Finally, the most likely explanation for the difference between the studies is that in the previous experiments [10–12], the movement patterns of the animals were quite isotropic — leading to isotropic, circular place fields — whereas in the experiments of Hayman *et al.* [2], the movement patterns were highly anisotropic, with mostly horizontal movement components (Figure 1A, blue lines). Similarly, the visual inputs in previous studies seemed quite isotropic [10–12], while the visual inputs in the study by Hayman *et al.* [2] were quite anisotropic, with gray-colored uniform floors that provided little visual information in the vertical dimension, in contrast to the walls that were covered with many objects and provided a rich set of cues in the horizontal dimension [2]. This asymmetry in sensory inputs and in behavior may have led to the anisotropic, vertically elongated firing fields of place cells and grid cells in the study by Hayman *et al.* [2] (Figure 1A). In other words, the hypothesis is that isotropic movement patterns and isotropic sensory inputs lead to isotropic spatial representation [10,12], while anisotropic movement patterns and anisotropic sensory inputs lead to anisotropic spatial firing patterns [2].

How could one test this hypothesis? One possibility would be to perform recordings from place cells and grid cells in a mammal that can move freely and isotropically through real three-dimensional space: Namely, record from the brains of flying bats. On two-dimensional planes, place cells in bat hippocampus and grid cells in bat entorhinal cortex exhibit remarkably similar spatial activity patterns to those of two-dimensional place cells and grid cells in rats [10,16]. In flight, bats exhibit highly complex three-dimensional flight maneuvers [17,18]. Therefore, the prediction is that in bats flying freely in three-dimensional space (Figure 1B, blue line), the three-dimensional place fields of hippocampal neurons should be isotropic, with roughly spherical shape (Figure 1B). Such experiments require the development of either wired or wireless telemetric recording techniques in freely flying bats — methods which we recently developed in our laboratory [19]. It remains to be seen whether this prediction for isotropic firing fields indeed holds true in the case of three-dimensional spatial representation in the brain of freely flying bats.

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Face Recognition: Vision and Emotions beyond the Bubble

A new study of how neurons in the human amygdala represent faces and their component features argues for a holistic representation.

Hanlin Tang[1] and Gabriel Kreiman[1,2,3]

Visual input from the retina travels through a cascade of processes in the neocortex to the highest echelons of the brain, eventually feeding into areas that govern memory, emotion, cognition and action. An important step to explaining these higher brain functions is to first understand and quantitatively characterize the neuronal circuits behind the transformation of the pixel-like visual input to the complex behaviorally relevant format in higher brain centers.

As reported recently in *Current Biology*, Rutishauser *et al.* [1] courageously attacked this question by recording the activity of individual neurons in the human brain while subjects view and act upon images of faces. The researchers focussed their study on the amygdala, a region of the brain that receives direct visual input from the inferior temporal cortex and plays a central role in processing emotions [2]. Higher brain centers that govern complex behavior are typically difficult to study, and the amygdala is no exception. Studies in rodents and non-human

primates can take advantage of electrophysiological techniques to monitor the activity of individual neurons, but it is not always trivial to design behavioral paradigms that tap into the rich repertoire of human emotions. Non-invasive studies of the human amygdala suffer from poor spatial and/or temporal resolution. Rutishauser *et al.* [1] combined the best of both worlds by examining neuronal activity in epileptic patients in whom electrodes had been implanted for clinical reasons [3,4]. This type of recording can provide insights about human cognition at the level of individual neurons and local circuits.

Previous single unit studies have revealed that neurons in the primate amygdala (in humans and monkeys) respond to complex visual shapes, including faces and other stimuli [5–8]. However, it was not clear whether these responses require visual presentation of the whole stimulus, or whether certain parts or features of the stimulus are sufficient to elicit a selective response. Because the amygdala is involved in recognizing emotions, the integration of different features into a whole percept may provide clues about how emotions are processed. Rutishauser *et al.* [1] hypothesized that the representation in the amygdala may have 'holistic' characteristics: that is, that neurons might be particularly sensitive to whole stimuli as opposed to stimulus parts. The authors used an experimental paradigm in which face images are presented through 'bubbles' such that only partial information is available to the viewer, who has to make a categorical discrimination based on the input.

What do neurons in the amygdala say about all this holistic business? Rutishauser *et al.* [1] found that several amygdala neurons prefer whole stimuli as opposed to specific parts or features. These neurons show surprising sensitivity in their firing rate responses to small degrees of occlusion in the stimuli, suggesting a 'holistic' representation. The responses are not necessarily monotonic and often defy our intuitions. In fact, the firing activity in response to stimulus parts does not reveal any immediately obvious relationship to the responses to the whole stimuli: the authors argue that the former cannot predict the latter. Intriguingly, in many instances, more information leads to smaller responses.

Given these puzzling observations, it is worth pondering the visual inputs to the amygdala and the degree to which the incoming information reflects features or wholes or both. Visual shape information is conveyed to the amygdala primarily through regions in inferior temporal cortex in monkeys [9] (less is known about the detailed neuroanatomical connections in humans). One possibility is that the input provides information about features and is combined in the amygdala in order to interpret the emotions conveyed by the whole stimulus. This notion is consistent with the results of several neurophysiological recordings in the macaque monkey inferior temporal cortex, where neurons seem to respond to complex shapes and features (for example, [10–13] among many others). Alternatively, regions of inferior temporal cortex that feed into the amygdala may contain neurons that share some properties with the ones reported by Rutishauser *et al.* [1], such as enhanced responses to whole objects [14].

It is not easy to interpret the neurophysiological responses without the aid of clear theoretical and computational models. The problem of object completion from partial information has received significant attention in the computational neuroscience literature. Object completion is relevant to the current study because the images were seen through bubbles, making object recognition from partial information a necessary step for a putative 'holistic' representation. Attractor networks show a remarkable ability to complete patterns by driving activity according to well-specified dynamical rules that guide the system from arbitrary starting points towards stored memories [15].

Some authors have speculated that the neuronal responses in the hippocampus are reminiscent of the dynamical patterns described by attractor networks [16]. The extent to which these similarities extend to the amygdala are not clear. These attractor network models rely on massive recurrent connectivity and contrast with other computational architectures where features are combined in purely feed-forward hierarchical fashion (for example, [17,18]). Several computational models of the ventral visual stream progressively build neurons that respond to more complex features using input from the parts represented in the previous layer [17–20]. It is conceivable (but far from clear) that hierarchical feature-based representations throughout the ventral visual stream encounter attractor network architectures at the highest echelons. It will be interesting and important for the field to reflect upon the type of computational principles that can give rise to the variety and non-monotonic nature of the responses reported by Rutishauser *et al.* [1].

The computational models also highlight the difficulties inherent in definitions about wholes and parts. In the current study [1], as in many other studies, there is an anthropomorphic distinction between wholes and parts. Further inspection shows that these definitions are far from trivial. Isn't a face a part of a whole individual? Or why not consider the eyes as a separate whole? Is 'F' a whole letter or is it part of the letter 'E'? Perhaps the distinction between features and wholes can be accounted for at least partly, by experience with particular combinations of features that tend to appear together in certain configurations. Simple null models may not know about 'whole objects', often work in feature spaces that are indifferent to the charm of faces and may not necessarily be able to distinguish emotions in the images. Inasmuch as these null models fail to explain the bewildering complexity and beauty of the neurophysiology in the amygdala, the current study elegantly forces us to go back and build more elaborate theories and algorithms.

One of the nice aspects of doing science is that good work can lead to more work. Thus, several questions emerge from the work of Rutishauser *et al.* [1]. As outlined above, the definition of 'wholes' and 'parts' is not trivial. It seems important to further understand the visual input to areas such as the amygdala so that we can better describe what computational properties are unique to the amygdala and which ones are

inherited from previous processing. The authors focus on face images, but the study leaves open the possibility that the amygdala can have similar responses to non-face objects. Is the "holistic" nature of the representation limited to faces [14]? The dynamics of the neuronal responses may provide further insights regarding the computational principles behind recognition and object completion. What type of computational models can give rise to the non-intuitive responses described in this study?
The inspiring work of Rutishauser *et al.* [1] opens the doors to a rich set of questions that deserve further investigation.

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Cell–Cell Junctions: α-Catenin and E-Cadherin Help Fence In Yap1

Metazoan cells translate adhesive events with neighbors into anti-proliferative signals in the nucleus. The cadherin–catenin adhesion complex has long been suspected of playing a key role in this process, and three recent papers suggest that it does so by modulating subcellular localization of the Hippo pathway component Yap1.

Brian S. Robinson and Kenneth H. Moberg*

Most metazoan cells spend their lives in close apposition with adjacent cells and must use a variety of communication tools to organize group activities and set standards for communal living. One key to a stable cellular neighborhood is preventing cells from over-proliferating and crowding out neighbors. A model of cellular crowd control has evolved, termed 'contact inhibition', in which intercellular adhesion events block proliferation. Cancer cells are rogues that by and large fail to abide by this rule. An understanding of the mechanisms underlying contact inhibition, and why certain mutations allow cancer cells to avoid it, has, however, remained incomplete. Three recent papers [1–3] now help to fill this gap by identifying E-cadherin and α-catenin, two protein components of the cadherin–catenin adhesion complex, as regulators of Yes-associated protein-1 (Yap1), a major oncogenic component of the Hippo tumor suppressor network. In doing so, these groups have illuminated what could be a central element of the contact inhibition mechanism.

Yap1 and Hippo

Yap1 and its homolog TAZ (transcriptional co-activator with PDZ-binding motif) are the main targets of the vertebrate Hippo growth regulatory pathway, which was first identified in *Drosophila* and shown to be a key regulator of organ size and tumorigenesis in other organisms, including vertebrates [4]. Canonical Hippo signals in vertebrate cells are transduced through two sequentially acting sets of kinases — Mst1 and Mst2 (Mst1/2) and Lats1 and Lats2 (Lats1/2) — to regulate phosphorylation of Yap1. Phosphorylated Yap1 (p-Yap1) is sequestered in the cytoplasm by 14-3-3 proteins [4,5], while unphosphorylated Yap1 shuttles into the nucleus where it interacts with context-specific partners to drive expression of pro-proliferative genes.