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Grid cells' need for speed

Citation for published version:

Gonzalez-Sulser, A & Nolan, MF 2016, 'Grid cells' need for speed' Nature Neuroscience, vol. 20, no. 1, pp. 1-2. DOI: 10.1038/nn.4460

Digital Object Identifier (DOI):

[10.1038/nn.4460](https://doi.org/10.1038/nn.4460)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Nature Neuroscience

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1 **Title:** Grid cells' need for speed

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12 **Abstract**

13 Grid firing fields of neurons in the entorhinal cortex are thought to require inputs
14 encoding running speed, but where do these speed signals originate? New results
15 suggest that glutamatergic projections from the medial septum are one of the inputs
16 that provide speed signals to the entorhinal cortex.

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19

20 **Main text**

21 To complete many everyday tasks, from foraging to running from predators, animals
22 must be able to keep track of where they are. This can be achieved by updating
23 internal estimates of location using information about speed and direction of
24 movement. Grid cells in the medial entorhinal cortex (MEC) are thought to be key to
25 this process, which is known as path integration. However while speed signals have
26 been recorded in the MEC¹, their origin is unclear. Two recent studies have
27 addressed the role of projections from the medial septum (MS)^{2,3}, a region previously
28 associated with generation of theta frequency network activity in the hippocampus
29 and entorhinal cortex.

30

31 In this issue of Nature Neuroscience Justus *et al.*² investigate whether glutamatergic
32 neurons in the MS provide the MEC with information about running speed.

33 Consistent with an earlier report based on recordings in rats⁴, Justus et al. found a
34 subset of cells in the MS that are speed sensitive. Intriguingly, they show that some
35 neurons in the MS increased their firing rate with increasing running speed, whereas
36 others decreased their firing rate (Fig. 1a). Justus et al. also discovered cells in
37 which theta frequency modulation of firing, as well as the overall firing rate, was
38 sensitive to running speed (Fig. 1b). Justus et al. then expressed a Ca²⁺ sensor in
39 the glutamatergic neurons in the MS and imaged population-level calcium signals
40 from their axon terminals in the MEC. They find that that the calcium signal in the
41 MEC is positively correlated with running speed. Therefore, glutamatergic neurons in
42 the MS appear to be a source of speed signals in the MEC.

43

44 How are glutamatergic signals from the MS integrated within the MEC? By making
45 patch-clamp recordings from MEC neurons in brain slices and activating MS inputs
46 optogenetically, Justus et al. show that pyramidal cells in superficial layers are

47 primary targets of glutamatergic inputs from the MS (Fig. 1e). The depolarization
48 generated by these inputs is proportional to the frequency at which they are
49 activated, suggesting they could relay rate coded speed signals. To further explore
50 this possibility, Justus et al. use a modelling approach in which spike patterns
51 recorded from speed coding neurons in the MS were replayed into reduced models
52 of pyramidal cells. These simulations suggest that pyramidal neurons in the MEC
53 could be speed sensitive cells, but are less likely to follow theta frequency
54 modulation of MS inputs. In contrast, simulated interneurons, because of their
55 shorter membrane time constant, effectively relay the theta frequency component of
56 MSDB inputs, but are relatively insensitive to running speed.

57

58 These results stimulate further questions about speed coding neurons in the MS and
59 their connections to the MEC. It is not yet clear if GABAergic or cholinergic neurons
60 that project from the MS to the MEC are also speed sensitive. The identity of
61 neurons with firing that is negatively modulated by speed is also unclear. While
62 cholinergic responses in the MEC so far appear to be quite rare^{2,5,6}, there are
63 prominent GABAergic projections from the MSDB that seem to specifically target
64 GABAergic interneurons in the MEC⁵⁻⁷ (Fig. 1e). Given that a substantial proportion
65 of the speed sensitive neurons in the MEC appear to be interneurons^{1,8}, it will be
66 important to establish the relative contribution of glutamatergic and GABAergic
67 projections to speed sensitive firing of identified cells in the MEC.

68

69 In a second recent study, Hinman *et al.*³ demonstrate that inactivation of the MS
70 differentially affects two independent speed signals in the MEC. They find that, just
71 as in the MS, running speed is encoded in the MEC both by spike frequency and by
72 changes in theta frequency oscillatory activity. However, whereas in the MS these
73 codes appear to be generated by the same neurons (Fig. 1b), in the MEC they
74 appear to be generated by different neurons. The oscillatory code in the MEC also
75 appears to differ in that the oscillation frequency (Fig. 1c) and the depth of theta
76 modulation (Fig. 1d) both increase with running speed. Intriguingly, Hinman et al.
77 demonstrate that rate coded speed signals in the MEC are enhanced by inactivation
78 of the MS, whereas the dependence of oscillatory signals on running speed is
79 reduced. These results suggest that inputs from the MS support oscillatory rather
80 than rate coded speed signals in the MEC.

81

82 How can the observation of a rate coded glutamatergic speed signal from the MS to
83 the MEC be reconciled with an increase in rate coded speed firing in the MEC
84 following inactivation of the MS? One possibility is that some computations in the
85 MEC involve integration of multiple speed-sensitive inputs. For example, neurons
86 found in the visual cortex also encode running speed⁹, while in the MEC grid firing
87 fields and speed coding were recently found to rely on visual input to a greater extent
88 than previously suspected⁸. Thus, if inputs from the MS converge on neurons in the
89 MEC that also receive visually driven speed signals, then the computation carried
90 out by MEC neurons may require that the input from the MS is also speed-sensitive.
91 Another possibility is that speed inputs from the MS may be required to coordinate
92 spike sequences that occur nested within the theta rhythm¹⁰, while other speed

93 inputs may drive rate coded speed firing and perhaps also path integration by grid
94 cells (or vice-versa).

95
96 What about the MS-dependent speed modulated oscillatory activity in the MEC?
97 Could the speed-dependent glutamatergic signals identified by Justus et al. play a
98 role? This seems possible. For example, if background synaptic activity in vivo
99 increases the membrane conductance of pyramidal cells receiving glutamatergic
100 inputs, then the resulting reduction in their integration time constant might enable
101 them to respond to speed and theta modulated components of MS firing.
102 Alternatively, depolarisation driven by rate coded glutamatergic speed signals may
103 promote membrane potential oscillations by increasing the electrical driving force for
104 theta modulated GABAergic input received either directly from the MS, or indirectly
105 via local interneurons. Disentangling these and other possibilities will likely require
106 further detailed analysis of circuitry connecting the MS and MEC, it's activity during
107 running behaviours and the consequences of targeted manipulation of genetically
108 defined subsets of MS neurons.

109
110 Finally, what are the implications do the findings from Justus et al. and Hinman et al.
111 have for mechanisms of grid cell firing? While most models of grid firing require
112 signals encoding speed and heading direction as inputs, they differ in the nature of
113 the speed signal. In continuous attractor network models, the speed is encoded by
114 firing rates. Although the neurons generating these inputs need not be in the MEC,
115 some of the speed-sensitive neurons reported by Hinman et al. appear consistent
116 with requirements of these models. In oscillatory interference models, speed is
117 encoded in the frequency of oscillatory signals and some of the firing patterns
118 reported by Hinman et al. appear consistent with these models. Hinman et al.'s
119 finding that the MS is required for both grid firing and speed-dependent oscillations
120 could be interpreted as convergent evidence for interference models. However, the
121 discovery by Justus et al.² of rate coded speed inputs from the MS to the MEC,
122 suggests that effects of inactivation of the MS might also be consistent with attractor
123 network models.

124
125 In summary, recent experimental evidence argues for multiple sources of speed
126 input to the MEC. Glutamatergic projections from the MS are a first identified source
127 of speed signals, while speed-dependence of MEC firing following inactivation of the
128 MS suggests the existence of additional speed inputs to the MEC. While the exact
129 role of speed inputs in grid firing remains unclear, increasingly precise circuit
130 investigations, such as that by Justus *et al.*, combined with systematic analyses of
131 speed coding introduced by Hinman et al., provide a powerful framework for further
132 investigation. Future studies will likely need to untangle the apparent complexities of
133 network connectivity and combine them with elucidation of grid cell input and output.

134 135 **References**

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167 **Figure 1. Glutamatergic inputs providing input for neuronal speed codes in**
168 **MEC. a-d.** Different neuronal codes generate distinct activity patterns representing
169 fast and slow running speed. Coding occurs through the frequency of spike firing (a)
170 or by spiking timing (black bars) relative to network oscillations (red lines) **e.** Circuit
171 diagram of projections from different cell types in the MS to specific synaptic targets
172 in MEC. Note: Large arrows denote more frequent synaptic targets in MEC and small
173 arrows denote less frequent ones. Abbreviations: ACh: cholinergic, Glut:
174 glutamatergic, GABA: GABAergic, Pyr: pyramidal, FS: fast spiking interneuron.

