

Letter

On pattern separation
in the primate,
including human,
hippocampusEdmund T. Rolls^{1,2,3,*}

In a recent article, Quiroga argued that pattern separation may not occur in the human hippocampus [1]. This argument was based on neuronal recordings in the human hippocampus that showed that many neurons respond to overlapping representations and thus may not reflect pattern separation. However, it is important to assess why pattern separation is especially important in specific parts of the hippocampus such as the dentate gyrus and CA3 (Figure 1), and to assess the type of investigation needed to support the claim that pattern separation does not occur in the human hippocampus, by comparing the currently available findings in humans with those in other primates.

First, pattern separation is needed in CA3 cells of the hippocampus because for these cells to operate as an attractor network associating the components of the episodic memory together, it is important to have relatively uncorrelated activity in the neuronal population for each memory; that is, the patterns of activity for each memory must be separated. Otherwise, the memory capacity (i.e., the number of memories that can be stored and recalled) is reduced [2–4]. Pattern separation therefore needs to be tested in the dentate gyrus, because this area is believed to perform the pattern separation by competitive learning and by the low contact probability of dentate granule cells via mossy fibres with CA3 cells [3–5]. Quiroga did not describe any comparison with the

sparseness of representations in different parts of the human hippocampal system or between the hippocampus and neocortex [1], but in macaques it has been shown that representations in the hippocampus are more sparse than in three neocortical areas [6], in line with the pattern separation hypothesis [3,4].

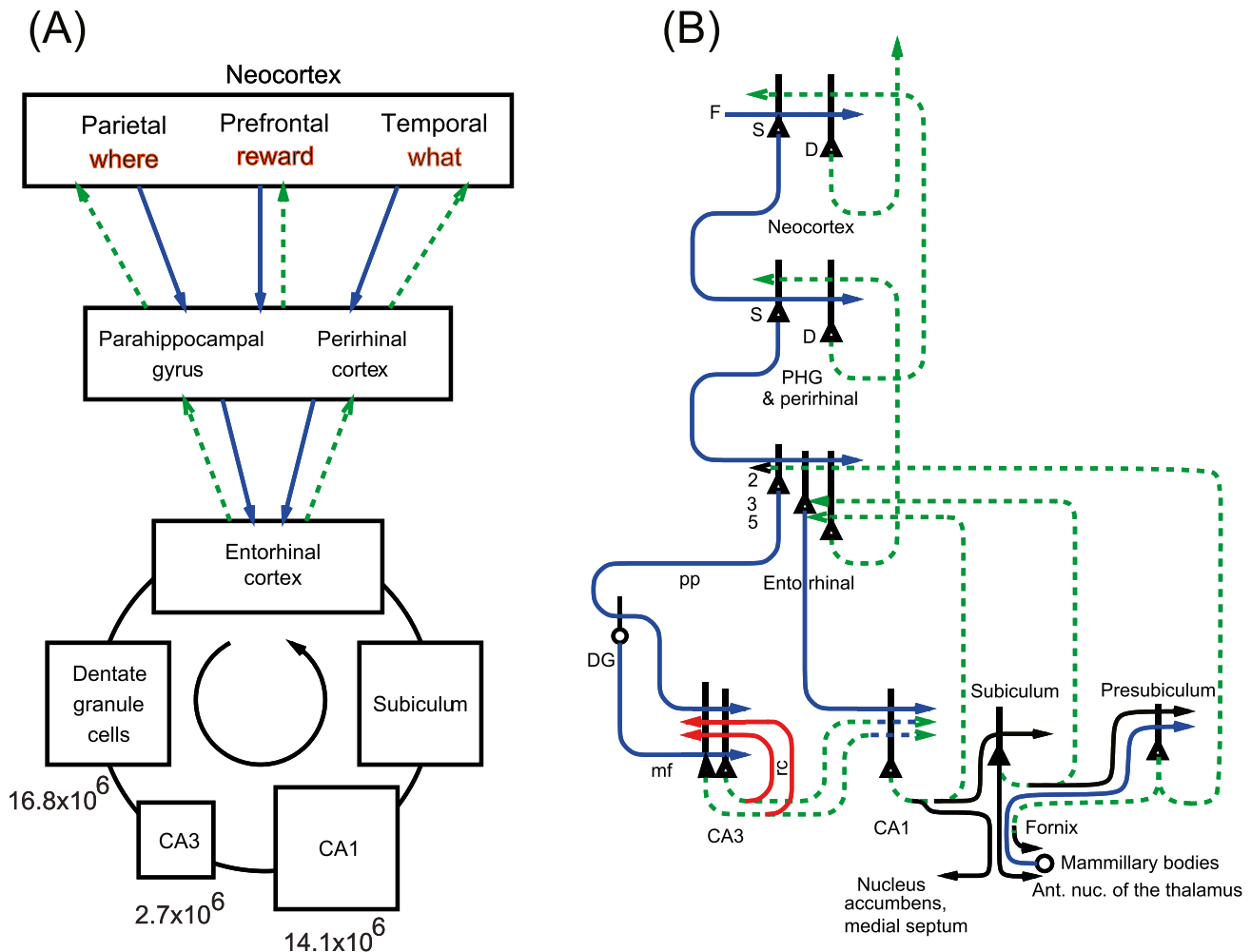
Second, when investigating hippocampal memory function, it is important to utilise an episodic memory task in which some of the components, such as ‘where’, ‘what’ (including reward value), and/or ‘when’ (e.g., temporal order), are learned in one trial [3,5,7]. In macaques, object-in-scene and reward-in-scene tasks that could be learned in one trial were used and neurons formed the necessary associations [8–10], but the person–place association task used in humans was different and often took approximately six trials to learn (Figure 2 in [1]), so was not a prototypical episodic memory task. Furthermore, most studies of concept cells did not use an episodic memory task at all [1].

Third, it was argued that conjunctive representations found in the human hippocampus (in which representations of, for example, different people overlapped) indicate that pattern separation is not present [1]. In fact, the critical requirement is that before an episodic memory is learned, disjunctive (i.e., separate) representations of the essential components [‘where’ with ‘what’ (including reward) and/or ‘when’] are present, so that they can be associated together in CA3 on a single trial in which an episodic memory is formed (Figure 1). After learning the episodic memory, the representations will appear to be conjunctive because presentation of either the ‘where’ or ‘what’ component will result in the whole representation being recalled in CA3. The neuronal responses recorded in a one-trial episodic memory task in macaques were consistent with this, in that different

single neurons could respond to one or other of the ‘what’ or ‘where’ components, or to either after learning [8,9], but this was not tested in the human investigations described by Quiroga [1]. Instead, representations of people were described as ‘not disjunctive’ because neurons responded best to one person but responded also to some other associated people. This however is how coding within a class (e.g., people within the ‘what’ domain) occurs in cortical systems and is described as sparse distributed coding across a whole population of neurons. In this type of coding, neurons respond best to one stimulus within a class (e.g., a face of one person), less well to another stimulus (e.g., a face of a second person), with lower and lower responses to other stimuli (e.g., faces of other people, of body parts, etc.) [3,6]. This type of coding, found throughout the cortex, is advantageous with respect to the storage capacity of neuronal networks, and to completion, generalisation, and fault tolerance [3].

Fourth, the argument that pattern separation might not be useful in humans because of a combinatorial explosion with too many neurons being required to represent all possible combinations of objects and places [1] is irrelevant with respect to memory storage in an autoassociation network in the CA3 neurons of the hippocampus, because it has been established that the memory storage capacity of an autoassociation network is not determined by the number of neurons in the network or by the number of combinations that they might represent, but instead by the number of recurrent collateral synapses on any one neuron in the autoassociation network and the sparseness of the representation, in this case in CA3 (Figure 1) [3,11].

The points made by Quiroga [1], therefore, do not address the issue of whether pattern separation is present in the human hippocampus for episodic memory. It is



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Figure 1. Connections of the hippocampus and pattern separation. Inputs reach the hippocampus from different parts of the neocortex (A) through the perforant path (pp) that makes synapses with the dendrites of the dentate granule cells (DG) (B). The DG cells are hypothesized to produce pattern separated representations in CA3 by operating as a competitive network that projects via the sparse mossy fibre inputs to the CA3 cells. The recurrent collateral system of the CA3 cells (red) is proposed to operate as a single attractor network to associate separate 'where' with 'what' or reward representations in one trial for episodic memory. The CA3 pyramidal cells project to the CA1 pyramidal cells that are hypothesized to produce conjunctive representations from the separate representations of 'where' and 'what' in CA3. These conjunctive CA1 representations are efficient as the first stage of the multistage recall process back to the neocortex (green). Time and temporal order are also important in episodic memory, and may be computed in the entorhinal-hippocampal circuitry [7]. The thick lines above the cell bodies represent the dendrites. S and D – superficial versus deep layer pyramidal cells. F – forward inputs to neocortical neurons from earlier neocortical areas. The numbers of neurons in different parts of the hippocampal trisynaptic circuit in humans are shown in (A), and indicate many DG cells, consistent with expansion encoding and the production of sparse uncorrelated representations prior to CA3. The hippocampal theory and supporting neurophysiological and related evidence are described elsewhere [3,5,7,11].

hoped that the points made here and elsewhere [12] will lead to fruitful tests of the hippocampal pattern separation hypothesis in humans in future. Important foundations for and developments of the concepts about pattern separation in the hippocampal system, and disjunctive versus conjunctive representations in it,

are described further elsewhere [3–5], with the aim to provide a foundation for future research into the episodic memory system.

Acknowledgements

There is much other relevant research on the roles of the human and primate hippocampus in memory and

navigation by many others including A.D. Ekstrom, I. Fried, N. Suthana, C. Stark and M.A. Yassa that could not be referred to here because of length limitations, but that research on memory and navigation is referred to in papers and supplementary material available at <https://www.oxcns.org> and in [3,12]. Dr Sylvia Wirth (Lyon) is thanked for stimulating discussions on the likelihood and nature of pattern separation in the primate brain.

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