Odor Memories: The First Sniff Counts

A new study which combined associative memory tests with functional magnetic resonance imaging of the brain has identified a potential neural correlate of the special association that is formed when an odor is first paired with a visual object.

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Odor memories in humans are likely to be processed by a separate memory system with distinctive features that make odor memories different from visual or auditory memories [1,2]. Two peculiarities of odor memory fascinate scientists and poets alike: the vividness of odor-evoked memories; and the difficulty of remembering a smell. Odor-evoked memories are more vivid and emotional than memories evoked by stimuli in other modalities. Because the best known description of this phenomenon is found in Marcel Proust's novel *In Search of Lost Time*, this phenomenon is often called 'Proust effect'. On the other hand, memories of odors *themselves* are elusive. Some have argued that smells cannot be remembered at all — Vladimir Nabokov wrote in his debut novel *Mary* "Memory can restore to life everything except smells".

Early research into the curious nature of smell memories relied on self-reported smell experiences and behavioral measures of odor memories. Functional brain imaging offers a new tool to objectively study how we remember odors by mapping activity in the brain while we remember. In this issue of *Current Biology*, Yeshurun *et al.* [3] report a study in which functional magnetic resonance imaging was used on subjects performing associative memory tests to study odor memories. Specifically they address the psychological phenomenon called 'resistance to interference' [4], or rather: what makes the first association of an odor with an object stronger than later associations of the same odor with a different object? Their results suggest that the hippocampus is involved in the formation of persistent odor associations.

Resistance to interference of odor memories was first described by Lawless and Engen [5], who showed that over a two-week period the first of two associations to an odor were retained far better than the second. They concluded that "If the storage system offers only one permanent link on a first-come first-served basis, subsequent learning will have little effect. The original associations will persist as long as they are unaffected by simple time-dependent decay processes". In another set of experiments, Zucco [1] showed that the persistence of first-learned associations is specific for odor memories in an experiment that exposed subjects to olfactory, visual, or acoustic stimuli and then asked to rate the pleasantness of different stimuli. Afterwards, the subjects had to recognize the original stimuli. Their ability to recognize odors was not impaired by having to sniff a different set of odors between learning and retrieval; however, their ability to recognize sounds or pictures *was* impaired by distracting sounds or pictures.

Psychophysical experiments that demonstrate the persistence of first-learned odor associations agree well with studies that suggest that the very first odor experiences in a human life in the womb and during breast-feeding persist throughout life. Positive associations with odors in the amniotic fluid and in breast milk that reflect the mother's diet have been shown to persist for several decades [6,7]. This process — the resistance to interference of a positive association with a food odor — may form the foundation of cultural and ethnical food preferences that are difficult to change later in life.

In the experiments reported by Yeshurun *et al.* [3], subjects had to associate the same visual objects first with one set of stimuli and later on the same day with a different set of stimuli. They used four groups of stimuli: pleasant odors (lemon or peach), unpleasant odors (manure or fish), pleasant sounds (guitar or waterfall), and unpleasant sounds (chalk or drill). A week later, the subjects were presented with the visual objects again and had to indicate which smell or sound was brought to mind first by the different visual objects. In addition to these behavioral measures, brain activity was imaged while subjects looked at the visual objects and recalled the associated odor or sound.

The brain imaging revealed that the hippocampus was more active when the subjects associated the visual object with the odor that was paired with it first than when they associated the visual object with the odor that was paired with it later. This activity in the hippocampus could be due to the neuronal processes that make first-learned odor associations persistent. This hypothesis is strongly supported by the finding that the effect is not found with sounds. The hippocampal activation is *not* stronger when the first-learned sound is associated with the visual object than when the sound that was later learned is used. It is therefore likely that Yeshurun *et al.* [3] have discovered the neuronal correlates of the special character of first-learned odor associations.

On the basis of previous research [1,5] and the new brain imaging data [3] one would expect that the first-learned odor has formed a stronger association than the odor that was associated later. However, the situation is complicated by the fact that the subjects in whom neuronal correlates of the special character of first odor associations were identified did not show behavioral evidence that first odor associations are indeed special — they showed no difference in the strength of association. Instead, Yeshurun *et al.* [3] discovered that the *pleasantness* of the associated stimulus has a strong influence on its resistance to interference. Associations of visual objects with unpleasant odors or sounds are much more persistent than associations with pleasant odors or sounds. This very large effect may well overshadow any effect of sensory modality in the experimental design of Yeshurun *et al.* [3]. This finding also qualifies the previous research into resistance to interference in which the stimuli were not balanced for pleasantness.

In our subjective every-day experience, it is apparent that odor memories are fundamentally different from other memories; however, the phenomenon has proved to be notoriously difficult to study under controlled laboratory conditions. Yeshurun *et al.*'s [3] approach of combining associative memory tests with functional magnetic resonance imaging allowed them to study how odor memories are different at the neuronal level. The identification of brain regions implicated in the formation of first-learned associations between odors and objects opens the door for research that will explicate the role of olfactory processing, emotion, and long-term memory in this intriguing phenomenon.

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DOI: 10.1016/j.cub.2009.09.046

Phagocytosis: Invitation to a Feast

How does a macrophage find an apoptotic cell for ingestion? A recent study shows that ATP and UTP released from the dying cell serve as important chemoattractants for macrophages and are key contributors to the efficient clearance of apoptotic cells *in vivo*.

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The deletion of excess, previously used, unwanted or damaged cells is essential in metazoa for development, metamorphoses, tissue homeostasis, responses to injury and for the development and regulation of innate and adaptive immunity. It is achieved by the induction of various forms of programmed cell death (PCD), of which apoptosis is the best known. Critical to the overall process, however, is the subsequent recognition and removal of the dying cell in a manner that can distinguish between PCD and cell death induced by external agents, toxins, physical damage or, particularly, infectious agents. For the former, a quiet efficient removal is the norm whereas, for the latter, the animal needs to (and does) mount a protective response that can encompass engagement of the various innate and adaptive immune processes with which it is endowed. In mammals, this is represented by the commonly noted but also overly simplified distinction between the non-inflammatory and non-immunogenic response to apoptotic cells *versus* the pro-inflammatory and pro-immunogenic effects of cells dying by non-PCD (often loosely described as necrotic) pathways.

Dying cells are removed by uptake into phagocytic cells. In simpler invertebrates, such as nematodes, this is largely achieved by recognition by, and uptake into, neighboring tissue cells, and in fact this near-neighbor removal can also occur in mammals, as exemplified by post-lactation remodeling of the mammary gland or, for that matter, the constant daily removal of retinal outer rod segments, each achieved by epithelial cells. But in animals with more professional and mobile phagocytes, these have taken on the major role in recognition, phagocytosis and digestion of the cells undergoing PCD. Many studies have addressed these processes and shown them to involve unique mechanisms of uptake (often involving ingestion of intact cells that can be as large as 20μm in diameter), unique sets of receptors and bridge molecules (opsonins), and unique intracellular signaling pathways, with remarkable evolutionary conservation of the entire process [1–3]. However, the important question of how the mobile phagocyte finds (is attracted to) the cells undergoing PCD has received much less attention. This is the subject addressed in the recent paper by Elliot *et al.* [4] which reports identification of the nucleotides ATP and UTP as prime candidates for what have been colloquially called 'find me' signals, following the various use of 'eat me' and 'don't eat me' for apoptotic cell uptake or inhibitory signals, respectively.

The approach taken by Elliot *et al.* [4] was to show release of chemotactic factors for macrophages from apoptotic cells *in vitro*, confirm with macrophage attraction into skin pouches in mice, identify candidate molecules released from the apoptotic cells and finger the likely receptors on macrophages that were responsible. To complete the story, they showed that removal of the factors or blockade of the candidate receptors reduced clearance of apoptotic cells in an *in vivo* model cell removal system following massive lymphocyte apoptosis in the thymus, which was first described by Scott *et al.* [5]. Their extensive series of experiments led to the identification of ATP and UTP as responsible molecules for apoptotic cell attraction of macrophages. These nucleotides are released from a variety of cells undergoing apoptosis in a caspase-dependent fashion, apparently before the cells undergo loss of plasma membrane permeability. They induce macrophage chemotaxis *in vitro* and *in vivo*, and apoptotic cell supernate induction of the macrophage attraction was shown to be abrogated by introduction of apyrase to hydrolyze the nucleotides. Overexpression of CD39 — a mammalian ecto-enzyme involved in natural nucleotide inactivation — was shown to have a similar blocking effect.