Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Hippocampal CA1 Subregion as a Context Decoder

Sebastian A. Barrientos and Vicente Tiznado

Centro Interdisciplinario de Neurociencias, Pontificia Universidad Católica de Chile, and Laboratorio de Circuitos Neuronales, Departamento de Psiquiatría, Centro de Investigaciones Médicas, Facultad de Medicina, Pontificia Universidad Católica de Chile, 8330024, Santiago, Chile

Review of Allen et al.

In many circumstances, making an appropriate behavioral decision requires the integration of previous experiences with information about the current situation. Episodic memory is the cognitive process by which temporally organized events are encoded, stored, and recalled. In humans and other animals, the ability to form episodic memories depends on the hippocampus, and hippocampal integrity is required for retaining and recalling this information (Scoville and Milner, 1957). All experiences that we remember are constituted of spatial and temporal information regarding surrounding events, which form the context of any situation. Hippocampal neural activity is thought to be involved in the neural representation of those contextual features at both population and single-cell levels.

The neural representation of spatial features of context and its involvement in memory has been extensively studied since the discovery of "place cells" in the hippocampus (O'Keefe and Dostrovsky, 1971). The hippocampus also encodes information about specific items in space (Komorowski et al., 2009; Manns and Eichenbaum, 2009), as well as the time elapsed between discrete stimuli (MacDonald et al., 2013). The encoding of temporal features is relevant because an essential aspect of episodic memory is the recognition of sequences of events, a process that is disrupted by hippocampal lesions (Fortin et al., 2002). If the hippocampus is crucial for the processing of temporal aspects of memory, how does it do it? Furthermore, how does it encode detailed information about a temporal sequence of events? How is this encoding related to the rest of memory-associated processing that occurs in the hippocampus?

A recent study published in the *Journal of Neuroscience* (Allen et al., 2016) moves us closer to understanding how the hippocampus participates in the detailed encoding of ordinal information about a sequence of stimuli, which the authors refer to as the "temporal context." Specifically, the authors trained rats in a nonspatial sequence memory task that they had previously characterized behaviorally in rats and humans (Allen et al., 2014). In this task, a sequence of odors was presented in a previously learned order ("Inseq") or in a different, unknown order ("Outseq"). Rats had to indicate whether each odor was presented in the learned sequence (Inseq) or out of sequence (Outseq) to obtain a reward, while neuronal activity was recorded in the CA1 area. To further characterize the memory-based encoding of sequences, rats were challenged with the following three types of tests in different sessions: the previously learned sequence (Well-trained); a novel sequence (Novel1); and the novel sequence presented a second time (Novel2).

Allen et al., 2016 found that ~25% of the recorded hippocampal CA1 neurons showed differential activity patterns for Inseq or Outseq stimuli. Furthermore, most of these cells, termed "sequence cells," responded preferentially to Outseq compared with Inseq stimuli. The authors confirmed this observation at the population level, finding that the activity of neural ensembles could be used to predict the sequence of stimuli. These CA1 neurons likely convey mnemonic information, since the number of sequence cells was well correlated with the performance of the animal. In the low-performance Novel1 session, the proportion of sequence cells found was considerably lower than in the high-performance sessions (Well-trained and Novel2).

Within the population of sequence cells, Allen et al., 2016 found a variety of activity patterns. They found neurons that fired during the entire sequence ("general cells"), and others that responded to specific odors and their position in the sequence ("conjunctive cells"). For example, one conjunctive cell showed maximal activity for the third odor of an Outseq sequence. Other subgroups of neurons fired specifically when the deviant odor in an OutSeq sequence was repeated ("repeat cells") or was changed to another ("skip cells"). These results show that CA1 neurons can encode both general and detailed information about a sequence of events.

Additionally, Allen et al., 2016 looked at local field potential oscillations in both theta (4–12 Hz) and slow-gamma (20–40

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Correspondence should be addressed to Sebastian A. Barrientos, Laboratorio de Circuitos Neuronales, Centro de Investigaciones Médicas, Facultad de Medicina, Pontificia Universidad Católica de Chile, Marcoleta 391, 8330024, Santiago, Chile. E-mail: snbarrie@uc.cl.

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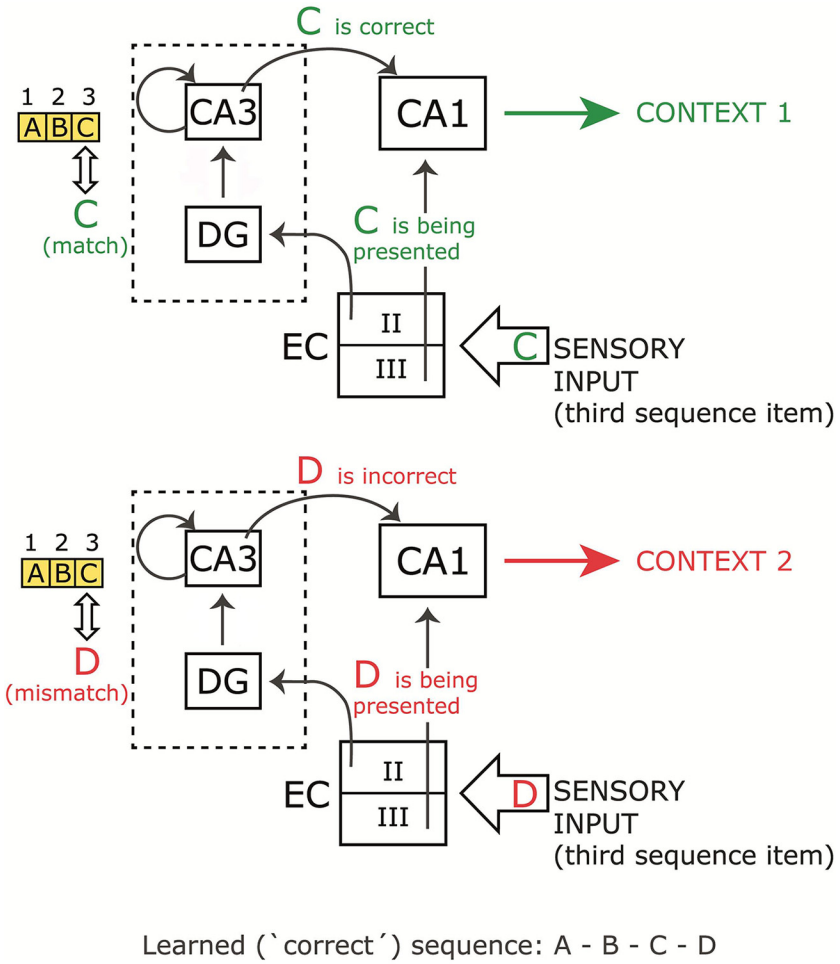

Figure 1. Example and proposed mechanism about CA1 neuron representations in Allen et al.'s study. The animal learned to associate a certain outcome with a sequence of four odors presented in the following order: A, B, C, and D (Context 1). The example shows how the information of the third item of a sequence flows within the hippocampal circuit in two different scenarios. Top, C is presented as the third item. Sensory information about item C is delivered from EC to CA1 by two parallel paths. EC layer II efferents provide input to the CA3–DG circuit, where recurrent synapses of CA3 allow the matching of incoming information about item C with the third item of the previously stored sequence. The resulting activity from this match in CA3 is sent to CA1, converging with the direct input from EC layer III, which triggers an abstract representation of context 1. Bottom, D is presented as the third item. In this case, the CA3–DG circuit does not recognize it as the third item of the sequence, resulting in the disambiguation of the overlapping sequences (ABC vs ABD), generating a distinct output pattern to CA1 that, in conjunction with the direct input from EC, triggers the representation of another context.

Hz) frequency bands. They found that the power of slow-gamma oscillations was larger during Inseq compared with Outseq sequences. In contrast, theta power was not modulated by the identity of the sequence. Such specificity of oscillatory activity was shown to be dependent on temporal context memory since gamma amplitude was also high for both the Well-trained and Novel2 sessions, but not for the Novel1 session.

Why is it interesting to look at CA1 activity? Besides being the primary output of the hippocampus, CA1 is thought to integrate information arriving from the following two parallel paths originating in the entorhinal cortex (EC): a direct EC–CA1 projection; and an indirect EC projection through CA3 and dentate gyrus (DG; Fig. 1). The resulting matching or mismatching of information from those two projections would elicit a representation of familiar or novel items. The results by Allen et al., 2016 reinforce this notion and provide interesting insights into its mechanism.

Regarding the direct EC projection, current evidence suggests that EC provides sensory information about the current situation (van Strien et al., 2009). This direct input from EC to CA1 originates in layer III of the EC and makes synaptic connections on the apical shaft of CA1 cells. Evidence from both modeling and empirical data suggests that this input is not enough by itself to trigger action potentials in CA1 neurons, unless they receive convergent CA3 inputs (Jarsky et al., 2005; Bittner et al., 2015), a point that reinforces the notion of CA1 cells reflecting the result of an integrative computation between two incoming inputs. The second input contributing to CA1 computation is the projection from layer II of the EC to the DG and CA3. Computational models propose that DG can accomplish pattern separation through the detection of subtle differences in EC inputs, whereas recurrent connections of CA3 are involved in the recall of previously stored information and pattern completion (McClelland and Goddard, 1996; Rolls and Kesner, 2006). This suggests that CA3 and DG together might support associative recognition of previously learned spatial or temporal contexts (Wood et al., 2000; Ginther et al., 2011; Neunuebel and Knierim, 2014). CA3 is believed to be part of the circuit that encodes sequences, because CA3-lesioned rats cannot recognize an altered spatial sequence (Hoang and Kesner, 2008). Together, these data indicate that since CA1 activity is the result of both CA3 and EC inputs, the representation of sequences in CA1 could arise from a conjunctive operation similar to what has been hypothesized recently for the human hippocampus (Davachi and DuBrow, 2015). Information about temporally discontinuous stimuli could be delivered from EC layer II to the CA3–DG circuit, where each item is compared with an already known sequence. Detected similarities/differences are contrasted in CA1 with incoming inputs from EC layer III, which are then translated into different context-enriched neural representations that are communicated to other brain regions (Fig. 1).

Allen et al., 2016 found a higher proportion of sequence cells in Outseq trials than in Inseq trials. In this regard, a similar experiment in humans showed that mismatched items within a learned sequence elicit higher hippocampal activity than the original sequence (Kumaran and Maguire, 2006). This selective responsivity likely involves repetition suppression, a habituation-like process induced by the repeated presentation of stimuli.

What questions remain to be answered? Further exploration of the specific contributions of CA3 and DG could disclose finer aspects of the mechanism. It is also extremely relevant to explore behavioral scenarios in which the subject does not recognize the context adequately. Previous work from the same group points to an unexplored portion of

the data that could be revealing in this respect. Indeed, in their behavioral article (Allen et al., 2014), the authors showed that not all Outseq sequences were equally difficult. Subjects had a much harder time recognizing out-of-place items if they were positioned in late, instead of early, portions of the sequence. Allen et al., 2016 do not report neural correlates of these behavioral difficulties, which may have resulted from inaccurate pattern completion or separation performed by the CA3–DG circuit. The inverse approach of diminishing or interfering with neural activity to cause specific behavioral errors would also be highly informative.

Allen et al., 2016 show that the hippocampus participates in the encoding of an essential feature of episodic memory, the detailed course of a sequence. These results support the notion that information from several regions converges in the CA1, which is required to form accurate representations of the context (Rolls and Kesner, 2006; Takahashi and Sakurai, 2009). The discovery of sequence cells broadens the spectrum of features of experience that the hippocampus encodes and retrieves. The major output of the hippocampus, the CA1, can thus deliver information about temporally ordered events, such as specific item–position conjunction within the sequence and specific alterations of a known sequence.

In a larger picture, we think that the processing of both spatial and temporal contexts by CA1 cells shares a similar mechanism. If this is true, it would suggest that the hippocampus is crucially involved in the coding of the entire spatiotemporal context in which each situation occurs. The challenge of integrating all the different lines of evidence into a single coherent framework of hippocampal function gets an additional valuable input from the study by Allen et al., 2016.

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