

Knowing your place: Subfield specific involvement in hippocampal spatial processing

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Abstract—Spatial navigation is a critical part of animal behaviour. Experimental data show that some cells in the hippocampus of animals engaged in exploration respond preferentially to particular physical locations. These place cells give us an important indication of hippocampal participation in spatial processing. Recent work has examined differences in place field representations between hippocampal subfields. We discuss these findings and show, using a computational model, how known aspects of hippocampal physiology can explain these differences.

I. INTRODUCTION

Place cells, found in the CA1 and CA3 regions of the hippocampus and the entorhinal cortex (EC), appear to code for specific physical locations. We firstly discuss experimental results relating to place cells, focussing specifically on recent data on how representations of place are formed differentially in CA3 and CA1.

We then present results from a model of place cell formation and modulation by environment, showing that several experimental properties of place cell formation arise from basic hippocampal physiology. These properties include NMDA receptor knockout effects and differences in representation correlation between CA3 and CA1. We also discuss how these results confirm existing research and suggest experimental possibilities that could be used to gain a better understanding of hippocampal function.

II. BACKGROUND

A. Discovery of place fields

Place cells were discovered by O'Keefe and Dostrovsky in 1971 [1] when recordings of extracellular potentials from rat CA1 neurons showed that some neurons increased their firing rate during navigation of particular spatial regions. These "place cells" form rapidly upon exposure to a new environment and are re-activated on reexposure to the same environment. Place fields overlap, such that at a given point in space, many place cells will be active [2]. In addition, this representation is distributed such that physically proximal hippocampal cells are not correlated in firing patterns [3] - there appears to be no topographic mapping of physical locations onto parts of the hippocampus.

We define a place cell to be a cell that fires preferentially when an animal is at a certain physical location, and a place field to be the physical region of space within which the cell will fire. A place representation is the set of place cells concurrently activated at a given point in space.

B. Theta rhythms, phase precession and inference of location

Theta frequency oscillations are an important part of hippocampal information processing, particularly in relation to spatial exploration. In 1993, O'Keefe and Recce discovered that the phase of a place cell's firing relative to the local theta oscillation shifts as the animal moves through the field [4]. This phase precession effect allows for a much finer coding of position than is given by the place cells alone [5].

C. Differences between hippocampal subfields

Although there are many theories which assign specific functionalities to different subfields within the hippocampus, there is a lack of experimental evidence to clearly delineate these functionalities. Although there are known physiological differences, one of the most notable being that CA3 is highly reciprocally connected, it is difficult to demonstrate clear functional differentiation - both CA3 and CA1 form place cell representations, for example.

1) *Connectivity differences*: How CA3 and CA1 place representations interact is not clear. CA1 is strongly driven by CA3, and, as we shall see, place fields in CA1 are affected by neuronal change in CA3. However, CA1 also receives input from the EC layer III cells (via the temporoammonic pathway), and this input is sufficient to activate place fields [6]. From this we can deduce that there are separate (but interacting) mechanisms of place cell formation in CA3 and CA1.

Research has shown that place cells can be found in CA3, CA1 and the EC. Initial results [7] seemed to suggest that place cells were more focussed (such that place fields were smaller) in the EC, but later work contradicted this and it is now widely accepted that the most localised representations are found in CA3.

Experiments on the effect of NMDA receptor¹ knockout

¹N-methyl-D-aspartate - one of the brain's primary excitatory neuroreceptors.

in the CA3 region have shown that without CA3 NMDA receptors, place cells in CA1 form more slowly and are less focussed (place fields are larger) [8]. However, place cells still form, and after a period of off-line learning, place fields become as well developed as those in the control animals. Place cell formation in CA3 appears to be prevented entirely by NMDA receptor knockout.

2) *Representational stability in CA3 and CA1*: Recent research has specifically examined these differences, specifically in the context of place field formation. [9] shows that place fields form more slowly in CA3 than CA1, while [10] and [11] demonstrate that small environmental changes cause larger changes in the field representation in CA1 than CA3. [11] is of particular interest. The authors consider a paradigm where rats run around a circular track, with distal cues. The cues are then rotated relative to the track, and the effect on place field representations is measured. Results show that the degree of correlation between CA3 representations as the cues rotate is higher than that of CA1 representations.

A possible explanation for these phenomena is that the reciprocal connections within CA3 allow representations to form as attractor states, such that small deviations from the stored representation are corrected by recall, while CA1 representations respond directly to inputs, without interference from previous stored representations.

D. Summary of differences between CA1 and CA3 place fields

We know that:

- Place fields develop more slowly in CA3 than CA1.
- Knockout of CA3 NMDA receptors causes place cells to form more slowly (and for place fields to be initially less focussed) in CA1.
- Small environmental shifts cause representations in CA1 to change more rapidly than those in CA3.

E. Inputs to the hippocampus

The structure and coding of the inputs that are used to construct place fields are not known in detail, but some work has been done that illustrates that visual input is a partial, but not complete activator of place cells [12]. It is also known that place cells require some motor feedback – if an animal is constrained such that it cannot move but is placed in an environment for which it has already formed a place representation, the representation will not be reactivated.

In our simulation, we assume some pre-processing of inputs, rather than modelling it explicitly.

F. Motivation for simulation

There are a number of simulation models that attempt to answer questions relating to the formation of place fields, phase effects, and how these relate to memory encoding (for example, see [13]). However, experimental results demonstrating clear differences between CA3 and CA1 place field representations are sufficiently new for there to be little modelling work to explain these differences.

These differences of representational stability between regions form a problem eminently suited to a simulation approach. We can use the known structures of the hippocampal subfields to construct a model that can determine whether the physiological differences alone can explain the differences in field correlation (specifically whether the CA3 recurrent connectivity is enough to explain the difference in representational stability), or whether it may also be necessary to consider other factors. Additionally, the quantitative nature of the problem (populations of place cells, degrees of correlation etc.) allows us to make strong predictions for experiment.

III. SPECIFICS OF THE NEURON, PLASTICITY AND HIPPOCAMPAL MODELS AND SIMULATION METHODOLOGY

A. Neuron model

The single neuron used by the model is a compartmental spiking neuron based on a model by Wang[14], using the neuron equation there². The model simulates a number of neuroreceptors, two excitatory (NMDA and AMPA) and two inhibitory ($GABA_A$, $GABA_B$ - classes of γ -Aminobutyric acid receptor), an after-hyperpolarisation (AHP) current and an intrinsic sodium current. Most constants are similar to those used in [14], some AMPA and NMDA conductances slightly altered to compensate for the smaller numbers of neurons used here.

B. Plasticity model

We use a detailed model of spike time dependent plasticity, based on a separation of plasticity components into separate potentiation and depression processes. This results in a dependence of synaptic strength change on inter-spike interval similar to that observed in [15], such that plasticity is dependent on a causal relationship between neuron firings (effectively a causal Hebbian model). The model is explained in much greater detail in [16].

C. Network model

Our hippocampal model has cell fields each consisting of 225 excitatory neurons and 50 inhibitory cells. The synapses between the DG and CA3 (the perforant path), EC and CA1 (temporoammonic pathway) and CA3 and CA1 (Schaffer collaterals) are all subject to bidirectional synaptic plasticity as described above. The model can be seen in Figure 1.

Inputs to the network consist of blocks of neurons, changing every 100ms. The entire sequence lasts for approximately one second, and represents traversal of a circular track. We show an example of the input sequence in Figure 2. The inputs repeat for 40s. Activity of the network's interneurons is modulated by theta frequency input from the septum. This modulation imposes theta frequency activity on the network as a whole.

² $C \frac{dV}{dt} = I_{LEAK} + I_{AHP} + I_{NMDA} + I_{AMPA} + I_{GABA_A} + I_{GABA_B} + I_{NaP}$ - the AMPA and NMDA currents are glutamatergically activated, two channel kinetic currents, the NMDA current being voltage gated, the NaP current is an intrinsic sodium current and the AHP current is an adaptation current based on calcium depletion by output spikes

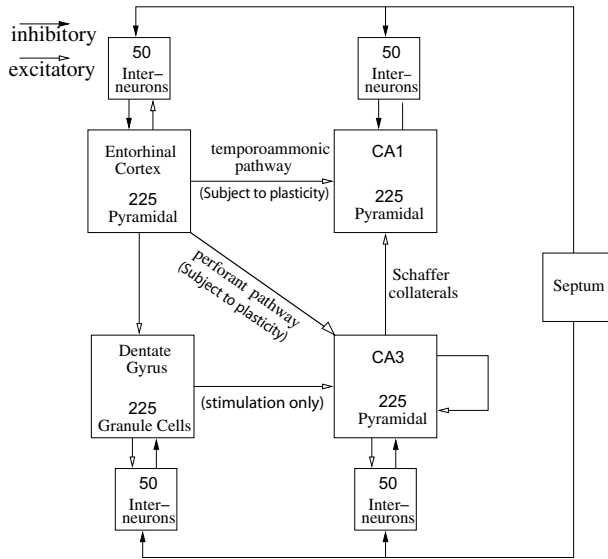


Fig. 1. Network model details showing primary connections and numbers of simulated neurons in each module

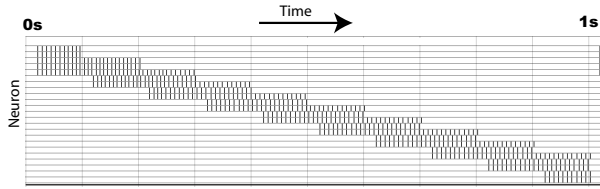


Fig. 2. Spike trains from entorhinal cortex showing input sequence

Connections between regions are primarily non-topographic, with 10-30% connectivity. CA3 is recurrently connected, with approximately 25% connectivity. This is considerably higher than the actual CA3's recurrence (approximately 4%), but is necessary to compensate for our much smaller number of neurons than the real CA3.

Our simulations will consider the following problems:

- Formation of place cells and representations, particularly the relative speed of formation of representations in CA1 and CA3 (do representations form faster in CA1?)
- The dependence of CA1 place cells on CA3 NMDA receptors.
- Effect on representations of introduction of additional environmental cues.

We will describe the specific methodologies used to address these problems individually in the next section, where we also look at the simulation results.

IV. RESULTS

Here we present results of the simulations, looking at firing patterns, place cell formation, speed of representation development and correlations between place field representations.

A. Place cell formation

At the start of the simulation, response to the inputs is determined by a random spread of initial connections and

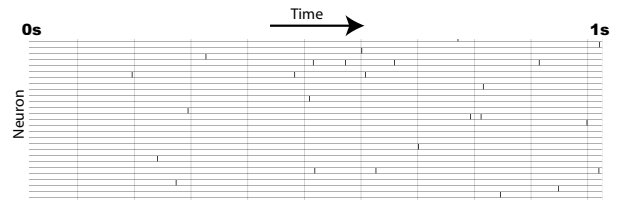


Fig. 3. Initial uncorrelated firing

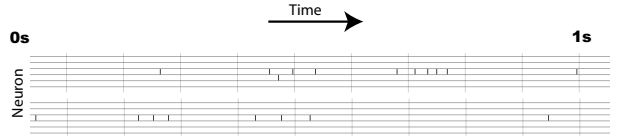


Fig. 4. After learning, some cells have developed sensitivity to particular inputs

neuronal noise – there is no marked response to particular inputs (see Figure 3).

After a period of learning, some cells develop sensitivity to particular inputs, firing preferentially when those inputs are present – the cells have developed place fields. We can see two cells with place fields in Figure 4. 20-30% of cells in CA3 and CA1 develop place fields.

B. Speed of place cell development – CA3 vs CA1

Next we wish to look at the relative rate of development of place cells in CA1 and CA3. To do this, we define a quantitative measure of representation development by:

- 1) Calculating a continuous version of neuronal firing rate functions (using a Gaussian filter function) for pyramidal cells in the input layer of the EC, CA3 and CA1.
- 2) Calculating correlations between the firing rates of each input neuron (in the EC) and pyramidal cells in CA3 or CA1. Neurons with firing functions highly correlated with specific inputs are considered to show a place field for that input.
- 3) Counting the number of neurons with a correlation above some threshold. This gives a quantitative measure of the number of place cells in a representation.

Given this technique for measuring the number of place cells, we can examine how this number evolves over time for both CA1 and CA3. Doing so, we see in Figure 5 that CA1 place fields develop faster than CA3 place fields, as experimental results indicate. In our model, this difference is due primarily to the relative rates of synaptic plasticity at perforant path and temporoammonic synapses.

Note on timescales: It is difficult to determine precisely the timescales of place cell formation from experimental evidence. We do not expect that our timings exactly represent real place cell formation, rather they demonstrate relative rates of formation.

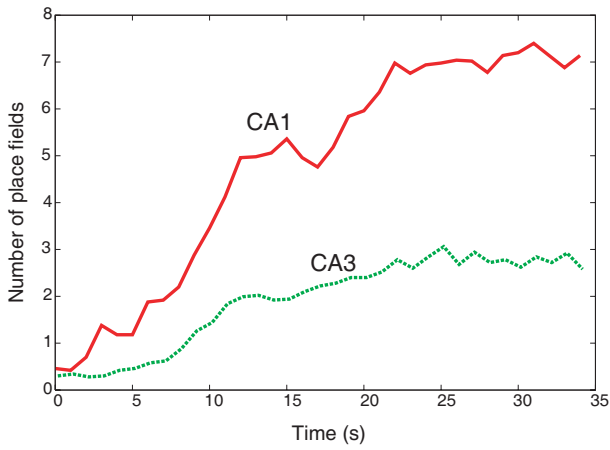


Fig. 5. Development over time of place cells in CA1 and CA3 regions

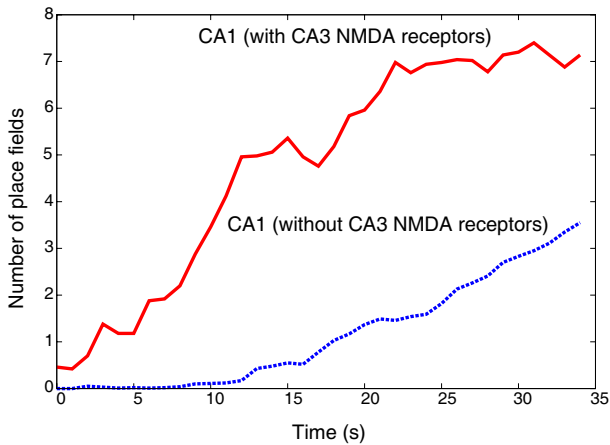


Fig. 6. Effect of CA3 NMDA receptor knockout on CA1 place field development

C. CA1 dependence on CA3 NMDA receptors

The work of Nakazawa et al [8] shows that without CA3 NMDA receptors, CA1 place fields develop much more slowly. We can simulate the effects of knocking out CA3 NMDA receptors by setting the conductance of NMDA mediated channels to zero for CA3 neurons and also preventing plasticity at CA3 synapses (since this plasticity is dependent on NMDA receptor activation).

When this is done, we can evaluate the change in rate of place cell growth using the measure defined in the previous section. Doing so, we can see in Figure 6 that CA1 place cells develop much more slowly without CA3 NMDA receptors.

D. Difference in representation correlation

Finally, we look at the difference in correlation between representations in CA1 and CA3.

1) *Measurement of place representation correlation:* To determine the effects on place cell representation of modification of the network inputs, we must define a quantitative measure of correlation between two representations. To do this we:

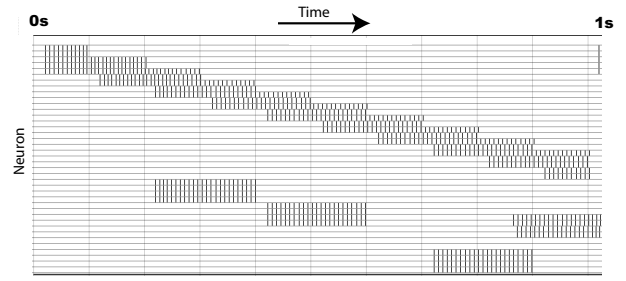


Fig. 7. Spike trains from entorhinal cortex showing cues and inputs

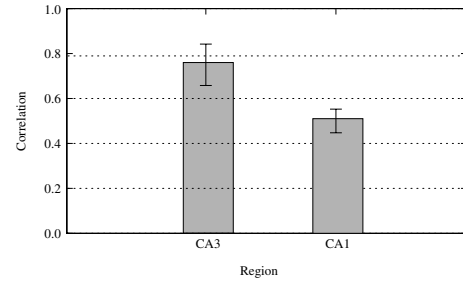


Fig. 8. Correlation between representations before and after introduction of extra cues into input

- 1) Calculate the set of place fields using the method described in Section IV-B (thresholded correlations of the EC input and CA3 and CA1 response firing functions), both before and after the change in input conditions.
- 2) Calculate the overlap between these representations by taking the total number of shared place fields divided by the total number of place fields.

This provides a quantitative measure of representational correlation.

2) *Introduction of environmental cues:* To simulate the effect of a partial environmental change, we can introduce “cues” into the simulated hippocampus, representing the presence of external objects outside the track on which an animal might run. We can see these cues alongside the network inputs in Figure 7. In this simulation, the cues are introduced into the simulated environment after 40s, and the network’s output for the next 20s is measured.

3) *Representation changes:* Measuring the difference in representation correlation between CA3 and CA1 after introduction of the cues shows us that CA3 representations have a higher correlation than CA1 representations (see Figure 8).

As we saw in Section IV-B, CA1 representations change more rapidly than those in CA3, so we should also examine the difference in representation correlation with no addition of cues (to test the possibility that the difference in correlation is due only to the different rates of representational change in CA1 and CA3 over time). Looking at Figure 9 we see that, although CA1 representational correlation is lower than that of CA3 when the inputs are constant, the difference is less than that in the case where cues are introduced, suggesting that an

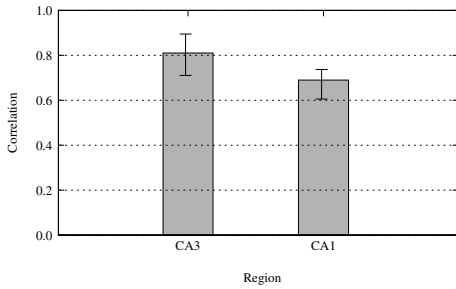


Fig. 9. Differences in representation correlation that arise only because of changes in representation over time

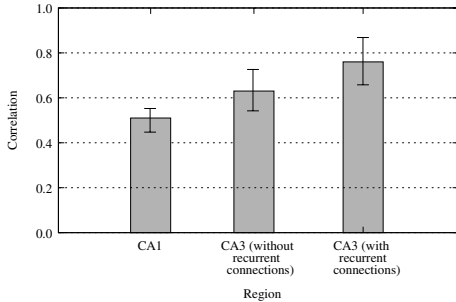


Fig. 10. Correlation between representations before and after introduction of extra cues into input, showing the effect of removing CA3 recurrent connections

additional mechanism is responsible for the differences.

To test the hypothesis that this difference arises as a result of the stabilising effects of CA3 recurrent connections, we can stop plasticity of CA3 recurrent synapses, and examine the effects on correlation. Looking at Figure 10 shows us that this does indeed reduce the CA3 representational correlation.

This does not, however, reduce the correlation to the level shown in CA1, so there may be additional factors involved.

V. DISCUSSION

We have seen that our model confirms experimental results for differences in place field formation between CA1 and CA3.

A. Formation of place cells

In our model, place cells form by associative plasticity on synapses between cell fields. Initial activity generated either by noise or afferent input causes neuron firing, after which connections to those neurons become strengthened, causing them to respond to particular inputs. After “simple” place cells have formed (responsive only to a single input), associative plasticity allows these cells to become responsive to other inputs temporally close to the initial generator of response.

B. Speed of formation of place fields

Our model confirms experimental evidence that place fields form more rapidly in CA1 than CA3 - the initial gradients of the development graphs are steeper in CA1. In our model this is due to the faster learning rate of synapses between the EC and CA1 than the perforant path input to CA3 (by a factor of

~ 2), and stronger initial connections to the CA1. There is not yet clear evidence for this faster learning (difficult to measure experimentally at the moment). However we posit that when techniques become available, the rate of plasticity at synapses to CA1 will be found to be greater than those to CA3. As a development of the model, a longer simulation would show whether the number of place cells in CA3 would reach the number in CA1.

C. CA1 place field dependence on CA3 NMDA receptors

We have seen both from experimental evidence [8] and our model simulation that without CA3 NMDA receptors, CA1 place fields develop much more slowly. We suggest that CA1 responsive fields are formed primarily by plasticity of the temporoammonic pathway (the direct input from the entorhinal cortex), but that the Schaffer collateral input is necessary to excite CA1 neurons such that associative plasticity can then form the place cells as described above.

The developmental difficulty then arises because, without CA3 NMDA receptors, both NMDA mediated excitatory synaptic transmission and NMDA dependent synaptic plasticity are blocked in CA3 neurons. This greatly reduces activity and prevents the formation of place cells, and this reduced activity stops the Schaffer collateral synapses from providing synaptic input to excite CA1 neurons enough for associations using the temporoammonic pathway to be formed. Place cells still develop slowly, since there is some activity in CA1 neurons from both noise and temporoammonic stimulation, but the growth rate is much lower.

D. Differences in representational stability

As shown in experiment, changes to the environment such as the introduction of external cues to a running track cause changes to place field representations. These changes are greater in CA1 than CA3 (although total changes to the environment seem to cause larger changes in CA3 than CA1).

Our model shows that CA3 recurrent connections are partially, but not totally responsible for this change. As we discuss above, the more rapid development of CA1 place fields probably arises from quicker plasticity of the temporoammonic pathway, and this quicker plasticity also explains why CA1 representations are less correlated upon changes of external environment (since they change more quickly).

E. Implications for separate functionality of CA3 and CA1

Although much speculation has occurred about the roles of the separate cell fields in the hippocampus, there has so far been little direct evidence of explicit functional differences between regions. The results from studies of place fields are some of the first to actually provide such evidence.

The observed results, specifically that CA1 field representations change more rapidly in response to changing inputs than those of CA3, suggest underlying differences in the physiological purpose of the two fields.

One possible explanation is that CA1 place fields are necessary for simple spatial exploration of a new environment

(and must therefore develop quickly and also respond rapidly to environmental changes). CA3 fields are part of a longer term spatial memory system (hence CA3's involvement in spatial working memory) and, as such, need to form stronger, more stable representations, resulting in a slower reaction to environmental changes.

VI. CONCLUSIONS, EXPERIMENTAL PREDICTIONS AND FURTHER RESEARCH

We have demonstrated a possible mechanism by which place cells develop. In CA3, development arises as a result of perforant path input modified by CA3 recurrent connections and in CA1 development is due to temporoammonic plasticity from activation of CA1 neurons via the Schaffer collateral synapses. Because the connections from EC to CA1 are initially stronger and plasticity is quicker CA1 place cells form more rapidly (these differences in learning rate are a hypothesis of our model and so lead to one of our predictions below). Removal of CA3 NMDA receptors reduces CA3 activity, and therefore activation of CA1 via the Schaffer collaterals, slowing CA1 place field development.

The extensive recurrent connectivity of CA3 makes its place field representations more stable to environmental changes than those of CA1 which, combined with CA1's more rapid plasticity, explains the correlation difference from changing inputs. CA1's rapidly changing response allows it to respond to current spatial input, while CA3's slower development makes it more suitable for part of a spatial memory system.

A. Predictions for experimental research

We have included as part of our model hypothesis, a faster learning rate for connections to CA1 than to CA3, and we therefore predict that if these learning rates are measured experimentally, CA1 plasticity will be found to be more rapid than that of CA3. Additionally it may be possible to test the hypothesis that CA1 place fields are involved in active exploration, by showing that disruption of these place fields reduces navigational ability.

Since we suggest that the increased stability of CA3 place field representations arises primarily from CA3 recurrent connections, we predict that if these connections were knocked out, CA3 place representations would be less stable to environmental change. This knockout may be possible by administration of scopolamine, an acetylcholine antagonist that, in CA3, diminishes effects of recurrent synapses and rate of synaptic plasticity. We predict that this would reduce the stability of the CA3 place fields.

B. Possibilities for further model development

While our model gives a basic explanation of how the two inputs to CA1 are integrated, the situation in the real brain is much more complex. Neuromodulatory effects, particularly that of dopamine [17], are important to the hippocampus' operation, and could be added to our model.

As mentioned in Section II-E, motor feedback appears to be necessary for the activation (and possibly development of)

place fields. A possible extension of our model would be simulation of the pre-processing of input to the EC, to show that removing motor input prevents place cell activation.

C. Summary

We have shown that our model of place cell formation replicates experimental results showing differences in place fields between CA3 and CA1, and explains how these differences are due partly to the different physiological structures of CA1 and CA3, particularly CA3's recurrent connectivity.

We have also suggested additional reasons for the differences and explained how the differences might reflect the underlying functions of the separate cell fields. We have made predictions for experimental verification.

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