In What Sense, if Any, do Hippocampal "Time Cells" Represent or Encode Time?

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Overview

The first part of this poster is a conceptual discussion of the notion of a time cell. It is argued that some neural structures must encode time in a more fundamental way than the time cells do. I introduce the term "i-timecode" for this fundamental representation. The second part places the conceptual discussion in a context of certain wellknown empirical findings in humans. The third and last part presents two main alternative approaches when formulating a theory of the i-timecode. These are: mapping time to space, and transforming time to the frequency domain (or a mixed domain). I also present a version, in gross outlines, of the second approach. In it, neural oscillations are given a role that is quite different from those which they, in the contemporary discussion of time cells in the hippocampus, have been hypothesized to play.

Background in the current discussion, and another concept of time code

Recent experimental evidence shows that the principal cells of hippocampal area CA1 are activated in sequence during remembered experiences. The conclusion has been drawn (Eichenbaum 2014) that these cells "encode the temporal structure of /remembered/ events". Most of the evidence for hippocampal time cells is based on rodent experiments involving remembered locations, and the activated cells are the even more well-known place cells. Hence it has been argued that the latter encode both space and time.

Let us for this occasion suppose that the brain is a deterministic system. Then any temporal sequence of states of any brain structure must be predetermined by some state of the brain before or coincident with the beginning of the sequence, together with the input to the brain during the unfolding of the sequence. Since we are here talking about sequences that unfold in the absence of perceptual input, we may drop the last clause of the previous sentence. I will refer to the relevant pre-dermining state as the i-timecode, for "instantaneous time code".

It might well be that the i-timecode for spatial memory always resides in the hippocampi, at least for mice and possibly for men. I will discuss this possibility shortly, but first note that the empirical data presented about the "time cells" do not show that it is fulfilled. These data rather illuminate the need for an i-timecode: how does it come (i.e., what is the originating state for the happening) that the principal CA1 cells are activated in sequence during remembered experiences? Neither does the found interaction with hippocampal neural oscillations provide an i-timecode.

Why the i-timecode of the human brain does not always reside in the hippocampi

It is of some interest to discuss whether the i-timecode is always to be found in the hippocampi. Let us focus on the human case. It is a prominent characteristic of the Amnestic Syndrome that the person who is afflicted with it does not lose her memory of the very last seconds. That is why she can always (given no other complicating circumstances) repeat a heard short sequence of numbers, both forwards and backwards. So this ability is not dependent on intact hippocampal circuits. What is lost for the Amnestic Syndrome patient is "only" that which slips out of her attention, and that is lost (more or less) for good.

Now, a most important set of "replay" phenomena involves the very last seconds, for example in the auditory domain. Of course repeating a heard sequence of numbers is in itself an example of such replay. Another one is the fact that one can clearly "hear" a sequence of tones after it has physically stopped sounding, or the last few syllables of another person's speech. If the patient with Amnestic Syndrome couldn't perform the latter feat, it would be impossible to communicate verbally with her. And it seldom is. Hence the human i-timecode cannot always reside in the hippocampi. I would bet that the same holds for the mouse i-timecode, but I cannot prove it.

> **Fig. 1 (left):** The first bars of Beethoven's Fifth Symphony. Can you hear them?

Fig. 2 (right): Another, most important case of "replay". When walking on a dwindling path, you need not keep your eyes on it all the time. When instead looking at the beautiful landscape, or even with your eyes shut, you will still "see" the path before you, and this "sight" will continue to guide your steps. It will even update, in the standard case fairly correctly, while you "walk" according to it!

Four points can be made here. First, the "replay" involves the motor system at least as much as the perceptual one. Or expressed more adequately, there is no purely perceptual system!

Second, the updating of the "internal model" shows that it is not a matter of pure re-play. Instead the information about the recently seen scene is integrated with other information and automatically transformed into a dynamic sensory-motor anticipation that, in the standard case, presents you with an objectively correct and possibly changing perspective within the correct coordinate frame. Stretching the famous principle of charity, one might say that this was exactly what the early champion of the "replay" theory, the philosopher David Hume, meant by saying that copies of impressions may be combined to form new ideas. Compare also the fact that memories are often updated when they are retrieved (Alberini ed. 2013). Maybe there are no pure memories, since it is an essential function of memory to adapt to the organism's present situation and needs?

Third, these dynamic anticipations make a good case for the so-called "stimulus substitution" theory of learning (Mackintosh 1964). The anticipatory state is a fullblown substitute for the stimuli that should have been at hand but are not. Also, it can be argued that this very concrete substituting is one of the most important functions of memory, as seen from a biological standpoint.

Fourth, my educated guess is that any patient with Amnestic Syndrome (and no other serious brain damage) can manage this paradigmatically spatio-temporal task – but she will probably not find her way back easily.

The case of waking up in a dark unfamiliar room and managing to orient in it for quite a while after just lighting it up for half a second is maybe more dramatic but less important from an ecological point of view.

For an early discussion of dynamic anticipation and the possible mechanisms behind it see Malmgren (1996).

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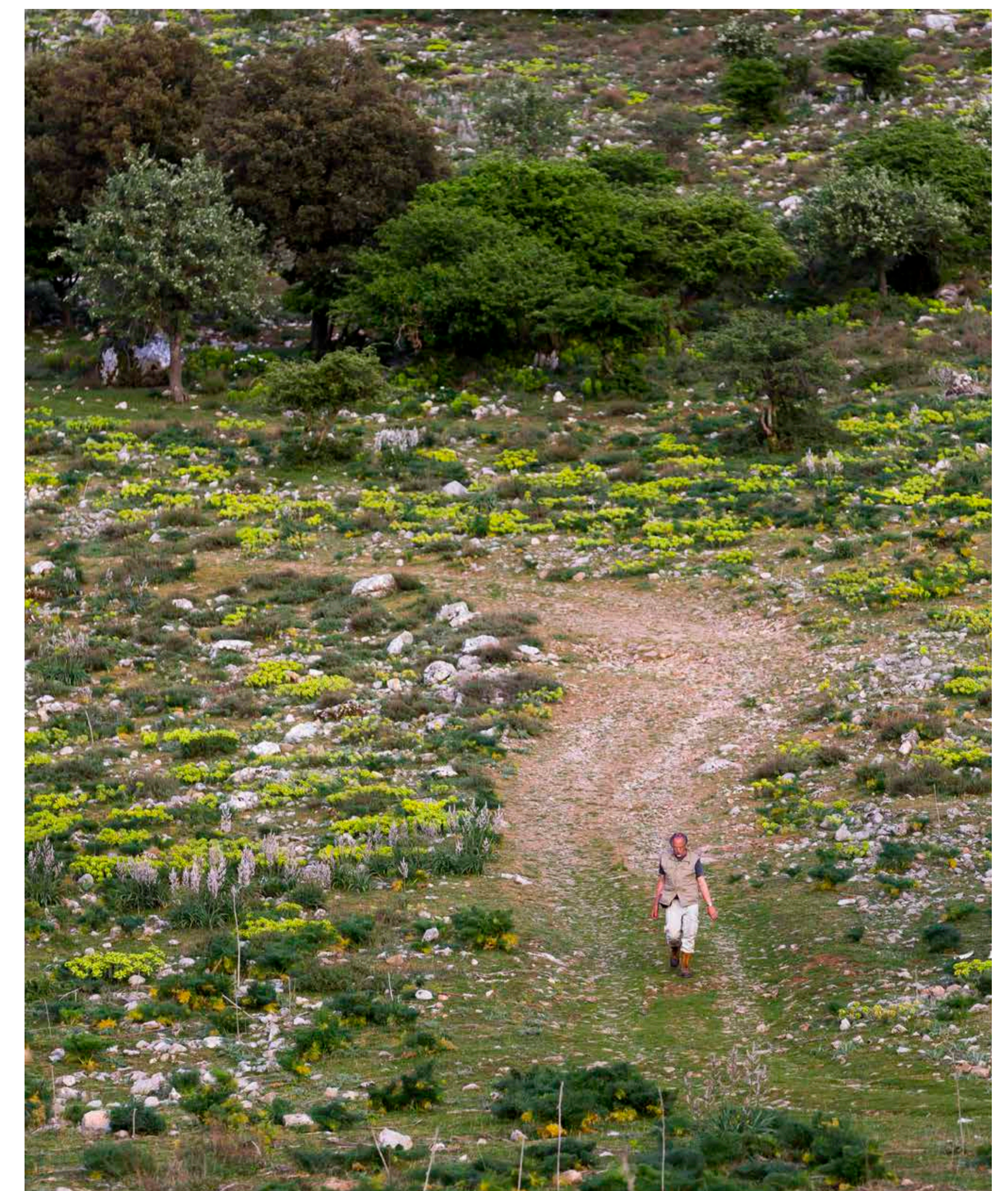
The nature of the i-timecode

What is the intrinsic nature of the i-timecode, and where is it located? According to the received view, long-term episodic memories are stored in sets of synaptic strengths in cortical networks that at least in the case of non-spatial memories are located outside the hippocampus. So when such memories are retrieved and replayed, these synaptic strengths are the i-timecode, or at least they form an essential part of it. Again, even if the hippocampi are necessary for the retrieval, the i-timecode is not a hippocampal state.

For short-term (or working) memory it has been argued that synaptic strengths in firing chains or recurrent neural networks in the hippocampus could provide the needed code. However, one fact tells strongly against these ideas. It is the abovementioned phenomenon of very fast learning, exemplified by our ability to immediately and exactly mentally replay or even physically reproduce a heard, short tonal sequence. Such learning requires quicker adaptations than those possibly provided by changed synaptic strengths.

Two possible solutions

There is good evidence that the auditory input travels along many parallel patways before reaching the primary auditory cortex. It is prima facie plausible that these different signals do not take the same time to reach their target. So one can describe the auditory cortex as equipped with incoming delay lines. A possible explanation of the phenomenon of "hearing" the last syllables spoken is that all the incoming messages are presented together to auditory consciousness, but with the older, more slowly transmitted messages tagged as older. This means that the i-timecode resides in the current state of that part of the auditory cortex in which auditory consciousness is located. Note that this explanation has a natural extension to motor control: fast, pseudo-ballistic movements such as hitting a tennis ball properly might be pre-programmed (i.e. determined by a motor i-timecode) in all its details through delay lines. See Malmgren (2003) for an detailed exposition if these ideas.

However this kind of solution would be extremely expensive (in term of needed wetware) for all but very short sequences. I will therefore end this exposition with a speculation that to my knowledge has not been put forward before. This in spite of the fact that neural oscillators play a very large roll in the current debate.

Envisage the sensory cortices as containing a large bank of independent, spiking neural oscillators with different but fixed frequencies and modifiable phases. They may be single, spontaneously firing neurons or whole circuits of neurons with a regular output. Regard a train of incoming, essentially binary (single spikes) sensory signals, and imagine that it causes a number of these oscillators to phase-lock to the frequencies that the signal sequence contains. The latter idea is not in any sense new; among other things it is closely related to a wellknown theory about neural entrainment in music perception (Large & Kolen 1994), but the latter is concerned with phase-locking of local field potential oscillations as manifested in the EEG rather than of neuronal spiking.

However, I also speculate that there is a certain mix of excitatory and inhibitory feedback connections from the bank of oscillators to the sensory structure where the input just arrived, such that the original input sequence will be replayed there in case of no further sensory input (and given a few other conditions). Hence the collective state of the involved oscillators at the end of the input sequence is the i-timecode for this replay.

How could that be? First note that since the neural oscillators are independent they will all remain in their reseted phase after input has ceased. Hence there will be peaks of collective activity corresponding to the locked phases. This means that the bank continues to implement a spectral and phase analysis of the input sequence. It "only" remains to add that the outputs of the oscillators sum in a way that make them do the kind of work that a Fourier or wavelet transform does, namely reconstructing the original sequence, but also extremely fast and at the same time very precisely. This is a very large order, and Fourier certainly would not work, but there are many other possible transforms that could be involved. See Principe (2015) for some exciting suggestions. This is not my own field of competence, so I have to leave it to others to judge whether my speculation is worth taking seriously.

References

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There is of course a huge relevant literature, but because of lack of space I had to keep the list at (or even below) the minimum.

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