Single-Neuron Recordings in Epileptic Patients

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Intracranial recordings in epileptic patients

Epilepsy is one of the most common neurological disorders affecting almost 1% of the population.[1] Patients suffering from epilepsy that do not improve with medication may be considered for resective surgery and, based on clinical criteria combined with neuroimaging and video-telemetry, may be implanted with intracranial electrodes to accurately localise the seizure originating area – the 'ictal onset zone'- and evaluate the prognosis of the potential surgical intervention.[2] Although the mechanisms of epileptic seizures are still far from being completely understood, intracranial electroencephalographic (EEG) recordings have given invaluable information, among others, to identify electrophysiological patterns at seizure onset, to determine the seizure focus and the routes of seizure spread, etc.[1 4] Besides their clinical importance, intracranial recordings also allow the study of neural activity in the living human brain, thus providing unique insights about different brain functions.[5]

For clinical reasons, intracranial recordings are often done in the medial temporal structures.[2] The medial temporal lobe (MTL) comprises the hippocampus, amygdala, entorhinal cortex and parahippocampal cortex. These areas are known to be involved in high level cognitive processes, such as memory formation,[6 7] and it is therefore very interesting to study how neurons in the MTL behave in different tasks and conditions. However, for neuroscientists interested in studying the principles of neural coding, the main limitation of intracranial EEG recordings arise from the fact that the EEG is a measure of the average electrical activity of large neural populations and, consequently, they only give indirect and ambiguous evidence of the behaviour of single neurons. Ideally, to get a deeper understanding of how neurons encode information in these areas, one would like measure the activity of single-neurons directly.

Single neuron recordings in humans

Using tungsten microelectrodes implanted during surgery in epileptic patients undergoing anterior temporal resections, just before the tissue removal, Ojemann and colleagues recorded single cells while the patients performed language tasks, such as object naming and word reading.[8] In this pioneering study, these authors found that single cells significantly changed their firing, thus showing some relation with language and memory.[8] Using microwires placed at the end of intracranial depth electrodes, a recording setup was developed at the University of California, Los Angeles (UCLA) that allows not only the recording of intracranial EEG but also of multiple single-neurons and local field potentials i.e. the mean field potential generated by the activity of neurons and synapses in the vicinity of the recording electrode.[9] The possibility of recording multiple single neurons in these areas allows the extraordinary opportunity to study directly the neural correlates of different brain functions in conscious human subjects, who – in contrast to animals – can give detailed feedback of their experience and behaviour. Moreover, human subjects can just be asked to perform a certain task and, at least in general, do not need extensive training as in the case of animals. In this respect, it should be noted that monkeys are usually over-trained to perform a task, a fact that may affect the interpretation of results since these could be attributed to the particular behaviour under study or to training effects.[10]

With the human single neuron recording setup developed at UCLA, it was shown that the firing of single neurons in the hippocampus and the amygdala discriminated faces from inanimate objects.[9] A following study demonstrated the presence of category-specific neurons in the human MTL: a neuron responding to faces, another one responding to objects, another one responding to animals, etc.[11] In another study, subjects were asked to imagine previously seen images and it was found that MTL neurons selectively changed their firing according to the image that was imagined.[12] Interestingly, most of the visually responsive neurons had the same selectivity when pictures were imagined – i.e. in the absence of the visual stimuli – thus suggesting that in MTL there is a common substrate for processing visual information and visual recall.[12]

Abstract neurons in the human medial temporal lobe

With the same experimental setup described above, several improvements allowed the identification of much larger number of neurons, especially those that fire very sparsely and are usually hard to detect. These developments led to the finding of neurons with invariant visual responses in the human MTL.[13] For example, a neuron in the hippocampus fired consistently to presentations of 7 different pictures of the actress Jennifer Aniston and not to about 80 pictures of other persons or objects. Another hippocampal neuron fired selectively to different pictures of the actress Halle Berry and even to the presentation of her name written in a computer screen. These findings show a very sparse, explicit and abstract representation by MTL neurons.

Figure 1: Raster plots of a single neuron in the right entorhinal corte that fired selectively to pictures of the World Trade Center. Trials where the pictures were (were not) recognised are displayed in blue (red). Responses changed dramatically depending on whether the picture was recognised or not, and far outlasted the stimulus presentation duration (shown in the left hand side).

Neural correlates of conscious perception

By progressively shortening the stimulus duration (264ms, 132ms, 66ms and 33ms) and showing the pictures at the threshold of recognition, it has recently been shown that the MTL neurons described above can follow the conscious perception of the pictures with 'all-or-none' responses.[14] For example, Figure 1 shows a single-unit in the right entorhinal cortex of a subject that fired selectively to pictures of the World Trade Center. From a nearly silent baseline activity the neuron responded with up to 10 spikes per second. The response of this neuron to the other 15 pictures shown in this experiment was not significant. The patient reported not recognising the picture of the World Trade Center in all trials with 33ms duration and in eight trials with other durations (in red). Corresponding with the behavioral report, there was no observable response during trials where the picture was not recognised. The difference between recognised and non-recognised trials was remarkable for the 66ms presentations, where it is clear that the neuron fired in an "all or none" fashion. In fact, for the three trials in which the picture was recognised, the neuron fired five to eight spikes between 300ms and 1000ms after stimulus onset and for the five trials in which the picture was not recognised the neuron did not fire a single spike.

What is the function of these MTL neurons?

Given the relatively long latency of the human MTL responses reported here – at about 300ms – it is highly likely that these neurons are not part of the recognition process per se. This is in agreement with lesion studies in the hippocampal formation and substantial evidence from patient H.M. and others.[6,7] In fact, patient H.M. – the most studied patient in neuroscience history – was subject to a bilateral hippocampal resection, which at the time (in the 1950s) was though to cure him from his epilepsy. After surgery, H.M. seemed to have a completely normal behaviour without the hippocampus, given his intact ability to recognise different people, but it soon became apparent that he was not able to form new memories. The fact that the MTL cells described here have very strong and abstract visual responses is in line with the interpretation that they may be underlying the link between consciously perceived inputs and memory, since we tend to remember concepts rather than irrelevant details.[13,15]

Conclusion

Recordings in patients suffering from epilepsy, implanted with intracranial electrodes for clinical reasons, have provided invaluable information about normal and pathological brain function. Here we have showed how much information can be obtained from single neuron recordings while awake and behaving patients perform different perceptual and cognitive tasks. The recordings described here were in the medial temporal lobe structures, which are crucial for memory processes. But this approach in not limited to the medial temporal lobe, since similar type of recordings are possible (and clinically justified) in other cortical and subcortical structures, such as the subthalamic nuclei for deep brain stimulation. The possibility of recording the activity of single neurons in these areas opens a window of new opportunities to directly tackle some of the most important and, so far, elusive questions in neuroscience. ◆

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