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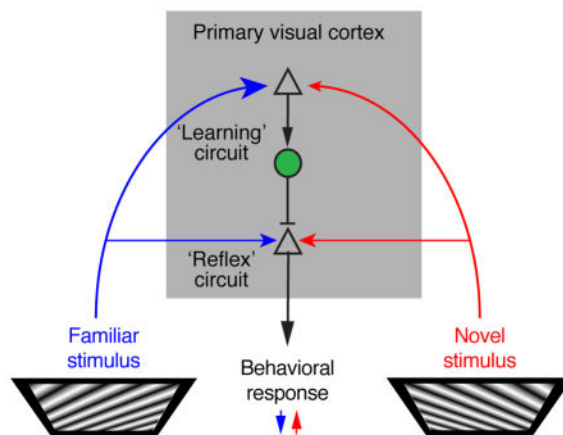
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*Curr Opin Neurobiol.* 2015 December ; 35: 57–65. doi:10.1016/j.conb.2015.06.008.**Visual recognition memory: A view from V1****Sam F. Cooke and Mark F. Bear**

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**Abstract**

Although work in primates on higher-order visual areas has revealed how the individual and concerted activity of neurons correlates with behavioral reports of object recognition, very little is known about the underlying mechanisms for visual recognition memory. Low-level vision, even as early as primary visual cortex (V1) and even in subjects as unsophisticated as rodents, promises to fill this void. Although this latter approach sacrifices interrogation of many of the most astounding features of visual recognition, it does provide experimental constraint, proximity to sensory input, and a wide range of interventional approaches. The tractability of rodent visual cortex promises to reveal the molecular mechanisms and circuits that are essential for a fundamental form of memory.

**Graphical Abstract**

Visual object recognition is a deeply studied phenomenon, regarded as perhaps the major adaptive function of vision, our dominant sense. This complex process depends upon innate

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The authors declare no conflict of interest.

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features of our brain that, through evolution, have been shaped by the statistics of our environment. It also depends upon the effects of visual experience and as such provides a wonderful example of how the brain stores and retrieves memory. The majority of work on object recognition has been carried out in higher-order visual cortex of monkeys, and has focused on neural correlates of what is known as high-level vision, characterized by the maximum tolerance to variation in viewing conditions. This feature, which is often described as invariance, is indispensable for the successful exploration of natural environments. As yet, it is also an unattainable marvel for those building machines to perform sophisticated object recognition for real-world applications.

Here we do not address this issue of invariance and how it is achieved, because this topic has been covered in great depth previously [1–6]. Instead, we will focus on object recognition as a memory process that, in its most simple form, may provide insight into how information is stored in the neocortex for long periods of time in a retrievable form. There are, nevertheless, several key findings from high-level visual recognition in primates that must be discussed before focusing on lower-level forms encoded in rodent V1.

### **The visual ventral stream: An object analyzer**

The cortical visual system in primates has been divided into dorsal and ventral streams, serving different roles in visual processing [7–9]. Here we focus on the ventral stream, which runs from the occipital cortex through multiple nodes in the inferior temporal cortex and is required for object recognition. The headwater of the stream is V1, which receives visual information, relayed by the lateral geniculate nucleus (LGN), from the retina. Neurons within V1 respond selectively to visual primitives such as orientation, direction and spatial frequency, and have a fine-grained retinotopic organization [10]. Representations of visual stimuli are thought to be gradually built in a feed-forward manner through V2 [11], V4 and into a series of sub-regions of infero-temporal cortex (IT), considered the highest order purely visual cortical area [1, 3]. IT feeds visual information to perirhinal cortex (PRC), an important site of multimodal sensory integration [12]. At each stage of the ventral stream the neural response latency to visual stimulation increases due to more intervening synapses [13], receptive field sizes becomes larger due to convergence of inputs from multiple retinotopic positions [14] and tuning becomes progressively more and more complex for selected combinations of features, reaching its zenith in IT [2]. Thus, while neural responses in V1 are a fair approximation of the pattern of light landing on the retina (although see [15–18]), in IT they represent individual objects in the outside world, responding with a degree of tolerance that allows recognition of the same object even when observed from two viewpoints that cast strikingly different patterns of light upon the retina. The focus of research in understanding recognition memory has therefore, not surprisingly, been in higher order areas.

### **High-level visual recognition**

Lesions limited to IT result in object recognition deficits [19]. Although there is heterogeneity in the response properties of neurons at every level of IT [20, 21], neurons generally respond to progressively more complex stimuli along a posterior-anterior axis [2].

The anterior tip of IT is now hypothesized to store prototype representations of individual objects [22]. The most complex of all stimuli that elicit preferential responses from neurons in IT are faces [23–25]. Some ‘face’ cells respond best to individual facial features presented alone, such as eyes, while others require that several facial features be presented simultaneously in a normal configuration. Importantly, though, there is little evidence that individual IT neurons respond to a shape, object, face, or individual in an entirely invariant fashion [1, 3] (but see ref [26]). The prevailing view is that representations of individual objects are generated by activity distributed among large numbers of neurons within IT, combining features, configurations and viewpoints through an as yet not fully understood process of binding to approximate invariant recognition [27, 28]. It is argued that this distributed storage system allows for a far greater memory capacity, ease of retrieval, and pattern completion that enables generalization and a high resistance to noise [29].

Monkeys are capable of selecting between two familiar stimuli based on how recently they were seen. This recency judgment, a form of working memory, correlates with a suppression of activity of IT cells to previously viewed stimuli [30, 31], in some cases regardless of intervening stimulus presentations [32, 33]. IT responses may also be suppressed to familiar stimuli relative to novel stimuli [32–34]. Such reductions in response rate occur independently of reward-expectation or behavior, supporting the idea that neurons in IT can serve as adaptive filters for familiar objects. In theory, this filtering would favor the passage of information about unexpected or novel objects [32]. What happens to these individual neurons in the long-term is not known because it is not possible to record from the same neuron from day to day. However, evidence for the continuance of response suppression over days comes from comparisons of novel and familiar stimulus sets. In these cases, novel stimuli evoke a greater response than do familiar stimuli in neurons most selective for those individual stimuli [33, 34].

Although monkeys are valuable subjects for gaining understanding of the neural correlates of high-level recognition memory, there is still much to be understood about the underlying physiology and molecular mechanisms. One obstacle is identification of the site of underlying plasticity. Modifications of electrical activity in any area of cortex may simply be a read-out of changes occurring elsewhere, and this problem is compounded as more synapses intervene between stimulus and response. To gain more insight into mechanism, there is an obvious benefit to studying rodents because their cortical wiring diagrams are simpler and the range of experimental approaches is far greater.

## **A ventral visual stream in rodents?**

There is now good evidence that rats, at least, are capable of something close to invariant object recognition [35][36]. There is also growing experimental evidence for the existence of separated visual cortical pathways in rodents with a hierarchical arrangement similar to that seen in primates [37–43], although further work is required to understand the degree of homology [41, 42, 44–46]. Many experiments on object recognition in rodents have focused on PRC, which, although far from being purely visual, inherits object selectivity through vision from the ventral visual stream in primates [47]. A large range of experiments have been conducted testing the impact of PRC lesions on object perception and recognition

memory in rodents [48, 49] and observing the response of neurons in this area to the presentation of objects, both familiar and novel. Many of these experiments have eschewed the operant conditioning approaches that were initially used to tackle the problem [50][51, 52] in favor of variations on an assay of long-term visual habituation that takes advantage of rodents' natural tendency to explore novelty over familiarity (Figure 1).

The stimuli of greatest significance to animals are those that either signal reward or punishment. Novel objects have the potential to deliver both and, therefore, animals attend to them. Likewise, animals ignore familiar objects that are repeatedly experienced without consequence. This familiarity is an important form of memory and serves as an alternative to operant conditioning as a means to understand recognition processes. In rats and mice, familiar object recognition has emerged as a robust and relatively high-throughput means of studying recognition (e.g. [53, 54]). This assay relies upon preferential exploration of a novel object that is presented at the same time as a familiar object. It is an advantageous experimental approach because it relies on a pervasive and spontaneously occurring behavior. In addition, novel object exploration requires only a brief period of habituation to the apparatus and familiarization with one object prior to a test of memory. There is no requirement for the formation of reliable association between stimuli/objects and reward or punishment, which can take a long time to develop in rodents, particularly in mice [55, 56]. The PRC is required for discrimination of novel from familiar stimuli [48, 49]. In anesthetized or head-fixed awake rats, visual presentations of familiar objects evoke less activity in PRC neurons than novel objects, and these neurons exhibit suppressive effects of recency [57], echoing observations made in monkey IT [32–34, 58]. Models of how this may occur invoke Hebbian long-term potentiation (LTP) of feed-forward inhibition [59] or synaptic long-term depression (LTD) [60]. The weight of evidence suggests that an LTD-like process is involved as blockade of metabotropic glutamate receptors in PRC, which are necessary for a form of LTD [61], prevents long-term familiar object recognition [62] and LTD of this sort is occluded in *ex vivo* preparations of PRC after object exploration [63]. The participation of LTD in familiarity is consistent with the idea of adaptive filters put forward by Miller, Li and Desimone for primates [32].

### Early visual cortex: Perception or memory?

Based on lesion experiments in rats, Karl Lashley proposed that all of neocortex participates equally in memory storage [64]. However, a visual memory obviously cannot be formed without sight. Lesions of primary sensory cortices may have their apparent effect on memory due solely to a profound impact on perception, not a loss of stored information. This viewpoint prevails today based on a sizeable body of work in monkeys: These studies led to the concept that posterior, lower-order elements of the ventral visual pathway, such as V1 and V2, were immutable feature detectors required for object perception but not memory, while anterior, higher-order regions, such as IT and PRC, were required for memory rather than perception [65–68]. However, there is little that is unique to higher-order visual cortical areas to suggest that they are any more plastic or well suited to information storage than V1 and there are those who disagree with the concept of specialized memory systems in the brain [69]. Indeed, there is now evidence that primary sensory cortices are highly plastic in adults and capable of storing memory (e.g. [18, 70]). It

is perhaps true that under real-world conditions, the burden on higher-order recognition memory is greater than that on lower-order. The large range of viewpoints and conditions tolerated by neurons in IT and PRC in recognizing objects is more useful in most situations than the complete lack of invariance that neurons in V1 exhibit. However, animals will use lower level strategies if they are useful [71] and the participation of lower order areas in these types of recognition tasks is born out by experimental observations [72]. The major advantage of studying rodent visual recognition in general, and low level visual cortex in particular, is the opportunity to identify the precise locus and mechanisms of cortical memory encoding.

### Orientation-selective habituation: Recognition memory at its simplest

Mice do not have excellent vision [73] but they use vision as a major sense in exploring their environment [74]. In an open arena flanked by computer monitors, mice will spontaneously orient toward and explore the monitor that displays a novel visual stimulus, *e.g.*, a high contrast, phase reversing grating of a particular orientation [75]. Interest in this stimulus, which predicts neither reward nor punishment, wanes with repeated exposure over several days. However, subsequent presentation of the same grating with a novel orientation is sufficient to again trigger active exploration. This phenomenon has been termed orientation-selective habituation (OSH), and serves as a convenient behavioral readout of visual recognition of the familiar stimulus.

Phase reversing, oriented gratings reliably evoke neural responses in V1 which can be measured with either unit recordings or visual evoked potentials (VEPs). Simultaneous recording of units and VEPs with electrodes in layer 4 of mouse V1 confirms that the magnitude of the evoked potential, reflecting excitatory synaptic currents, is well correlated with peak firing rate. Thus VEPs, which can be easily recorded over days in awake animals using chronically implanted electrodes, offer a convenient measure of cortical responsiveness to visual stimuli. Recordings of VEPs in awake head-fixed mice viewing the oriented gratings previously viewed in the open arena reveal, perhaps unexpectedly, that the familiar stimulus orientation evokes a substantially *larger* response than does a novel orientation. This phenomenon has been called stimulus-selective response potentiation (SRP).

Head fixation is used to record VEPs because it gives the experimenter good control of visual stimulation parameters, *e.g.*, spatial frequency and orientation. Head fixed mice also respond behaviorally to presentation of novel gratings with movements of the forepaws, probably reflecting the innate orienting response. These movements, termed vidgets (visually induced fidgets) can be simply measured with a piezo-electrical device. Daily recordings of vidgets and VEPs in V1 in response to the same stimuli demonstrate the timecourse of OSH and SRP (figure 2). After several daily sessions, a familiarity test is performed by comparing responses to the experienced and a novel stimulus orientation. Vidgets are reduced and VEPs are increased in response to the familiar stimulus relative to the novel.

SRP in mouse V1 has been studied extensively following its initial description in 2006 [76–80]. This form of plasticity features a pronounced increase in the magnitude of VEPs and unit firing in layer 4 of the binocular region of V1 and shares core molecular features with the experimental phenomenon of LTP [76, 78]. Induction and expression of SRP occur locally in V1. It is prevented by manipulations of NMDA receptors and AMPA receptor trafficking that are restricted to V1 [75, 76] and it is reversed by local V1 microperfusion of the ZIP peptide [78] which also reverses LTP [81], albeit via poorly understood mechanisms [82–84].

The observation that SRP and OSH occur simultaneously in response to the same visual experience begs the obvious question of whether they are different manifestations of the same underlying plasticity in V1. Three main lines of evidence support the hypothesis that SRP and OSH share mechanisms. First, similar to SRP, OSH can be induced selectively through one eye, indicating that the supporting plasticity occurs prior to integration of input from the two eyes. Second, V1-specific manipulations of NMDA receptors prevent OSH as well as SRP. Third, infusion of the ZIP peptide into V1 renders mice unable to discriminate familiar and novel oriented stimuli. These findings place the mechanism for encoding and expression of OSH in V1.

In principle, a simple sign reversal is all that is required to account for OSH by SRP. If the vidget is driven by activity in the deep layers of V1, then augmentation of responses in the superficial layers could suppress vidgets via feedforward inhibition. This simple model is supported by the finding that selective activation of inhibitory interneurons, restricted to V1, is indeed sufficient to completely suppress the vidget (Figure 3).

As mentioned, exposure of mice to gratings of a single orientation in the open arena causes OSH of the orienting response, and SRP of the VEP. It also causes habituation of the vidget responses in the head-fixed animals. This observation is consistent with a memory retrieval process of familiarity, which is context-independent and depends on non-hippocampal plasticity, as compared to recollection, which is context-dependent and thought to require additional hippocampal plasticity [85]. Thus, OSH presents as a form of low-level recognition memory that is reliant upon information storage in V1, but which may capture the mechanistic essence of high-level recognition memory.

### **Increases and decreases in neural activity with familiarity**

One major difference between these observations in V1 and those made in IT and PRC, is that activity in V1 is elevated in response to familiar orientations but reduced in higher-order cortices to familiar objects [32–34, 58]. It is possible that the rules of plasticity vary from region to region. For example, evidence strongly suggests that mechanisms of LTP in V1 support SRP and OSH [75, 76, 78]. In contrast, the decrease in activity in PRC as stimuli become familiar has been attributed to mechanisms of LTD [62, 63, 86, 87]. The fact that cells decrease in activity as animals habituate to sensory stimuli makes sense in many ways: These stimuli are of little importance to the animal and they need not motivate any subsequent behavior [88–92]. Thus, overall, one might expect to see greater neural responses to stimuli that promise reward or punishment, or novel stimuli that hold the



possibility of signaling either, than to stimuli that have been proven by experience to be inconsequential.

One interesting consideration is the cortical layer within which cells have been recorded. Neurons in thalamo-recipient layer 4 of cortex, as recorded in SRP, may be modified very differently by familiarity than neurons in the deep layers, which may have been oversampled in previous studies because they are larger and easier to isolate. As mentioned, it is possible that synaptic potentiation occurs through experience in layer 4, and through a process of feedforward inhibition, leads to suppression of cortical output in these deeper layers [92] (figure 3). This is a question that will require further investigation.

A second important consideration is the nature of the stimuli that are being viewed in these experiments. Phase reversing stimuli have been used to investigate SRP [75, 76, 78, 93]. This contrasts with most experiments interrogating visual recognition memory in which static images are presented or actual objects that can be freely explored. When monkeys viewed similarly dynamic stimuli, in the form of fast sequences of two-dimensional objects, recorded neurons in IT responded more strongly to those they were familiar with than those that were novel [94, 95]. Moreover, enhanced event-related potentials to familiar stimuli were also recorded in human occipital cortex [94]. Again, this is an area of work that merits a great deal of further investigation.

## Conclusions

The question of how we use vision to recognize familiar stimuli remains open. The major body of work elucidating this process has focused on higher order visual cortical areas such as IT and PRC, providing evidence that these regions report and are critically required for real-world object recognition. The underlying process has been difficult to understand, partly because these regions receive highly processed information. More recent work suggests that cortical areas early in visual processing, including V1, are equally plastic and store recognition memory that allows for the detection of novel stimuli if challenged appropriately. If the goal is to study object recognition and the remarkable degree of tolerance to viewpoint and conditions that our visual system achieves, then clearly it does not make sense to confine investigation to V1 of non-foveal animals with inferior vision, such as rodents. On the other hand, if the goal is to understand how the brain stores information in a retrievable form for long periods of time, then there is great value in studying recognition memory in mice, because the widest possible array of experimental techniques can be applied. There is also great benefit in studying primary sensory cortices. These regions are experimentally tractable because they receive relatively unprocessed information, and are well understood in terms of form and function. In particular, habituation and the familiarity that results are fundamental forms of learning and memory that are important to all species, and can be assayed with simple experimental approaches akin to the already established assay of novel object detection. These processes deserve to be studied in depth.

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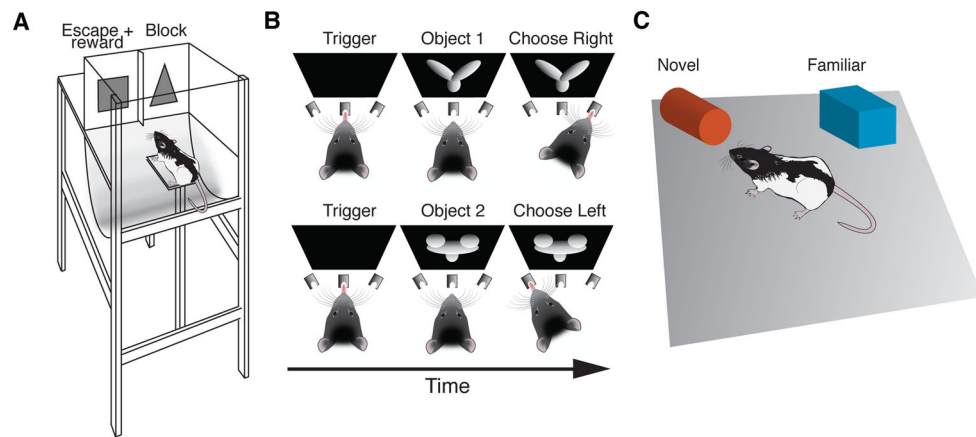
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**Highlights**

- Habituation is a well established and robust assay to study visual recognition memory
- Synapses in V1 are modified as mice habituate to familiar stimuli
- Local manipulations of synaptic plasticity in V1 disrupt encoding and retrieval of memory





**Figure 1.**

Assays of visual recognition memory in rodents. **A)** Famous work by Karl Lashley used a forced choice assay in which rats learned to jump to safety and reward by selecting one of two simultaneously presented stimuli. Failure to remember the stimulus associated with escape resulted in a fall into netting below the apparatus and no reward. The use of a platform and precipitous drop enabled the maintenance of the rats viewpoint at a fixed equidistance from both stimuli. Lashley [50] and others [96] have used this assay and different variations on operant discrimination tasks [51, 52] to demonstrate that pigmented rats have pattern vision, and are capable of visual recognition memory. Most importantly they demonstrated a great degree of tolerance to changes in luminance and scale, as well as repetition, occlusion and clutter. **B)** More recent work has shown that rats are capable of something close to true invariant object recognition [35]. This again uses an operant conditioning approach in which a rat positions its own head at a designated viewpoint in front of a computer screen to trigger a trial. This initiation step ensures that the stimulus is viewed from a consistent position. The animal then learns to receive a reward to the left or right depending on the object presented from a single canonical viewpoint. In a second step, a small subset of novel virtual rotations and altered lighting are presented so the rat learns to generalize its response depending on the object presented. Eventually, tolerance to a very wide range of transformations can be assessed by scoring the correct decision of the rat to go left or right, revealing a startling degree of invariance to viewpoint and lighting conditions. **C)** A very well established assay of familiar object recognition and, thereby, novel object detection in rodents simply makes use of their tendency to explore novelty. Once habituated to the behavioral arena, subject are initially presented with two similar objects to explore. Once these objects have become familiar within a single 5–10 minute exploration session animals are removed and one of the objects is replaced with a novel object. After a designated time period (determined by the longevity of memory that is being studied) the subject is returned to the arena and the degree of preferential exploration of the novel object reflects the degree to which the familiar object is recognized. This assay is relatively high throughput and has become very popular due to the lack of training required in the subjects. It has been used as a basis of understanding the role of the perirhinal cortex (PRC) in recognition memory. A drawback of the assay is the lack of experimental constraint, as the viewpoint of the mouse is not fixed. Mice use all of their senses to explore the objects and,

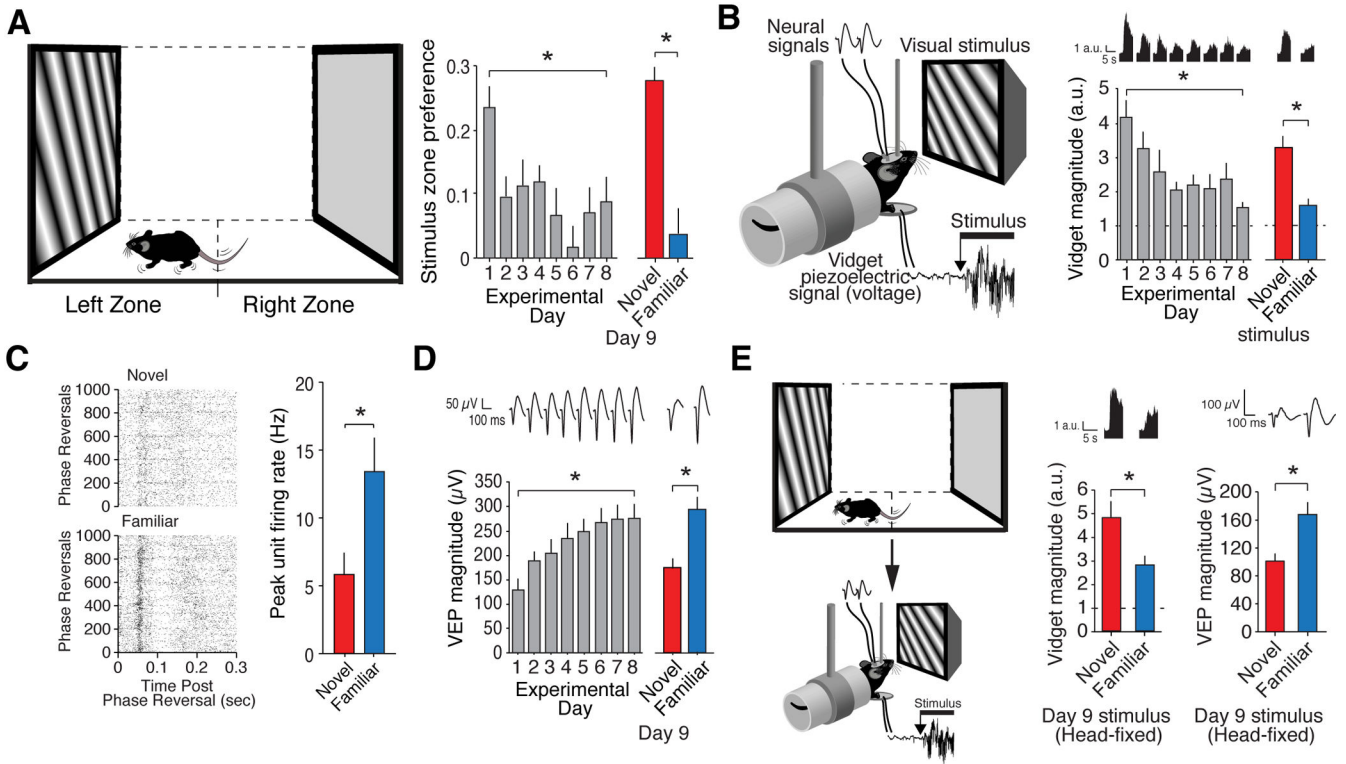
because somatic sensation is generally dominant over vision in rodents may not be the most direct assay of visual recognition.

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**Figure 2.** Orientation-Selective Habituation. **A)** Mice presented with a high-contrast phase reversing sinusoidal grating stimulus on one side or the other of a 40–40 cm square arena tend to orient to the grating stimulus and explore it extensively. This exploratory behavior gradually decreases over days, reflective of a long-term habituation process as they familiarize themselves with the stimulus. After eight days of habituation mice show a clear lack of interest in the familiar stimulus (blue), but exhibit pronounced exploration of a novel stimulus (red), which is altered only in orientation. **B)** This orientation-selective habituation (OSH) is re-capitulated in head-fixed mice viewing a similar stimulus. A piezo-electrical device placed under the forepaws of the mice can be used to measure behavior elicited by the onset of the sinusoidal grating stimulus. The recorded behavior, described as a vidget (visual-induced fidget), habituates over a similar time-course to exploratory behavior in freely-moving mice. During a test session of randomly interleaved presentations of familiar (blue) and novel orientations (red) after eight days of habituation, vidgets of significantly greater magnitude are elicited by the novel orientation. **C)** Head-fixation enables both control over the animal’s view of the stimulus and the application of a wide-range of recording approaches and interventional techniques. Recordings of unit activity in thalamo-recipient layer 4 reveal a surprising elevation of unit firing rate to the familiar stimulus compared with the novel, in contrast to the effects on behavior: Example raster plots are shown on the left and averaged peak firing rate on the right. **D)** Visual evoked potentials (VEPs) can be recorded from layer 4 with chronically implanted electrodes. The stability of this recording approach over days allows for the observation of a form of plasticity known as stimulus-selective response potentiation (SRP), in which the magnitude of the VEP driven

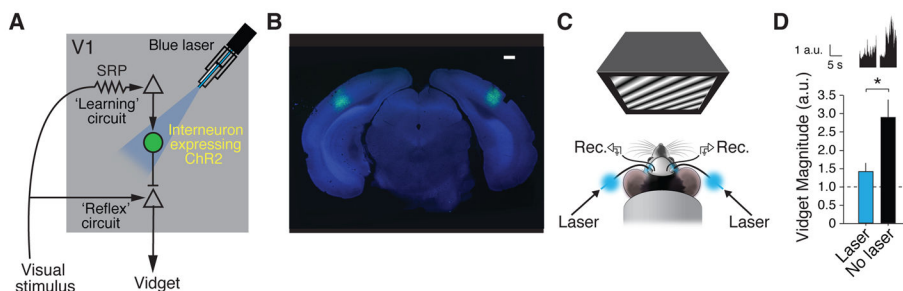
by a progressively familiar stimulus is potentiated. During the test session on day 9, again in striking contrast to the behavior, the familiar stimulus (blue) evokes VEPs of greater magnitude than the novel (red). **E**) When mice habituate to an oriented stimulus in the open arena this habituation transfers to head-fixation, under which conditions the mice have never previously experienced the stimulus, suggesting both that there is some commonality between the vidget and the orienting/exploratory behavior observed in the freely moving mice, and that OSH is context-independent. SRP is also observed after OSH in the open arena, as recorded under head-fixation, indicating that a common physiological process underlies learning in both settings.

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**Figure 3.**

Elevated feedforward inhibition as a means of habituation. **A)** A very simple model of long-term habituation, inspired by Sokolov [90] and others [89, 91], proposes that there are separate ‘reflex’ and ‘learning’ pathways, the former of which mediates a basal behavioral response and the latter of which is strengthened through experience. Habituation results from a feedforward inhibition, activated by the ‘learning’ pathway, which suppresses output of the ‘reflex’ pathway. In the case of orientation-selective habituation (OSH), we propose that potentiation occurs in the superficial layers of cortex, measured as SRP, and that feedforward inhibition suppresses output of a parallel direct pathway that passes through the deep layers of cortex. This is an anatomically plausible arrangement [97]. In the simplest of all cases this parallel organization and feedforward suppression might be accomplished in V1 alone, although the spirit of the model could be maintained within a much more extensive circuitry. An obvious first test of this model would be to selectively activate inhibition using optogenetics, with the prediction that behavioral output should be suppressed. **B)** This prediction has been tested by bilaterally expressing Channelrhodopsin-2 in only the parvalbumin-positive inhibitory interneurons in binocular V1 (green)[75]. **C)** Illumination of V1 with blue light activates interneurons. **D)** In head-fixed mice, the visually-driven behavioral output, termed a vidget, is almost completely suppressed only when the interneurons are activated. There are additional predictions of this model that remain to be satisfied: SRP should be spared if ChR2 could be restricted to only feedforward inhibition, inactivation of feedforward inhibition should lead to a recovery of the vidget driven by familiar stimuli, and activation of deep layers should directly drive a vidget. More work is required to test these predictions.