

Insights on Vision Derived from Studying Human Single Neurons

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Investigating the living brain, and in particular relating its activity to behavior is one of the most important challenges in neuroscience. Researchers use many different techniques to explore this relationship. Careful observation of patients with brain lesions or neuroimaging methods such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or near infra-red spectroscopy (NIRS) are examples of procedures which allow researchers to make inferences about brain activity in a non-invasive way. However, the most widely used such tool, fMRI, measures a blood oxygen dependent (BOLD) signal that is only indirectly related to the signal of interest, neural activity. Consequently, the BOLD contrast reflects hemodynamic changes rather than neuronal activity (Kim and Ogawa 2012). The relationship between BOLD and neural activity is complex and with the exception of primary visual cortex (V1) poorly understood (Logothetis et al. 2001; Logothetis and Wandell 2004). In contrast, the EEG signal reflects directly the (although averaged) activity of neurons, but it is highly filtered due to the large distance between the neuronal sources and the electrodes on the scalp. Thus, despite their undisputed utility in expanding our knowledge about the human brain, current non-invasive techniques do not permit direct study of activity such as local field potentials (LFPs) and spiking activity in individual neurons.

In rare clinical situations, invasive intracranial recordings are a necessary step in the diagnosis or treatment of illness, e.g. in patients suffering from drug resistant epilepsy or Parkinson's disease. These situations represent a rare opportunity for researchers to record electrophysiological signals directly from inside the human brain much like those usually restricted to animal models.

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So far, most research utilizing single unit recordings in humans has focus on areas of the medial temporal lobe (MTL), in particular the hippocampus, amygdala, entorhinal cortex, and parahippocampal cortex. This is because the MTL is a routine target for depth electrode studies in patients suffering from drug resistant epilepsy. In this review, we will summarize key findings on how individual neurons in the MTL respond to visual stimuli and what has been discovered about the human visual system based on such recordings.

It is important to keep in mind the limitations of such invasive work conducted in human subjects. Subjects suffer from brain pathology, which means that these studies are never carried out on data from a healthy brain. The data we discuss all originates from epilepsy patients who are being investigated for possible surgical treatment of their drug resistant seizures. This raises the question to what extend these results generalize to non-epileptic subjects. For example, studies showed that some abnormalities in brain activity can be observed even in cortical areas not deemed epileptic (Engel et al. 1982; Bettus et al. 2011). Despite these limitations, it is remarkable that the type of findings we review in this chapter have been highly reproducible across a wide variety of patients with different kinds of epilepsy. This makes it very unlikely that these findings are abnormalities caused by epilepsy, because these would be expected to vary considerably according to their exact pathology. Also, since the location of the epileptic focus is not known in advance, electrodes are implanted in many areas which after the fact are deemed non-epileptic. Thus, eventually many of the recordings are made in healthy tissue unrelated to the seizure focus or network. Comparing data recorded within and outside of the seizure focus is a valuable tool to assess the sensitivity of a finding to epilepsy. Such comparisons have generally revealed little difference, with some notable exceptions that provide insights into specific deficits attributable to epilepsy (see Fig. SII in Rutishauser et al. 2008). Lastly, in spite of these limiting factors, human intracranial recordings have reproduced many key discoveries previously made in animal models, such as highly invariant and tuned visual neurons described in this chapter.

1 Latency

An important metric which can be quantified directly using human single neuron studies is the latency of neuronal responses. The most comprehensive knowledge about latencies is available for the different parts of the MTL. For example, Kreiman et al. quantified latencies in response to visual stimuli (pictures on a screen) for neurons in the amygdala, entorhinal cortex and hippocampus (Kreiman et al. 2000a). Onset latencies (defined as a significant increase of firing rate above baseline) for the amygdala were 240 ms, for entorhinal cortex 209 ms and for hippocampus 239 ms. Interestingly, latencies were not significantly different between the different areas. In a more recent study by Mormann et al. (2008) another method—analyzing distribution of interspike intervals (Hanes et al. 1995)

—was used to estimate the latency of single unit responses. Similarly to the earlier study, latencies were long (~ 400 ms) and there was no significant difference between amygdala, entorhinal cortex and hippocampal units. Notable, the latency of neurons recorded from the parahippocampal cortex had a significantly shorter latency of 270 ms. Anatomically, one would expect this difference because the parahippocampal region is the major input to the entorhinal cortex (Suzuki and Amaral 1994). More puzzling is the lack of latency differences between the other areas. A potential explanation are the monosynaptic connections between amygdala, entorhinal cortex, and hippocampus (Suzuki 1996), but it remains unclear why other connections that are also monosynaptic result in a large latency difference. The most interesting, and puzzling, result is the ~ 100 ms gap between onset latencies of the parahippocampal cortex and other regions. It has been suggested that this is due to a recurrent process within parahippocampal region (Quiroz 2012).

Latencies of neuronal responses from areas other than MTL have also been reported. In one study, single neuron responses to action execution and observation were studied in areas MTL and supplementary motor cortex (SMA) (Mukamel et al. 2010). Neurons in SMA had similar latencies as neurons in the MTL during action observation, but responded significantly faster than neurons in the MTL during action execution. Interestingly, neuronal latencies of units recorded in ventral prefrontal cortex were significantly shorter (faster) than those observed in the MTL (Kawasaki et al. 2005): latencies as short as 120–170 ms were observed in response to presentation of emotional visual stimuli. This fast response could indicate that prefrontal cortex modulates visual processing in other areas, including temporal cortex and the amygdala, via feedback projections (Sugase et al. 1999; Adolphs et al. 2014).

2 Visual Selectivity of Neurons in the Human MTL

Along the visual stream, selectivity becomes more complex (Gross 1994; Logothetis and Sheinberg 1996; Tanaka 1996; Grill-Spector and Malach 2004). In early stages of visual processing, such as in V1, neurons are tuned to simple visual features such as oriented bars. In contrast, neurons in higher visual areas such as V4/V5 are selective for directions of motion and neurons in inferotemporal cortex (IT) are selective for even more complex stimuli such as hands and faces (Gross 1994; Logothetis and Sheinberg 1996; Tanaka 1996). In even higher level visual areas of the MTL, such as the hippocampus and amygdala, visual selectivity is even more specific such as for particular aspects of faces such as eye contact (Leonard et al. 1985; Miyashita et al. 1989; Mosher et al. 2014). In humans, this area is where most is known about the selectivity of individual neurons. In 1997, Fried et al. (Fried et al. 1997) published one of the first comprehensive studies on the highly specific selectivity of human MTL neurons to complex visual stimuli, such as Ekman faces (Ekman and Friesen 1976). A key result was that single units in the

MTL could discriminate faces from inanimate objects. Following up on this initial discovery, Kreiman et al. (2000a) characterized the responses of single human MTL units for sets of pictures grouped into different semantic categories such as objects, animals, cars, and faces. The key finding was that most visually selective cells responded to all stimuli of a category, even if the different stimuli (pictures) belonging to this category looked visually very different. This indicated that these neurons are highly invariant to visual variation. While such highly invariant tuning has been found in numerous areas of the human MTL, there are some interesting inter-areal specializations that have been described. For example, Mormann et al. (2011) has demonstrated that neurons in the right but not left amygdala are significantly more likely to be tuned to pictures of animals. Importantly, the selectivity of such neurons can extend much beyond that of semantic categories. In a seminal study by Quiroga et al., neurons were identified that responded only when a specific individual, object or landmark were shown in an image (Quiroga et al. 2005). This study was composed of two parts. In the first part of the experiment, around 90 images of people and objects familiar to the subject were presented in a screening session to identify candidates for selective units. Next, variations of the images which elicited a strong response in the screening session were used in a later session. Results from the second part of this experiment showed that MTL neurons were highly selective for pictures representing a particular person, object or landmark but not for other pictures. Figure 1 shows an example of a unit exhibiting this remarkable property.

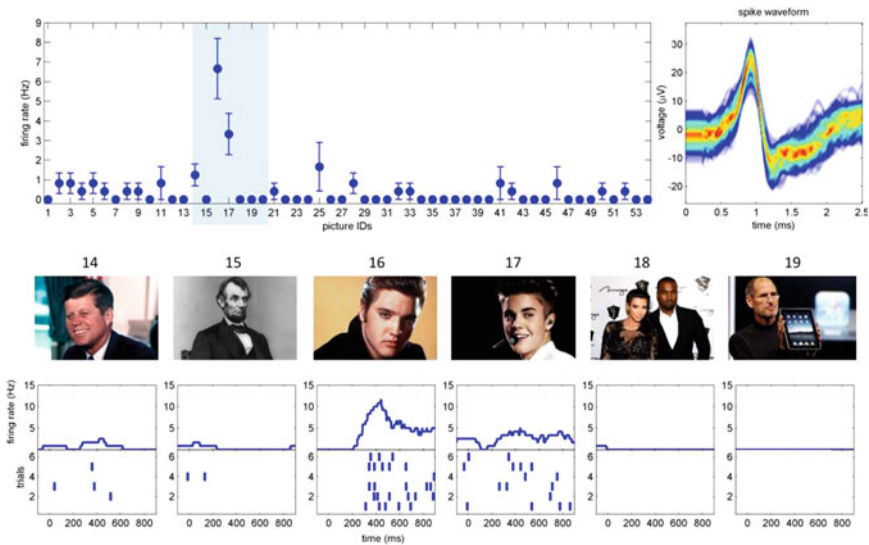


Fig. 1 Example of a highly selective response of an individual amygdala neuron. 54 different images were presented (“picture ID”), to most of which the neuron did not respond. However, to some images (such as ID 16) this unit responded very strongly (ID 16 is a picture showing Elvis Presley). Unpublished data

In another study the selectivity of putative pyramidal cells and interneurons in the MTL was assessed (Ison et al. 2011). Units were classified as putative pyramidal cells and interneurons based on their baseline firing rate and features of the extracellular waveform. Putative pyramidal cells were found to be much more selective than interneurons, a finding which was valid across different regions of the MTL, although the highest selectivity was observed in the hippocampus as compared to amygdala, entorhinal cortex and parahippocampal cortex. This gradient corresponds to the major signal pathways through the MTL (Suzuki and Amaral 1994), indicating that neuronal selectivity for visual stimuli increases successively at each stage in visual processing. Different analysis methods have supported this hierarchical gradient of selectivity (Mormann et al. 2008): parahippocampal neurons, on average, responded to five different stimuli whereas neurons in entorhinal cortex and hippocampus responded, on average, to only two stimuli. Mormann et al. (2008) also revealed a positive correlation between selectivity and latency, which further supports the concept of a mechanism of hierarchical processing in which in every step of processing of visual information the representation of a stimulus becomes more precise and selective (Grill-Spector and Malach 2004). The studies summarized so far show that MTL neurons respond to only small numbers of all possible stimuli. This indicates that each stimulus is encoded by a relatively small neuronal assembly (Quian Quiroga et al. 2008) and this data therefore support a sparse coding hypothesis (Olshausen and Field 2004; Barlow 2009). This theory proposes that a given percept in the brain is represented by the activity of a small population of specialized neurons. In contrast, an alternative view is distributed population coding (Decharms and Zador 2000), which suggests that a percept is represented by the activity of large numbers of broadly tuned neurons.

3 Invariance

Another remarkable feature of MTL neurons is their invariance. In their 2005 study, Quian Quiroga and colleagues (2005) presented to subjects not only different images of the same object or person but they also used pencil sketches, caricatures of this person or object or even letter strings with their names. What they discovered was that even if those pictures had nothing in common visually (but were linked semantically), specific and selective neurons still showed an increase firing rate when presented with these stimuli. This result suggested that neurons responded to an abstract representation of the meaning of the object or individual rather than to any visual property of the picture. This phenomena has also been confirmed using a decoding analysis (Quian Quiroga et al. 2007) that demonstrated that it is possible to decode the identity of the person presented in a picture. In contrast, it was not possible to estimate which specific picture of the person was presented. Noticeable, the selectivity for the identity of a person is not limited to the visual modality but extends to auditory input as well. In one of the experiments, pictures and an audio playback of a voice reading the names of this images were used (Quian Quiroga

et al. 2009). The results showed that there was no significant difference in selectivity of cells in MTL when comparing visual and auditory input. The strength of this multimodal invariance was different among different parts of the MTL. In the parahippocampal cortex, half of the responsive neurons showed visual invariance but none of this unit showed multimodal invariance. In entorhinal cortex, 70 % of all visually responsive neurons were visually invariance and 35 % were, in addition, multimodally invariant. In the hippocampus, even more neurons were invariant: 86 % showed visual invariance and 38 % multimodal invariance.

This systematic variability of multimodal invariance is compatible with the hierarchical structure of the MTL (Mormann et al. 2008; Ison et al. 2011).

4 Grandmother Cells

The highly invariant, sparse and specific responses of neurons in the MTL triggered a renewed discussion about the concept of so called “grandmother cells” (Ison and Quiroga 2008; Quian Quiroga et al. 2008; Quian Quiroga 2013). A grandmother cell is a hypothesized neuron that responds only to a complex, specific stimulus such as the image of one’s grandmother. The concept of grandmother cells was originally proposed by Jerry Lettvin (Gross 2002), although unknown to Lettvin a few years earlier the same concept was introduced by the polish neurophysiologist Jerzy Konorski who used the term “gnostic” cell due to the Greek term “gnosis” for knowledge (Konorski 1967). The grandmother cell hypothesis is an extreme view of the sparse coding hypothesis (Olshausen and Field 2004; Barlow 2009), which proposed that a given percept in the brain is represented by the activity of a small neuronal population and in the extreme case only a few or even only one neuron. As summarized above, the results obtained from single units recordings in the human MTL support the sparse coding hypothesis. This raises the question of whether it is possible that ultimately, on the very last stages of visual processing, a percept could be represented by the highly specific activity of only a few neurons?

This question is difficult to answer with the current experimental setups used in research involving epilepsy patients. Because of time and stability constraints, only a limited number of pictures can be tested (typically less than 200). Consequently, it is impossible to dismiss the possibility that a given neuron that responded only to a particular picture during the experiment would not also respond to a different, but never shown, image. Nevertheless, there are several arguments against the grandmother cell hypothesis. Using Bayesian probabilistic analysis of a data set consisting of 1425 MTL units from 34 sessions Waydo and colleagues (Waydo et al. 2006) estimated that out of the approximately 10^9 (Harding et al. 1998; Henze et al. 2000; Schumann et al. 2004) neurons in the human MTL, approximately 2 million are involved in representing each individual concept. This estimate is far larger than that predicted by the grandmother cell hypothesis. Furthermore, estimating that average an person can distinguish between 10000 and 30000 objects (Biederman and Bederman 1987), we can assess that one neuron should respond to ~50–150

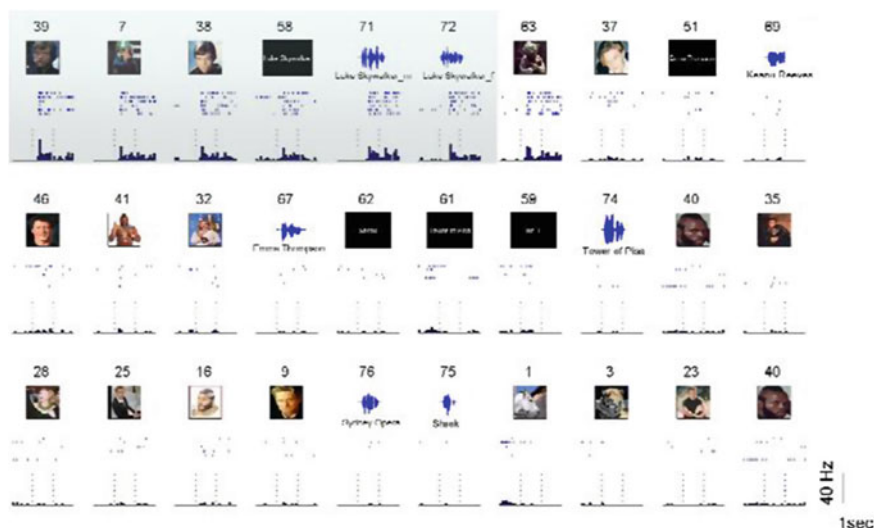


Fig. 2 Example single Unit recorded in the entorhinal cortex that responded selectively to pictures of Luke Skywalker, as well as the written and spoken name. The same unit showed also selectivity to Yoda—other character from movie “Star Wars”. Modified from (Quian Quiroga et al. 2009)

distinct objects (Waydo et al. 2006; Quian Quiroga et al. 2008). It was also shown that some of the units indeed responded to very different objects. For example, a unit in entorhinal cortex that responded to Luke Skywalker from the Star Wars movie series was also activated by a picture of Yoda, another character appearing in the same movie (Quian Quiroga et al. 2009) (Fig. 2).

Similarly, another neuron responding to Jennifer Aniston also responded to Lisa Kudrow, both actresses in the TV series “Friends” (Quian Quiroga et al. 2005). In conclusion, it thus appears that these units responded to related but distinct concepts rather than to one specific object. This feature of MTL neurons led to the proposed term “concept cell” (Quian Quiroga et al. 2005; Quian Quiroga 2012) to appropriately describe these highly selective neurons.

5 Topography of Tuning

Another import piece of information which was obtained from individual human neurons concerns the topography of tuning properties of neurons. In many sensory systems in the brain, a topographic organization of neurons can be observed at least in lower levels (Hubel and Wiesel 1962; Simons and Woolsey 1979; Shou et al. 1986; Talavage et al. 2000). For example, in the visual system nearby neurons in the thalamus, as well as in the early visual cortices receive inputs from

neighbouring parts of the visual field (Hubel and Wiesel 1962; Shou et al. 1986). This topographic organization can still be observed in higher order visual areas (Tanaka 1996; Kreiman et al. 2006; Tsao et al. 2008). In contrast, human MTL neurons do not show any apparent topographical organization. Neighboring neurons, such as those recorded on the same microwire, are typically tuned to unrelated concepts (Quiari Quiroga et al. 2009; Mormann et al. 2011). This phenomenon is similar to that shown for place cells in the rodent hippocampus, where nearby units can encode totally different and non-overlapping place fields (O’Keefe and Nadel 1978).

6 Internally Generated Responses and Consciousness

Human recordings from MTL neurons are an ideal setup for studying internally (i.e. without sensory stimulation) generated responses because neurons are tuned to very specific high-level concepts and human subjects can easily follow instructions to produce certain thoughts such as “think about Bill Clinton”. Similarly, concept cells represent a great opportunity to study awareness due to their tuning for specific abstract representations. Indeed there are many experiments studying these phenomena in patients. In one of these studies subjects were asked to imagine previously viewed images (Kreiman et al. 2000b). Results of this experiment showed that the selectivity and tuning for internally imagined pictures were very similar to selectivity during sensory stimulation: 88 % of neurons which were selective during perception and imagery had the same tuning in both situations. In another study subjects viewed short (5–10 s) video clips and were later asked to freely recall these clips and immediately report when a specific clip “came to mind” (Gelbard-Sagiv et al. 2008). Again, neurons in the MTL showed similar tuning during perception and during free recall (imaginary). This phenomena was subsequently utilized in an experiment in which subjects attempted to use knowledge of their own neuronal activity to alter pictures presented on a screen (Cerf et al. 2010). In this biofeedback study, subjects were presented with hybrid “morphs” of two images. For each of the two pictures at least one selective neuron was previously identified. The subject’s task was to enhance one of the pictures by focusing their thoughts on it. A real-time decoder used the firing rates of MTL neurons to control the visibility of each image. Without any prior training, subjects succeeded in driving the visual stimulus towards one of the two images in over 70 % of trials entirely by focusing their thoughts on a given image. This result shows that internally generated responses can overwrite responses triggered by sensory input.

In an early study of visual awareness utilizing recordings from the MTL (Kreiman et al. 2002), the flash suppression method (Wolfe 1984; Sheinberg and Logothetis 1997) was used to alter perception of a visual input. With this method, the percept of an image presented to one eye only can be removed from awareness by the rapid presentation (“flash”) of a different image to the other eye. The results of this study demonstrated that 70 % of the visually selective neurons followed the

perceptual alternation. Strikingly, none of the selective neurons responded to the suppressed percept. This phenomena has also been studied using a backward masking paradigm. This revealed that visually tuned neurons fired whenever a picture was correctly recognized. In contrast, the same neurons remained at baseline when the picture was not recognized. Additionally, there was no difference in the evoked firing rate of visually selective cells regardless of whether the stimulus was presented for 33, 66 or 132 ms. All that was necessary is that the subject recognized the image, regardless of presentation duration. More recently, a face adaptation paradigm was used to study conscious perception (Quian Quiroga et al. 2014). In this paradigm, perception of an ambiguous hybrid face is biased by a preceding presentation of one of the faces that make up the hybrid (morphed) face. This preceding face (the “adaptor”) biases perception toward the other, non-adapted, face. The hybrid faces were constructed from two familiar faces, to at least one of which a selectively tuned neuron was previously identified. Analysis of the neuronal firing patterns again demonstrated that the neuronal response followed the subjective percept, even if the physical input was exactly identical for two different percepts (Fig. 3).

A similar phenomena has also been observed during the perception of emotional faces (Wang et al. 2014). In this experiment, neurons in the amygdala were identified which signaled the presence of the emotion in a face (such as happy or fearful). Remarkably, these same neurons signaled the subjective judgment of emotions shown by the subjects rather than the stimulus features. For example,

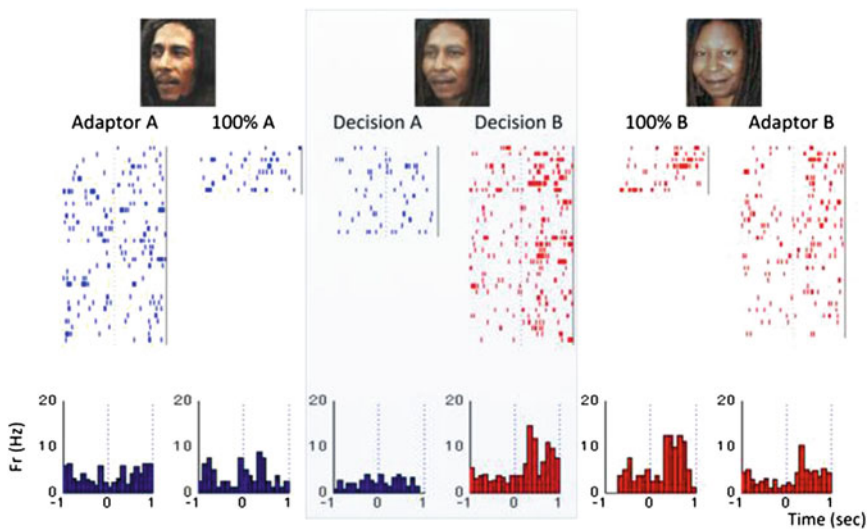


Fig. 3 Responses of a neuron recorded in the hippocampus that is tuned to an image of Whoopi Goldberg (100 % B) but not to Bob Marley (100 % A). The response was larger when the hybrid picture was recognized as Whoopi Goldberg (Decision B). Adapted from (Quian Quiroga et al. 2014)

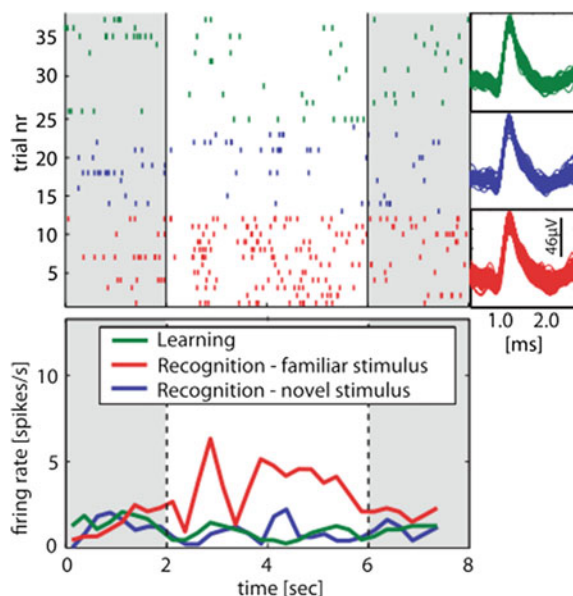
when a patient thought a happy face was fearful, the neuronal response followed the subjective percept of fear.

Together, these results support the argument that neurons in the human MTL might play a role in forming conscious percepts. However, lesion studies neither report perceptual deficits nor impairment of moment-to-moment awareness resulting from MTL lesions. In contrast, such studies of patients with MTL lesions show major deficits in memory formation and consolidation (Scoville and Milner 1957; Milner et al. 1968; Squire et al. 2004). For example, patient H.M. exhibits superior performance compared to age match control group in the Mooney face perception task, in which subjects need to recognize faces in chaotic-looking black and white patterns (Milner et al. 1968). Similarly, patients with bilateral lesions of the amygdala exhibit deficits in the recognition of emotions but not in other visual-perceptual discrimination tasks nor in consciousness processes (Tranel and Hyman 1990; Adolphs et al. 1994, 2005). This data thus suggest that activity of cells in the MTL is not required to create conscious percepts (Quiñan Quiroga 2012). So what other function could those neurons have?

7 Memory

As lesions of the MTL lead to significant impairments in acquiring new memories (Scoville and Milner 1957; Milner et al. 1968; Squire et al. 2004), it was hypothesized that concept cells could play an important role in the process of acquiring new memories (Quiñan Quiroga 2012). Some of the characteristic of these neurons supports this hypothesis (Quiñan Quiroga 2012). For example, the high degree of invariance of these neurons corresponds to the fact that humans have a tendency to remember concepts and forget details (Quiñan Quiroga et al. 2005). They also tend to be activated to relevant concepts for a given subject such as pictures of their family, themselves (Viskontas et al. 2009). Additionally, these cells respond to multimodal stimuli and they are also activated by internal processes. This indicates that their function may lay beyond perception (Kreiman et al. 2000b; Gelbard-Sagiv et al. 2008; Quiñan Quiroga et al. 2009; Cerf et al. 2010). Indeed, research concerning long term memory utilizing recordings of single unit MTL supports the crucial role of MTL neurons in forming new memories (Rutishauser et al. 2006, 2008, 2010). While this research has been reviewed extensively elsewhere (Rutishauser et al. 2014), we briefly summarize a few key findings relevant to the present discussion. In a series of experiments, subjects were shown a sequence of unfamiliar (novel) images. After a delay (10–30 min), during which subjects performed a distraction task, another sequence of images was presented. This second set contained both the images shown previously as well as unfamiliar (novel) images. The task of the subjects was to indicate for each image whether it has previously been seen before (old) or not (new). This is thus a typical declarative

Fig. 4 Hippocampal neuron which increases its firing rate to familiar stimuli. *Green trials*—shows response during learning phase, *Blue trials*—shows response to novel stimuli during test recognition session, *Red trials*—shows response during recognition session to stimuli already presented during learning phase. Modified from Rutishauser et al. (2006)



memory task, requiring an intact MTL. Analysis of units in the amygdala and hippocampus revealed two subpopulations of neurons (Rutishauser et al. 2006, 2008). The first subpopulation increased their firing rate to pictures which had previously been presented (Fig. 4) whereas a second subpopulation responded only for novel pictures.

These differences could be observed as fast as 10 min after initial encoding and lasted at least 24 h (the shortest and longest period tested). In one of the variants of the experiment, subjects saw pictures in one of four quarters of the screen during the learning session and were asked to memorize not only which pictures they saw but also their position on the screen (Rutishauser et al. 2008). The group of neurons that increased their firing rate for familiar pictures increased their firing rate even more when the spatial position was correctly remembered by the subject. In contrast, the firing rate increase was of reduced magnitude if the subject failed to remember (recall) the spatial position. This data demonstrates a role of these neurons in the declarative memory process and suggests that these neurons encode a continuous strength-of-memory-gradient. Interestingly, it was possible to predict which pictures will later be remembered and which will be forgotten based on the response of neurons during the encoding phase (Rutishauser et al. 2010). The best predictive feature was the extent of phase locking to theta-band (3–8 Hz) oscillations of a subset of neurons. Thus, if during encoding of a particular picture theta phase locking was strong, the image was likely encoded and thus later remembered. In contrast, weak phase locking predicted that the image would be forgotten. This result shows the first direct demonstration of the crucial interplay between neuronal activity and ongoing oscillation in the process of forming new memories. Another interesting discovery made

by Rutishauser et al. was that novelty/familiar responses were not visually tuned (Rutishauser et al. 2008, 2015). Instead, an individual novelty/familiarity coding neuron signaled whether a stimulus has been seen before or not regardless of the visual category of the presented picture. This is in stark contrast to the highly tuned neurons summarized earlier, indicating that these neurons are different. Thus, this neuronal response could be utilized as general novelty detector that signals the significance of a stimulus and facilitate its memorization (Lisman and Otmakhova 2001).

8 Closing Remarks

During the last two decades, research based on recoding single neurons in the human brain have greatly advanced our understating of cognition, memory, and perception. Early experiments largely replicated and extended to humans findings previously made only in animal models, in particular macaques. This is important because it validates the animal model. More recently, fundamental new discoveries only possible in humans have been made. Among those are the crucial new insights provided on the exquisite tuning, invariance and sparseness of visually responsive neurons summarized in this chapter. Unfortunately, little is known about the response of neurons in the human visual cortex due to the inability to routinely record from these areas in humans. Nevertheless, recordings from higher-level areas in the MTL have revealed a surprising number of interesting insights for vision and awareness and are thus highly valuable. Lesion studies of the MTL only have a limited impact on perception and visual awareness, but result in major memory impairments. Similarly, single unit research summarized in this chapter has revealed an important role for MTL neurons in the memory formation process. Together, this data supports the hypothesis that the highly specific visual responses observed in the MTL subserve memory formation or retrieval rather than perception as such. However, it should also be noted that the perceptual studies performed with MTL-lesioned subjects are rather crude and one can thus not exclude the possibility that the right experiments have not yet been done to uncover perceptual or perhaps awareness deficits in patients with MTL lesions.

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Computational and Cognitive Neuroscience of Vision

Zhao, Q. (Ed.)

2017, VII, 315 p. 85 illus., 71 illus. in color., Hardcover

ISBN: 978-981-10-0211-3