OPINION

Concept cells: the building blocks of declarative memory functions

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Abstract | Intracranial recordings in subjects suffering from intractable epilepsy — made during their evaluation for an eventual surgical removal of the epileptic focus — have allowed the extraordinary opportunity to study the firing of multiple single neurons in awake and behaving human subjects. These studies have shown that neurons in the human medial temporal lobe respond in a remarkably selective and abstract manner to particular persons or objects, such as Jennifer Aniston, Luke Skywalker or the Tower of Pisa. These neurons have been named 'Jennifer Aniston neurons' or, more recently, 'concept cells'. I argue that the sparse, explicit and abstract representation of these neurons is crucial for memory functions, such as the creation of associations and the transition between related concepts that leads to episodic memories and the flow of consciousness.

More than 2,000 years ago, Aristotle argued that our thoughts are based on internal representations of the external world, and he distinguished between sensation (the image impinging on the retina) and perception (the interpretation we give to the stimulus)[1]. Nowadays this view constitutes one of the most basic principles of brain function. The sight of a familiar person or the sound of this person's voice, for example, triggers a cascade of brain processes that creates a representation leading to the recognition of the person, the recollection of details related to him or her and the generation of new memories.

The study of how neural populations give rise to such exquisite processes has been a subject of active research for decades. In particular, a large number of studies have established that neurons in the ventral visual pathway (FIG. 1) are involved in visual recognition[2–5]. Along the ventral visual pathway there is an increase of selectivity to complex features and visual invariance[2–5]: neurons in V1 (the first cortical visual processing area) represent the minute details that compose an image, whereas neurons in the inferotemporal cortex respond to a high-level representation of the image.

From the inferotemporal cortex there are massive projections to the medial temporal lobe (MTL)[6–8]. Evidence from animal studies[9–11], patient H.M.[12–15] and other patients with lesions in the hippocampus and the MTL[11,16,17] have clearly demonstrated the key role of the MTL in the creation of declarative memories, their consolidation and recall[10,11,16,18–22]. What has remained less studied, however, are the processes and neuronal representations that determine how the perception of external stimuli leads to the creation of the conceptual, internal representations of Aristotle and to the formation of new memories. As our thoughts rely on constructions we make about the external world, both perception and memory are based on the meaning we attribute to what we sense or recall. This attribution of meaning is subjective: it involves abstraction or, in other words, extracting relevant features and leaving aside an immense number of details[4,23–26]. In this Perspective I argue that the recently identified 'Jennifer Aniston neurons' — or 'concept cells' (REF. 27) — in the MTL are the pinnacle of this abstraction process and provide the conceptual representation of stimuli that underlies declarative memory functions.

Concept cells

Patients suffering from intractable epilepsy may be implanted with intracranial electrodes for clinical reasons, and this provides a unique opportunity to record the activity of multiple single neurons in conscious human subjects performing different tasks (BOX 1). The exact location of the electrodes often includes the MTL, given its involvement in certain forms of epilepsy[28]. Initial studies showed selective MTL neuronal responses to particular words and faces[29] and to infrequent stimuli in an oddball task[30]. Neurons in the human MTL were also found to respond to conjunctions of stimulus features (such as gender and facial expressions[31]), associated word pairs[32], the category of the stimuli[33], the degree of novelty and the familiarity of images presented to the subjects[31,34,35], and were found to be active during visual imagery[36] and recall[37]. The use of stimulus sets optimized for each subject (according to their own preferences and background), screening sessions to determine which pictures elicit responses in any of the recorded neurons, and optimal data processing (namely, spike detection and sorting (BOX 1)) has made it possible to identify sparsely firing neurons in the human MTL with very selective responses — the Jennifer Aniston neurons, or concept cells, which are characterized below.

Visual and multimodal invariance. Neurons in the human MTL typically show a high degree of visual invariance[27] — that is, they show similar firing in response to an individual or object, regardless of the size or viewing angle, in contrast to the limited robustness to basic image transformations that is found in cortical visual areas in animals[4,5] (but see REF. 38). For example, one of the first such neurons found in the hippocampus fired to seven different pictures of the actress Jennifer Aniston and not to 80 other pictures of known and unknown people, animals and places — hence the name Jennifer Aniston neurons. In a subsequent session, the same neuron also responded to Lisa Kudrow (whose picture was not shown in the first session), a co-star in the television series *Friends*. Another hippocampal neuron in the same patient responded selectively to

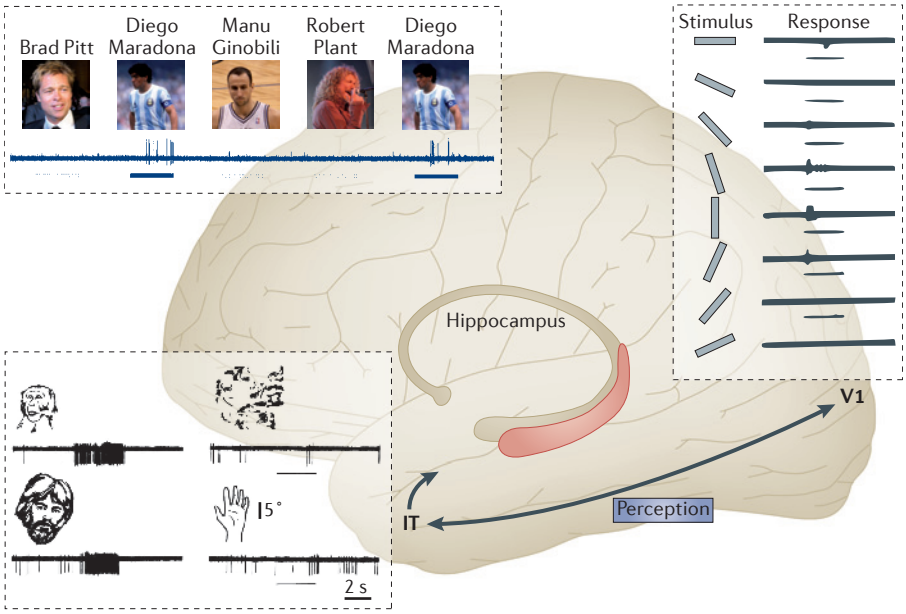


Figure 1 | **Visual perception and memory pathway.** Neurons in V1 — the first cortical visual processing area — respond to local orientations; in the case of this example neuron, a vertical bar[120,121]. This information is further processed along the ventral visual pathway; the neuronal representation in V1 is combined into more complex patterns in higher areas, and in the inferotemporal cortex — the final purely visual area — neurons fire selectively to the sight of faces[122,123]. The inferotemporal cortex has numerous connections to the medial temporal lobe (which includes the hippocampus), in which neurons were found to respond selectively to persons or objects, such as, in the example shown, the football player Diego Maradona[27,40]. The bottom left inset is reproduced, with permission, from REF. 124 © (2008) Elsevier. The top centre inset is reproduced, with permission, from REF. 125 © (2012) MIT Press. The right inset is reproduced, with permission, from REF. 126 © (1959) Wiley.

four different pictures of the Sydney Opera House and to five pictures of the Bahai Temple in India, which the patient confused with the Sydney Opera House (as verbally confirmed after the recording). Another neuron responded to Halle Berry — even when she was masked as Catwoman, a character she played in one of her movies — and yet another neighbouring neuron responded to Mother Teresa[27]. The fact that neighbouring neurons fire to seemingly unrelated concepts, like Halle Berry and Mother Teresa, is indeed common[39,40] and supports the idea of a non-topographic organization of the MTL.

These and many other examples[27,40] suggest that MTL neurons encode an abstract representation of the concept triggered by the stimulus. This claim was tested more conclusively by presenting the written names of these persons or objects to the subjects, and it was found that a large proportion of MTL neurons did indeed respond to both the pictures and the written names of a particular individual (or object). For example, the hippocampal neuron that fired selectively to pictures of Halle Berry responded also to the letter string "HALLE BERRY" (and not to other names). Moreover, the selective responses of these neurons could be triggered by stimuli in other sensory modalities, such as the name of a person pronounced by a synthesized voice[40] (FIG. 2).

Latency of medial temporal lobe responses. The response onset of MTL neurons was more than 100–150 ms later than what would be expected if it resulted from direct feedforward projections from the inferotemporal cortex. Indeed, visual responses in the monkey inferotemporal cortex occur about 100–150 ms after stimulus onset[41], whereas a detailed analysis of the latency of hundreds of (human) MTL neurons showed that responses in the hippocampus, amygdala and entorhinal cortex had a mean latency of about 300–400 ms, with those in the parahippocampal cortex occurring about 50–100 ms earlier[40,41]. The difference in these latencies is consistent with a hierarchical structure of the MTL (see below). Moreover, the relatively large gap between the responses in the inferotemporal cortex and parahippocampal cortex, as well as that between the responses in the parahippocampal cortex and the rest of the MTL, suggests the existence of lateral processing. Such lateral processing could be involved in the transformation of percepts into cognitive entities that can be processed and stored into memory (see below). It is also conceivable that other areas that interact with the MTL — for example, the prefrontal cortex, given its role in categorization[42] — may be involved in this process.

Sparse coding. The responses of MTL neurons are typically very selective, in the sense that these neurons fire to very few of the stimuli presented to the subject (FIG. 2). In contrast to visual cortical areas, in which it is common to find neurons that fire to a relatively large number of stimuli[43,44], in the human MTL, neurons typically respond to no more than 2–3% of the stimulus set[27,39]. As human MTL neurons fire to very few stimuli, each stimulus has to be encoded by a sparse network of relatively few MTL neurons. However, there should be more than one neuron per concept, as the probability of finding the 'one and only neuron' encoding a particular concept in a single experiment is tiny; so if we find a neuron firing to Jennifer Aniston, there must be more. On the basis of the number of responsive units in a recording session, the number of stimuli presented and the total number of recorded units, it has been estimated that in a population of about 10^9 neurons in the MTL, less than ~10^6 are involved in the representation of a given concept (such as Jennifer Aniston or Halle Berry) and, conversely, that each of these MTL neurons may encode up to a few dozen of the 10,000–30,000 things a person can recognize[45]. However, both of these estimations should be taken as upper limits — the true values may be a couple of orders of magnitude lower — because it is difficult to detect very selective neurons (BOX 1), which results in a bias towards observing broadly tuned neurons[46,47]. In addition, the images used were of concepts that were very familiar to the patients (for example, pictures of the patients themselves, family members, experimenters and celebrities) so as to increase the probability of triggering responses. Indeed, personally relevant items were shown to elicit the largest number of responses in the human MTL (and most of the 10,000–30,000 things a person can recognize may not be represented in the MTL at all, as these may not be salient enough to trigger memory processes, see below)[48].

Explicit representation of concepts. At the level of V1 there is an implicit representation of complex visual stimuli, such as pictures of persons or objects, in the sense that it is not possible to infer which stimulus is

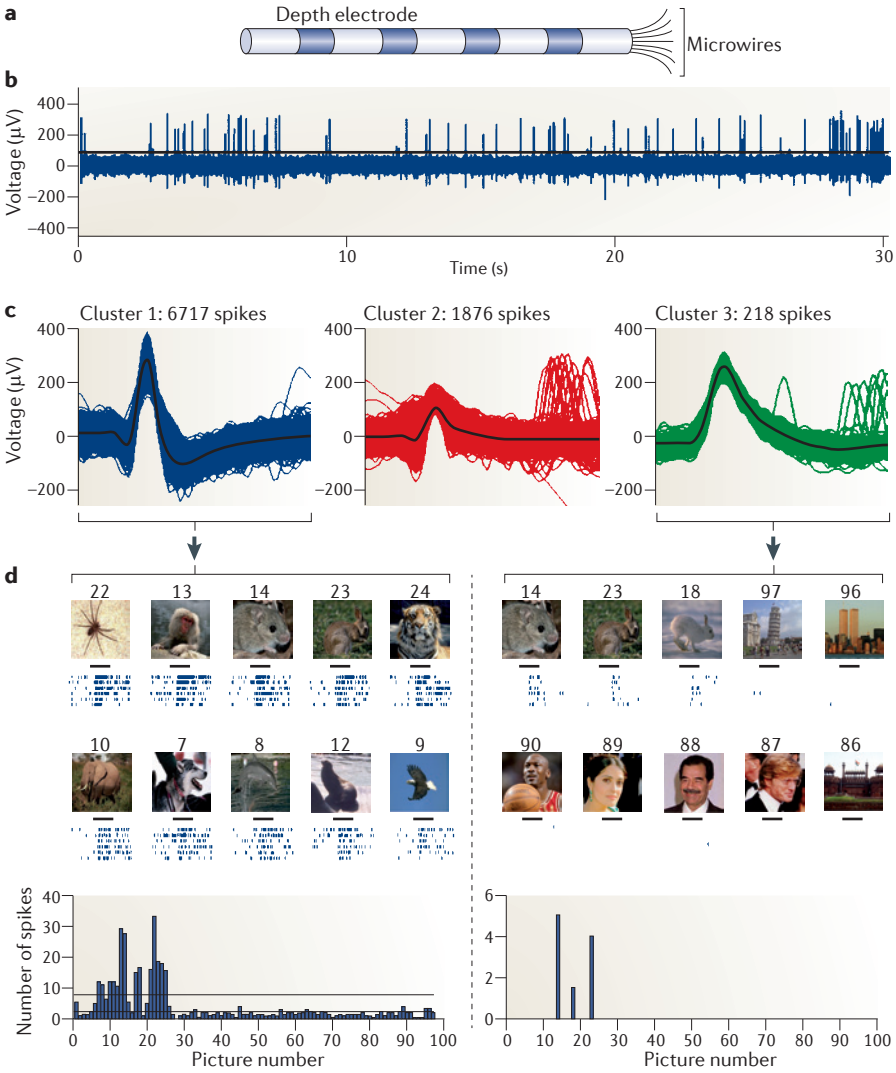
present from the activity of a single neuron. By contrast, in the MTL this representation becomes explicit: a single neuron can tell us whether a given (complex) stimulus is present or not. This can be quantified in an objective way by evaluating the ability to predict the presented stimuli from the firing of the neurons, using decoding algorithms[49]. From the very selective firing of MTL neurons, it was indeed possible to infer which picture was shown to the subject with a success rate way above chance. Just an average of four spikes, fired between 300 ms and 600 ms after stimulation in a handful of neurons, were sufficient to make such predictions[39]. Moreover, in agreement with a very sparse representation, the decoding performance increased linearly with the number of neurons included in the analysis, in contrast to the nonlinear increases found in earlier visual areas[43,50,51] (such nonlinear increases mean that, on average, each responsive neuron contributes to the representation of a large number of stimuli). In general, the decoding algorithm could not distinguish between different pictures of the same individual[39], underlining the idea that MTL neurons encode concepts rather than particular details.

The predictions made from the firing of MTL neurons were not always perfect — their accuracy depended on the noise level, trial-to-trial variability, the stimulus set used and the number of stimuli the neurons fired to — but they were significantly better than chance. If an MTL neuron fires to more than one stimulus (as it is often the case), then we may not be able to distinguish among these stimuli, but the neuron nevertheless gives us information about the stimulus being present (namely, that it is one of a few possible stimuli). The findings that predictions based on the activity of relatively few neurons were already significantly better than chance and that the prediction accuracy increased linearly with the number of neurons argue for an explicit representation in the MTL. This is in contrast to implicit representations in, for example, V1, in which the firing of a single neuron encodes local details and tells us nothing at all about the identity of complex stimuli. In other words, from the firing of a V1 neuron we cannot tell whether the stimulus is a given person, a landscape, an animal or an object, because the neuron fires to a very large number of stimuli and in a different manner if these stimuli are slightly changed.

A recent study designed on the basis of these results showed that patients could modify the firing of individual MTL

Box 1 | **Single neuron recordings in humans**

Neurophysiology recordings in humans are typically limited to non-invasive procedures, such as electroencephalography or functional MRI. There are, however, a few exceptional cases in which, for clinical reasons, it is possible to obtain single-cell recordings in humans. Among these, patients with epilepsy refractory to medication may be implanted with intracranial depth (grid or strip) electrodes to localize the epileptic focus[116]. After the implantation of the electrodes, patients are continuously monitored over several days until a sufficient number of seizures has been recorded and a clinical decision about the surgery can be reached. In the early 1970s, recordings from single neurons in these patients were first performed by inserting microwires through the depth electrodes[117]. Part **a** of the figure shows a sketch of these electrodes, part **b** shows the continuous (high-pass filtered) data and the threshold for spike detection obtained from a microwire located in the amygdala of one patient and part **c** shows the spike shapes of three different units identified from this recording after spike sorting[118,119]. Panel **d** of the figure shows the responses of the first and the third neuron (in blue and green, respectively, in part **c**). The black bars show the presentation time of the stimuli (1 s). The first neuron was activated by pictures of animals and did not respond to other type of stimuli, such as faces or places. The third neuron was much more selective and fired only to three out of 97 pictures: the mouse, the squirrel and the rabbit. Note that without optimal spike sorting this neuron could have been missed because first, the three spike shapes overlap, and second, the third neuron fired only 218 spikes during the ~30-minute recording and its activity could be masked by the other two units, which fired approximately 40 times more spikes in this time. Moreover, this neuron could have been missed if the stimulus set had not included these three particular animals. On the basis of their spike widths and firing rates, the first neuron could be, in principle, classified as an interneuron and the third one as a pyramidal cell. It has indeed been found that interneurons tend to fire to a larger number of stimuli, which — by suppressing the firing of other neurons — may constitute a mechanism for generating the very selective responses of pyramidal cells[54].



neurons to project their thoughts onto an external display[52]. In this case, subjects were presented with a hybrid, semi-transparent superposition of two images — each of which having at least one neuron responding to it, as determined from previous screening sessions. The activity of the responsive MTL neurons was decoded in real time and then used to control the relative opacity and transparency of each of the images. In almost 70% of the trials, and without any prior training, the subjects could make a target picture clearer, fading out the other one, by voluntarily modifying the firing of the responsive MTL neurons. For example, in an experiment starting with the presentation of a 50–50 hybrid picture of Marilyn Monroe and Josh Brolin (two American actors), in 15 out of 16 trials, the subject could successfully convert the hybrid image into Marilyn Monroe or Josh Brolin (as specified by a target presentation at the beginning of the trial) within a few seconds, just by thinking about one or the other person[52]. Interestingly, the subjects' internal thoughts could override the influence of the visual stimulus on the neurons' firing. For example, during the presentation of a hybrid image with 70% Marilyn Monroe and 30% Josh Brolin, the firing of the Josh Brolin-responsive neuron was higher when the subject focused on the concept 'Josh Brolin' than when he focused on 'Marilyn Monroe', even though the visual stimulus was exactly the same in both cases. These firing rate changes were not the effect of a broad modulation in a given area — such as could be expected from, for example, changes in overall attention — because the subjects could also change the firing of nearby neurons in different ways, typically increasing the firing of the neuron that responded to the picture they were focusing on and decreasing the firing of the neuron that responded to the other picture[52].

Another study, in which the images were presented very briefly, at the threshold of conscious recognition, showed that the responses of MTL neurons are mostly all-or-none, in the sense that a neuron fires whenever the picture eliciting its firing is recognized and remains at baseline levels (or completely silent) if it is not[53] (FIG. 3). In other words, MTL neurons can explicitly signal whether a stimulus is recognized. Given the limited set of pictures used in this experiment (only 16 per session), in some cases the subjects could guess which picture was presented using visual cues (for example, the background colour), which led to priming effects — that is, as the experiment

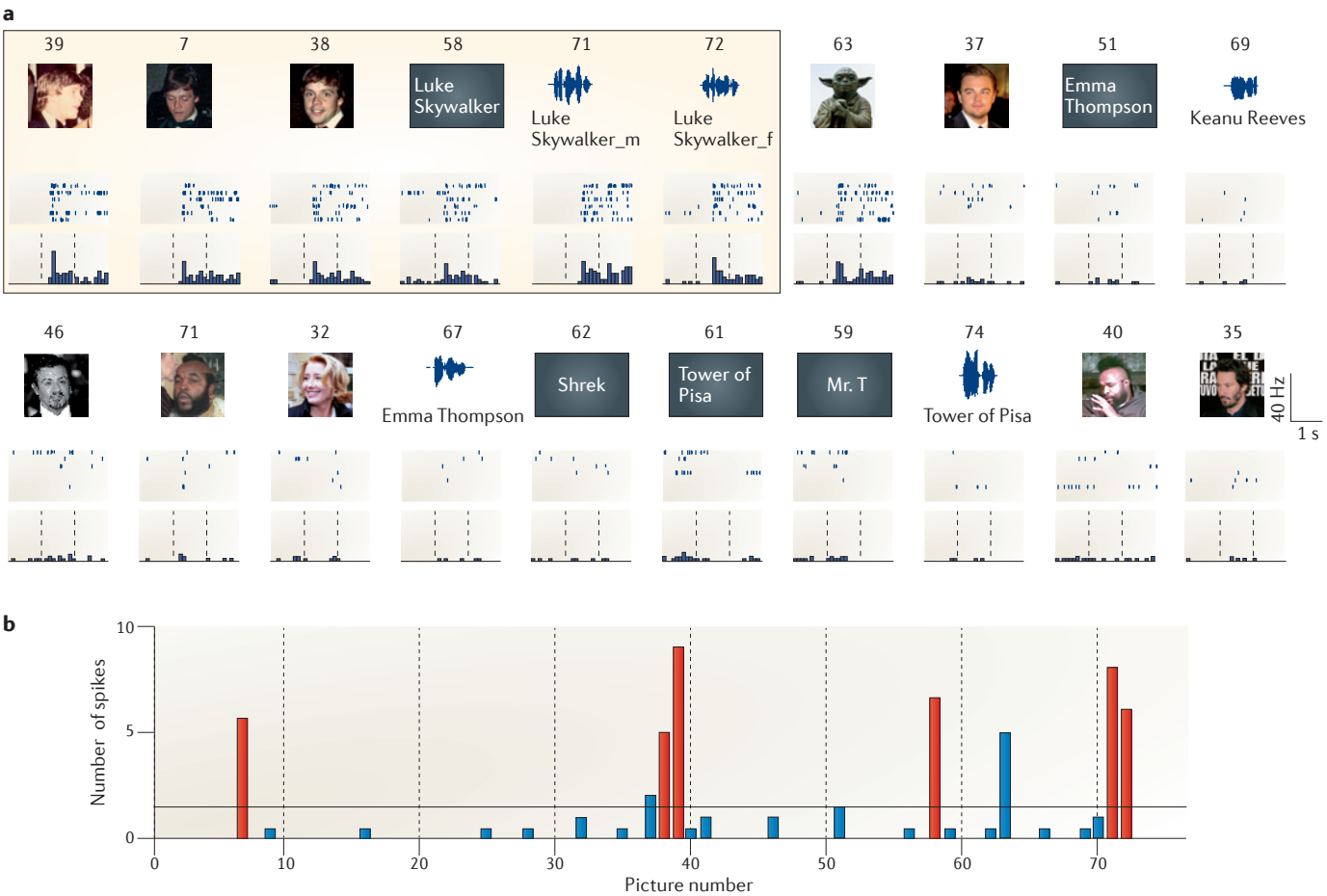


Figure 2 | **Example of a neuron with multimodal invariance. a** | Responses of a neuron in the entorhinal cortex to various pictures and to written and spoken words. Owing to space restrictions only 20 out of 76 responses are displayed. For each stimulus, the raster plot for the six trials and the peristimulus time histograms are shown. The neuron fired, from a nearly silent baseline, selectively to pictures of Luke Skywalker from the movie *Star Wars* (stimuli 39, 7 and 38), his name written on the computer screen (stimulus 58) and his name pronounced by a male and a female synthesized voice (stimuli 71 and 72, respectively). This neuron also fired to Yoda (only a single picture of Yoda was presented; stimuli 63), another character from the movie *Star Wars*. The vertical dashed lines mark stimulus onset and offset, 1 s apart. **b** | Median number of spikes (across trials) for all stimuli. The bars in red correspond to presentations of Luke Skywalker. The horizontal line marks 5 standard deviations above baseline firing. Owing to copyright issues, some of the original images used are replaced here by similar ones. The figure is reproduced, with permission, from REF. 40 © (2009) Cell Press.

progressed the patients became better at recognizing the pictures[53]. So, even if the face on a picture was not seen, other visual cues were sometimes enough for the subjects to correctly guess which picture was being shown, and this triggered the firing of the responsive neuron just as when the picture was presented for longer times.

Hierarchical processing in the MTL

The MTL comprises several interconnected areas that are organized in a hierarchical structure[6–8] (FIG. 4). Briefly, the parahippocampal and perirhinal cortices receive direct inputs from sensory cortical areas and send this information to the entorhinal cortex, which in turn projects to the hippocampus, at the top of the MTL hierarchical structure. The amygdala has direct connections to the other MTL areas and to the sensory cortex.

Neurons in the parahippocampal cortex show about double the number of visual responses (to the stimuli presented in an experiment) compared to the rest of the MTL, which is in agreement with the lower selectivity of neurons in this area. Indeed, there is an increase in selectivity of neurons along the MTL, with the lowest selectivity found in the parahippocampal cortex and the highest in the hippocampus[41,54] (FIG. 4). There is also an increase in visual invariance along the MTL: 52% of the responsive neurons showed visual invariance in the parahippocampal cortex, 59% in the amygdala, 70% in the entorhinal cortex and 85% in the hippocampus[40]. In line with these results, the number of neurons with multimodal responses increases along the MTL: no neuron in the parahippocampal cortex had responses to sound or text presentations, whereas about one-quarter of the responsive neurons in the amygdala and half of the responsive neurons in the entorhinal cortex and the hippocampus responded to sound and text (in addition to pictures)[40]. Altogether, these results show that along the anatomical hierarchical structure of the MTL, there is an increase in response latency, selectivity, invariance and multimodal convergence. This suggests an increase of abstraction along the MTL hierarchy that leads to the encoding of the meaning of the stimulus. This conceptual representation reaches its pinnacle at the hippocampus, but to a varying degree is also present in other MTL areas. Indeed, earlier MTL and cortical areas contribute to the build-up of such coding, which, as I argue in the next section, is crucial for memory functions.

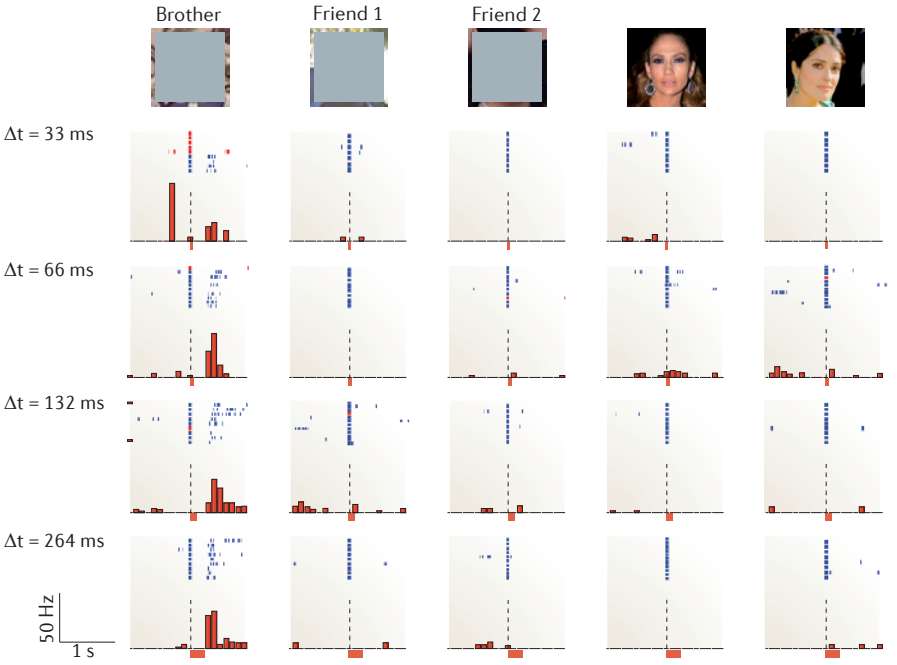


Figure 3 | **Example of all-or-none responses with conscious perception.** A neuron in the hippocampus that fired selectively to a picture of the patient's brother (pictures covered for privacy). Each stimulus was presented for four different durations, which are shown at the left of the figure and indicated by the light red bars at the bottom of the peristimulus time histograms. Trials in which the pictures were and were not recognized are identified with blue and red markers, respectively, at time zero in the raster plots. For each duration, the peristimulus time histograms show the average response to all (recognized and non-recognized) trials. From a nearly silent baseline, the neuron increased its firing to up to 50 Hz only when the patient recognized the picture of his brother: note the dramatic difference between the recognized and non-recognized trials, especially for the 33 ms presentations. The figure is reproduced, with permission, from REF. 53 © (2008) National Academy of Sciences.

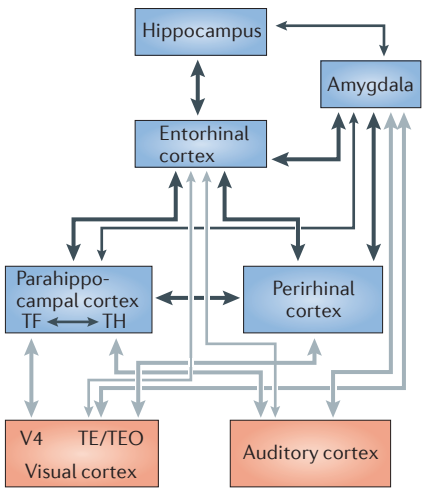
What is the function of concept cells?

Explicit representation of meaning. Converging evidence from the evaluation of patient H.M. and many other studies have shown that the hippocampus, and the MTL in general, is not necessary for visual perception (although some authors argue that the perirhinal cortex is involved in the perception of conjoint features[55–57]) but that it is crucial for the acquisition of declarative memories[10–12]. Considering this role, and the fact that the MTL receives direct projections from the ventral visual pathway and other sensory areas[6–8], one can infer that concept cells in the human MTL, particularly in the hippocampus, encode the meaning of a stimulus for memory functions. More specifically, I propose that a hippocampal neuron firing to a picture of Jennifer Aniston during an experiment is (along with other neurons encoding the same concept) not necessary to recognize her, but it is rather crucial to create new associations and memories, enabling the subject to, for example, later remember having seen Jennifer Aniston's picture during the experiment. This interpretation is supported by the facts that: first, these neurons have a relatively long latency[40,41], suggesting lateral processing to extract the meaning of the stimulus; second, they tend to fire to personally relevant concepts, namely, those that the subject may care to store in memory[48]; third, they have a high degree of invariance, which is in agreement with the fact that we tend to remember concepts and forget irrelevant details[27,58]; fourth, they have a sparse, explicit and non-topographic representation[39], which is ideal for memory functions such as creating new associations[59,60]; and fifth, their function is beyond sensory processing, given that their firing can be triggered by different stimulus modalities[40] or internal processes in the absence of external stimulation[36,37,52].

As the meaning attributed to the things around us is subjective[23], it is likely that the meaning encoded by concept cells is subjective as well, in the sense that it depends on the relevance and connotation that the stimulus has for the subject (for example, the neuron that fired to both the Sydney Opera House and the Bahai Temple, described above, probably did so because

these were the same concept for the subject). This subjective meaning would, in turn, determine the level of categorization or individualization with which the concept will be encoded and eventually stored in memory. Although the MTL is not involved in perception and although categorization may be performed in other areas (including the prefrontal cortex[42]), concept cells fire explicitly to the conscious perception of the stimulus[53]. Therefore, I propose that the firing of a concept cell may bring the particular concept into awareness so that it can be embedded within related facts and circumstances, thus enabling the creation of associations, memories and the flow of consciousness (see below). In other words, I propose that the semantic representations encoded by concept cells constitute the building blocks for declarative memory functions.

Associations, memory and the flow of consciousness. The importance of the MTL for the acquisition of declarative memories and associations has long been established from lesion studies in humans[11,12,61] and unit recordings in animals[21,62–69]. In line with these studies, it is common to find neurons in the human MTL that respond to concepts that are related to each other[40,70]; in other words, if one of these neurons responds to more than one concept, these concepts tend to be related. For example, a neuron fired to Luke Skywalker and Yoda, both characters of *Star Wars*[40] (FIG. 2); another neuron fired to both Jennifer Aniston and Lisa Kudrow, who were co-stars in the same television series; another neuron fired to two basketball players; another one to the Eiffel Tower and the Tower of Pisa; and so on[27,39,40]. Moreover, several neurons responded to one or a few researchers involved in the experiments with the patients. Given that none of these researchers was previously known to the patient, this suggests that concept cells can form invariant responses and associations relatively quickly[40]. In line with this observation, a recent study showed that concept cells can change their firing to encode newly created associations after only one or a few presentations of the associated stimuli[71]. Moreover, a study using video presentations showed that the firing of multiple neurons in the human hippocampus rapidly becomes temporally correlated, which may reflect the encoding of an association of consecutive events[72].



	Parahippocampal cortex	Amygdala	Entorhinal cortex	Hippocampus
Selectivity	4.7%	2.4%	1.7%	1.7%
Response latency (ms)	245	298	334	311
Responsive units	18%	10%	10%	8%
Visual invariance	52%	59%	70%	85%
Text responses	0%	18%	59%	48%
Sound responses	0%	32%	47%	48%

Figure 4 | **Hierarchical processing in the human medial temporal lobe.** The medial temporal lobe consists of the hippocampus, entorhinal cortex, parahippocampal cortex, perirhinal cortex and amygdala. On the basis of anatomical studies in monkeys[6–8], the connectivity within the medial temporal lobe and with the visual and auditory cortex are marked with black and grey arrows, respectively. The table shows, for the four areas in which recordings have been performed in humans, the selectivity and latency of neuronal responses to pictures of people, places and objects, the percentage of responsive units (that is, those that fired to at least one picture), units with visual invariance, and units that also responded to text and sound presentations[40,41]. Along the hierarchical anatomical structure of the medial temporal lobe, there is an increase in the latency of the responses, selectivity, invariance and number of multimodal responses. The highest degree of selectivity and invariance is found in the entorhinal cortex and the hippocampus, which indicates that 'concept cells' — that is, neurons that encode the meaning of the stimulus — are mostly located in these areas. TE, temporal area TE; TEO, temporal occipital area TEO; TF, temporal area TF; TH, temporal area TH. The figure is reproduced, with permission, from REF. 40 © (2009) Cell Press. Data in the table are from REF. 40.

As mentioned before, concept cells do not act in isolation but as part of sparse cell assemblies[45,58,73]. It is then tempting to argue that the association of related concepts relies on overlaps in the networks representing them (FIG. 5). For example, within a cell assembly firing to Luke Skywalker, some neurons may also fire to Yoda[40] (as was the case for the neuron in FIG. 2). Other 'Luke Skywalker neurons' may also fire to Darth Vader, another character of *Star Wars*. Then, it is possible that if the 'Luke Skywalker network' is activated — in response to an external stimulus or internal processes — the subject will become aware of the concept 'Luke Skywalker' and, as a result of the overlap of the Luke Skywalker network with the cell assemblies encoding Yoda or Darth Vader, the network encoding one of these related concepts may in turn become active. Another network overlapping with these three concepts could encode a broader category, such as the concept of *Star Wars*, which would not necessarily be associated with a single image but would be preferentially activated when seeing all these figures together.

In this model, concepts that are, at first, unrelated, could be rapidly linked through Hebbian synaptic plasticity[74]. A similar association mechanism may underlie the learning of somebody's name (that is, associating a name with a face) or, more generally, the link between different sensory modalities (for example, the look and the smell of a rose). Indeed, except in the parahippocampal cortex, MTL neurons fire to pictures of persons as well as to their written and spoken names[40]. Different cortical areas process these three types of stimuli, and MTL neurons, which receive input from these cortical areas, might link them into single concepts — at least in the first instance, as these associations may be later stored in the cortex. Thus, viewing a person's picture, or reading or hearing his or her name, may trigger responses in a subset of the cell assembly encoding this particular concept — that is, the subset of neurons that receive direct projections from the cortical area activated by the stimulus — and this will in turn activate the whole assembly through pattern completion[59].

Consecutive transitions between cell assemblies (FIG. 5) bring related semantic concepts into awareness, one after the other, and thereby create a flow of consciousness, like the recall of Marcel Proust's past memories in a stream of thought triggered by the taste of a madeleine. According to this model, the recall of information should also involve interactions with different cortical areas, in which more detailed

representations — for example, the features of a face — are stored. Concept cells may then provide a conceptual, sketched representation underlying the flow of thought that is linked to (and binds together) rich representations of memories stored in the cortex. This proposal shares similarities with the idea that the hippocampus indexes memory storage sites in the neocortex[75] and combines the different traces that constitute a memory[20]. A similar mechanism may underlie the generation of episodic memories — the ability to remember personal experiences[76] — which are formed by the association of consecutive events[77,78].

It cannot be ruled out that other areas may be also involved in creating transitions between concepts. However, the MTL seems to be crucial: it has been noted that patients with MTL lesions are impaired at accessing and combining contextual information and providing detailed accounts of past experiences[16,17,79–81]. For example, three such patients, H.M., W.R. and K.C., were shown to have a relatively preserved semantic memory but were incapable of recalling personally experienced events[17,79,80]. Moreover, patients with bilateral hippocampal damage are impaired at imagining new experiences: compared to control subjects, they are able to imagine only fragmented events without an environmental context[82,83].

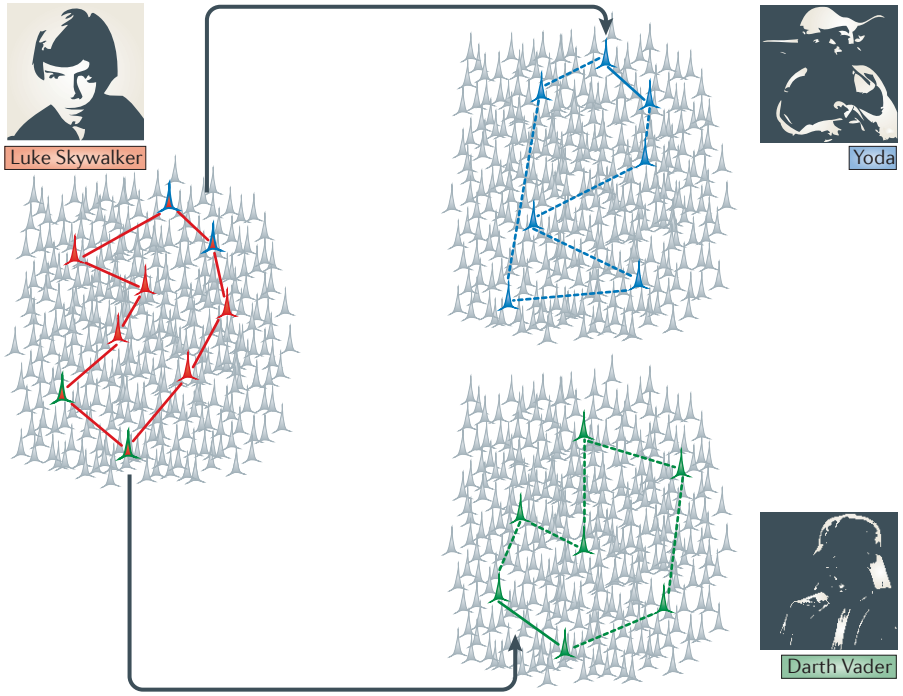


Figure 5 | **Sparse representation of concepts in the medial temporal lobe.** On the left is a hypothetical cell assembly encoding the concept 'Luke Skywalker' (marked in red). Of these neurons, some also fire to Yoda (identified with a blue line contour), and some others fire to Darth Vader (identified with a green line contour). The activation of the 'Luke Skywalker cell assembly', for example, after seeing his picture, can then trigger other associated concepts, such as Yoda or Darth Vader, through the firing of the neurons with an overlapping representation and pattern completion[59]. Such partially overlapping representation could be the basis of the encoding and learning of associations and episodic memories.

From distributed to sparse coding. Evidence from different sensory systems and species suggests that the neural representations of complex stimuli are distributed in primary sensory areas and are sparser in higher areas[46,84,85]. In the human MTL, concept cells show a dramatic increase in selectivity to complex features, compared to neurons in the ventral visual pathway[27,58]. Does this ultra-sparse representation lead to 'combinatorial explosion'? In other words, are there enough neurons in the MTL to encode all possible concepts: such as Jennifer Aniston in front view, wearing a red dress, together with Brad Pitt? The key point is that selectivity occurs together with invariance: large populations of neurons in primary sensory areas may fire differentially to minute stimulus changes, whereas MTL neurons seem to fire to a concept, ignoring such differences. Moreover, concept cells respond to personally relevant items[48]: that is, those that are salient enough to be memorized.

The ultra-sparse representation by MTL neurons raises the question of whether they should be considered to be grandmother cells: that is, one or relatively few neurons encoding only one concept[86], also known as a localist representation. As discussed above, in the MTL concepts are represented by sparse cell assemblies, not by just one neuron per concept. Moreover, although it is in principle possible that an MTL neuron (together with others) could encode only one concept, this is experimentally impossible to prove because it can never be ruled out that a neuron that fires to a particular concept would have also fired to some other stimuli that were not used in the experiment. In fact, it is common to find MTL neurons that respond to more than one concept[40,70,73]. It is therefore not possible to assert that concept cells are grandmother cells, but we can nevertheless say that these neurons have a very sparse and abstract representation of concepts; they do not encode details.

Modelling studies pioneered by Marr[59] have shown that a sparse and explicit coding, as shown by these neurons, is ideal for fast learning and for the creation of new memories and associations. This contrasts with distributed representations in the cortex, which are better suited for the slow learning of shared structures of the stimuli, categorizations and generalizations[60,87–89]. In fact, it has been proposed that the brain may use a complementary learning system approach: the fast-learning hippocampal system is used to learn facts of everyday life based on single exposures, and the neocortical system consolidates this information and embeds it within information from past experiences at a much slower pace, thus avoiding interference between different memories[60,89].

Relationship with place cells

There are striking similarities between concept cells in the human MTL and place cells in the rodent hippocampus, which fire whenever the rat crosses a particular location in the environment (the neuron's 'place field')[90]. First, like human MTL neurons[39], place cells are very selective and, from a very low baseline, fire strongly to their preferred stimulus (in this case, a particular place field)[91]. Second, place cells give an explicit representation of the environment that allows an accurate prediction of the animal's location[91] — similar to the explicit representation of concepts by human MTL neurons that allows the prediction of the stimulus seen by the subject[39]. Third, place cells show attractor dynamics: their firing changes abruptly when environmental

shapes are changed incrementally[92]. This is reminiscent of the all-or-none responses of human MTL neurons, which dramatically change their firing upon picture recognition and could set up on an attractor (by the activation of a network representing a given concept) from a few visual cues[53]. Fourth, place cells maintain their tuning after the light is turned off[93] — that is, their firing can be triggered in the absence of visual information — just like the firing of concept cells can be elicited by imagery[36], internal thoughts[52] or recall[37]. Fifth, place cells can be formed within minutes[91], and concept cells can also encode new concepts and associations relatively quickly[40,71] (for example, in one study, MTL cells responded to researchers the patient did not know a couple of days before the experiment took place[40]). Finally, the rat hippocampus has a seemingly random connectivity[94] that leads to a non-topographic organization, meaning that neighbouring neurons do not necessarily have neighbouring place fields[95,96]. Although we cannot directly assess this issue in the human hippocampus, it is common to find that neighbouring neurons — the activities of which could be separated after spike sorting — respond to completely unrelated things (for example, Halle Berry and Mother Teresa)[39,40]. Notably, such non-topographic organization is ideal for a fast learning of new associations[59].

Both concept cells and place cells can be linked to memory process, and the difference between them may simply reflect the different types of stimuli that are salient to each species: whereas for humans it is important to recognize faces (among other things) and associate information about different people and concepts, for rats it is more important to memorize environments. Along these lines, it has been suggested that the spatial representation given by place cells in rodents is analogous to the representation of semantic memories in humans[97] and that the sequential firing of place cells when a rat travels[98–104], plans[103,104] or replays[98,100–102] a certain trajectory is like an episodic trace, in which the timing of the event is provided by theta phase precession[97]. In line with this view, it has been shown that hippocampal lesions in rats impair the recall of sequences of odours[105]. Following this argument, concept cells can be seen as representing semantic memories — which are also encoded in the neocortex but perhaps in a more distributed manner — and such semantic representations may be crucial for memory functions, such as generating new associations and episodic memories. In fact, episodic memories involve the association of concepts (or events, such as: 'yesterday it was hot, I went to the cinema and later had an ice cream')[76], which, I argue, relies on the semantic representations by concept cells.

Consolidation and plasticity

The role of the hippocampus and the MTL in memory has long been established through evidence from patient H.M.[12,13,15] and many other studies[10,11], showing that MTL lesions lead to anterograde amnesia. The standard consolidation model states that the MTL is crucial for the consolidation of memories into the cortex and, once consolidation has taken place, the MTL is not necessary for their retrieval[10,11]. Other authors have challenged this view, arguing that semantic memories do indeed consolidate in the cortex, but the recall of episodic memories always relies on the hippocampus[16,20]. According to this view, named multiple trace theory, the hippocampus is always necessary for binding different neocortical representations of an event to recall the full richness of episodic memories; this is in contrast to semantic memories, which are stored in the cortex and are independent of contextual information[20]. In the context of this discussion, it is interesting to consider whether concept cells in the human MTL are involved in consolidating information into the cortex and change their tuning according to the things that are particularly relevant at a given time — that is, they no longer respond to a concept after its related memory is consolidated in the cortex — or whether they provide a more stable representation that remains present after consolidation. Unfortunately, we cannot directly address this question because recordings in humans are limited to a few days, and long-lasting tuning changes can therefore not be assessed. Moreover, it is very difficult to track the same neurons across days, as electrodes may move from one day to the next. Nevertheless, a recent study provides evidence of relatively stable representations by concept cells[106]. The analysis of several hundred responses recorded in 26 patients showed that concept cells fire to their preferred stimulus from the first presentation onwards. Therefore, these concepts — which had not necessarily been active in the recent

Glossary

Attractor
A state or set of states towards which neighbouring states converge. In neuroscience, percepts and memories are thought to act as attractors of neuronal representations.

Cell assembly
A network of functionally connected neurons that is activated by a specific mental process (for example, a visual stimulus or the retrieval of a memory).

Combinatorial explosion
A problem in which the number of possibilities increases exponentially. A combinatorial explosion argument has been raised to disprove the possibility of grandmother cells, as there are not enough neurons in the brain to encode all possible concepts and their instances (for example, grandmother smiling, grandmother drinking tea, grandmother wearing a red pullover, and so on).

Declarative memory
Also known as explicit memory, this is the memory of things that can be named and consciously recalled — things that one can be explicitly aware of.

Episodic memory
A form of declarative memory that involves personally experienced events and situations.

Grandmother cell
A neural representation in which relatively few neurons encode for only one thing. Grandmother cell coding is the extreme version of sparse coding.

Grid cells
Neurons in the rodent entorhinal cortex that fire when the animal is at one of several specific locations in an environment and that are organized in a grid-like manner.

Lateral processing
Recurrent processing within a given brain area.

Medial temporal lobe
(MTL). A system of anatomically connected structures that is critical for declarative memory. It comprises the hippocampus, amygdala and the entorhinal, parahippocampal and perirhinal cortices.

Non-topographic organization
A representation in which nearby neurons represent disparate things. It contrasts with a topographic organization, in which nearby neurons encode similar stimulus features or motor outputs (and connect to nearby neurons in other areas).

Oddball task
A task in which subjects have to detect an infrequent deviant stimulus (the oddball or target) that is randomly placed in a sequence of frequent non-target stimuli.

Pattern completion
The process by which a whole-cell assembly is activated from partial inputs.

Semantic memory
A form of declarative memory that involves the memory of facts and knowledge about the world.

Theta phase precession
A phenomenon in which place cells fire at increasingly earlier phases of the underlying theta oscillation when approaching the place field.

past — were already encoded by these neurons before the experiment took place. In other words, there was no reassignment of the concept to a random set of neurons (as would have been the case if the hippocampal representation would have completely decayed after consolidation in the cortex), which would have taken at least a few trials to establish. Moreover, although there was a systematic decay of the response strength with stimulus repetition, this decrease reached an asymptotic value way above the baseline firing activity[106]. It should, however, be noted that this asymptotic convergence was shown for a few repetitions in experiments lasting only about half an hour, and we cannot rule out that further decreases may occur in a longer timescale.

Given the proposed relationship between place cells and concept cells described above, we can also consider additional, yet indirect, evidence supporting the view that the representations by concept cells are relatively stable, as it has been shown that place cells maintain the same tuning properties for months (unless the environment is changed)[107]. Moreover, learning and plasticity in the rodent hippocampus is mediated by changes in synaptic strength through long-term potentiation (LTP)[108], and pharmacological and genetic manipulations that affect LTP can produce unstable place fields that in turn lead to spatial learning impairments[109–112]. On the basis of this evidence, one could postulate that the coding by concept cells should be relatively stable, as an unstable representation by concept cells in the human MTL would give rise to memory deficits. However, this interpretation should be taken with caution because: first, the analogy between spatial memory in rodents and memory process in humans is still a matter of dispute[16,69,113,114]; and second, although there is a cortical declarative memory representation in humans, it is not clear whether a cortical memory representation of space exists in rodents (that is, besides the one given by place cells in the hippocampus and grid cells in the entorhinal cortex). It should also be noted that this proposal argues in favour of neither the standard consolidation model nor the multiple trace theory, as in both models the human MTL could retain a stable representation of concepts, independently of whether memories (especially episodic) are consolidated in the cortex; with the former model the MTL representation of concepts will be redundant after consolidation —as it will also exist in the cortex — whereas with the latter it will always be necessary for the retrieval of episodic memories.

It is possible that concept cells cease to encode a given concept if it becomes irrelevant for the subject. Indeed, the brain may implement an optimal balance between stability (to avoid the situation of having a given concept represented in a different set of neurons each time) and plasticity (to adapt to changes and efficiently encode the relevant concepts). Concept cells may provide a semantic representation for memory functions in the MTL that remains relatively stable for as long as the concept continues to be relevant. The representation of these concepts in the MTL allows the establishment of new associations between them. As time passes, the number of neurons encoding a given concept may diminish if it becomes irrelevant, and this may constitute a key neural mechanism of forgetting.

Conclusions and open questions

Our thoughts are based on abstractions and the attribution of meaning to what we sense or recall. Concept cells in the human hippocampus are the pinnacle of this abstraction process and provide a sparse, explicit and invariant representation of concepts, which, I have argued, are the building blocks for memory functions, such as the creation of associations, episodic memories and the flow of consciousness. This interpretation is supported by a large number of studies showing the role of the MTL in memory and the creation of associations, and also by the specific characteristics of concept cells discussed above.

Single-cell studies in humans are limited in terms of the location and number of recording sites for obvious ethical reasons. In spite of these limitations, it has been possible to show that there is a hierarchical processing in the MTL leading to the generation of multimodal conceptual representations. Animal models and, in particular, the further understanding of the relationship between concept cells and place cells in rodents may provide further insights into the processes of memory formation and into how such an abstract representation arises from the activity of upstream areas. The analogy with place cells is a quite compelling but far from resolved matter. In addition, an open question remains: what would be the human analogue of grid cells found in rodents[115]? Further studies may also elucidate the mechanisms underlying the remarkably robust onset of response in concept cells, at about 300 ms, which is considerably later than responses in high-level visual areas. Such robust and late response latency may enable the MTL to receive information from different cortical areas simultaneously to create a unified percept.

Concept neurons are part of cell assemblies encoding particular concepts. It would therefore be interesting to determine how neurons that encode the same concept communicate with each other: is it through the precise synchronized timing of spikes or through a simultaneous increase of firing within some particular time window? It would also be interesting to study how the firing of a given cell assembly may lead to the firing of another one encoding an associated concept, as has been found for place cells in rats[97,103,104]. Other questions for future research concern the stability and malleability of the representation by concept cells in the MTL and how, and to what degree, the information encoded by concept cells consolidates in cortical areas. Finally, it remains an intriguing question whether such abstract representations are specific to humans or also occur in other higher mammals to create the incredibly rich variety of our memories and thoughts.

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