about the outcome of the behavior. Cortical states in mice could also be far more anatomically restricted than we currently appreciate. At a broad level, neuromodulators or thalamic input might set the tone for global changes in cortical state, hence the active states in S1 and V1 during pupil dilation. On top of this, subcircuits might be locally activated through the activity of corticocortical and/or thalamocortical connections. Activation could therefore be targeted to subcircuits processing features of the environment that are relevant to behavior—a situation that would again closely resemble models of selective attention (Harris and Thiele, 2011). A full description of waking cortical states in mice will require a deeper analysis of multiregion recordings in combination with high-resolution monitoring of multiple limbs and sense organs.

The correlation of activated cortical states with pupil dilation in the absence of movement is an important observation, but what is its role in visual perception? Two recent studies have shown that visual perception is improved in running mice (Bennett et al., 2013) and during activated states induced by optogenetic stimulation of cholinergic axons in visual cortex (Pinto et al., 2013). It will now be exciting to examine visual perception during pupil dilation in stationary and running mice. The combination of high-resolution behavioral monitoring with neuronal recordings and manipulations in awake, head-restrained mice is opening a window onto a bigger vista—an understanding of the roles of specific types of cortical neurons in the internal control of sensory processing and perception.

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Concept Cells through Associative Learning of High-Level Representations

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In this issue of *Neuron*, Quian Quiroga et al. (2014) show that neurons in the human medial temporal lobe (MTL) follow subjects' perceptual states rather than the features of the visual input. Patients with MTL damage however have intact perceptual abilities but suffer instead from extreme forgetfulness. Thus, the reported MTL neurons could create new memories of the current perceptual state.

Neurons along the ventral visual pathway respond with varying degrees of specificity to subjects' perceptual decisions. In situations where the visual input and the subjective percept can be experimentally dissociated, most neurons in early visual areas respond to low-level stimulus properties, whereas approximately 90% of neurons in higher-level inferotemporal (IT) cortex are modulated by the subjects' perceptual report (Logothetis, 1998). Neurons from area TE of IT feed into medial temporal lobe (MTL) structures that include the hippocampal formation and the entorhinal, perirhinal, and parahippocampal cortices (Suzuki and Eichenbaum, 2000). A new study in this issue of *Neuron* by Quian Quiroga et al. (2014) shows that "concept cells" in the human MTL closely follow subjective awareness.

Several studies have demonstrated the presence of "concept cells" in the human MTL (Quian Quiroga, 2012). Concept cells are highly selective neurons that seem to represent the meaning of a given stimulus in a manner that is invariant to different representations of that stimulus. For example, a single neuron in the human hippocampus was found to selectively respond to several different pictures of the actress Halle Berry, even when she was disguised as Catwoman, the role she played in one of her movies. The same neuron also responded to the letter string "HALLE BERRY" but not to other letter strings. Later studies showed that these "concept cells" were also activated when stimulus information was provided in other sensory modalities, for example, hearing the name of a person spoken aloud (Quian Quiroga, 2012). These invariant, multimodal responses are in contrast to the more stimulus-specific responses observed in visual area IT and suggest that MTL neurons encode stimulus information in an abstract form, such that various instances of a given stimulus can activate these neurons.

In the new study, Quian Quiroga et al. (2014) ask whether concept cells encode the perceptual reports of subjects when visual inputs are ambiguous. Human subjects were presented with ambiguous images created by morphing two different pictures (for example, a morph between Presidents Bill Clinton and George Bush). Before viewing the morphed image, subjects viewed an adaptor image (a picture of Clinton or of Bush) and then reported with whom the morphed image corresponded. As expected from previous adaptation studies, exposure to the adaptor image biased subjects' perception, with the result that the subsequent morphed image was identified as the opposite of the adaptor. Thus, in this paradigm, the very same morphed image could be identified either as Clinton or Bush depending on which adaptor stimulus was used. By recording from a neuron selective to Clinton or Bush, Quian Quiroga et al. (2014) could then examine how the neuron's response varied with the perceptual report of the subject.

Quian Quiroga et al. (2014) recorded from 62 neurons in different MTL structures and, consistent with the evidence for high-level representations in MTL neurons, found that rather than merely signaling the visual input, the activity of MTL neurons correlated with the subjects' perceptual decision. Strikingly, in many cases, the responses to the morphed images were indistinguishable from the responses to the original nonmorphed image, both when considering the magnitude as well as the latency of responses (although Quian Quiroga et al., 2014 are careful to point out that this null result could be due to the large variability in responses across neurons). That is, in our example of the Clinton neuron above, on trials when the morphed images were identified as Clinton, the Clinton neuron's response was no different from its responses to the nonmorphed image of Clinton, regardless of the degree of morphing. Thus, these neurons appear to respond in an all-or-none manner, their response reflecting the conscious percept of the subject, regardless of the ambiguity in the visual input.

These findings along with results from studies employing the mental imagery (Kreiman, 2007), binocular rivalry (Kreiman, 2007), change detection (Reddy et al., 2006), and masking (Quian Quiroga, 2012) paradigms reveal that the activity of MTL neurons correlates strongly with conscious vision, rather than the visual features of the input stimuli. What could be the functional role of these neurons? On the face of it, these neurons have properties that almost make them look like potential candidates for being the elusive neural correlate of consciousness (NCC) (Crick and Koch, 1990). However, this seems implausible since patients with bilateral MTL damage show no obvious problems in perceptual awareness and consciousness (Squire et al., 2004). This suggests that the NCC lies upstream of these MTL neurons.

Instead, patients with MTL damage exhibit profound memory impairments and MTL structures have long been known to play a key role in recognition and associative memory processes (Squire et al., 2004; Suzuki and Eichenbaum, 2000). Single-neuron studies in the nonhuman primate have revealed that MTL neurons signal the learning of associations or relationships between stimulus pairs. A preferred cue as well as its learned paired associate activated pair-coding neurons in perirhinal cortex (Naya et al., 2003), and the learning of arbitrary associations between stimuli and spatial locations has been observed in hippocampal neurons (Wirth et al., 2003). fMRI studies have also shown that the MTL encodes associations between stimuli even when subjects are unaware of the temporal contingencies between them (Schapiro et al., 2012). This ability of MTL neurons to encode associations between initially unrelated stimuli presented in close temporal proximity could underlie the formation of concept cells. Indeed, the statistics of the world ensure that different representations of a given stimulus (e.g., a person's face and hearing her name pronounced) co-occur frequently. A simple associative learning mechanism in conjunction with the statistical regularities of the world could result in MTL neurons encoding different forms of a given stimulus, thus exhibiting the property of invariance, a key feature of concept cells (Figure 1).

The new study by Quian Quiroga et al. (2014) unequivocally demonstrates that MTL concept cells follow the visual percept of the subject. However, as we have argued above, MTL neurons are unlikely to be the direct correlates of subjective awareness. Instead, it is probable that, in cooperation with neocortex, these neurons play a key role in transforming the current perceptual state of the subject into long-term memories. As mentioned above, the activity of most neurons in IT cortex correlates with subjective visual awareness. This information about the perceptual state of the subject enters the MTL in the perirhinal cortex (Suzuki and Eichenbaum, 2000). Patients with MTL damage have difficulty creating new memories, and lesion studies have shown that connections from MTL structures to neocortex are necessary for establishing and maintaining long-term memories in area TE (Higuchi and Miyashita, 1996). Thus, it is plausible that the functional role of concept cells is to create new memories of the current perceptual experience of the subject based on information they receive about high-level representations in cortex. In addition, the abstract nature of concept cell responses implies that the new memories could be linked to other memories of the same stimulus, such that future viewings of the stimulus could potentially activate all memories related to this stimulus.

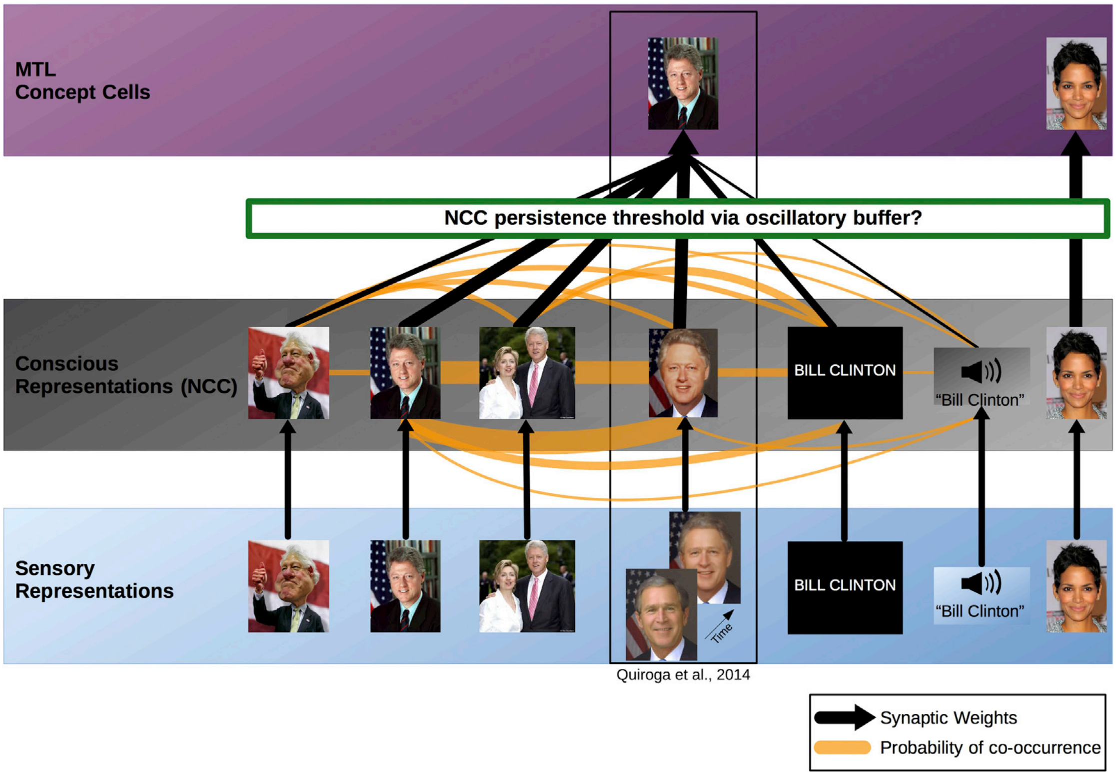

Figure 1. Associative Learning of High-Level Representations in MTL Concept Cells
In earlier processing areas, sensory representations contain information about the input stimuli. For example, in the new study by Quian Quiroga et al. (2014) the activity of neurons in these areas would reflect the low-level visual features of the morphed image. These stimulus representations feed into higher-level representations (NCC) where firing activity is correlated with subjects' perceptual awareness (for example, the percept of Bill Clinton in the morphing paradigm). As a result of statistical regularities in the real world, different stimuli co-occur with different probabilities, as indicated by the thickness of the orange lines. Thus, while the probability of co-occurrence of different pictures of Bill Clinton is high (as depicted by the thicker orange lines), the probability of Bill Clinton and Halle Berry co-occurring is presumably very low (and thus not depicted in this figure). Concept cells in the MTL are situated at the summit of the processing stream and receive information from higher-level areas about the perceptual state of the subject. MTL cells could learn associations between different stimuli with a learning rule in which the synaptic weights (thickness of the black lines) grow with the probability of co-occurrence. Stimuli that are more likely to co-occur would activate the same MTL neuron resulting in abstract, invariant representations, a hallmark of MTL concept cells. The functional role of these MTL neurons could be to establish the current perceptual experience of the subject into long-term memories, possibly selecting only those experiences for which the corresponding activity patterns in cortex persist for at least a certain minimum duration.

One intriguing possibility is that MTL neurons select patterns of activity in neocortical structures that are sufficiently long lasting to merit long-term storage in episodic memory. Studies using rapid sequential visual presentation (RSVP) show that high-level processing is possible even when the input image changes 75 times a second (Potter et al., 2014). Single-unit recording studies have also demonstrated that even at such high presentation rates, IT neurons can show a brief "blip" of activity each time the cell's preferred stimulus is presented (Keysers et al., 2001). But not all such briefly presented stimuli are remembered. Perhaps, MTL circuits are designed to only store patterns that remain active in cortex for a certain minimum duration, for instance, at least 100–200 ms (Thorpe, 2012). The hippocampus could thus act as a gatekeeper, letting information through into episodic memory only if the corresponding cortical representations persist beyond this temporal threshold. This process of pattern selection could explain why MTL neurons have such long latencies relative to neurons in the neocortex. An elegant way of implementing such a pattern selection mechanism could be to use an oscillatory buffer in which any neural representation that is maintained on two consecutive oscillatory cycles would be selected for memory storage. Such a (wildly speculative) mechanism could rely on the prominent theta oscillations observed in MTL structures.

In conclusion, evidence is accumulating that "concept cells" carry high-level, abstract stimulus information. The new study by Quian Quiroga et al. (2014) nicely underscores this idea by demonstrating that these cells track the high-level perceptual report of subjects, even when the incoming stimulus information is noisy or ambiguous. As we have argued above, these MTL cells are most likely postperceptual, not required for supporting perception, but for encoding the current percepts into new episodic memories.

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The Hippocampal Cacophony: Multiple Layers of Communication

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Locally generated gamma oscillations synchronize spikes, but the nature of coupling between regions remains unclear. In this issue of *Neuron*, Schomburg et al. (2014) show that afferent gamma input fails to entrain hippocampal output, suggesting limited propagation of gamma waves.

The timing of signals in the brain is important for information transfer. Such temporal coding is facilitated by neural oscillations in many frequency bands, which provide a temporal framework within which information can be bound or segregated via oscillatory cycles (Buzsáki and Wang, 2012). Gamma oscillations (>30 Hz) in particular tightly synchronize the spiking output of a region, making a response in the downstream region more likely to be elicited than if the signals arrived asynchronously. This is known as coincidence detection, which is a widely accepted consequence of gamma activity (König et al., 1996). Additionally, downstream regions also produce gamma oscillations during information transfer, and it has been postulated that gamma oscillations that are coherent between the upstream and downstream regions facilitate successful information transfer between the two regions (Fries, 2005). New compelling evidence in this issue of *Neuron*, however, found that spiking of Cornu ammonis 1 (CA1) pyramidal neurons was not entrained by afferent gamma input, questioning whether this latter theory applies to hippocampal gamma oscillations.

CA1 in the hippocampus has spatially segregated inputs and different gamma oscillations that occupy distinct frequency bands (Csicsvari et al., 2003; Colgin et al., 2009), therefore making CA1 an excellent place within which to study gamma oscillations. Adopting a tour de force approach, Schomburg et al. (2014) implanted high-density silicon shanks containing an impressive total of up to 256 sites into the dorsal hippocampus of rats. This allowed for simultaneous recording of both gamma oscillations and spikes from all layers of CA1 and also along the majority of CA1's transverse (proximodistal) axis of the dorsal hippocampus. The high recording density increases the likelihood of capturing activity from matching dendritic and somatic compartments of the same neurons, which is an important factor to consider when interpreting the acquired data. CA1 receives afferent input from layer 3 of the entorhinal cortex (EC3) and CA3 of the hippocampus, from which they also recorded in concert with CA1. Complementing this state of the art technology, the investigators used advanced methods of source separation. Specifically, independent component analysis (ICA) was used in addition to conventional current-source density (CSD) analysis to pinpoint the precise location of gamma oscillations. ICA allows for the separation of linearly mixed sources into their independent components (Fernández-Ruiz and Herreras, 2013). This is useful when heterogeneous signals occur at the same site, such as gamma oscillations in CA1, where ICA has been employed to isolate and study the different current generators (Korovaichuk et al., 2010).