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Single unit approaches to human vision and memory

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Research on the visual system focuses on using electrophysiology, pharmacology and other invasive tools in animal models. Non-invasive tools such as scalp electroencephalography and imaging allow examining humans but show a much lower spatial and/or temporal resolution. Under special clinical conditions, it is possible to monitor single-unit activity in humans when invasive procedures are required due to particular pathological conditions including epilepsy and Parkinson's disease. We review our knowledge about the visual system and visual memories *in the human brain at the single neuron level*. The properties of the human brain seem to be broadly compatible with the knowledge derived from animal models. The possibility of examining high-resolution brain activity in conscious human subjects allows investigators to ask novel questions that are challenging to address in animal models.

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Current Opinion in Neurobiology 2007, **17**:471–475

This review comes from a themed issue on
Sensory systems
Edited by Peter Mombaerts and Tony Zador

Available online 20th August 2007

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2007.07.005

Introduction

Most of our knowledge *at the neuronal level* about the visual system comes from studies in animal models such as macaque monkeys, cats, rats or mice. Human studies are largely restricted to non-invasive tools including scalp electroencephalography, imaging or lesions. These techniques have provided important insights about the anatomy and function of different brain areas. Unfortunately, the spatial resolution ranges from mm to cm and, therefore, typical measurements report some indirect assessment of the average activity over at least millions of neurons. Some of these measurements also show a slow temporal resolution, which may extend up to two orders of magnitude slower than the neuronal firing time scales.

Under some circumstances, it is possible to record neuronal spiking activity in the human brain. These invasive measurements are carried out in patients that have electrodes implanted for clinical reasons. The most typical scenarios involve either patients with movement disorders such as Parkinson's disease (e.g. [1]), patients with psychiatric diseases including depression and obsessive compulsive disorder (e.g. [2]), patients with forms of epilepsy that are resistant to treatment [3,4] and patients with tetraplegia [5]. We focus here on studies on epileptic patients because the work relates more directly to vision and memory.

Visual information impinging on the retinae is conveyed to visual cortex through the lateral geniculate nucleus in the thalamus. In cortex, two main pathways can be distinguished: a dorsal 'where' pathway and a ventral 'what' pathway [6]. Visual information is then conveyed to areas in the medial temporal lobe (MTL) and to frontal cortex areas. Most single-unit recordings in epileptic patients focus on areas of the MTL including the entorhinal cortex, parahippocampal gyrus, hippocampus, subiculum and amygdala. The MTL structures receive input from multiple modalities and play an important role in the formation of memories [7–9].

Here we discuss the recording of single neuron activity in humans, what has been learnt about visually evoked responses and the relationship to visual memory formation.

Recording spiking activity in the human brain

In many cases, intracranial recordings from the human brain involve the use of large subdural grid electrodes or intracranial EEG measurements (e.g. [10–13]). These recordings show better spatial delimitation than scalp EEG measurements but they are far from neuronal resolution. Invasive recordings of spiking activity in humans date back to the 1950s [13–15]. Thin microwires (about 40 μm in diameter, 1 MΩ impedance) are invasively implanted during surgery. The number of electrodes and their location depend on clinical considerations. Recordings in patients are restricted to areas that are clinically relevant (e.g. areas which are suspect of causing epileptic seizures).

In some cases, investigators record neuronal activity *during* surgery [13,16–18]. These acute recordings involve difficult experiments because they need to be performed in the context of brain surgery. The information gathered from these recordings (combined sometimes with elec-

trical stimulation) can be used to make clinical decisions about the areas to resect.

In other cases, electrodes are chronically implanted for approximately one week [19]. The patients stay in the hospital and the electrodes record activity until sufficient information about the seizure onset foci is accumulated. The microwires are not moved by the clinicians after surgery (until they are removed). These recording conditions provide more time to collect data and also allow for the possibility of following up neuronal activity over longer periods of time.

While most experiments attempt to correlate physiological measurements with the visual input, recordings in humans can evaluate how neuronal signals represent subjective percepts [20]. Multiple converging pieces of evidence show that humans are largely unaware of a large fraction of activity in their brains. Distinguishing subjective perception from the visual input has been challenging in animal models. Still, significant progress has been made recently by extensively training animals to report their percepts (e.g. [21]). Invasive recordings from the human brain offer the potential of directly asking questions about perception at high spatial and temporal resolution [22,23•].

Everything we know about single neuron activity in the human brain comes from studies in patients. However, it should be noted that in many cases, electrodes are placed in areas that are far from the epileptic focus based on *a posteriori* analyses.

Visually-evoked single neuron activity

Ascending through the visual hierarchy, neurons show progressively longer latencies, larger receptive field sizes and higher degrees of complexity in the preferred features. In higher visual areas, such as inferior temporal cortex, a neuron may respond selectively to complex objects [24–27]. So far, only rarely have investigators monitored spiking activity in early visual areas in humans [13–15]. The overall properties of lateral geniculate thalamic and occipital human neurons seem to be generally compatible with the observations in animal models (based on recordings from tens of neurons only) [28]. LGN neurons show latencies of about 30 ms; occipital neurons showed latencies of about 60 ms and were tuned to certain spatial frequencies. In area V5/MT (an area specialized for visual motion, not to be confused with the medial temporal lobe, MTL), coherent visual motion evoked a strong spiking response with a latency of about 110 ms [29]. The neuronal activity could distinguish between stationary and moving stimuli and also between coherent and incoherent motion stimuli.

Responses to faces and to a perceptual matching task were observed in the superior and middle temporal gyrus [17,18]. Neurons in the lateral temporal cortex also responded selectively during a visual spatial memory task [16]. Neurons in human medial temporal lobe areas also show strong selectivity preferences upon presentation of different complex visual stimuli. For example, neurons respond selectively upon visual presentation of photographs depicting human faces [30,31] and can discriminate between faces and household objects [32,33]. In a more extensive set of images that included human faces denoting emotional expressions (see also [34]), human faces from famous people including photographs and line drawings, household objects, spatial layouts, animals, vehicles and abstract patterns, MTL neurons showed selective responses to either broad categories of objects or to specific objects within those categories [35] (see also [36]). MTL neurons also responded to specific views and landmarks while the subjects were engaged in a virtual maze navigation task [37]. Some MTL cells also modulated their activity in response to conjunctions of behavioral goals, place in the environment and specific views.

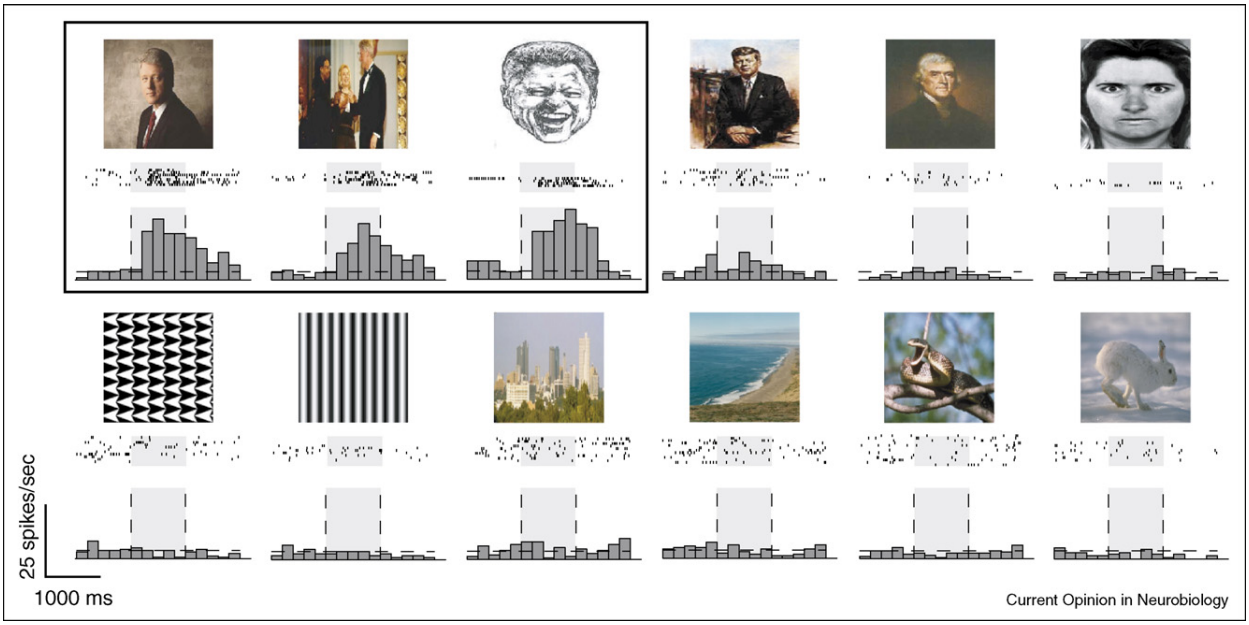
Visually evoked responses were also found outside visual cortex and the MTL. For example, visual presentation of aversive stimuli evoked responses in the ventral prefrontal cortex [38]; responses after eye movements (which could potentially be visually evoked responses) were found in the subthalamic nucleus [39•].

Selectivity and invariance in object recognition

One of the essential characteristics of visual recognition is the high selectivity and strong robustness to stimulus transformations. The combination of invariance and selectivity constitutes one of the main achievements of the primate recognition machinery [25–27]. The selective responses of neurons in the MTL show robust tolerance to strong changes in the input images. For example, broadly tuned neurons show responses to multiple different objects within a category [35]. During the virtual navigation task described above, neurons that were activated when the subject was in a particular location within the environment showed robustness to the particular ways of defining the place [37].

A particularly remarkable degree of invariance in the MTL neuronal responses was recently demonstrated by Quian Quiroga and colleagues [40••]. Upon finding a neuron responding to a particular face or object, subjects were shown several images containing modified versions of the particular face or object. Many MTL neurons showed robust invariance to these transformations (an example is shown in Figure 1). The striking degree of sparseness and selectivity of these responses has prompted some investigators to suggest that these may represent 'grandmother' neurons, that is, neurons that respond in a very specific fashion to a single object [41]. However, careful analyses suggest that each neuron is

Figure 1



Example of selectivity and invariance in the human MTL [40••] showing the responses of a single unit in the right amygdala of an epileptic patient. Depth electrodes were implanted to localize areas responsible for seizure onset [3,4,13,19]. Here we show the responses of the unit to 12 of the 53 images that were presented during this session (the neuron did not respond above baseline for any of the other stimuli which are not shown here). The raster plot shows the spikes aligned to stimulus presentation (shaded box). The post-stimulus time histograms below the raster plots show the average activity of the neuron across the repetitions of each image (bin size = 200 ms). The horizontal dashed line shows the average activity of the unit during the entire experimental session.

likely to respond to many objects/concepts and that individual objects/concepts may be represented also by many neurons [40••,42•].

The representation of visual memories

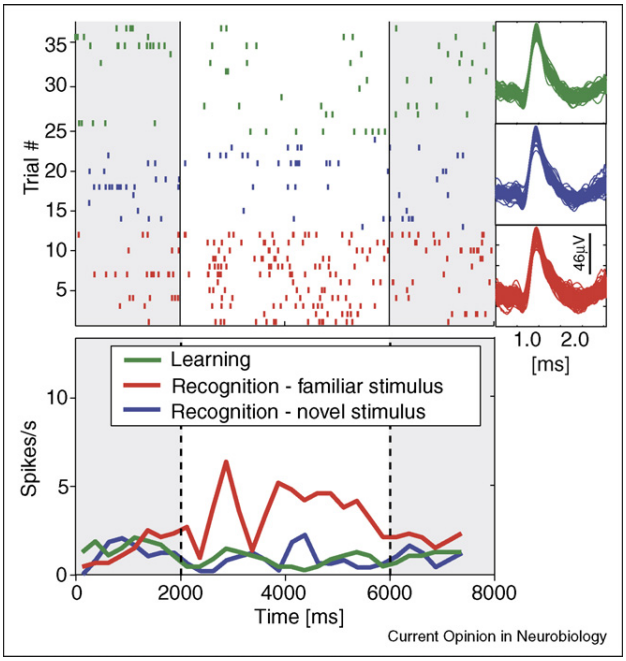
Several pieces of evidence suggest that the highly selective responses by MTL neurons should not be exclusively attributed to visual recognition or visual perception. These responses could well reflect a role of the MTL in memory trace formation, memory consolidation and information retrieval: (i) The MTL receives information from different modalities [8]; (ii) Subjects with MTL lesions or excisions show profound deficits in the formation and consolidation of novel declarative memories. Yet, the visual recognition capabilities seem to remain largely intact [7–9]; (iii) The latencies of human MTL neurons are rather long for immediate visual object recognition [26]; (iv) Assuming parsimony and extrapolating from animal studies, extensive evidence from molecular and physiological experiments strongly suggest a prominent role for the MTL in memory formation and consolidation (e.g. [8,9]), (v) Electrical stimulation in the human MTL can disrupt memory formation [43].

There is a close link between memory and recognition [25,26,44]. Most models of visual object recognition postulate a comparison between the incoming input and existing templates or centers from radial basis function units (e.g. [25–27,44]). Consistent with this notion, recordings in the human MTL suggest that these neurons may play an important role in memory processes.

In a word-pair association task, the activity of hippocampus neurons during the association/encoding phase could predict whether the subjects would remember those word pairs [45]. In another study, neurons in the human MTL were selectively activated when subjects mentally recalled information about an image that had been visually presented several seconds before [46]. After seeing images presented on a monitor, the subjects were instructed to mentally recall one image or the other. Several MTL neurons modulated their activity in a selective fashion during visual recall ([46] see also [47]).

An important first step in the formation of new memories may be the distinction between familiar and novel information. Repeating a stimulus within a short time (seconds) does not seem to have an effect on the MTL neuronal responses ([30], see however [48•] for longer intervals). Fried and colleagues recorded single neuron activity in response to visual presentation of faces and objects, some of which had been shown to the subjects about 10 hours before the recordings and observed that many neurons could differentiate between familiar and

Figure 2



Responses of a single unit in the hippocampus of an epileptic patient during learning and recognition of visually presented images. Subjects were shown 12 different images (learning phase, green). *Each image was shown only once during learning*. After 30 min, subjects were shown either the same images (recognition phase, red) or novel images (recognition phase, blue). The raster plot (top) shows the spikes aligned to stimulus onset (at t = 2000 ms). The post-stimulus time histogram (bottom) shows the average activity of the neuron during each phase. The spike waveforms (top, right) show that the recording was stable during the experiment. This neuron enhanced its activity upon presentation of familiar stimuli. Modified with permission from [49••].

novel stimuli [32]. How much information is needed to label an object as 'familiar' or 'novel'? Rutishauser and colleagues showed subjects only a single instance of each of 12 possible images during a learning phase; 30 min later, they presented subjects with familiar and novel stimuli ([49••], see also [48•]). Several hippocampus neurons could distinguish whether the image had been shown before or not (see example in Figure 2). A decoding analysis using a statistical classifier showed that the population of neurons could correctly indicate whether a stimulus was familiar or not even when the subject made an incorrect behavioral response, emphasizing that the neurons did not represent the decision process but, rather, directly reflected the actual memory of previous presentation.

Conclusions

The study of single neuron activity in the human brain offers the potential to bridge between high-resolution studies in animal models and low-resolution studies in human subjects. The motivation for inserting electrodes in the human brain comes from clinical considerations such as the need to map where seizures are coming from and the function of brain areas that may need to be removed. For this reason, data is non-uniformly distributed in the brain and most of the information comes from areas in the medial temporal lobe structures. By and large, the observations in visual cortex seem to be broadly compatible with knowledge derived from recordings in animal models. Single neuron recordings in human patients offer the possibility of asking questions that are very challenging to address in studies in animals. This includes the possibility of directly studying at high spatial and temporal resolution questions about the relationship between vision and language, the formation of episodic visual memories, single-trial learning and the relationship between neuronal activity and subjective perceptual sensations.

Acknowledgments

We thank Yigal Agam and Ueli Rutishauser for comments and Ueli Rutishauser for preparing Figure 2. We acknowledge the support of the American Epilepsy Foundation.

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