, S., and Rinberg, D. (2020). Manipulating synthetic optogenetic odors reveals the coding logic of olfactory perception. Science *368*, eaba2357.

Connor, E.G., McHugh, M.K., and Crimaldi, J.P. (2018). Quantification of airborne odor plumes using planar laser-induced fluorescence. Exp. Fluids *59*, 0.

Crimaldi, J.P., and Koseff, J.R. (2001). High-resolution measurements of the spatial and temporal scalar structure of a turbulent plume. Exp. Fluids *31*, 90–102.

Crimaldi, J., Lei, H., Schaefer, A., Schmuker, M., Smith, B.H., True, A.C., Verhagen, J.V., and Victor, J.D. (2022). Active sensing in a dynamic olfactory world. J. Comput. Neurosci. *50*, 1–6.

Cury, K.M., and Uchida, N. (2010). Robust odor coding via inhalation-coupled transient activity in the mammalian olfactory bulb. Neuron *68*, 570–585.

Dasgupta, D., Warner, T.P.A., Erskine, A., and Schaefer, A.T. (2022). Coupling of mouse olfactory bulb projection neurons to fluctuating odour pulses. J. Neurosci. *42*, 4278–4296.

Demir, M., Kadakia, N., Anderson, H.D., Clark, D.A., and Emonet, T. (2020). Walking Drosophila navigate complex plumes using stochastic decisions biased by the timing of odor encounters. Elife *9*, 1–31.

Devine, D.V., and Atema, J. (1982). Function of chemoreceptor organs in spatial orientation of the lobster, Homarus americanus: differences and overlap. Biol. Bull. *163*, 144–153.

Esquivelzeta Rabell, J., Mutlu, K., Noutel, J., Martin del Olmo, P., and Haesler, S. (2017). Spontaneous rapid odor source localization behavior requires interhemispheric communication. Curr. Biol. *27*, 1542–1548.e4.

Feldman, J.L., Del Negro, C.A., and Gray, P.A. (2013). Understanding the rhythm of breathing: so near, yet so far. Annu. Rev. Physiol. *75*, 423–452.

Findley, T.M., Wyrick, D.G., Cramer, J.L., Brown, M.A., Holcomb, B., Attey, R., Yeh, D., Monasevitch, E., Nouboussi, N., Cullen, I., et al. (2021). Sniff-synchronized, gradient-guided olfactory search by freely moving mice. Elife *10*, 1–39.

Fischler-Ruiz, W., Clark, D., Joshi, N., Devi-Chou, V., Kitch, L., Schnitzer, M.J., Abbott, L.F., and Axel, R. (2021). Olfactory landmarks and path integration converge to form a cognitive spatial map. Neuron *109*, 4036–4049.e5.

Geffen, M.N., Broome, B.M., Laurent, G., and Meister, M. (2009). Neural encoding of rapidly fluctuating odors. Neuron *61*, 570–586.

Gire, D.H., Kapoor, V., Arrighi-Allisan, A., Seminara, A., and Murthy, V.N. (2016). Mice develop efficient strategies for foraging and navigation using complex natural stimuli. Curr. Biol. *26*, 1261–1273.

Grimaud, J., and Murthy, V.N. (2018). How to monitor breathing in laboratory rodents: a review of the current methods. J. Neurophysiol. *120*, 624–632.

Gumaste, A., Coronas-Samano, G., Hengenius, J., Axman, R., Connor, E.G., Baker, K.L., Ermentrout, B., Crimaldi, J.P., and Verhagen, J.V. (2020). A comparison between mouse, *in silico*, and robot odor plume navigation reveals advantages of mouse odor tracking. eNeuro 7, https://doi.org/10.1523/ENEURO.0212-19.2019.

Hepper, P.G., and Wells, D.L. (2005). How many footsteps do dogs need to determine the direction of an odour trail? Chem. Senses *30*, 291–298.

Hopfield, J.J. (1991). Olfactory computation and object perception. Proc. Natl. Acad. Sci. Unit. States Am. *88*, 6462–6466.

Hurst, J.L., and Beynon, R.J. (2004). Scent wars: the chemobiology of competitive signalling in mice. BioEssays News Rev. Mol. Cell. Dev. Biol. *26*, 1288–1298.

Huston, S.J., Stopfer, M., Cassenaer, S., Aldworth, Z.N., and Laurent, G. (2015). Neural encoding of odors during active sampling and in turbulent plumes. Neuron *88*, 403–418.

Jackson, B.J., Fatima, G.L., Oh, S., and Gire, D.H. (2020). Many paths to the same goal: balancing exploration and exploitation during probabilistic route planning. ENeuro *7*, 1–11.

Jacobs, L.F., Arter, J., Cook, A., and Sulloway, F.J. (2015). Olfactory orientation and navigation in humans. PLoS One *10*, 1–13.

Jones, P.W. and Urban, N.N. (2018). Mice Follow Odor Trails Using Stereo Olfactory Cues and Rapid Sniff to Sniff Comparisons. bioRxiv 293746, https://doi.org/10.1101/293746.

Jordan, R., Fukunaga, I., Kollo, M., and Schaefer, A.T. (2018). Active sampling state dynamically enhances olfactory bulb odor representation. Neuron *98*, 1214–1228.

Justus, K.A., Murlis, J., Jones, C., and Cardé, R.T. (2002). Measurement of odor-plume structure in a wind tunnel using a photoionization detector and a tracer gas. Environ. Fluid Mech. *2*, 115–142.

Kepecs, A., Uchida, N., and Mainen, Z.F. (2006). The sniff as a unit of olfactory processing. Chem. Senses *31*, 167–179.

Khan, A.G., Sarangi, M., and Bhalla, U.S. (2012). Rats track odour trails accurately using a multi-layered strategy with near-optimal sampling. Nat. Commun. *3*, 703.

Kim, A.J., Lazar, A.A., and Slutskiy, Y.B. (2011). System identification of Drosophila olfactory sensory neurons. J. Comput. Neurosci. *30*, 143–161.

Lewis, S.M., Xu, L., Rigolli, N., Tariq, M.F., Stern, M., Seminara, A., and Gire, D.H. (2021). Plume dynamics structure the spatiotemporal activity of glomerular networks in the mouse olfactory bulb. Front. Cell. Neurosci. *15*, 633757.

Li, A., Gire, D.H., Bozza, T., and Restrepo, D. (2014). Precise detection of direct glomerular input duration by the olfactory bulb. J. Neurosci. *34*, 16058–16064.

Li, C., Dong, H., and Zhao, K. (2018). A balance between aerodynamic and olfactory performance during flight in Drosophila. Nat. Commun. *9*, 1–8.

Liu, A., Papale, A.E., Hengenius, J., Patel, K., Ermentrout, B., and Urban, N.N. (2020). Mouse navigation strategies for odor source localization. Front. Neurosci. *14*, 1–16.

Mafra-Neto, A., and Cardé, R.T. (1994). Fine-scale structure of pheromone plumes modulates upwind orientation of flying moths. Nature *369*, 142–144.

Marin, A.C., Schaefer, A.T., and Ackels, T. (2021). Spatial information from the odour environment in mammalian olfaction. Cell Tissue Res. *383*, 473–483.

Mathis, A., Mamidanna, P., Cury, K.M., Abe, T., Murthy, V.N., Mathis, M.W., and Bethge, M. (2018). DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. Nat. Neurosci. *21*, 1281–1289.

McAfee, S.S., Ogg, M.C., Ross, J.M., Liu, Y., Fletcher, M.L., and Heck, D.H. (2016). Minimally invasive highly precise monitoring of respiratory rhythm in the mouse using an epithelial temperature probe. J. Neurosci. Methods *263*, 89–94.

Meister, M. (2015). On the dimensionality of odor space. *eLife, 4, e07865*, pp. 1–12. https://doi.org/10.7554/eLife.07865.

Moore, P., and Crimaldi, J. (2004). Odor landscapes and animal behavior: tracking odor plumes in different physical worlds. J. Mar. Syst. *49*, 55–64.

Moore, P.A., and Atema, J. (1991). Spatial information in the three-dimensional fine structure of an aquatic odor plume. Biol. Bull. *181*, 408–418.

Mori, K., Nagao, H., and Yoshihara, Y. (1999). The olfactory bulb: coding and processing of odor molecule information. Science *286*, 711–715.

Murlis, J., Elkington, J.S., and Carde, R.T. (1992). Odor plumes and how insects use them. Annu. Rev. Entomol. *37*, 505–532.

Murlis, J., Willis, M.A., and Cardé, R.T. (2000). Spatial and temporal structures of pheromone plumes in fields and forests. Physiol. Entomol. *25*, 211–222.

Mylne, K.R., and Mason, P.J. (1991). Concentration fluctuation measurements in a dispersing plume at a range of up to 1000m. Q. J. R. Meteorol. Soc. *117*, 177–206.

Parabucki, A., Bizer, A., Morris, G., Munoz, A.E., Bala, A.D.S., Smear, M., and Shusterman, R. (2019). Odor concentration change coding in the olfactory bulb. eNeuro. https://doi.org/10.1523/ENEURO.0396-18.2019.

Poo, C., Agarwal, G., Bonacchi, N., and Mainen, Z.F. (2021). Spatial maps in piriform cortex during olfactory navigation. Nature *601*, 595–599.

Porter, J., Craven, B., Khan, R.M., Chang, S.J., Kang, I., Judkewitz, B., Volpe, J., Settles, G., and Sobel, N. (2007). Mechanisms of scent-tracking in humans. Nat. Neurosci. *10*, 27–29.

Radvansky, B.A., and Dombeck, D.A. (2018). An olfactory virtual reality system for mice. Nat. Commun. *9*, 839.

Radvansky, B.A., Oh, J.Y., Climer, J.R., and Dombeck, D.A. (2021). Behavior determines the hippocampal spatial mapping of a multisensory environment. Cell Rep. *36*, 109444.

Raiser, G., Galizia, C.G., and Szyszka, P. (2017). A high-bandwidth dual-channel olfactory stimulator for studying temporal sensitivity of olfactory processing. Chem. Senses *42*, 141–151.

Rajan, R., Clement, J., and Bhalla, U. (2006). Rats smell in stereo. Science *311*, 666–670.

Rebello, M.R., McTavish, T.S., Willhite, D.C., Short, S.M., Shepherd, G.M., and Verhagen, J.V. (2014). Perception of odors linked to precise timing in the olfactory system. PLoS Biol. *12*, e1002021.

Reddy, G., Murthy, V.N., and Vergassola, M. (2022a). Olfactory sensing and navigation in turbulent environments. Annu. Rev. Condens. Matter Phys. *13*, 191–213.

Reddy, G., Shraiman, B.I., and Vergassola, M. (2022b). Sector search strategies for odor trail tracking. Proc. Natl. Acad. Sci. U. S. A. *119*, 1–8.

Reeder, P.B., and Ache, B.W. (1980). Chemotaxis in the Florida spiny lobster, Panulirus argus. Anim. Behav. *28*, 831–839.

Reisert, J., Golden, G.J., Matsumura, K., Smear, M., Rinberg, D., and Gelperin, A. (2014). Comparing thoracic and intra-nasal pressure transients to monitor active odor sampling during odor-guided decision making in the mouse. J. Neurosci. Methods *221*, 8–14.

Riffell, J.A., Sanders, E., Hinterwirth, A.J., Abrell, L., Shlizerman, E., Medina, B., and Kutz, J.N. (2014). Flower discrimination by pollinators in a dynamic chemical environment. Science *344*, 1515–1518.

van Rijzingen, I.M.S., Gispen, W.H., and Spruijt, B.M. (1995). Olfactory bulbectomy temporarily impairs Morris maze performance: an ACTH(4-9) analog accellerates return of function. Physiol. Behav. *58*, 147–152.

Schmuker, M., Bahr, V., and Huerta, R. (2016). Exploiting plume structure to decode gas source distance using metal-oxide gas sensors. Sensor. Actuator. B Chem. *235*, 636–646.

Schwenk, K. (1994). Why snakes have forked tongues. Science *263*, 1573–1577.

Shraiman, B.I., Siggia, E.D., Shralman, B.I., and Siggia, E.D. (2000). Scalar turbulence. Nature *405*, 639.

Shusterman, R., Smear, M.C., Koulakov, A.A., and Rinberg, D. (2011). Precise olfactory responses tile the sniff cycle. Nat. Neurosci. *14*, 1039–1044.

Smear, M., Shusterman, R., O'Connor, R., Bozza, T., and Rinberg, D. (2011). Perception of sniff phase in mouse olfaction. Nature *479*, 397–400.

Smear, M., Resulaj, A., Zhang, J., Bozza, T., and Rinberg, D. (2013). Multiple perceptible signals from a single olfactory glomerulus. Nat. Neurosci. *2013*, 1687–1691.

Stierle, J.S., Galizia, C.G., and Szyszka, P. (2013). Millisecond stimulus onset-asynchrony enhances information about components in an odor mixture. J. Neurosci. *33*, 6060–6069.

Szyszka, P., Stierle, J.S., Biergans, S., and Galizia, C.G. (2012). The speed of smell: odor-object segregation within milliseconds. PLoS One *7*, 4–7.

Szyszka, P., Gerkin, R.C., Galizia, C.G., and Smith, B.H. (2014). High-speed odor transduction and pulse tracking by insect olfactory receptor neurons. Proc. Natl. Acad. Sci. Unit. States Am. *111*, 16925–16930.

Tariq, M.F., Lewis, S.M., Lowell, A., Moore, S., Miles, J.T., Perkel, D.J., and Gire, D.H. (2021). Using head-mounted ethanol sensors to monitor olfactory information and determine behavioral changes associated with ethanol-plume contact during mouse odor-guided navigation. eNeuro *8*, https://doi.org/10.1523/ENEURO.0285-20.2020.

Thesen, A., Steen, J.B., and Døving, K.B. (1993). Behaviour of dogs during olfactory tracking. J. Exp. Biol. *180*, 247–251.

Uchida, N., and Mainen, Z.F. (2003). Speed and accuracy of olfactory discrimination in the rat. Nat. Neurosci. *6*, 1224–1229.

Vergassola, M., Villermaux, E., and Shraiman, B.I. (2007). "Infotaxis" as a strategy for searching without gradients. Nature *445*, 406–409.

Verhagen, J.V., Wesson, D.W., Netoff, T.I., White, J.A., and Wachowiak, M. (2007). Sniffing controls an adaptive filter of sensory input to the olfactory bulb. Nat. Neurosci. *10*, 631–639.

Vickers, N.J. (2000). Mechanisms of animal navigation in odor plumes. Biol. Bull. *198*, 203–212.

Wachowiak, M. (2011). All in a sniff: olfaction as a model for active sensing. Neuron *71*, 962–973.

Wallace, D.G., Gorny, B., and Whishaw, I.Q. (2002). Rats can track odors, other rats, and themselves: implications for the study of spatial behavior. Behav. Brain Res. *131*, 185–192.

Weissburg, M.J., Dusenbery, D.B., Ishida, H., Janata, J., Keller, T., Roberts, P.J.W., and Webster, D.R. (2002). A multidisciplinary study of spatial and temporal scales containing information in turbulent chemical plume tracking. Environ. Fluid Mech. *2*, 65–94.

Welker, W.I. (1964). Analysis of sniffing of the albino rat. Behaviour *22*, 223–244.

Wesson, D.W., Donahou, T.N., Johnson, M.O., and Wachowiak, M. (2008). Sniffing behavior of mice during performance in odor-guided tasks. Chem. Senses *33*, 581–596.

Wu, Y., Chen, K., Ye, Y., Zhang, T., and Zhou, W. (2020). Humans navigate with stereo olfaction. Proc. Natl. Acad. Sci. U. S. A. *117*, 16065–16071.

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