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COMMENTARY

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An integrative view of human hippocampal function: Differences with other species and capacity considerations

Rodrigo Quian Quiroga [1,2,3,4]

[1]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

[2]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

[3]Centre for Systems Neuroscience, University of Leicester, Leicester, UK

[4]Department of neurosurgery, clinical neuroscience center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Correspondence
Rodrigo Quian Quiroga, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.
Email: rqqg1@leicester.ac.uk

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Abstract

We describe an integrative model that encodes associations between related concepts in the human hippocampal formation, constituting the skeleton of episodic memories. The model, based on partially overlapping assemblies of "concept cells," contrast markedly with the well-established notion of pattern separation, which relies on conjunctive, context dependent single neuron responses, instead of the invariant, context independent responses found in the human hippocampus. We argue that the model of partially overlapping assemblies is better suited to cope with memory capacity limitations, that the finding of different types of neurons and functions in this area is due to a flexible and temporary use of the extraordinary machinery of the hippocampus to deal with the task at hand, and that only information that is relevant and frequently revisited will consolidate into long-term hippocampal representations, using partially overlapping assemblies. Finally, we propose that concept cells are uniquely human and that they may constitute the neuronal underpinnings of cognitive abilities that are much further developed in humans compared to other species.

KEYWORDS
concept cells, conjunctive coding, engram, episodic memory, human intelligence, neural coding

1 | INTRODUCTION

Over the years, a vast number of studies provided evidence that the human hippocampus is involved in declarative memory (Squire et al., 2004; Squire & Zola-Morgan, 1991), working memory (Kaminski et al., 2017; Kornblith et al., 2017), semantic (Reber et al., 2019) and conceptual relationships (Bausch et al., 2021; Constantinescu et al., 2016), the coding of associations (Ison et al., 2015; Reddy et al., 2015) and spatial navigation (Ekstrom et al., 2003; Jacobs et al., 2013; Moser et al., 2017), among others, and that, just focusing on relatively recent works with human single cell recordings, it contains a plethora of neuron types, going from place cells (Ekstrom et al., 2003), grid cells (Jacobs et al., 2013), concept cells (Quian Quiroga et al., 2005), mirror neurons (Mukamel et al., 2011), novelty and familiarity cells (Rutishauser et al., 2006; Rutishauser et al., 2008; Viskontas et al., 2006), category cells (Kreiman et al., 2000a; Mormann et al., 2011; Mormann et al., 2017), number cells (Kutter et al., 2018), cells encoding semantic relationships (Bausch et al., 2021; Reber et al., 2019), time cells (Reddy et al., 2021; Umbach et al., 2020), neurons detecting boundaries between episodes (Zheng et al., 2022), and so on. But can a single area of the brain perform so many different functions, especially considering that CA3—arguably the most critical substructure of the hippocampus, with recurrent connections that allow establishing associative networks—has only 2.8 million neurons (Amaral & Lavenex, 2007)?

On top of that, it has long been argued that hippocampal neurons show pattern separation—that means, an orthogonalization of the neuronal representations of similar, overlapping memories, in order to avoid interference (Yassa & Stark, 2011). According to this principle, the hippocampal neuronal representation corresponding to the memory of, for example, meeting a colleague at a conference, involves a different set of neurons compared to the one of meeting the same colleague elsewhere. At the single neuron level, pattern separation is implemented through conjunctive coding (Eichenbaum et al., 1999; Eichenbaum & Cohen, 2014; Rolls & Wirth, 2018), with neurons responding distinctively to different conjunction of features, in order

to create unique assembly representations—following the previous example, having neurons responding to the colleague in the context of the conference but not in the other place and vice versa.

Pattern separation has been proposed to be a key process of memory coding which is largely supported by theoretical and modeling studies, direct single neuron recordings in rats and monkeys, and noninvasive recordings (fMRI, electroencephalography [EEG]) in humans (Kesner & Rolls, 2015; Leal & Yassa, 2018; Rolls, 2016; Yassa & Stark, 2011). However, pattern separation exacerbates the capacity problem mentioned above. So, not only we have many different types of neurons and functions in the human hippocampus, but just focusing on memory processing, according to pattern separation, distinct and largely orthogonal assemblies are assigned to memories involving the same persons in different contexts.

In this opinion, I will describe an integrative model of hippocampal function that explains the variety of responses observed in this area, and that it is plausible when considering capacity limitations. For this, I will first revisit memory capacity considerations, will then describe single neuron recordings in the hippocampus and the main properties of "concept cells" found in this area. Based on these results, I will then propose a model of memory coding based on partially overlapping assemblies, challenging the notion of pattern separation, and stressing key differences with what has been described in the hippocampus of other species. I will then revisit memory consolidation and the distinction between episodic and semantic memory, and I will finally argue that concept cells provide the building blocks of episodic memory and that these neurons and their coding mechanism is exclusively human and may be a cornerstone of human cognitive abilities.

2 | CAPACITY CONSIDERATIONS

Episodic memory has been historically considered a mental time travel in which past experiences are revisited (Tulving, 2002). We have the feeling of recalling our past as in a movie, but how much do we actually remember? And related to this, how many memories can our brain store? What is its capacity?

In spite of the fact that it is very difficult and subjective to estimate memory capacity—for example, what constitutes a memory after all?—these questions have attracted the attention of scientists for long (for an excellent review, see Dudai, 1997). Toward the end of the 19th century, Francis Galton used introspection cued by specific words, and estimated that he remembered hundreds, perhaps thousands, but not tens of thousands memories (Galton, 1879). A few years later, Ebbinghaus quantified how memories decay with time, with his famous "forgetting curves" (Ebbinghauss, 1885), and at the beginning of the 20th century, psychologist Gustav Spiller took the monumental task of writing down all the events he recalled from different stages of his life, concluding he had about 10,000 memories in 35 years (Spiller, 1902). (Incidentally, the arguments of Spiller were a source of inspiration for writer Jorge Luis Borges, who conceived "Funes the memorious," a man who remembered absolutely everything and was, according to Borges, unable to think, generalize or abstract; Quian Quiroga, 2012a.)

Nearly a century after Galton, Crovitz, and Schiffman refined the cued introspection method and found a log–log relationship between memory retention and the elapsed time (Crovitz & Schiffman, 1974), which integrating over a period of 20 years gave a total estimate of 224 remembered memories (Crovitz et al., 1991). Dudai reviewed estimations of remembered personal memories and, following studies by Linton (1978) and later by Wagenaar (1986)—who used the recollection of events they experienced written in personal diaries—concluded that Crovitz and colleagues underestimated autobiographical memory capacity and that a more accurate estimation of memory recall is about thousands "core episodes" (i.e., the minimal chunk of an episodic memory that characterizes an episode and is enough for its retrieval) in a lifetime (Dudai, 1997), which is consistent with the previous estimation by Spiller (between about 10,000 and 20,000 for an adult person), given that Spiller counted separately the main elements of each episodic memory, whereas Linton, Wagenaar, and Dudai considered each episodic memory as one.

While the question of how much we remember has been the realm of psychology and results should be taken order of magnitude estimations, considerations about the brain's capacity to store and retrieve memories have been mainly studied by physicists and computational neuroscientists. The seminal work of Hopfield showed how memories can be stored by fully connected attractor networks (with all neurons connected to each other and each memory pattern being an attractor) and that the capacity of these networks scales as 0.14 the number of neurons (Hopfield, 1982). In the original Hopfield model, memory patterns were distributed among the nodes of the attractor network and later studies showed that the factor 0.14 could be raised up to 2 when using sparse patterns (Gardner, 1987). Further insights were given by Treves and Rolls (1991, 1994), who, using an attractor network to model area CA3 of the hippocampus—an area characterized for recurrent connections, which the authors proposed to be the main substrate for the encoding and retrieval of episodic memory—estimated the effect of diluted connectivity (i.e., considering the physiological constraint that neurons are not all connected to each other), to conclude that the network capacity is proportional to the number of recurrent connections between the neurons, not to the number of neurons itself, and inversely proportional to the sparsity of the stored patterns. Then, considering a mean number of 12,000 recurrent synapses per neuron and a sparsity of 0.02 in the rat CA3, they estimated that this area can store up to 36,000 patterns (Treves & Rolls, 1991).

In conclusion, the theoretical calculations of memory storage capacity of area CA3, in the order of several tens of thousands or more, seems largely sufficient to store the number of autobiographical memories, of the order of thousands, estimated by introspection and related methods used in the psychology literature (Dudai, 1997). However, the theoretical calculations described above are not free of assumptions (e.g., homogeneous connectivity) and, once we have presented evidence provided by single neuron recordings in humans, we

will see that the actual storage capacity of area CA3 is more limited, thus imposing a major challenge to understand how memories are encoded in the hippocampus.

3 | HUMAN SINGLE NEURON RECORDINGS

Noninvasive recordings, such as EEG, magnetoencephalography (MEG), and fMRI, are used with human subjects for obvious ethical reasons, but, while these methods provide insights into the activation of brain areas during different tasks, they can only offer an indirect and vague measure of the activity of individual neurons (Logothetis, 2008; Logothetis et al., 2001). In contrast, extracellular recordings provide direct access to study the firing of multiple neurons but, since they require the implantation of electrodes inside the brain, they can usually be performed only in animals, and the lack of direct verbal feedback limits our understanding of what is going on in the animal's brain. Moreover, the types of experiments and questions that can be addressed with animals are limited because they often need extensive reward-driven training to perform different tasks, far from the natural conditions of how these behaviors occur in real-life and, furthermore, if the ultimate goal is to understand the human brain (but this need not necessarily be the case), it is possible that findings in other species may not apply to humans.

In very particular cases it is, however, possible to perform invasive recordings of individual neurons in patients with epilepsy refractory to medication, who are implanted with intracranial electrodes to determine the location of the epileptic focus and then evaluate the possibility of its surgical resection (Quian Quiroga, 2019; Rey et al., 2015). These patients typically stay for several days at the hospital ward, offering the extraordinary opportunity to record the activity of multiple single neurons while they perform different tasks.

Compared to noninvasive studies, the most obvious advantage of single-neuron recordings is the possibility to measure directly the neurons' responses and provide mechanistic evidence underpinning brain functioning. This can validate or falsify theories that cannot be resolved with noninvasive methods. For example, in line with the finding of neurons responding to faces in the monkey temporal cortex (Freiwald & Tsao, 2010; Gross, 2008; Gross et al., 1972; Tsao et al., 2006) and human fMRI findings (Grill-Spector et al., 2017; Kanwisher, 2017; Kanwisher et al., 1997), neurons in the human occipitotemporal cortex showed strong responses to faces (Decramer et al., 2021). Likewise, in the human parahippocampal cortex, neurons were found to respond strongly to specific places (Mormann et al., 2017), consistent with the fMRI responses observed in the "parahippocampal place area" (Epstein & Kanwisher, 1998). On the other end, human single neuron recordings can also challenge previous theories, as they have, for example, been argued not to show hippocampal "pattern separation" (Quian Quiroga, 2020) (see below), contrasting to what has been described in other species (Kesner & Rolls, 2015; Knierim & Neunuebel, 2016; Rolls, 2013, 2016) and indirect evidence obtained with EEG and fMRI in humans (Leal & Yassa, 2018; Yassa & Stark, 2011). Moreover, single neuron recordings provide findings that cannot be observed at the population level with EEG, MEG, and fMRI, both in humans and other species (Quian Quiroga, 2019). In particular, single neuron recordings in the macaque visual system have shown a microstructure of the neuronal responses that could not be observed in the voxel activity (Issa et al., 2013), and information about face identity given by neuronal responses in the macaque face patches was not retriable from the fMRI data (Dubois et al., 2015). Moreover, in the human medial temporal lobe (MTL), single neuron recordings have shown the presence of neurons responding sparsely to very few pictures (Quian Quiroga et al., 2005; Quian Quiroga et al., 2007), and due to the lack of spatially clustered responses in the MTL (i.e., nearby neurons tend to respond to completely different stimuli; De Falco et al., 2016), these findings could not be observed with fMRI or noninvasive recordings, which reflect coherent mass activations (Logothetis, 2008).

The main disadvantage of human single-neuron recordings compared to noninvasive methods is the fact that the recordings are done in a clinical setting, with a relatively limited time to perform experiments and a sparse coverage of the areas involved in the specific function under study, given that the number and location of the implanted electrodes is determined exclusively by clinical criteria (Quian Quiroga, 2019; Rey et al., 2015). Moreover, the sparsity of the responses (Mormann et al., 2008; Quian Quiroga et al., 2007) makes it very difficult to simultaneously record neurons belonging to the same assembly (e.g., encoding a particular person) and, therefore, assembly properties have to be inferred based on statistical considerations (Quian Quiroga, Kreiman, et al., 2008; Waydo et al., 2006). In addition, human single-neuron recordings are performed in epileptic patients and findings could in principle be attributed to this pathology or an effect of the medication. However, this is unlikely because similar types of responses are found in recordings close to the epileptic focus and in more distant areas (Mormann et al., 2008), and results are also similar for patients with different types of epilepsy, involving different pathophysiological mechanisms (Niedermeyer, 1993). Effects of the medication can be also ruled out because similar results are obtained in patients with different medications and dosages, and at different days of the intervention, considering that the medication is gradually tapered down during the time the patient is in the hospital, to increase the chances of recording seizures.

4 | CONCEPT CELLS

Single neuron recordings in the human MTL have shown the presence of strong and very selective responses. For example, Figure 1a shows the responses of two neurons recorded in the hippocampus of a patient, while he passively looked at 150 pictures, presented 15 times each, in pseudorandom order. Both neurons responded only to one of the 150 pictures, thus showing very high selectivity. In fact, even if pictures of persons or items familiar to the patients were used in these experiments to maximize the chances of getting responses (Viskontas et al., 2009), it has been shown that human MTL neurons

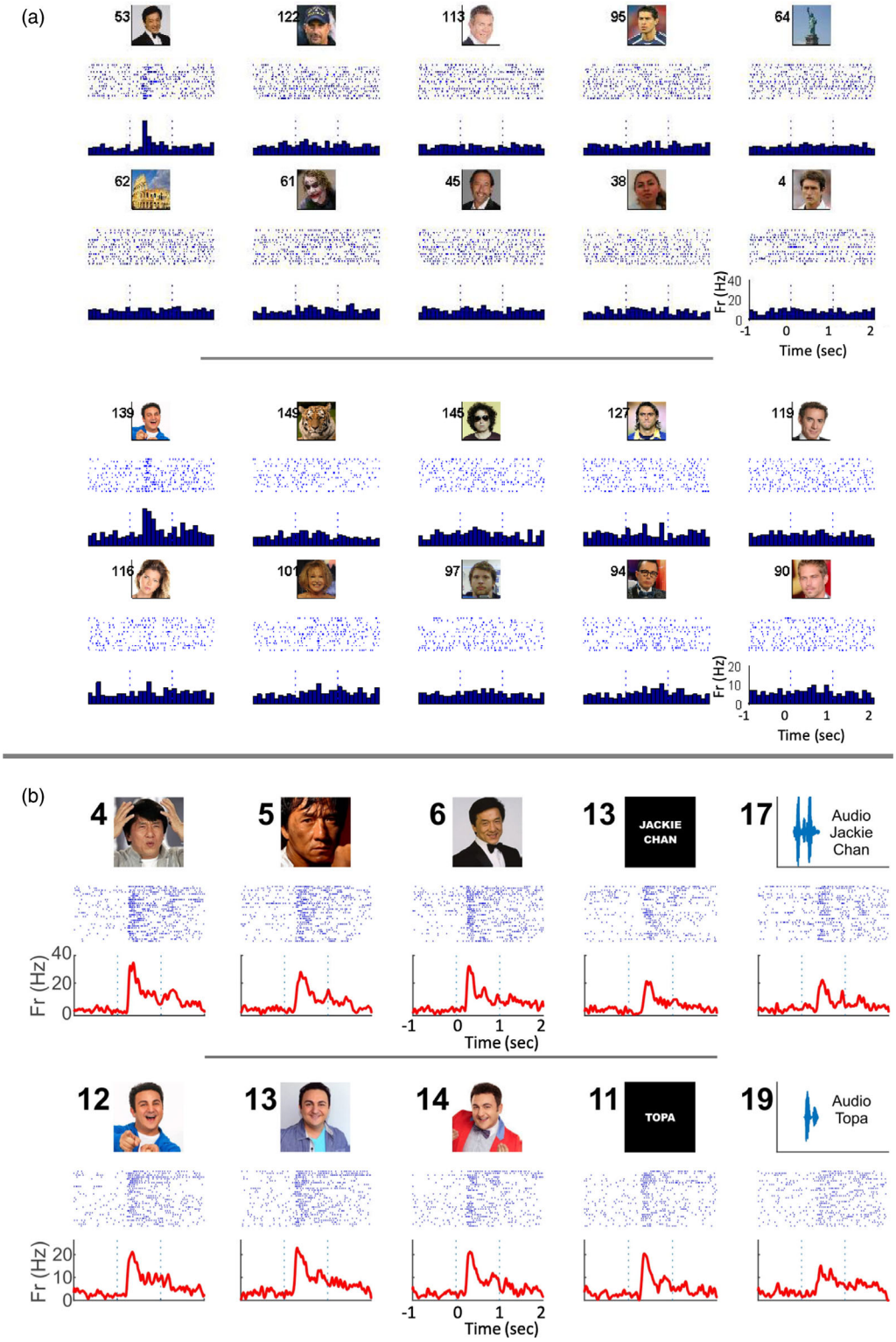

FIGURE 1 (a)) Responses of two hippocampal neurons during a screening session. The neuron on top responds to a picture of actor Jackie Chan and the one on the bottom to a picture of Argentinean TV host "Topa." In both cases, the largest 10 out of 150 responses are shown (there were no significant responses for the other 140 pictures presented). For each response, the stimuli presented are shown on top, the raster plots (first trial on top) in the middle, and the peristimulus time histograms on the bottom. (b) Responses of the same two hippocampal neurons in a follow-up session, in which different pictures and the written and spoken names of the individuals were shown. The neuron on top respond to all three pictures of Jackie Chan and his name and, likewise the one below responded to the pictures of Topa and his name. Despite their differences (shown in different postures, with different expressions, etc.), the responses to the pictures of Jackie Chan were indistinguishable from each other in terms of both their strength and their latency (same for the pictures of Topa). For both neurons, there were no significant responses to the other 15 stimuli (pictures and names of other persons) presented in the same experiment.

typically respond to a very small fraction of the presented stimuli (Quian Quiroga, 2012b; Quian Quiroga et al., 2007). In the examples of Figure 1a, it can also be observed a very long latency of the responses, at about 300 ms, which is typically the case for human MTL neurons (Mormann et al., 2008; Quian Quiroga et al., 2005), and it is much later than the latencies expected for visual perception processes (Kirchner & Thorpe, 2006; Mormann et al., 2008; Thorpe et al., 1996; Thorpe & Fabre-Thorpe, 2001).

The results of "screening sessions," as the one in Figure 1a, in which subjects just viewed a large number of pictures, have been used in follow-up paradigms performed shortly after (trying to maximize the chance of recording from the same neurons), using the pictures that triggered responses in any of the recorded neurons (Quian Quiroga, 2019; Rey et al., 2015). In these follow-up experiments, it has been shown that hippocampal neurons do not just respond to the details of the pictures presented, but rather to the person (or item) featured in the pictures (Quian Quiroga et al., 2005). Figure 1b shows the result of one of these follow-up experiments, using the screening results obtained with the neurons of Figure 1a. We observe a similar response for the 3 pictures of the persons eliciting the neurons' responses (there were no responses for 15 pictures and names of other people) and to the persons' written and pronounced names, thus showing that the MTL neuronal responses go beyond a specific sensory modality, as they can be triggered both by visual and auditory stimuli (Quian Quiroga et al., 2009).

4.1 | Concept cells represent the meaning of the stimulus

Using the pictures eliciting responses in screening sessions, other experiments explored how MTL neurons respond in conditions of difficult or ambiguous perception. In one of these studies, pictures were presented very briefly, at the threshold of conscious perception, and it was found that the responses of MTL neurons were mostly all-or-none, in the sense that a neuron fired whenever the picture eliciting its response was recognized and remained at baseline levels (or completely silent) when it was not, even if the stimulus presentation was exactly the same in both cases (Quian Quiroga, Mukamel, et al., 2008). Figure 2a shows two of these neurons. The neuron on the left panel was nearly silent during baseline (or the presentation of other pictures), it responded only when the picture of the World

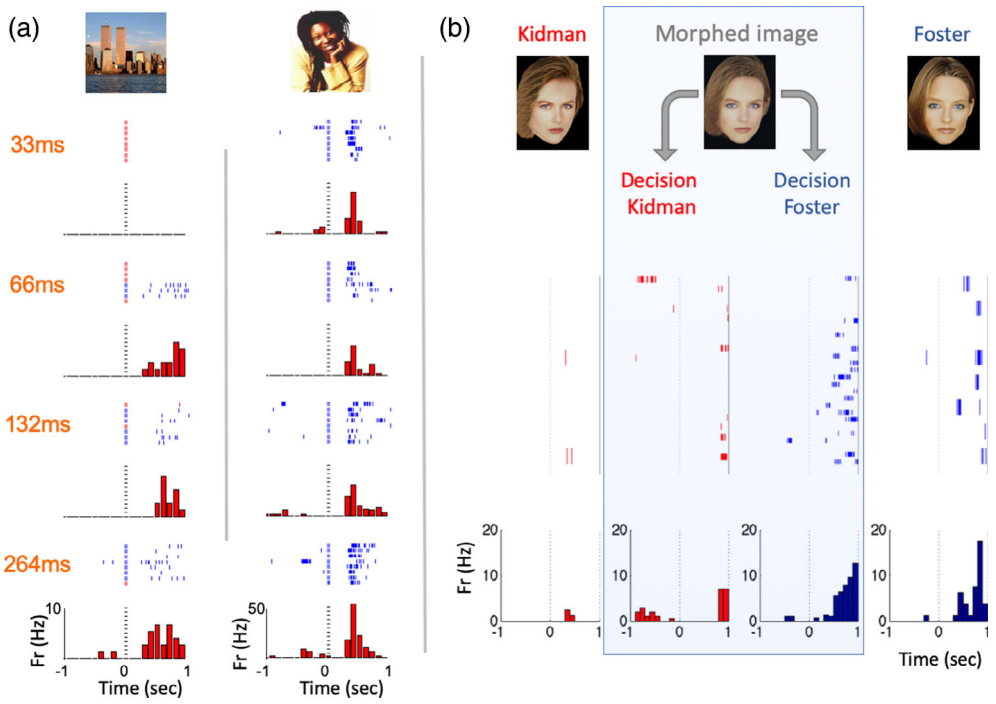

FIGURE 2 (a)) Raster plots and peristimulus time histograms of a neuron in the entorhinal cortex that responded to a picture of the World Trade Center (left) and another neuron in the hippocampus that responded to a picture of actress Whoopi Goldberg (right). Both neurons did not respond to any of the other 15 pictures presented in the experiments (not shown for space reasons). The different presentation durations are shown at the left of each plot. Trials where the pictures were (were not) recognized are displayed with a blue (red) mark at time 0. For the neuron responding to the World Trade Center, there is a marked difference in the responses when the picture was recognized compared to when it was not (66 ms being at the threshold of recognition). For the neuron responding to Goldberg, the patient reported recognizing her in every trial (likely using visual cues for very short durations) and the neuron responded similarly in all cases. (b) Raster plots and peristimulus time histograms of a neuron in the hippocampus that responded to a picture of actress Jodie Foster (right), but not to one of Nicole Kidman (left). The response to the ambiguous morphed image (center plots) was larger when the subject recognized it as Foster compared to when the subject recognized it as Kidman.

Trade Center was recognized by the subject and remained silent when it was not (red and blue markers at time zero, respectively). The neuron on the right, was also nearly silent during baseline and responded to actress Whoopi Goldberg. In this case, the patient reported recognizing her in all trials. Given the limited set of pictures used in these experiments (16 per session), the fact that the patient could recognize the picture of Goldberg even with 33 ms presentations, which is too short for face recognition, can be attributed to the use of basic cues such as the overall yellow tone compared to the other pictures. Using these cues and the recognition of the face at longer durations, it is striking that the neuron responded similarly at all presentation durations (Quian Quiroga, Mukamel, et al., 2008).

In another study, the images of persons that gave neuronal responses in the screening sessions were morphed with the images of other persons that did not (Quian Quiroga et al., 2014). Figure 2b shows the responses of a neuron in the hippocampus tested with these stimuli, which fired to a picture of Jodie Foster, but not to one of Nicole Kidman. When the morphed image between Foster and Kidman was presented, the neuron responded only when the subject recognized the ambiguous picture as Foster and remained nearly silent when he recognized it as Kidman. Note also that the response was similar to the original picture of Foster and to the morphed one (as long as the subject recognized it as Foster). In fact, considering the whole pool of neurons analyzed in this study, there was not a significant difference between the responses to the pictures of the persons triggering the neurons' responses and the morphed pictures, when recognized as the response-eliciting person (Quian Quiroga et al., 2014), which contrast to the graded responses to morphed faces reported in monkey IT cortex (Leopold et al., 2006) (see also (Chang & Tsao, 2017)).

Summarizing, MTL neurons represent the meaning of the stimulus, rather than the stimulus itself, irrespective of its specific sensory features. This attribution of meaning is subjective and can dramatically vary together with the MTL neuronal responses, depending on how the subject perceives the stimulus. In other words, what matters is not the stimulus but how the subject perceives it—that is, how it will be remembered (see next sections). So strong is the detachment from the details of the sensory inputs, that the firing of these neurons can not only be triggered by completely different pictures of the same person, but also by the person's written and pronounced name (Quian Quiroga et al., 2009), and even during free (Gelbard-Sagiv et al., 2008) or cued recall (Ison et al., 2015), in the absence of sensory inputs.

4.2 | Concept cells encode associations

Episodic memory relies on establishing associations between concepts (persons, places, items) (Eichenbaum, 2004; Quian Quiroga, 2012b; Wallenstein et al., 1998). Several works on humans and other animals have shown the involvement of the MTL in coding associations (Berger et al., 1976; Day et al., 2003; Eichenbaum, 2004; Graf & Schacter, 1985; Mayes et al., 2007; Quian Quiroga, 2012b; Rolls & Wirth, 2018; Wallenstein et al., 1998; Wirth et al., 2003; Wirth et al., 2009; Yanike et al., 2004). In line with this evidence, concept cells represent familiar concepts (Viskontas et al., 2009), that means, the type of persons and other things we form memories about. Furthermore, we tend to forget irrelevant details and remember concepts, which is exactly the type of information encoded by these neurons. In addition to this, it has been shown that concept cells respond to associated concepts. For example, Figure 3a shows a neuron in the hippocampus that responded to actor Leslie Nielsen and to two pictures of an airplane. In terms of visual features, these images are very dissimilar, but at the conceptual level, they are related due to the movie Airplane! (which was known to the patient), featuring Nielsen. The responses of the neuron to the pictures of Nielsen and the two airplanes were indistinguishable from each other, both in terms of their strength and latency, as it was the case for most (~80%) MTL neurons that responded to more than one concept (Rey et al., 2018). This shows a binary coding not only for the responses to different pictures of the same person, as shown above (Figure 1b), but also for the associated persons or items that each neuron responds to (Rey et al., 2020).

To quantify the observation that MTL neurons tend to respond to associated concepts, two metrics were used: first, subjects were asked to rank how much pairs of pictures were related to each other (including those that gave responses in the same neurons and others as control), and second, an "association score" was defined from the number of hits obtained when doing an internet search of two concepts together, normalized by the product of the number of hits given by each concept separately (De Falco et al., 2016). The left and middle columns of Figure 3b depict the results of these two metrics, both showing that the association scores between the pictures to which a neuron responded to were significantly higher than those between other picture pairs. Moreover, this difference was significantly higher for the metric given by the patients' responses, because the patients established subjective relationships based on their own episodic memories that are not necessarily shared by other internet users. In fact, MTL neurons represented idiosyncratic associations between specific concepts (e.g., responding to a particular actor and a particular place but not to other actors and other places) that could not be explained by the familiarity of the stimuli, visual similarities between the pictures, or broad semantic categorizations (e.g., actors, musicians) (De Falco et al., 2016).

Exploiting the fact that nearby neurons recorded from the same electrode can be separated after spike sorting (Quian Quiroga, 2019; Rey et al., 2015), the left bars of Figure 3b show that items to which nearby neurons responded to did not tend to be associated. This demonstrates a lack of topographic organization in the MTL, which is ideal to rapidly establish relationships between any arbitrary items, as it is expected for episodic memory, and that contrasts with the topographically organized information in primate visual neocortical areas (Tanaka, 1996). Moreover, Figure 3c shows the probability of finding responses to two given concepts as a function of the association

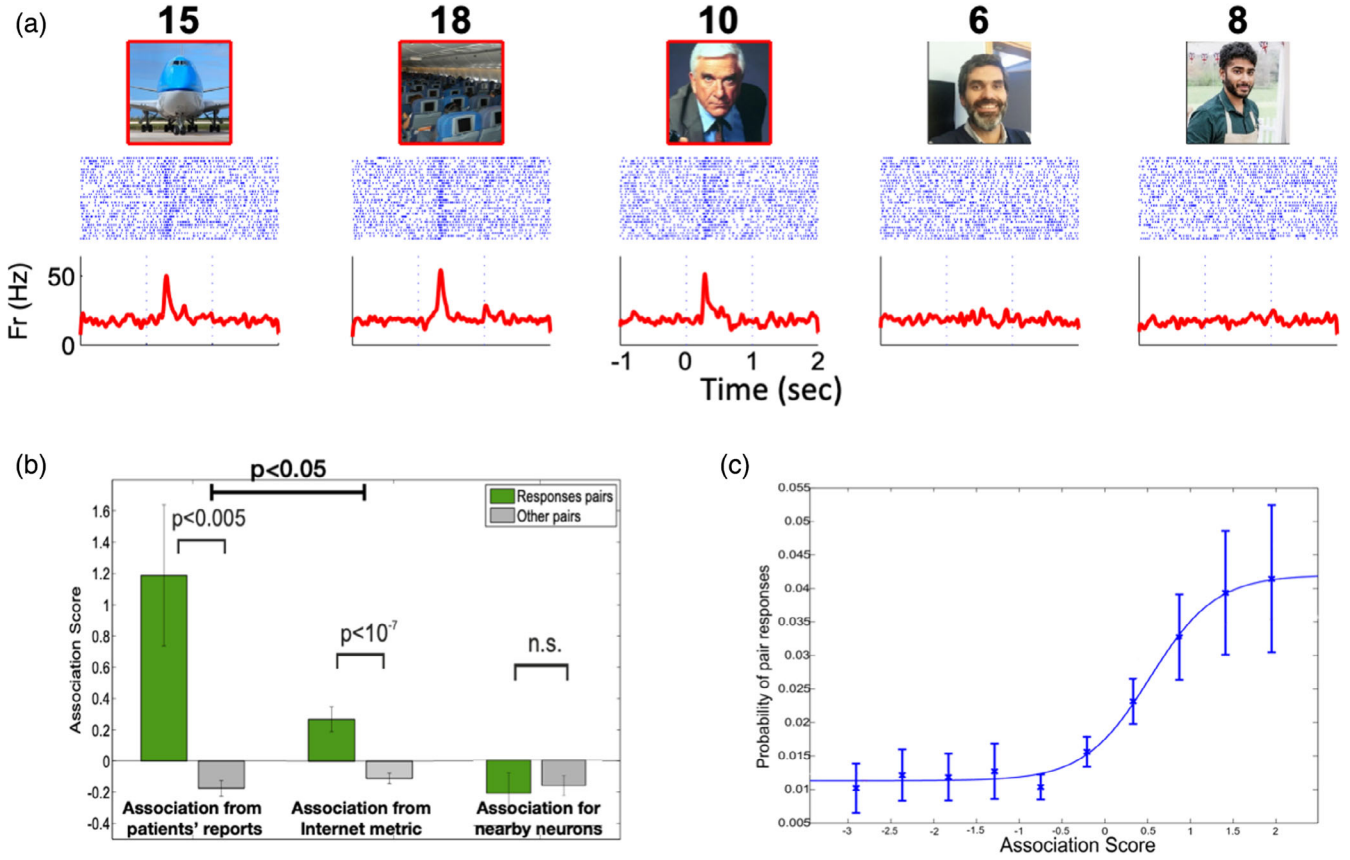

FIGURE 3 (a)) Responses of a neuron in the hippocampus that responded to actor Leslie Nielsen and to two pictures of an airplane. The neuron encodes the association between Nielsen and the airplane pictures due to the movie Airplane!, featuring the actor, and did not respond to any of the other stimuli presented (for space reasons, 5 out of 20 responses are shown and there were no significant responses to the other pictures). As in Figure 1, the responses to Nielsen and the airplane pictures were indistinguishable from each other, both in terms of their strength and latency. (b) Mean association score for pairs of pictures to which individual neurons responded to, and other picture pairs, based on the patients' scores (left) and on an internet search association metric (middle), and mean association score between pictures eliciting responses in nearby neurons, showing a non-topographic organization (right). Values are normalized using a Z score. (c) Probability of responses to pairs of pictures as a function of their degree of association using the internet search metric. Error bars denote *SEM*.

between them, which increases monotonically, until reaching an asymptote of about 4% for highly associated concepts (De Falco et al., 2016).

To further test whether concept cells are involved in episodic memory, a pair association task was used where, for each person to whom a neuron initially responded to (as determined from previous screening sessions), an association with an arbitrary place was created by showing an artificial image created with Photoshop of the person in the place. Neurons initially firing to a person showed a significant increase in firing to the presentation of the associated place (without the person) but not to other places that were associated with other persons (the associations also worked the other way around; neurons initially firing to a place started firing to the person associated with it and not to other persons) (Ison et al., 2015). As an example, Figure 4a shows a response of a hippocampal neuron that (before learning) initially responded to actor Josh Brolin and not to the Eiffel Tower. After seeing the image of Brolin by the Eiffel Tower, the subject learnt the association between the two stimuli and the neuron continued responding to Brolin, also responded to the Photoshop image of Brolin by the Eiffel Tower (which is not surprising since Brolin was in the picture), but also started responding to the Eiffel Tower without Brolin (Ison et al., 2015). The normalized population responses of these neurons are shown in Figure 4b, where we observe a small decrease of the responses to the preferred stimulus after learning, due to repetition suppression, as described in previous studies (Pedreira et al., 2010; Rey et al., 2015). In contrast, for the non-preferred associated stimulus there was a clear increase of the neurons' responses after learning. Figure 4c shows the normalized average responses to the associated stimulus as a function of the relative trial number, aligned to the time of learning (trial 0). As seen in this plot, the increase in the response to the associated stimuli was abrupt and happened at the exact time of learning the associations, sometimes after a single presentation (Ison et al., 2015). This is in line with an involvement of these neurons in the encoding of new episodic memories, which are typically formed after single, unique experiences. Finally, Figure 4d shows that after learning the responses to the associated stimuli were similar in the different tasks and conditions of the experiment.

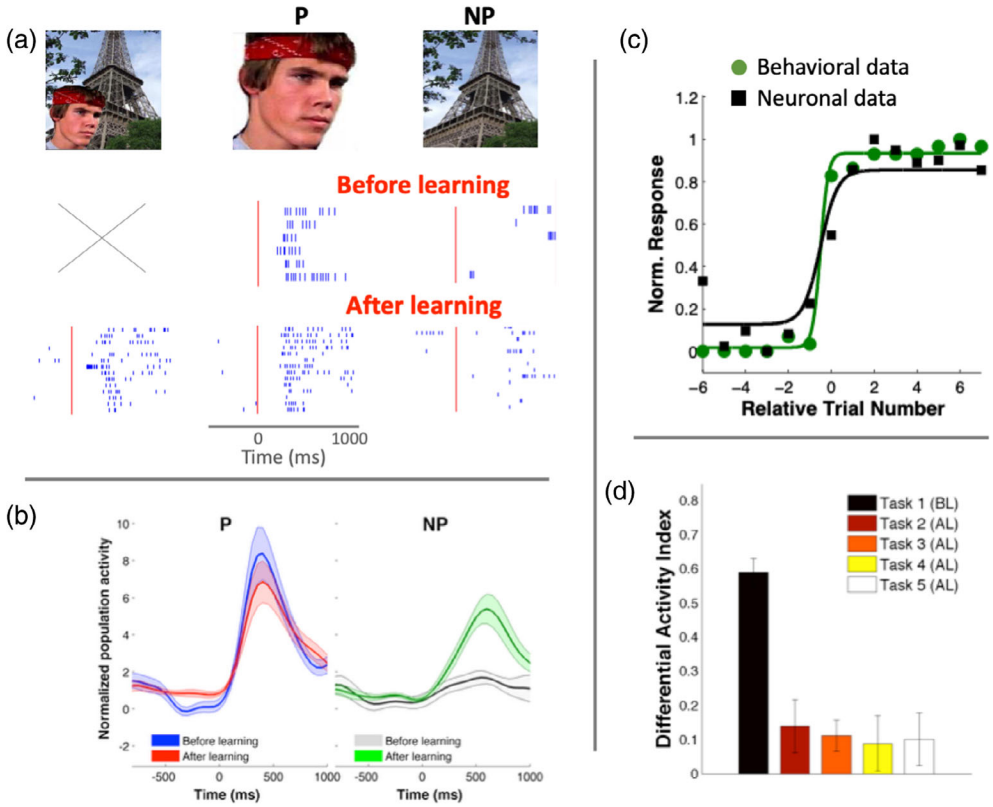

FIGURE 4 (a)) Responses of a neuron in the hippocampus that initially responded to actor Josh Brolin (preferred picture [P]) and not to the Eiffel Tower (non-preferred picture [NP]) before (top) and after learning (bottom). After learning, the neuron continued responding to Brolin, responded to Brolin in the Eiffel Tower, and also responded to the Eiffel Tower without Brolin. (b) Normalized grand average responses to the P and NP pictures. The responses to the P pictures decreased due to repetition suppression, whereas those to the NP pictures showed an increase after learning, encoding the new associations. Shaded areas denote *SEM*. (c) Normalized behavioral and neuronal responses to the NP pictures, aligned to the time of learning (trial 0). Note the step increase of the neuronal responses at the precise time of learning the associations. (d) Differential activity index (difference between P and NP responses) before (BL; task 1) and after learning (AL; tasks 2–5). The difference observed before learning was reduced after learning due to the increase of the NP associated responses. No significant differences were present after learning, suggesting that the responses were not task dependent. Task 1/2, picture presentations before/after learning; task 3, testing of the associations; task 4, recall; task 5, passive viewing of the pictures.

5 | MEMORY CODING WITH PARTIALLY OVERLAPPING ASSEMBLIES

The evidence presented in the previous section suggests that concept cells encode associations using partially overlapping assemblies. Figure 5 illustrates the idea. Suppose that you have fortuitously encountered Jennifer Aniston in two different occasions: one time by the Eiffel Tower, and another time by the Tower of Pisa. The first "core episode" (using Dudai's terminology mentioned above) is given by the association between Aniston and the Eiffel Tower (and perhaps other associated items that were part of this experience), which at the neuronal level is encoded by having some of the neurons responding both to Aniston and the Eiffel Tower, whereas the second core episode is given by the association of Aniston with the Tower of Pisa, which, likewise, is encoded by having some neurons encoding both concepts. If you later see Aniston on TV, you will have an activation of the cell assembly representing her and you may evoke the memory of Paris, by coactivating the Eiffel Tower assembly, or the memory of Italy, by coactivating the assembly representing the Tower of Pisa.

The key parameter determining how associations are coded with this model is the degree of overlap between the assemblies, which was estimated to be about 4% for associated concepts (Figure 3c) (De Falco et al., 2016). This value is consistent with the one obtained modeling partially overlapping assemblies using an attractor network, showing that there are two critical values of the overlap, *C_min* and *C_max*, that determine whether associations can be successfully retrieved (above *C_min*) but without merging the attractors and having a unitized representation (above *C_max*) (Gastaldi et al., 2021).

Episodic memories go way beyond the encoding of a few associations and the coactivation of one or the other group of hippocampal assemblies will also coactivate neocortical representations linked to one or the other memory. The hippocampal representations of concepts, and associations between them, provide a basic sketch of episodic memories—that is, the neuronal substrate of the "core episodes"—which is given by the coactivation of a set of associated

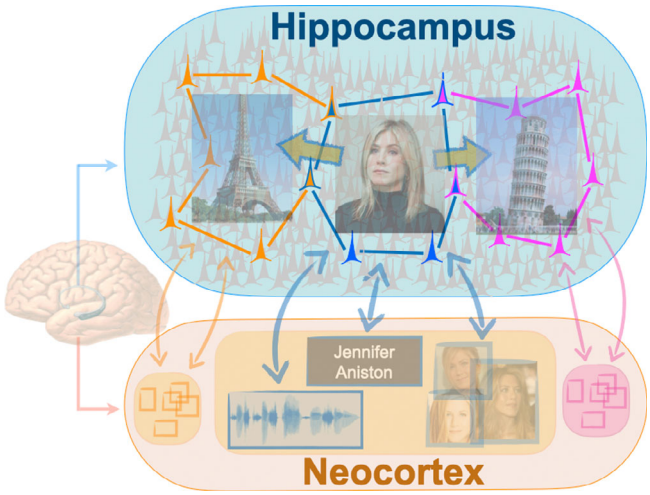

FIGURE 5 Top: encoding of associations in the hippocampus with partially overlapping assemblies. An assembly of concept cells responding to Jennifer Aniston (marked with blue lines) shares neurons with other one representing the Eiffel Tower (in orange/blue) and with another one representing the Tower of Pisa (in pink/blue). A first function of concept cells is to encode the associations between concepts (with shared neurons), representing the core episodes of episodic memories; in this case, a memory of Aniston in the Eiffel Tower and another one of Aniston in the Tower of Pisa. The core episodes can then be reactivated with the coactivation of associated assemblies. A second function of concept cells is to link and also coactivate different neocortical representations related to the specific core episode that is evoked.

assemblies that distinguishes the different memories involving a particular person, or different memories occurring at a particular place (other things you may have experienced in Paris or Pisa), and so on.

Within this framework, I postulate that concept cells have two main functions: first, to provide the neuronal substrate for the activation of associated hippocampal assemblies that represent specific episodic memories (and also allow the flow of consciousness going from one associated concept to the other), and second, to coactivate distant neocortical representations associated to the particular memory, in line with the view of the hippocampus as a pointer to neocortex, linking distant representations (e.g., the face and written or spoken name of a person, etc.) (Teyler & Discenna, 1986).

6 | DIFFERENCES WITH OTHER SPECIES

In comparison to the responses in the hippocampus of other species (studied mainly in macaques and rats), the human hippocampal responses show three key distinctive features: (i) a very late response latency, (ii) multimodal invariance, and (iii) no context modulation.

6.1 | Late response latency

While the response latencies to picture presentations are at about 150 ms in the macaque hippocampus (Jutras & Buffalo, 2010; Rolls et al., 1989; Rolls et al., 2005; Yanike et al., 2004), the latency in humans is double, about 300 ms (Mormann et al., 2008; Rey et al., 2018). It could in principle be argued that this difference is due to a slower visual processing in humans compared to monkeys. However, responses in high level visual areas are at about 100–150 ms both in monkeys (for a summary, see table 1 in Mormann et al., 2008) and humans (Davidesco et al., 2014; Decramer et al., 2021; Jacques et al., 2016; Liu et al., 2009). Therefore, while in the monkey visual system the response onsets are dictated by a cascade of feedforward activations (Thorpe & Fabre-Thorpe, 2001) that from high level visual areas send the information directly to the hippocampus (n.b.: we refer to response onsets, which does not mean that there is not feedback processing the monkey visual system), visual information in humans is much further processed before reaching the hippocampal memory system.

But what determines when exactly the human hippocampal neurons should start firing? The long latency of the single neuron responses were shown to be shortly preceded by a local field potential (LFP) deflection in the theta range (Rey et al., 2014), with an onset that covaries with the one of the single neurons (Rey et al., 2018). This LFP deflection thus opens a temporal window for MTL neurons to fire and also provides a mechanism to synchronize inputs from different sensory systems, which take different times to process the stimulus (Rey et al., 2014). It is currently unknown whether such LFP evoked response is present in monkey hippocampal recordings.

6.2 | Multimodal invariance

Human hippocampal neurons show a very high degree of visual and multimodal invariance (Quian Quiroga, 2012b; Quian Quiroga et al., 2005; Quian Quiroga et al., 2009). To be more specific, in most cases (about 80%), and as shown in Figure 1b, the responses to different pictures of the same concept are indistinguishable from each other, both in terms or response strength and latency (Rey et al., 2020). This binary coding contrast to the typical finding of graded responses in the neocortex (Logothetis & Sheinberg, 1996; Tanaka, 1996). In particular, neurons in the monkey inferotemporal (IT) cortex respond to complex visual features, such as specific objects or faces, and show some degree of invariance to changes in size, position, and 2D rotations (Gross, 2008; Logothetis & Sheinberg, 1996; Rolls, 2000; Tanaka, 1996). However, in this context invariance is taken as a preserved selectivity with different variations of the stimuli—that is, the neuron continues to have a stronger response to a particular face or item, but without necessarily implying the same neuronal response across variations, as found with the human MTL recordings. In monkey IT, it is indeed typical to observe a clear tuning with graded responses (Logothetis & Sheinberg, 1996; Tanaka, 1996), which can be used to distinguish the presented stimuli (Gross, 2008; Hung et al., 2005; Kiani et al., 2007).

The responses to the written and spoken names are also very strong and to the same persons (concepts) whose pictures elicit the firing of the neurons. However, they are only present in 40% of the

cases (Rey et al., 2020), which means that the patients may not be familiar with the names of some persons (although they may know who they are and have recollections related to them), may call them differently, or the fact that names involve a completely different neocortical processing that might be less effective in triggering the activation of the corresponding MTL assemblies.

The degree of abstraction of the human single cell responses increases along the hierarchical structure of the MTL, reaching its pinnacle in the hippocampus (Quian Quiroga, 2012b). In monkeys, there is also an increase of abstraction along the ventral visual pathway, with neurons in high level visual areas maintaining a preserved selectivity to simple image transformations, such as changes in size, position, or 2D rotations (Logothetis & Sheinberg, 1996; Tanaka, 1996). However, as mentioned above, preserved selectively is not the same as invariance—that is, neurons in IT visual cortex show a graded coding to image transformations, in contrast to the binary coding observed in humans (Rey et al., 2020). Moreover, in monkeys the response selectivity is not preserved with 3D picture rotations (e.g., a front and profile view of a face) or when using different pictures of the same individual or object (Logothetis & Sheinberg, 1996; Tanaka, 1996).

The findings in monkeys mentioned in the previous paragraph are in high level visual areas and one wonders if abstract responses, as those found in humans, can be encountered in the monkey (or rat) hippocampus. A study in the monkey hippocampus replicated the protocol used to find concept cells (Quian Quiroga et al., 2005), analyzing single neuron responses to pictures of very familiar individuals (other monkeys in the colony, pictures of researchers interacting with the animals, etc.) and their voices. However, no neurons with such a degree of selectivity and visual or multimodal invariance were found (Sliwa et al., 2016). Moreover, the responses to the voices were not correlated to the ones of the pictures of the same individuals (i.e., they were in different neurons, which was never the case in humans), as it was also shown by another study in the monkey face patches (Khandhadia et al., 2021).

6.3 | No context modulation

The responses of human hippocampal neurons to specific persons (or items or places) are basically the same in different contexts and tasks (Quian Quiroga, 2019, 2020). This is actually the reason why screening sessions are performed to identify what the neurons respond to: because the responses observed during passive viewing in the screening sessions (Figure 1a) (Quian Quiroga et al., 2005) are maintained in follow-up experiments, in which, among others, similar responses were observed to various pictures of the same persons (Figure 1b) (Rey et al., 2020), or in visual perception tasks using backward masking (Quian Quiroga, Mukamel, et al., 2008) and morphed pictures (Quian Quiroga et al., 2014) (Figure 2), or in working memory tasks (Kaminski et al., 2017; Kornblith et al., 2017), during free recall (Gelbard-Sagiv et al., 2008), when subjects were asked to just think about the person triggering the neuron's responses (Cerf et al., 2010; Kreiman et al., 2000b), or performed a pair association task (Figure 4) (Ison et al., 2015) that gave similar neuronal activations when the subjects saw the persons triggering the responses on their own or in specific locations (Figure 4a), learned and recalled the associations (tasks 2 and 4 in Figure 4d), or passively viewed the pictures (task 5 in Figure 4d). In line with this evidence, it was also found that the responses of MTL neurons were similar in a recognition memory and a categorization task, contrasting with task modulations observed in frontal lobe neurons (Minxha et al., 2020).

The lack of context modulations observed in the human hippocampal neurons contrasts markedly with findings in the monkey and rat hippocampus. In fact, the responses of neurons in the monkey hippocampus are, to a large extent, modulated by the task performed by the animals and tend to respond to specific conjunctions of objects, viewpoints, positions, reward locations, contexts, tasks, and so forth (Baraduc et al., 2019; Cahusac et al., 1989; Gulli et al., 2020; Miyashita et al., 1989; Rolls et al., 2005; Rolls & Wirth, 2018; Wirth et al., 2017). The object-view cells, as well as the cells responding according to a particular location in a state space comprising the animal's position, view and task context, are indeed excellent examples of the conjunctive coding observed in the monkey hippocampus (Rolls & Wirth, 2018).

In the rodent hippocampal formation, neurons respond to the spatial location of the animals—particularly, place cells in the hippocampus and grid cells in entorhinal cortex (Moser et al., 2017). As in the human hippocampus, place cells also show some degree of abstraction because, in open arenas, they fire to specific locations irrespective of the trajectory of the animal. However, a key difference with the human hippocampal responses is that these neurons tend to remap and change their responses according to the task and context—that is, the firing of the neurons changes when altering the environment (Alme et al., 2014; Colgin et al., 2008; Fyhn et al., 2007; Moser et al., 2017), the task performed by the animal (Bower et al., 2005; Markus et al., 1995; Smith & Mizumori, 2006), when introducing associations with odors or items at specific locations (Komorowski et al., 2009; McKenzie et al., 2014; Wood et al., 1999), and when changing, among other factors, the animal's overall trajectory (Frank et al., 2000; Wood et al., 2000), trajectory planning (Pastalkova et al., 2008), reward location (Lee et al., 2006) or motivational state (Kennedy & Shapiro, 2009) (for reviews, see Eichenbaum & Cohen, 2014; Eichenbaum et al., 1999; Moser et al., 2017; Shapiro et al., 2006). In contrast to place cells, grid cells show regular geometrical patterns of activations that have been thought to provide a more stable representation (Fyhn et al., 2007; Moser et al., 2017). However, these neurons were also later found to change their firing patterns following physical changes in the environment (Krupic et al., 2015; Krupic et al., 2018) and other cognitive factors, such as the reward location (Boccara et al., 2019; Butler et al., 2019).

7 | CHALLENGING PATTERN SEPARATION

Human hippocampal neurons provide a more abstract, context independent representation, compared to what is found in the same area

in rats and monkeys. On a more theoretical basis, the context modulation (or conjunctive coding) observed in the rat and monkey hippocampal responses, at the assembly level gives rise to pattern separation—that is, the neuronal representation of overlapping inputs tends to be orthogonalized, creating nonoverlapping assemblies in order to avoid interference (Leal & Yassa, 2018; Rolls, 2016; Yassa & Stark, 2011). The notion of pattern separation has been supported by modeling studies (Kesner & Rolls, 2015; Kumaran et al., 2016; Marr, 1971; Rolls, 2016; Treves & Rolls, 1994), direct single neuron recordings in the rat and monkey hippocampus (Colgin et al., 2008; Fyhn et al., 2007; Kesner & Rolls, 2015; Knierim & Neunuebel, 2016; Leutgeb et al., 2007; Neunuebel & Knierim, 2014; Rolls, 2016; Rolls & Wirth, 2018; Vazdarjanova & Guzowski, 2004) and indirect evidence provided by fMRI and EEG recordings in humans (Leal & Yassa, 2018; Yassa & Stark, 2011). However, based on the evidence of context-independent representations in the human hippocampus described above, it has been argued that, in contrast to findings in rats and monkeys, hippocampal pattern separation may not be present in humans (Quian Quiroga, 2020). To clarify, the argument is that the human hippocampus should differentiate overlapping memories (such as the ones with a particular person in different situations/contexts) and fMRI data demonstrate that this is the case. However, such differentiation is not achieved through an orthogonalization of memory representations via pattern separation, but rather by the coactivation of distinct partially overlapping assemblies, each of them being context independent, as illustrated in Figure 5.

The encoding of memories via partially overlapping assemblies of Figure 5 is very different to pattern separation because each assembly encodes a specific concept (e.g., Jennifer Aniston, the Eiffel Tower, the Tower of Pisa) and not conjunctions of concepts (Jennifer Aniston at the Eiffel Tower, or Jennifer Aniston at the Tower of Pisa). This way, associations are encoded through overlaps between the context independent assemblies (that facilitate their coactivation), rather than by dedicated assemblies representing each specific memory separately. In other words, the model of Figure 5 does not tend to orthogonalize overlapping memories, as with pattern separation, because different memories involving, for example, Jennifer Aniston, share the activation of the same "Jennifer Aniston assembly" (Quian Quiroga, 2020).

A lack of hippocampal pattern separation in humans has interesting behavioral consequences. In fact, context independent representations may be optimal in terms of memory capacity (see below), a trade-off between pattern completion and memory distinction (but not through pattern separation), and to support cognitive abilities that are uniquely developed in humans, such as our power of inferential reasoning, generalization, metacognition and creative, abstract thinking (Quian Quiroga, 2020). The tradeoff is that such representation leaves details aside (at least in the hippocampus) and it seems more prone to errors and the creation of false memories, mixing information from different contexts, compared to having dedicated, largely nonoverlapping representations with pattern separation. With the model of partially overlapping assemblies it is also computationally more difficult to conceive precise sequences of activations supporting the "mental time travel" on which episodic memory is believed to rely on (Tulving, 2002). But on the other hand, with largely orthogonal, pattern separated assemblies, although it is very straightforward to implement a replay of chains of activations, as has been described in the rat hippocampus (Buzsaki, 2005; Diba & Buzsaki, 2007; Pastalkova et al., 2008), it is difficult to resolve sequence crossings (i.e., the same event shared between memories) or have generalizations and inferences (i.e., establishing relationships between different memories).

Summarizing, the absence of pattern separation in the human hippocampus suggests that episodic memory, lacking details and encoded with context independent assemblies, is more a reconstruction rather than a replay and, more generally, that the human hippocampal memory system is tuned to encode high-level relationships to achieve understanding (involving inferences, generalizations, etc.), instead of an accurate recollection.

8 | MEMORY CAPACITY REVISITED

In the previous sections, we saw that area CA3 of the hippocampus is modeled as an autoassociative network supporting episodic memory, and that the theoretical capacity for encoding memories in this area is of about 36,000 different patterns in rats (probably more in humans) (Treves & Rolls, 1991, 1994), which is much larger than the actual number of core episodes we remember from our lifetime experiences (Dudai, 1997). However, these theoretical calculations are not free of assumptions. In particular, they consider a homogeneous connectivity (and independent synaptic inputs to each neuron), something that does not seem to apply to the case of having assemblies of neurons strongly connected to each other, and with a relatively lower effective connectivity to neurons outside the assembly.

Based on results with human single neuron recordings, a Bayesian probabilistic argument that considered the number of responsive units in the screening sessions (Figure 1a), the number of stimuli presented and the total number of recorded units, it was estimated that about 1 in a thousand neurons represent a given concept (Waydo et al., 2006). Therefore, taking an estimate of 2.8 million neurons in the human CA3 (Amaral & Lavenex, 2007), this means that about 1000 different assemblies, each of them with a couple thousand neurons, could be stored in this area. However, this estimation should be taken as a lower limit because: first, it is difficult to detect very selective neurons, which results in a bias toward finding broadly tuned responses (Quian Quiroga, 2019; Rey et al., 2015); second, the selectivity values obtained in these experiments are bounded by the number of pictures presented (e.g., with 100 pictures, it is not possible to find a selectivity of less than 1%); and third, in the screening sessions, images of very familiar concepts were used to maximize the chances of getting responses (as hippocampal neurons respond predominantly to concepts that are familiar to the patients (Viskontas et al., 2009)) and a larger selectivity is expected for a more unbiased set of pictures.

Real life memory capacity estimations—perhaps about thousands (Dudai, 1997)—should be taken as order of magnitude, and are just about the number of things that cell assemblies in CA3 can encode. The capacity of CA3 seems, however, quite tight when considering pattern separation and that each episodic memory should be stored as a separate, largely nonoverlapping assemblies. This is exacerbated when considering that core episodic memories might be composed of a series of linked events, each event requiring a separate assembly to store it. Think of all the memories you have with your parents, close family members and friends; think also of all the distinct experiences you have at your house, your office, or the local pub you use to go with different people. Instead, the model of partially overlapping assemblies (Figure 5), which is a direct consequence of the responses observed in the human recordings (and not based on capacity or theoretical considerations), seems to allow a much larger capacity because distinct memories are encoded as overlaps between assemblies representing familiar concepts. This way, to encode, for example, the memories of N persons in M distinct contexts, instead of $N \times M$ assemblies needed with pattern separation, only $N + M$ assemblies are required—that is, the required number of neurons increases arithmetically, rather than geometrically.

9 | MEMORY CONSOLIDATION

The encoding of memories originally stored in the hippocampus may consolidate with time in the neocortex, thus alleviating the memory capacity limitations discussed in the previous section. Findings with patient H.M. and lesion studies in monkeys led to the proposal of the *standard consolidation model*, which states that declarative memory (comprising semantic and episodic memory, namely, the memory of facts and of personal experiences, respectively) are initially encoded in the MTL but then consolidate in the neocortex and, once consolidation has taken place, the MTL is no longer necessary for their retrieval (Squire et al., 2004; Squire & Zola-Morgan, 1991). Later works have offered an alternative view, named *multiple trace theory*, claiming that only semantic memory consolidates in the neocortex, whereas episodic memory always relies on the hippocampus (Moscovitch et al., 2005; Nadel & Moscovitch, 1997; Sekeres et al., 2018). In other words, both models agree that semantic memory consolidates with time in the neocortex, but whereas for the standard consolidation model episodic memory also consolidates in the neocortex, for the multiple trace theory the hippocampus provides a long-term representation that remains critical for episodic memory, which means that, after a hippocampal lesion, all the episodic memories, and not just the ones of recent years, are lost into oblivion.

Evidence supporting one or the other theory comes mainly from behavioral studies in patients with MTL lesions and fMRI studies (Moscovitch et al., 2005; Sekeres et al., 2018), which have, however, provided mixed results due to the variability of the precise location and extent of the lesions in the first case, and the fact that with fMRI is not possible to assess, at the single-cell level, the stability and plasticity of neuronal representations. The evidence provided by human single neuron recordings is also relatively limited because it is difficult to track the responses of the neurons across days and patients are typically implanted with intracranial electrodes for no longer than 1 or 2 weeks. However, evidence supporting a long-term role of the hippocampus in (episodic) memory is given by the fact that the neuronal responses obtained in the screening sessions are already obtained the very first time the patients see the picture eliciting the responses, meaning that the neuron was already encoding the concept before the experiment took place (Pedreira et al., 2010; Rey et al., 2015). This was also the case for the responses to associated concepts (obtained during passive viewing), reflecting the patients' own personal, episodic experiences (De Falco et al., 2016).

In the pair association task described in Figure 4, about 40% of the neurons initially responding to a particular concept, started firing to the associated one, whereas only 4% of the neurons fired to associated concepts during passive viewing (Figure 3c). This means that only about 1 out of 10 neurons initially encoding an association during the memory task may consolidate this information into a long-term representation, if the association is further revisited and will be remembered by the subject. Moreover, the largest proportion of MTL responses during the screening sessions was to experimenters that were initially unknown to the patients and performed experiments with them (Viskontas et al., 2009). In fact, the number of responses to the experimenters was even higher than the ones to well-known family members, thus showing that a large number of neurons encode novel, personally relevant persons and, as with the pair association paradigm, only few of these neurons may continue to encode these persons in the long term, if they are going to be remembered.

9.1 | Episodic and semantic memory

From the arguments in the previous section, it seems clear that the hippocampus keeps a long-term representation of concepts and associations between them, in line with the multiple trace theory. In other words, episodic memory is always dependent on the hippocampus whereas semantic memory relies on the neocortex. Later versions of this theory emphasized the dynamic evolution of memories, which led to the *trace transformation theory*, postulating that, in time, detailed episodic memories are transformed into variants that retain the gist of the memory (Dudai's "core episode") in the hippocampus, as well as schematic, semantic and perceptual representations in the neocortex, and that both hippocampal and neocortical systems interact in the retrieval of episodic memories (Gilboa & Moscovitch, 2021; Renoult et al., 2019; Sekeres et al., 2018).

The responses with human single neuron recordings described in the previous sections are consistent with this view, in which the hippocampus acts as a hub, encoding concepts and associations that constitute the gist of episodic memories, and that link to related representations in the neocortex (Figure 5). Making a distinction between episodic and semantic memory is, however, not always straightforward. In particular, the factual information related to a person's own past, what is known as "personal

semantics," may sometimes be considered episodic and sometimes semantic memory (Renoult et al., 2012). Taking the example of Figure 3a, does the response to actor Leslie Nielsen and the pictures of an airplane encode an episodic recall of the movie Airplane! or the semantic knowledge that Nielsen is the main actor of this movie?

Given the difficulty in making a clear-cut distinction between episodic and semantic memory, we propose that it might be more appropriate to focus on key differences between the hippocampal and neocortical representations, and then evaluate how these provide the neural underpinnings supporting the distinction between episodic and semantic memory. In particular, the associations encoded by human hippocampal neurons represent arbitrary relationships that are meaningful to the subjects, based on their own experiences, rather than semantic relationships (De Falco et al., 2016). Moreover, the lack of topographic organization in the human hippocampus (Figure 3b) is ideal for the fast formation of associations that underlie episodic memory, because it facilitates rapidly establishing associations between arbitrary concepts, and not just those corresponding to the same category, which is in line with the very rapid encoding of associations shown by these neurons (Figure 4c). This contrasts with the topographic and columnar organization observed in the neocortex (Mountcastle, 1957; Tanaka, 1996), which together with a more distributed population coding, is better suited to encode organized information and hierarchical structures that are characteristic of semantic memory and that can typically support relatively slow learning, so that the encoding of new associations does not disrupt established hierarchies and the organization of semantic information (McClelland et al., 1995). But even with a slow learning rate, some arbitrary associations may not fit within such hierarchical organization, and, as proposed by the multiple memory trace theory and trace transformation theory, this information will not consolidate in the neocortex and, therefore, there is a complementary hippocampal system to encode it. These arbitrary associations constitute the gist or core episode that allow making jumps in a memory narrative, which is in line with evidence showing the role of this area in coding associations between discontiguous, incongruent events (Staresina & Davachi, 2009; van Kesteren et al., 2013; Wallenstein et al., 1998), and the fact that patients with MTL lesions have a very limited recall and imagination, being able to provide only fractional accounts that are supported by neocortical structures (Hassabis et al., 2007), as when remembering a few isolated scenes from a movie but not the movie plot.

10 | AN INTEGRATIVE VIEW OF HIPPOCAMPAL FUNCTION

There has been a long ongoing discussion about the function of the hippocampus, mainly following two seminal and, in principle, disparate findings: first, the realization of the critical role of the hippocampus in declarative memory after its surgical removal in patient H.M. (Corkin, 2002; Squire & Zola-Morgan, 1991), and second, the finding of neurons encoding spatial locations, namely place cells (and later, entorhinal grid cells) in rodents (Moser et al., 2017). To reconcile these views, and following Tolman's earlier ideas (Tolman, 1948), it has been proposed that the hippocampus may have a more general role of organizing experiences according to multidimensional cognitive maps involving spatial, temporal and associational contexts (Schiller et al., 2015), and many authors have provided related theoretical frameworks linking the memory and spatial representation functions of the hippocampus (Bird & Burgess, 2008; Burgess et al., 2002; Buzsaki, 2005; Buzsaki & Moser, 2013; Maguire & Mullally, 2013; Rolls & Wirth, 2018; Wittington et al., 2020).

As discussed above, several studies have shown that the firing of place cells in rodents tend to change following physical alterations in the environment, as well as the context and task performed by the animals (Eichenbaum et al., 1999; Eichenbaum & Cohen, 2014; Moser et al., 2017; Shapiro et al., 2006). Such modulations provide contextual information related to the experience of the animal in the environment and it has therefore been argued that the hippocampus has a relational memory role, linking together the different elements constituting an experience (Eichenbaum et al., 1999; Eichenbaum & Cohen, 2014). Within this framework, the representation of spatial locations is one of many components of a memory, which is particularly prevalent in rodents, due to the importance of knowing their surroundings for their behavior, and the fact that rodents acquire information about the environment through exploration, whereas primates rely mainly on vision and eye movements to explore their surroundings (Rolls & Wirth, 2018).

Even if not as critical as in rodents, humans have also representations of specific locations that enrich their memories. In this respect, particular locations can be seen as concepts that are associated to different experiences, which are also encoded by partial overlapping assemblies—see the examples of the Tower of Pisa and the Eiffel Tower in Figure 5. But what about all the other functions attributed to the hippocampus described in the introduction? How can the same area be involved in so many disparate functions, going from memory coding, spatial representations, semantic relationships, working memory, or the coding of time, novelty and even numbers?

We have previously seen that hippocampal neurons encode new persons and associations, which may later consolidate into long-term representations, if they are relevant enough and are often revisited by the subject (see consolidation section). More in general, we can argue that the hippocampus provides a flexible machinery that temporarily processes different types of inputs, involving temporal, spatial, conceptual, memory relationships, and so on. Then, what appear to be different types of hippocampal cells and processes are just manifestations of the same general function, in line with Eichenbaum's relational theory (Eichenbaum & Cohen, 2014). However, the representation of the stimuli in temporary tasks is labile and the involved neurons could soon be recruited to encode something else after the experiment is done, unless the stimuli is rehearsed over and over again, becoming familiar and triggering specific memories (e.g., the memory of doing the experiment). This simple mechanism can then offer an adaptive and temporary code that is able to deal with different hippocampus dependent tasks, which may lead to representations

with partially overlapping assemblies for those items that are further rehearsed and continue to be relevant to the subject.

11 | WHY ONLY HUMANS HAVE CONCEPT CELLS?

Although the structure of the hippocampus is preserved across species—particularly in rodents, monkeys and humans (Clark & Squire, 2013)—I postulate that its coding principles and precise functioning is different in humans because it receives and processes different types of inputs compared to other species. In particular, the latency of human hippocampal responses is very late and, although there are direct feedforward connections from high level visual areas to the hippocampal system, the large latency gap between these structures indicates much further neocortical processing (at least compared to monkeys and possibly involving the prefrontal cortex (Eichenbaum, 2017)), in order to extract the meaning of the stimulus before the information reaches the hippocampus. This way, it is the meaning of the stimulus, rather than the stimulus itself, what it is processed by the human hippocampal memory system and it, therefore, makes sense to find the invariant and context independent representation by concept cells in the human hippocampus, because different pictures of the same person or the person's name have the same meaning for memory functions (since we tend to remember concepts and forget details).

Concept cells then represent the meaning of the stimulus for memory functions. They tend to respond to things (persons, places, items) that are very familiar to the subjects—that is, those that we form memories about. To be more precise and in order to compare across species, let us give an operational definition of concept cells. First of all, by concept we mean specific persons, places, objects, and not other more abstract notions, such as, reward, attention, and so forth (i.e., I will not argue that other species do not have neurons that could respond, for example, to reward in different conditions). In this sense, concept refers to a particular person (or place or item) irrespective of the sensory features of the stimuli (e.g., how exactly a person looks like in different pictures).

There are three main characteristics that define concept cells: (1) they show very selective responses, responding to very few of the presented stimuli (Mormann et al., 2008; Quian Quiroga, 2012b; Quian Quiroga et al., 2007); (2) they show a very high degree of (multimodal) invariance, mostly responding equally to different pictures and even the written and spoken names of specific persons, places, and so forth (Quian Quiroga, 2012b; Quian Quiroga et al., 2005; Quian Quiroga et al., 2009); and (3) they do not show context modulations, responding similarly in different tasks and conditions (Quian Quiroga, 2019, 2020).

Neurons with these characteristics are so far exclusively human. In rats, it was shown that while the animals interacted with other rats, although the presence of conspecifics altered the firing of hippocampal neurons, no cell responded selectively to individual rats (von Heimendahl et al., 2012). Further studies have shown a coding of "social memory" (i.e., a neuronal representation of conspecifics) in rodent hippocampal neurons (Hitti & Siegelbaum, 2014; Okuyama et al., 2016). However, these neurons were shown to represent the degree of familiarity with other conspecific, but without the degree of selectivity and invariance of concept cells—that is, it was not shown that these neurons respond selectively to a specific familiar conspecific (and not to other ones with a similar degree of familiarity), and with a response that is invariant to different views or presentations of the particular conspecific.

Arguably, the closest to concept cells are neurons in the monkey face patches that respond selectively to relatively few faces (Freiwald & Tsao, 2010; Tsao et al., 2006), apparently showing a coding similar to the one by concept cells. However, it was later demonstrated that these neurons actually respond to complex visual features, and not to specific individuals, according to the projection of the faces onto specific feature axes (Chang & Tsao, 2017). Absence of evidence is not evidence of absence, and it is still possible that in the future neurons similar to concept cells will be found in the hippocampus of other animals. However, it is remarkable that hippocampal responses in rats and monkeys show a completely different type of coding, relying on conjunctive coding and pattern separation, instead of the invariant and context independent representations found in humans.

But why only humans have concept cells? A major difference with other species is that humans have a refined use of language. Language allows exchanging information to communicate and teach elaborated thoughts, not only about the immediate circumstances of our surroundings, but also about past experiences and future plans (something that it is not possible without language). This way, language facilitates shared knowledge and the development of an incredibly complex culture. However, it is another, perhaps less noticed key advantage of language what makes concept cells unique to our species. This is the fact that language reinforces abstractions, to think about concepts detached of details and circumstances. Every noun, every verb, and every adjective is in itself an abstraction that provides a representation of meaning upon which we construct our high-level thoughts (Quian Quiroga, 2012a). Therefore, I postulate that, after tens and perhaps hundred thousand years of evolution, concept cells—and the mechanism of further neocortical processing that gives rise to extracting the meaning of the stimulus that is send to the hippocampal memory system—may have developed together with language, reinforcing abstractions and the machinery to facilitate unique cognitive abilities, including our capacity of generalization, imagination, metacognition and creative, abstract thinking.

12 | CONCLUSIONS

Single neuron recordings in the hippocampus performed for clinical reasons have provided new insights onto how memories are stored in the human brain. In particular, we have seen that concept cells encode concepts and associations between them, which are the building blocks of episodic memory. These neurons have two key functions:

first to link arbitrary concepts using partially overlapping assemblies and then provide a sketch representation of "core episodes," and second, to coactivate related sensory and semantic representations in the neocortex. We have also highlighted the main differences between the hippocampal and neocortical representations, particularly focusing on the fact that the hippocampus encodes arbitrary associations, which are the basis of episodic memory, whereas the neocortex encodes more ordered associations and hierarchies, which are the basis of semantic memory.

There are three defining features of concept cells, which up to now have not been found in other animals: high selectivity, multimodal invariance and no context modulation. The lack of context modulation gives rise to a completely different memory coding compared to other species, with partially overlapping assemblies, instead of pattern separation. This means that instead of forming dedicated assemblies representing new associations and memories, the neurons expand their tuning, representing the associations with overlaps between the context independent assemblies. We have also seen that the model of partially overlapping assemblies alleviates memory capacity limitations compared to pattern separation. In addition, we have proposed a unified view of hippocampal function, by which neurons in this area provide a flexible and temporary coding that can be used in various tasks and conditions—thus the finding of completely different types of hippocampal responses—and that, if the information is further revisited and consolidated, it will tend to form invariant and context independent hippocampal assemblies, representing those things that are relevant to the subject.

Finally, the claim that concept cells are unique to humans is, no doubt, very bold and intriguing. In this respect, a main goal of this article is to foster comparative studies across species in order to validate or falsify this observation and explore if, and to what extent, the properties of such neurons may explain the unique neuronal underpinnings of our memories, thoughts and intelligence.

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CONFLICT OF INTEREST

The author declares no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Rodrigo Quian Quiroga https://orcid.org/0000-0001-6534-3993

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