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2   # The representation of space in the brain

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16   ## Abstract

17   Animals can navigate vast distances and often display behaviours or activities that

18   indicate a detailed, internal spatial representation of their surrounding environment or a

19   'cognitive map'. Over a century of behavioural research on spatial navigation in humans and

20   animals has greatly increased our understanding of how this highly complex feat is achieved. In

21   turn this has inspired half a century of electrophysiological spatial navigation and memory

22   research which has further advanced our understanding of the brain. In particular, three

23   functional cell types have been suggested to underlie cognitive mapping processes; place cells,

24   head direction cells and grid cells. However, there are numerous other spatially modulated

25   neurons in the brain. For a more complete understanding of the electrophysiological systems

26   and behavioural processes underlying spatial navigation we must also examine these lesser

27   understood neurons. In this review we will briefly summarise the literature surrounding place

28   cells, head direction cells, grid cells and the evidence that these cells collectively form the

29   neural basis of a cognitive map. We will then review literature covering many other spatially

30   modulated neurons in the brain that perhaps further augment this cognitive map.

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Spatial representations in the brain

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36   The study of how organisms are able to navigate their environment is in many ways the

37   study of survival; all animals must navigate to find mates, shelter, food and water. For wild

38   animals this often means navigating large expanses of land, perhaps also with limited cues. For

39   example, Peters (1978) reports that in wooded areas masked by snow, wolves often take long,

40   complex, winding, unplanned paths when hunting - but they can still return directly to the distant

41   location of their pups. Elephants have similarly been recorded navigating distances over roughly

42   100 km a month (Leggett, 2006); during these trips they frequently visit isolated and distant

43   waterholes (Viljoen, 1989) despite navigating environments devoid of any stable landmarks.

44   Navigating large distances is often not enough however, as animals must also be able to

45   navigate flexibly and efficiently. Moustached tamarin (*Saguinus mystax*) and brown-mantled

46   tamarin (*Saguinus fuscicollis*) living in the South American rainforest for instance, often move

47   between foraging sites in such a way as to minimise the distance travelled between trees, even

48   taking into account the timing that particular trees begin to fruit (Garber, 1988; Janson et al.,

49   1981; Milton and Katharine, 1981). Efficient navigation also encompasses being able to take

50   unplanned routes however. Powell (1977) for instance, reports that fishers (*Martes pennanti*)

51   have a home range through which they have been observed taking novel, direct paths between

52   the nesting sites of prey animals. Often animals are even expected to navigate in completely

53   unknown territory. For example, captured Burmese pythons (*Python molurus bivittatus*) driven

54   more than 30 kilometres into the everglades of South Florida have been tracked heading

55   directly from their displacement site back to their home territory (Pittman et al., 2014). Similar

56   results have also been observed in Egyptian fruit bats (*Rousettus aegyptiacus*), these animals

57   frequently fly large distances to forage for food and when they are displaced from their territory

58   by distances of over 80 km they are able to navigate directly back to their home cave (Tsoar et

59   al., 2011).

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61   The purpose of laboratory experimentation is not to replace ethological observations

62   such as these, but to further advance our knowledge of how these processes may unfold and

63   particularly, how they may be represented in the brain. These experiments are always in much

64   smaller environments than those described above and almost always use rodents such as rats

65   and mice. Despite some criticism (Geva-Sagiv et al., 2015), this approach is indeed informative

66   about the processes at work in larger environments and rats do form a good basis for

67   researching them. Experiments have shown that, like other animals, rats can navigate back to

68   their home territory after being displaced (Innes et al., 2011), and radio tracking experiments

69   have demonstrated that wild rats navigate considerable distances (over half a kilometre) in

70   search of food and will also spend considerable time in open environments away from cover

71   (Taylor, 1978). This is likely an underestimation of their navigation ability, though, as these

72   animals were restricted to a small territory. In contrast, a rat released on an uninhabited island

73   near New Zealand navigated the entire island before settling on a home territory spanning a

74   hectare. Later, this same rat swam 100m to a nearby island (Russell et al., 2005). Having

75   observed these complex navigational feats in the wild, we are thus faced with the question of

76   how these animals, and others, navigate such large trips: as it turns out, laboratory research

77   suggests that the biological processes underpinning this spatial navigation can be very complex.

78   Early behaviourist psychological research into the behaviour of animals and humans, at

79   the start of the last century, concentrated on the relationship between stimuli and the responses

80   they evoke (Hull, 1950; Watson, 1919). It was not until forty years later that Edward Tolman

81   (1948) suggested the idea that there might be an internal representation of space, which he

82 called a 'cognitive map'. He based this proposal on a wealth of experimental evidence

83 pertaining to studies of the processes underpinning spatial navigation in rats. A debate ensued

84 between those researchers in support of this map hypothesis and those who instead embraced

85 the stimulus-response interpretation of behaviour, culminating essentially in a combination of

86 these two schools (Restle, 1957). Thirty years after Tolman's influential work, John O'Keefe and

87 Lynn Nadel (1978) revived Tolman's cognitive map hypothesis. This time it was built on a firmer

88 bedrock of behavioural experiments, but also on tantalising electrophysiological work conducted

89 over the preceding decade (O'Keefe and Dostrovsky, 1971).

90   This combination of behavioural and electrophysiological research began largely with

91 John O'Keefe, who in 1971 demonstrated, together with Jonathan Dostrovsky, the existence of

92 cells in the hippocampus of freely behaving rats that fired preferentially for specific spatial

93 locations in the animal's environment (O'Keefe and Dostrovsky, 1971). Later, in 1978, O'Keefe

94 published a highly-cited book with Lynn Nadel detailing how these 'place cells' could form the

95 neural basis of a spatial representation in the brain, or a 'cognitive map,' and went on to

96 elucidate the characteristics of these cells (O'Keefe and Nadel, 1978). A few years later a

97 second class of cell, first reported by James Ranck Jr. in 1984, and heavily researched since

98 the 1990s by Jeffrey Taube and colleagues, was demonstrated to respond purely to the

99 direction an animal is facing, in an almost compass-like manner (Taube et al., 1990a, 1990b).

100 This seemed to further support O'Keefe and Nadel's proposal about a mapping function for the

101 hippocampal system. Most recently, in 2005, May-Britt and Edvard Moser, together with

102 Marianne Fyhn, Torkel Hafting and colleagues, published findings demonstrating the existence

103 of cells that fire in a continually repeating hexagonal grid of fields across the surface of an

104 animal's environment (Fyhn et al 2004; Hafting et al., 2005). Many of the properties of these

105 'grid cells' have since been explored, and their relationship to place cells is a complex one

106   (Rowland et al., 2016), but it seems likely that at least one of their functions is to provide metric

107   information about how far the animal has been walking and in what direction. This confirmation

108   of the truly spatial nature of the entorhinal-hippocampal system led to the award of the 2014

109   Nobel Prize in Physiology or Medicine to O'Keefe and the Mosers for their discovery of "a

110   positioning system in the brain."

111   Thus, rather than fulfilling different niches, experimental psychology and cognitive

112   neuroscience have always been intertwined, each building on the progress of the other. Now we

113   know that many of the highly complex behavioural processes observed in humans and animals

114   reflect an equally complex world of cellular processes, which have observable

115   electrophysiological correlates. The three major spatial cell types described above appear to

116   form the backbone of a complex system that we are only just beginning to understand.

117   However, in the ensuing decades since place cells were discovered, a number of other cell

118   types have been encountered, both cortically and subcortically, that may also contribute to

119   spatial encoding. Many of these are less well described and less well known than the 'big three',

120   but may be no less important. In this review we aim to concentrate on these, with the hope that

121   illuminating them may provide insight into how the brain organizes its cognitive representation of

122   space. We will focus largely on the functional aspects of these neurons, for a more detailed

123   review of the anatomical aspects see Knierim (2006). First, however, we review the

124   hippocampus and place, head direction and grid cells.

The hippocampus

126   Initial interest in the hippocampus was sparked by the observed impact of hippocampal

127   damage, both accidental and intentional, on behaviour. One of the most influential cases in this

128 respect was that of a patient, Henry Molaison, known for many years only as patient H.M., who

129 suffered from epileptic seizures which were found to arise from structures in his medial temporal

130 lobe. In 1953 surgeons removed, bilaterally, H.M.'s hippocampal formation and a number of

131 adjacent structures (Corkin et al., 1997; Penfield and Wilder, 1958). Tragically, but of great

132 interest to many researchers, after this surgery H.M. was afflicted with severe anterograde

133 amnesia (Gabrieli et al., 1988; Scoville and Milner, 1957) which stayed with him until his death

134 in 2008. During his life, H.M.'s long-term memory and language skills were largely unaffected

135 (Kensinger et al., 2001), however, he was unable to form new episodic memories. It was

136 subsequently also discovered that he could not use a physical map to navigate in unfamiliar

137 surroundings (Corkin, 2013, 1984) and was impaired on a number of spatial tasks (Corkin,

138 1979; Morris, 1999; Teuber and Weinstein, 1956) for a review see (Corkin, 1984, 2002 or 2013).

139 This finding implicated the hippocampus as a structure which is crucial for the formation of new

140 memories, including (it later transpired) those that are spatial in nature. Subsequent to H.M.'s

141 affliction, interest grew in whether the hippocampus is related to the formation, consolidation or

142 retrieval of these memories, a question that is still not fully resolved.

143 Motivated by the findings of H.M. and other similar cases, animal researchers began to

144 search for animal models of hippocampal amnesia, resulting in the development by Olton and

145 colleagues of the radial maze, which was initially developed as a test of working memory (Olton

146 et al., 1980). Using the radial maze, Olton and colleagues showed that the task is highly

147 dependent on the hippocampus (Olton et al., 1978). While this could have suggested a role for

148 working memory in episodic memory formation, in fact O'Keefe and Nadel, motivated by the

149 findings described in the next section, suggested that the hippocampal dependence could be

150 due to the spatial nature of the task (O'Keefe and Nadel, 1978). The debate between working-

151 memory and spatial-map explanations for the effects of hippocampal lesions was finally settled

152   when Richard Morris developed the water-maze (Morris, 1984), and used it to show that the

153   hippocampus was necessary to solve the task even though it is mostly spatial and has no

154   working memory component (Morris et al., 1982).

155   Place cells

156   The excitement generated by the case report of patient H.M. led researchers to embark

157   upon electrophysiological investigations of the hippocampus. When O'Keefe and Dostrovsky

158   (1971) took advantage of a newly developed technique to record single, complex spiking (Fox

159   and Ranck, 1975; Ranck, 1973), pyramidal (Henze et al., 2000) neurons in the rat hippocampus

160   (Fig. 1A and Fig. 2) they found that the firing rate of many of these cells was modulated purely

161   by spatial location (Fig. 1B), and named them 'place cells'. Similar place-encoding neurons were

162   subsequently found in several other species including mice (Rotenberg et al., 1996), bats

163   (Ulanovsky and Moss, 2007), monkeys (Cahusac, Miyashita and Rolls, 1989; Rolls et al., 1998)

164   and humans (Ekstrom et al., 2003), suggesting a certain generality of the phenomenon,

165   although place cells have not been reported yet in non-mammals.

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167   Insert Fig. 1 [three cell types] near here
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170   Place cells were tremendously exciting because they revealed the formation, by the

171   brain, of an abstract, cognitive representation. Their properties have led to a great deal of

172   theorizing about how mammalian brains might construct a representation of space. Place cells

173   recorded in exploring rats fire maximally when the rat's head is in one specific region of the

174   environment, regardless of which way it is facing (and therefore what it can see). This area of

175   high firing rate is known as the cell's 'place field' (O'Keefe, 1979; O'Keefe and Conway, 1978;

176   O'Keefe and Nadel, 1978): typically, firing outside of the place field is absent. Place cells

177   recorded simultaneously, and therefore near to each other in the brain, often have place fields in

178   different areas of an environment, suggesting that the population of cells as a whole represent

179   the entire surface of an environment (O'Keefe, 1976; Wilson and McNaughton, 1994).

180   Furthermore, once the representation of an environment has formed it is stable across days

181   (Hill, 1978; Muller et al., 1987) and even weeks (Thompson and Best, 1990), although recent

182   evidence suggests that not all place cells are always stable (Mankin et al., 2015; Ziv et al.,

183   2013) possibly for interesting reasons to do with charting the passage of time.

184   What makes place cells fire where they do? Visual information is important, as the

185   location of a place cell's place field is often influenced by the distal cues or landmarks

186   surrounding the environment (Muller and Kubie, 1987; O'Keefe and Conway, 1978;

187   Yoganarasimha and Knierim, 2005). However, place cells still fire in the same locations in the

188   dark provided the rat remains in the apparatus (Save, Nerad, & Poucet, 2000; Zhang,

189   Schönfeld, Wiskott, & Manahan-Vaughan, 2014; Markus et al., 1994; Quirk et al., 1990) and

190   blind rats also have relatively stable place fields (Save, Cressant, Thinus-Blanc, & Poucet,

191   1998). This indicates that the place cell representation can be built in the total absence of visual

192   information provided the availability of other sensory cues such as olfaction and tactility. We

193   now know that these different sensory modalities are integrated both within and outside the

194   hippocampus (Jeffery, 2007). Thus, place fields represent higher order constructs assembled

195   from more primitive spatial ones such as direction, boundaries, and self-motion information (see

196   below). If the environment is altered or completely novel, the cells may completely change their

197   firing relationship and represent this environment in a unique way (Anderson and Jeffery, 2003;

198   O'Keefe and Conway, 1978); this process of place field alteration between different

199   environments is known as 'remapping' (Muller and Kubie, 1987). Together, these results further

200   support the idea that place cells may underlie spatial navigation and memory; place cells as a

201   population uniquely represent entire environments and these specific representations are

202   recalled whenever the animal encounters the environment in the future.

203   Although, as mentioned above, place cells have been found in several species, it

204   remains unclear how much of what has been discovered in rats and mice is universal, even

205   within mammals. Bats, whose ancestral lineage diverged from that of rodents around 65 million

206   years ago, have well-formed place fields that resemble rodent ones in most important respects

207   (Ulanovsky and Moss, 2007). However, the situation for primates appears to be slightly

208   different. Humans and other primates primarily use visual cues, such as landmarks, when

209   navigating (Ekstrom, 2015) and neuroimaging studies implicate the hippocampus and the

210   parahippocampal region in human navigation (Aguirre et al., 1996; Maguire et al., 1998; Spiers

211   and Barry, 2015). However, in humans and other primates, spatially modulated cells appear to

212   make up the minority of cells in these structures. Initial reports suggested that cells in the

213   primate hippocampus might instead respond to objects (Eifuku et al., 1995; Rolls, 2005; Rolls et

214   al., 1989), whole-body motion (O'Mara, Rolls, Berthoz and Kesner, 1994) or relate to the

215   direction of 'spatial view' – where the animal is looking, rather than where it is; (Rolls, 1999;

216   Rolls et al., 1997; Rolls and O'Mara, 1995). In humans only around 11-25% of neurons in the

217   hippocampus and parahippocampal regions appear to respond purely to spatial location, the

218   majority of these being in the hippocampus (Ekstrom et al., 2003; Miller et al., 2013). However,

219   most cells in that region of the temporal lobe encode many aspects of space conjunctively,

220   combining features such as current location, current view, current spatial goal or heading

221   direction (Ekstrom et al., 2003; Miller et al., 2013). Spatial view cells have not been observed in

222   rodents (but see de Araujo et al., 2001) perhaps because rodents have particularly poor

223   eyesight or because they explore environments directly rather than visually. Place cells in rats

224   are unable to form a stable representation for an environment unless it has been directly

225   explored (Rowland et al., 2011) which suggests that these animals may not have an inferred

226   allocentric representation for remote space, although recent research suggests that observing a

227   conspecific explore a novel environment can improve the stability of place cell representations

228   when later exploring the same environment (Mou and Ji, 2016). Instead, rats may have the

229   reverse representation; in the rodent superior colliculus (Cooper et al., 1998) and area V1 of the

230   visual cortex (Haggerty and Ji, 2015) cells fire in spatial locations where visual cues appear the

231   same. The firing of the latter cells seems to lead place cells temporally, suggesting that the

232   information from these may guide the activity of place cells. Thus, rats probably use remote

233   visual cues to inform the spatial activity of place cells, whereas the activity of spatial view cells

234   carries information about the remote visual cues being observed.

235   Head direction cells

236   The discovery of head direction (HD) cells came about in the aftermath of the original

237   place cell report, when researchers were still trying to understand the source of their spatial

238   firing. Ranck, Jr. (1985, 1984) reported finding, in the dorsal presubiculum of the rat, cells that

239   were modulated by the facing direction of the head, and a detailed description of the activity of

240   these 'head direction' cells was published shortly after (Taube et al., 1990a, 1990b, 1987). Head

241   direction cells fire maximally when an animal's head faces a particular direction in the azimuthal

242   (horizontal) plane (Fig. 1C and Fig. 2), this 'preferred direction' is independent of the animal's

243   current behaviour or position. Different head direction cells have different preferred firing

244   directions, equally distributed, such that as a population there is equal representation of all

245   directions, and no overall preferred direction (Taube et al., 1990b). Like place cells, the firing of

246   head direction cells has been shown to rely on the angular position of environmental cues

247   (Goodridge and Taube, 1995; Taube, 1995a; Taube et al., 1990b; Zugaro et al., 2000) if these

248   cues are stable (Knierim et al., 1995), but such cues are not necessary (Mizumori and Williams,

249   1993; Yoder et al., 2011). As with place cells, if distal cues are rotated or if the animal is moved

250   between environments then the preferred firing direction of all head direction cells realign or

251   rotate (Fig. 1C), and they do this coherently (Skaggs et al., 1995; Yoganarasimha and Knierim,

252   2005).

253   Head direction cells are found in a comparatively greater number of brain regions than

254   grid cells and place cells, and these structures seem to essentially comprise the classic Papez

255   limbic circuit (Taube, 1998), originally thought to be an emotion circuit and then later a memory

256   one. In rats the head direction 'signal' is thought to initially arise within the brainstem in the

257   dorsal tegmental nuclei (DTN) and lateral mammillary nuclei (LMN), where neurons sensitive to

258   angular head velocity can also be found. From here, the signal projects to the anterior dorsal

259   thalamus (ADN) and then to a variety of regions in thalamus and cortex. Regions in the

260   thalamus include antero-dorsal, lateral dorsal and reuniens nuclei, and cortical regions include

261   postsubiculum, entorhinal and retrosplenial cortices, parasubiculum, posterior parietal cortex

262   (see Fig. 8 for a schematic and Yoder et al., 2011 for a review). In other species, these cells

263   have also been observed in the primate presubiculum (Robertson et al., 1999), drosophila

264   central complex (Seelig and Jayaraman, 2015) and there is some evidence of directionally

265   sensitive neurons in the human entorhinal cortex (Jacobs et al., 2010), retrosplenial cortex and

266   thalamus (Shine et al., 2016).

267   # Grid cells

268   Unlike place cells in the hippocampus, many cells in the mEC fire in multiple discrete

269   and regularly spaced locations which form a triangular lattice or tessellated grid (Fig. 1D). These

270   'grid cells' are found close to the border between the mEC and postrhinal cortex (Fyhn et al.,

271   2004; Hafting et al., 2005) and in the pre- and parasubiculum (Boccara et al., 2010)(Fig. 2). Like

272   place cells, the firing of grid cells is partially dictated by external cues; when distal landmarks

273   are rotated, grid cell firing fields rotate by a corresponding amount (Hafting et al., 2005), and

274   deformation of the environment often causes partial deformation of the grid (Barry et al., 2007;

275   Stensola et al., 2012). However, unlike with place cells, in new environments the firing of

276   different grid cells remains coordinated, such that the grid patterns of grid cells rotate and move

277   together, maintaining a stable relationship (Fyhn et al., 2007). This has led to suggestions that

278   grid cells function cooperatively, by virtue of an interconnected matrix known as an attractor

279   network (McNaughton et al., 2006).

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281   Insert Fig. 2 [Anatomical regions] near here
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284   Grid cells do not appear to depend on extramaze cues to maintain a stable firing pattern.

285   In complete darkness the grid pattern persists undisturbed, provided (as with place cells) the rat

286   has not been disoriented; this has led many to suggest that grid cells may be involved in the

287   computations underlying self-motion calculation, also known as 'path integration' (Fuhs and

288   Touretzky, 2006; Fyhn et al., 2007; Hafting et al., 2005; McNaughton et al., 2006). This idea is

289   supported by the finding that lesions of the mEC result in path integration impairments (Allen et

290   al., 2014; Van Cauter et al., 2013). Given their mathematical and geometric properties it is

291 almost hard to believe these cells exist at all: however, they are not confined to the rat brain and

292 are also found in mice (Fyhn et al., 2008) and have recently been observed in bats (Yartsev et

293 al., 2011) and possibly also in humans (Jacobs et al., 2013). Evidence for their existence in

294 humans has also been demonstrated using functional magnetic resonance imaging techniques

295 (fMRI) (Doeller et al., 2010). The function and origin of these cells is still not greatly understood.

296 However, their activity is likely informed by two other cell types found in the mEC; speed cells,

297 which encode the movement velocity of the animal (Kropff et al., 2015), and a recent report of

298 'band cells' (Krupic et al., 2012 but see; Navratilova et al., 2016 and Krupic et al., 2015) which

299 fire in discrete bands of activity and may aid in the formation of the hexagonal grids of grid cells.

300   Place, head direction and grid cells have turned out to be only the beginning of what

301 promises to be a large array of diverse spatially modulated neurons, some of which have clear

302 real-world correlates but many of whose properties are obscure, or 'conjunctive ' (combine

303 several types of information). We turn next to some of these other cells, to see how their

304 properties could contribute to the building of a cognitive map, but first we look at a class of

305 neuron found throughout the brain, whose firing is more spatially diffuse, and yet seem to have

306 a critical role to play in spatial computations: interneurons.

307 ## Interneurons

308   Interneurons are a morphologically diverse class of typically high firing-rate neurons that

309 use the inhibitory transmitter gamma-Aminobutyric acid (GABA). They usually form local

310 networks of neurons that mostly control their neighbours via short-range, inhibitory connections,

311 and for a long time were thought only to have the relatively uninteresting role of modulating local

312   network activity so as to prevent runaway excitation and epileptic seizures. It is now thought that

313   some of them may have a much more computationally interesting role.

314   In each of the brain structures associated with spatial navigation there tend to be a

315   minority (around 10% of all neurons, for example, in CA1 region of the hippocampus) of high

316   firing neurons which are spatially insensitive (Freund and Buzsáki, 1998), and these are

317   typically interneurons. When recording in the CA1 region of the hippocampus of awake animals,

318   these cells are usually treated as a single class and are often ignored, on the basis that they are

319   modulatory rather than signal-carrying. However, hippocampal interneurons have been

320   suggested to consist of at least 21 distinct types (Klausberger and Somogyi, 2008; Somogyi and

321   Klausberger, 2005), each having specific temporal relationships to the local field potential

322   oscillatory signal known as theta rhythm, and so it seems increasingly likely that they have an

323   important computational role. It has become clear that understanding or modelling neural

324   networks will be impossible without an understanding of these intervening cell types (Sik et al.,

325   1997).This has been examined in two domains - space and time.

326   We begin with spatial information. Although initial reports described interneurons as

327   having no discernible spatial properties (Christian and Deadwyler, 1986), Kubie, Muller and

328   Bostock (1990) showed that hippocampal interneurons do have a coarse but repeatable spatial

329   specificity. This is relatively stable and even rotates with a visual cue like the place fields of

330   place cells. Similar results were also reported in different apparatus (Ego-Stengel et al., 2007;

331   Frank et al., 2001; McNaughton et al., 1983). Wilent and Nitz (2007) for example not only

332   confirmed that the firing of interneurons is spatially modulated, but that this firing can be as

333   informative as place cells. They also observed that some interneurons exhibit 'off fields', or an

334   area of significantly lower firing, that resembles an inverted place field; indeed the authors

335   suggest that this firing may result from interneuron and pyramidal cell interactions.

336   Is the information carried by interneuron firing more than might be expected from the

337   combined input of multiple place cells? Marshall et al. (2002) found that stimulation of a place

338   cell intracellularly can modulate the firing of monosynaptically connected interneurons and that

339   the spatial specificity of these interneurons is often the result of place cell inputs, suggesting

340   that this may not be the case. However, Hangya, Muller and Czurko (2010) simultaneously

341   recorded pairs of interneurons and CA1 place cells and found that even monosynaptically

342   connected neurons could have both similar and distinct spatial representations. These results

343   provide evidence that the spatial specificity of hippocampal interneurons is greater than could

344   be expected based purely on their inputs from place cells. It is the case however that in many

345   correlated cell pairs, interneurons have an off field, as reported by Wilent and Nitz (2007), that

346   corresponds to the location of a connected place cell's place field. This suggests that although

347   interneurons may possess spatial specificity of their own, a subpopulation of these cells are

348   probably involved with place cell firing in an inhibitory or excitatory way.

349   The other important domain in which interneurons have been extensively investigated is

350   in control of the timing of activity in networks. Klausberger and Somogyi (2008) found fine-

351   grained relationships between interneuron activity and theta rhythm, suggesting that the

352   coordinated activity of spatial neurons might be regulated by an orchestra of interneurons,

353   organised by a central conductor, the forebrain structure known as the medial septum. The

354   medial septum probably controls the timing of theta rhythm via long-range inhibitory projections

355   into hippocampus (Melzer et al., 2012). Timing is potentially important for spatial coding

356   because space and time are linked by velocity, since travel at a certain velocity for a certain

357   time translates a subject by a particular distance. It may be that one function of theta rhythm,

358   which varies in frequency with running speed (Jeewajee et al., 2008; McFarland et al., 1975), is

359   to convey a speed signal into the hippocampal formation. The question of whether this is due to

360   explicit encoding of running speed or is a byproduct of the sensory drive associated with

361   increased speed of movement through the sensory world has been debated. However,

362   stimulation of the medial septum, which drives the theta rhythm in hippocampus (Vertes and

363   Kocsis, 1997) directly affects running speed (Fuhrmann et al., 2015), and altering theta

364   frequency artificially has been shown to lead to a change in the running speed of mice (Bender

365   et al., 2015). These results suggest a specific locomotor role for theta, though whether this is on

366   the sensory/encoding side as well as the motor side remains to be determined.

367   As well as the local field potential, cells that are modulated by running speed are

368   common throughout the brain, but again, this might be due to the increased rate of sensory

369   drive rather than a functional role in speed encoding per se. Place cells for example show a

370   considerable amount of modulation by running speed (Czurkó et al., 1999; Kubie et al., 1990;

371   McNaughton et al., 1996, 1983; O'Keefe et al., 1998; Rivas et al., 1996; Sharp et al., 1990;

372   Whishaw, 1998; Wiener et al., 1989; Zhang et al., 1998); they oscillate at a higher frequency

373   and emit more spikes per theta cycle (Geisler et al., 2007). In the medial entorhinal cortex,

374   some of the grid cells in the deeper layers are modulated by speed as well as space - they are

375   known as 'conjunctive' (Sargolini et al., 2006; Wills et al., 2012). Primary visual neurons are also

376   - surprisingly - modulated by running speed (Niell and Stryker, 2010; Saleem et al., 2013).

377   However, it has also been suspected that some cells in the brain might code more purely for

378   speed. For example, O'Keefe reported an observation in hippocampus of a solitary 'speed cell'

379   (O'Keefe et al., 1998) whose activity was linearly related to running speed and could be

380   decoupled from effort, but attempts to find the source of this signal were not successful for many

381   years. Recently, however, Kropff et al reported that a large proportion of neurons in mEC are

382   tuned solely for running speed (Kropff et al., 2015). These cells are thought to be interneurons.

383   Putting this all together, a function for hippocampal interneurons in regulating spatial processing

384   might be to provide a speed signal that the system can use to update the self-localization signal.

385   One influential hypothesis for how this could be done is the oscillatory interference model first

386   suggested by O'Keefe and Recce (1993) and subsequently elaborated by Burgess, O'Keefe

387   and colleagues into a model that could also account for grid cell grids (Burgess et al., 2007).

388   The above ideas aside, the function of interneurons is still little understood, but it seems

389   clear that the brain has not created such a vast array of neuronal cell types for trivial reasons.

390   The next few years should see major advances in our understanding of these ubiquitous

391   neurons.

392   # Extrahippocampal place cells

393   This review is primarily concerned with spatial representations in the brain other than the

394   'big three' cell types, the simplest examples of which are perhaps neurons analogous to place

395   cells in brain areas outside the hippocampus (HPC). For example; both Quirk et al. (1992) and

396   Hargreaves et al. (2005) reported finding cells resembling hippocampal place cells in the medial

397   entorhinal cortex (mEC): the same structure where grid cells can predominantly be found (Fig.

398   3). However, it is not known if these cells were truly place-specific units like those in the

399   hippocampus or merely the isolated vertices of a grid cell's firing structure (Savelli et al., 2008).

400   Indeed, Hargreaves et al. (2005) were also able to record a grid cell, suggesting that their

401   electrodes were at least in a location where they can be found. Nonetheless, more recent

402   studies have confirmed the existence of what appear to be spatially modulated non-grid cells

403   which resemble hippocampal place cells in the mEC (Savelli et al., 2008) as well as spatially

404   modulated cells with multiple firing fields that do not seem to conform to the traditional grid cell

405   classification (Krupic et al., 2012; Latuske et al., 2015; Pérez-Escobar et al., 2016; Zhang et al.,

406   2013), especially in the deeper layers of the structure (Tang et al., 2015).

407   --
408   Insert Fig. 3 [Extrahippocampal place cells] near here
409   --
410

411   Spatial correlates have also been observed in the striatum, a structure closely connected

412   and compared to the hippocampus (discussed later). A small number of cells here appear to

413   encode the head direction (Mizumori et al., 2000; Ragozzino et al., 2001; Wiener, 1993) or

414   relative location of the animal (Wiener, 1993), but more recent studies have failed to find such

415   spatial encoding (Berke et al., 2009) instead suggesting that neurons here encode specific

416   motor responses or behaviours which may themselves occur in a specific spatial location.

417   Nonetheless, the activity of proposed striatal location-sensitive neurons closely follows that of

418   hippocampal cells (Yeshenko et al., 2004). Although, the striatum is thought to utilise contextual

419   information differently to the hippocampus as cells there remap more when the lights are

420   switched off during a navigation task (Mizumori et al., 2000). However, this is not the case when

421   visual cues are simply reorganised, suggesting that these cells may integrate visual information

422   or that they are more sensitive to the navigation strategy the animal is using (Shibata et al.,

423   2001; Yeshenko et al., 2004). In any case, the evidence of true place encoding anywhere near

424   the sensitivity of the hippocampus appears to be lacking in the striatum, this is compounded by

425   the fact that the few reports of spatial activity there always involve a spatial task where animals

426   execute specific responses for specific rewards, both of which we know are important correlates

427   of striatal activity.

428   The medial septum has received considerable attention recently, mainly because

429   inhibiting activity there disrupts entorhinal theta modulation (Jeffery et al., 1995) and grid cell

430   firing (Brandon et al., 2011; Koenig et al., 2011). However, cells in the nearby lateral septum

431   (LS) are reported to have spatial characteristics similar to those of place cells (Leutgeb and

432   Mizumori, 2002; Ryoi et al., 1998; Zhou et al., 1999)(Fig. 3). In contrast to place cells however,

433   these cells initially form orthogonal representations for different environments but later represent

434   them similarly, perhaps indicating a role in pattern completion processes. Evidence suggests

435   that spatially modulated neurons may also reside in the primate septal area (Kita et al., 1995;

436   Nishijo et al., 1997). However, damage specifically to the LS does not seem to impact behaviour

437   (Bland and Bland, 1986; Oddie et al., 1996) and so the function of these cells is still largely

438   unknown.

439   Some cells in the subiculum have similarly been likened to hippocampal place cells

440   (Sharp, 2006, 1997)(Fig. 3) but these seem to be more responsive to environment boundaries

441   (Stewart et al., 2014), opening the possibility that these cells were boundary vector cells

442   (discussed later). In any case, spatially modulated cells in the subiculum certainly seem to have

443   much less spatial selectivity than hippocampal place cells (Anderson and O'Mara, 2004; Barnes

444   et al., 1990; Martin and Ono, 2000) and may instead often encode a combination of positional,

445   directional and speed information (Muller et al., 1991; Sharp and Green, 1994). This finding,

446   coupled with the fact that the firing of these cells is relatively stable in complete darkness

447   (Brotons-Mas et al., 2010), might mean that these cells are more involved in path integration

448   processes than the specific place representations of hippocampal place cells.

449   Jankowski et al. (2015), however, report the observation of much more spatially

450   selective units, resembling hippocampal place cells, in the rostral thalamus (parataenial,

451   anteromedial, and nucleus reuniens), an area associated with episodic memory in humans

452   (Clarke et al., 1994; Mitchell et al., 2014; Van der Werf et al., 2003) and long term memory in

453   rats (Loureiro et al., 2012)(Fig. 3). Mink et al. (1983) also previously reported individual neurons

454   that seemingly responded to spatial correlates in the anteromedial thalamus. These cells are

455   stable within a session, but it is unknown if they maintain a consistent representation over time

456   or if they remap between environments or contexts. Further characterisation will be needed

457   before these cells can be fully compared to hippocampal place units (Jankowski et al., 2015).

458   Similarly, Jankowski and O'Mara (2015) report the existence of spatially modulated units

459   resembling hippocampal place cells in the anterior claustrum (Fig. 3). However, these represent

460   a low proportion of the cells recorded there (4.3%) and like many subicular cells some of them

461   are directionally modulated, suggesting a different role to hippocampal place cells that is

462   perhaps more closely related to visual processes.

463   Deshmukh and Knierim (2011) report the existence of units with spatial fields resembling

464   those of place cells in the lateral entorhinal cortex (lEC): however, these cells require the

465   presence of objects within the environment and are not well spatially modulated when objects

466   are not present (Deshmukh and Knierim, 2011; Hargreaves et al., 2005; Yoganarasimha et al.,

467   2010). These cells may thus provide hippocampal place cells with non-spatial information

468   (Deshmukh and Knierim, 2013; Manns and Howard, 2006) rather than form a unique spatial

469   representation outside the hippocampus. In rodents, the postrhinal cortex has been suggested

470   to fulfil a similar role to the parahippocampal area in primates (Burwell, Witter and Amaral,

471   1995) which is associated with processing spatial scenes (Epstein and Kanwisher, 1998). In

472   rodents its connectivity supports processing both spatial and non-spatial information (Whitlock,

473 Sutherland, Witter, Moser and Moser, 2008) and within the structure cells have been observed

474 to fire in a spatially modulated manner. However, these representations are not stable (Fyhn,

475 Molden, Witter, Moser and Moser, 2004) and do not rotate predictably when visual cues are

476 rotated, but have instead been suggested to represent an initial step in the progression towards

477 true place selectivity (Burwell and Hafeman, 2003). In another cortical structure, Lipton, Alvarez

478 and Eichenbaum (1999) report location-sensitive neurons in the orbitofrontal cortex (OFC). The

479 firing of many of these cells (72% of recorded neurons) discriminated multiple odour ports based

480 on their location. These cells did not usually encode purely location as many of them would also

481 modulate their firing rate based on the behaviour of the rat or the phase of the task, suggesting

482 that they may be integrating visuospatial processing and behavior. Further results from

483 Feierstein et al. (2006) suggest that pure location-dependent firing is unlikely in the OFC and

484 that cells there may have a locomotor rather than a purely spatial representation. Thus we see

485 that the precise spatial modulation of the hippocampal place cell may not be common outside

486 the hippocampus.

487 ## Boundary/border cells

488 Perhaps the relatively unique spatial representation in the hippocampus is due to the

489 variety of spatial inputs that project there. For example, another widely researched, but often

490 overlooked cell type responds purely to environmental boundaries (Fig. 4) - these cells have a

491 complex relationship with both place and grid cells that is still not greatly understood. Early

492 observations demonstrated that hippocampal place cell firing often appears to be determined, at

493 least partly, by the geometric constraints of an environment. By elongating a square

494 environment into a rectangle, place fields which were previously small and round were seen to

495 stretch in response to the wall changes, becoming long and distended in the same dimension,

496   albeit by a smaller amount (O'Keefe and Burgess, 1996). This led a number of researchers to

497   formulate a model of place cell firing which employed a class of cells known as Boundary Vector

498   Cells (BVCs): these cells were predicted to fire in relation to environmental boundaries, with

499   place cell firing arising as a result of a threshold sum activity of a subpopulation of these BVCs

500   (Barry et al., 2006; Burgess et al., 1997; Hartley et al., 2000).

501   --
502   Insert Fig. 4 [border cell] near here
503   --
504

505   Initial reports suggested that cells in the subicular formation of the rat may be responsive

506   to environment boundaries (Sharp, 1997; Sharp and Green, 1994) albeit with a weak overall

507   spatial modulation. Later studies have since revealed cells which at least partially fit the

508   description of the hypothesised BVCs, in areas as diverse as the subiculum (Barry et al., 2006),

509   presubiculum and parasubiculum (Boccara et al., 2010), mEC (Bjerknes et al., 2014; Savelli et

510   al., 2008; Solstad et al., 2008) and recently in the anterior claustrum (Jankowski and O'Mara,

511   2015) and rostral thalamus (Jankowski et al., 2015)(Fig. 4). These cells have a preferred firing

512   direction, much like head direction cells, but instead of firing maximally when the animal's head

513   is facing this direction a BVC will fire when the animal encounters an environmental boundary in

514   that direction from the animal. This firing is driven by the memory of the boundary's position

515   relative to the animal, based on self-motion information and not simply by perceptual cues

516   (Lever et al., 2009; Raudies et al., 2012; Raudies and Hasselmo, 2012). This consistent firing is

517   observed in every environment in which the cell is observed, if the animal's sense of direction

518   remains the same in each (Lever et al., 2009; Sharp, 1997). Environmental boundaries which

519   can drive BVC firing in this way may be walls, low ridges or vertical drops and the colour, texture

520   or odour of these does not seem to influence the cell's firing (Lever et al., 2009).

521   Within this group of spatially modulated neurons there is a great diversity of different

522   types. Initial models predicted that different cells would respond to different distances from

523   boundaries. However, border cells in the mEC seem to respond to boundaries not more than 10

524   cm away (Bjerknes et al., 2014; Solstad et al., 2008); the same seems to be true of boundary

525   cells in the claustrum (Jankowski and O'Mara, 2015). Subicular boundary vector cells, in

526   contrast, can be observed to have fields distant from their preferred boundary (Lever et al.,

527   2009) suggesting that these two types of cell may form discrete populations. Furthermore,

528   Stewart et al. (2014) report the existence of 'boundary-off' cells in the subiculum. These cells

529   fire in a way that resembles an inverted boundary cell, with activity covering an environment

530   *except* for an area near one particular boundary. Stewart et al. (2014) propose that these cells

531   may play a distinct role in navigation, suggesting that they may form another separate class of

532   boundary cells. So far, all of these boundary and border cells do not direct their activity (or lack

533   of activity) to all boundaries in all directions: they are selective only for those found at a specific

534   distance from the animal and at a particular allocentric direction. However, so called 'perimeter'

535   or 'annulus' cells in the rostral thalamus (nucleus reuniens and anteromedial

536   thalamus)(Jankowski et al., 2015), anterior claustrum (Jankowski and O'Mara, 2015), mEC

537   (Solstad et al., 2008) and mouse anterior cingulate cortex (Weible et al., 2012) break even this

538   rule and fire along all environment boundaries (Fig. 4). These cells are also accompanied by

539   corresponding boundary off counterparts that fire only in the centre of an apparatus (Weible et

540   al., 2009). These cells may mark yet another distinct population, perhaps forming a precursor to

541   boundary cells that is generally active near all boundaries.

542   # Object cells

543   Recognising if a stimulus is novel or familiar is often crucial to an animal's survival and

544   this is true as much of object recognition as it is of recognising an immediate threat - confusing

545   a slice of pizza for your hat may result in a short period of embarrassment but it's easy to see

546   how faulty or non-existent object recognition such as this could escalate quickly to be a life or

547   death matter, especially for animals. Furthermore, the recognition and memory of objects may

548   underlie features of episodic and 'episodic like' memory in humans and animals: it would be

549   difficult to forget the aforementioned pizza incident but it would likewise be impossible to

550   remember without also having access to a memory for the associated objects. Indeed, a more

551   recent view of the hippocampus is that it is involved in integrating a variety of stimuli in order to

552   potentially lay the framework for the creation of episodic or episodic like memory. In this view,

553   memory is comprised of spatial ('where') and nonspatial ('what') information (Knierim et al.,

554   2014) of which objects comprise a small part. The hippocampus is known to be involved in

555   processes far beyond purely spatial navigation (Eichenbaum et al., 1999) including the

556   discrimination of non-spatial cues such as objects (Clark et al., 2000; Fortin et al., 2004). For

557   instance place cells in the hippocampus have been shown to respond to the spatial location of

558   objects (Lenck-Santini, Rivard, Muller and Poucet, 2005) so this information is certainly being

559   utilised by the hippocampus and thus possibly also in the formation of episodic memory. It likely

560   originates in structures outside the hippocampus however; as nonspatial information is thought

561   to progress through the perirhinal cortex and lateral entorhinal cortices before entering the

562   hippocampus (Deshmukh et al., 2012; Witter et al., 2000; Witter and Amaral, 1991). We will

563   review some electrophysiological evidence of object related activity outside the hippocampus,

564   paying particular attention to those representations that are still spatial in nature.

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566   Insert Fig. 5 [object cell] near here
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568

569   It is important to remember that cells which are more active around or near specific

570 objects are not necessarily spatially modulated, these neurons may be encoding visual or tactile

571 information (Burke et al., 2012) or novelty (Wan et al., 1999; Zhu et al., 1995). Upon analysis

572 this phenomenon may appear spatial, but this is merely because the objects occupy a specific

573 spatial location (see O'Keefe, 1999 for a similar discussion) for an example see the dissociation

574 between representations in the perirhinal and lateral entorhinal cortex (Deshmukh et al., 2012).

575 However, a number of studies have highlighted cells that also possess spatial characteristics

576 which we will discuss here. For instance, about 5.5% of cells in anterior claustrum show a

577 sensitivity to objects: this firing begins immediately upon exploring the object and dissipates as

578 soon as it is removed (Jankowski and O'Mara, 2015)(Fig. 5). Firing persists in darkness or if the

579 object is replaced with a different one, meaning that it does not simply represent visual, texture

580 or other sensory features. Rather, these cells seem to encode the spatial location of objects in

581 the environment. In the absence of objects some of these cells are also spatially modulated and

582 resemble hippocampal place cells suggesting that they are encoding spatial information about

583 objects when they are present rather than their identity.

584   Similarly, lateral entorhinal cortex (lEC) cells are not well spatially modulated in a blank

585 environment (Deshmukh and Knierim, 2011; Hargreaves et al., 2005) or even in an environment

586 where many distal cues are provided (Yoganarasimha et al., 2010): however, when objects are

587 placed inside the environment many cells show activity resembling the object-sensitive cells in

588 the claustrum (Deshmukh and Knierim, 2011). In contrast to those cells though, units in the lEC

589   often maintain their object-related firing when the object is removed, providing evidence of a

590   spatial memory for the position of objects (Tsao et al., 2013)(Fig. 5). In support of this spatial

591   view, some of these neurons are sensitive only to specific objects or fire in the position of a

592   moved or missing object (Deshmukh and Knierim, 2011; Tsao et al., 2013): these object

593   memory 'trace responses' were not seen in the claustrum cells. However, units which show the

594   same trace response activity have been reported in lateral entorhinal cortex (Vandrey and

595   Ainge, 2016) and can also be found in the mouse anterior cingulate cortex (ACC) where cells

596   respond to the precise spatial location of a missing object for up to 30 days after initial exposure

597   to the environment (Weible et al., 2012, 2009)(Fig. 5). One interpretation of these findings is

598   that, as discussed above, these brain regions are involved in conveying object/place

599   associations to the hippocampus. Certainly, lesions of the lEC result in object recognition

600   impairments (Wilson et al., 2013).

601   ## Goal cells

602   Similar to object recognition, the representation of spatial and nonspatial goals is a

603   fundamental requirement of survival. Rarely do we navigate without a specific goal in mind,

604   even if it is only a subgoal on a longer journey or a simple place of regular interest such as the

605   supermarket. Without a representation of the supermarket however you would need to walk

606   aimlessly until randomly finding it every time you needed to buy milk. It is true that rats do not

607   need to buy milk very often, but they do have to find food, potential mates and shelter. Thus,

608   having a representation of these spatial goals can allow them to navigate quickly, efficiently,

609   safely and flexibly whenever necessary. However, finding a representation of spatial goals in the

610   brain has proven difficult and initial reports suggested that even the highly integrative spatial

611   map provided by place cells does not encode this information (Hölscher et al., 2003; Siegel et

612   al., 2008; Speakman and O'Keefe, 1990). Some studies suggested that the firing of place cells

613   at the beginning of a complex maze may be related to the future goal of the animal and that this

614   reflected the animal's anticipation of this location (Ferbinteanu et al., 2003; Frank et al., 2001;

615   Wood et al., 2000), however, recent evidence suggests that this firing is actually related to the

616   animal's future trajectory, not the goal (Grieves et al., 2016b). Other evidence suggests that

617   place fields may subtly shift towards spatial goals causing an overrepresentation of that location

618   (Hollup et al., 2001; Kobayashi et al., 2003; Dupret et al., 2010) or that some place cells may

619   fire preferentially just before reward attainment (Eichenbaum et al., 1987). However, these goal

620   representations are not as specific as one might expect or hope for. Early models actually

621   predicted the existence of 'goal cells' which would modulate their firing rate based on an

622   animal's distance from its current goal (Burgess et al., 1993; Burgess and O'Keefe, 1996;

623   Pfeifer, 1998). These cells, which were thought to perhaps reside in the subiculum, could be

624   used to navigate efficiently towards a goal location if the environment is not too complex. This

625   seems like a much more attractive way to represent spatial goals and some cells in frontal-

626   cortical regions may play a comparable role.

627   Despite direct hippocampal input (Jay and Witter, 1991), cells in the prelimbic area of the

628   medial prefrontal cortex (mPFC) do not typically encode location (Gemmell et al., 2002; Ito et

629   al., 2015; Jung et al., 1998; Poucet, 1997) though they may encode contextual information

630   (Euston and McNaughton, 2006; Hyman et al., 2012; Ito et al., 2015; Jung et al., 1998).

631   However, using a novel open field task where rats activate the availability of a food reward from

632   a location separate to the one where they actually consume the reward (Rossier et al., 2000),

633   Hok et al. (2005) found evidence of a quasi-spatial representation in the prelimbic/infralimbic

634   areas of the mPFC (Poucet et al., 2004)(Fig. 6). Specifically, many units there increased their

635   activity in the location of a spatial goal, despite this being spatially distinct from the location of

636   the reward. This representation perhaps informs hippocampal activity - where similar goal

637   related firing can also be observed in place cell firing (Hok et al., 2007; Poucet et al., 2004).

638   Although inactivation of the mPFC does not disrupt goal firing in place cells (Hok et al., 2013),

639   so the reverse flow of information may be true. These cells have very large firing fields located

640   on or near the goal location, characteristics which are both important features of the

641   aforementioned goal cells (Burgess and O'Keefe, 1996). However, further research will be

642   needed to clarify whether mPFC cells do hold a spatial representation of the goal or if they are

643   merely representing task-relevant stimuli (Hagler and Sereno, 2006) or goal-based action

644   selection (Matsumoto, 2003) in a spatial task, thus just giving the appearance of a spatial

645   response.

646   --
647   Insert Fig. 6 [goal cell] near here
648   --
649

650   Looking at the nearby obitofrontal cortex (OFC); initial evidence from primates

651   suggested that this structure may encode the economic significance of different behavioral

652   outcomes (Padoa-Schioppa et al., 2006). Indeed, recent evidence in rats also suggests that the

653   OFC may encode expectations or realisations about rewards (Steiner and Redish, 2012). In

654   terms of a spatial representation, cells seem to simply modulate their firing in relation to spatial

655   goals, perhaps giving the appearance of spatial coding (Steiner and Redish, 2012; Stott and

656   Redish, 2014). However, cells in the OFC may be spatially responsive to odour-place

657   associations (Feierstein et al., 2006; Lipton et al., 1999) and their firing may also be related to

658   future goal locations and response directions (Feierstein et al., 2006).

659   Another possibility is that already discovered cells actually fulfil this role. It has been

660   proposed for instance that the firing of grid cells in the medial entorhinal cortex could be

661   translated into a gradient signalling the distance to a spatial goal (Stemmler et al., 2015), but

662   this signal may not be represented itself by a specific cell. Alternatively, we may not need to

663   stray out into distal cortical regions in order to find a goal representation at all; more recent fMRI

664   data suggest that there may be such a representation in the human hippocampus (Howard et

665   al., 2014) but direct electrophysiological evidence in any animal of such a signal has remained

666   elusive. Preliminary evidence from research on bats, however, may provide a concrete example

667   of such a representation; these animals appear to have neurons that encode the precise spatial

668   location and allocentric direction of a goal even when it is obscured (Sarel et al., 2015). How this

669   representation is formed, utilised or adapted is still to be determined; likewise if a similar

670   representation is to be found in the human or rat brain is still unknown

671   # Conjunctive cells

672   So far we have seen examples of cells with specific representations of space, however,

673   many cells in the brain do not form a pure representation such as this, especially those cells in

674   structures associated with integrative processes. Many cells encode a number of environmental,

675   spatial or behavioural features simultaneously and are thus termed 'conjunctive cells'.

676   Concentrating on those cells that conjunctively encode spatial features, many of these are found

677   in the medial entorhinal cortex, but there are also examples in other brain regions too. Theta-

678   modulated place-by-direction (TPD) cells, for example, have been observed in the rat

679   presubiculum and parasubiculum. These cells fire in specific spatial locations but only when the

680   animal is facing in a particular direction (Cacucci et al., 2004)(Fig 7). Similar cells have also

681   been observed in the parasubiculum (Taube, 1995b) and retrosplenial cortex (Alexander and

682 Nitz, 2015; Cho and Sharp, 2001; Vedder et al., 2016)(Fig 7), there they are thought to integrate

683 this information with self-motion information. Many cells in the medial entorhinal cortex (mEC)

684 respond conjunctively to direction, location and running speed; for instance some grid cells may

685 also exhibit head direction correlates (Sargolini et al., 2006) or head direction cells may exhibit

686 strong spatial modulation (Tang et al., 2014)(Fig 7). Indeed, these conjunctive cell types were

687 being used in artificial navigation modules before they were discovered and may be necessary

688 for efficiently computing current location (Milford et al., 2006, 2010) suggesting that these cells

689 may fulfil an important role in spatial navigation processes.

690 --
691   Insert Fig. 7 [conjunctive cell] near here
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693

Movement- or action-sensitive cells

695 So far in this review we have focused on those cells that encode an animal's spatial

696 location: however, movement through space is a critical part of spatial processing, and many

697 cells in the brain encode movement, or encode space conjunctively with movement. Self-motion

698 information can be used to estimate spatial location through path integration processes if a

699 known reference point is provided (Mittelstaedt and Mittelstaedt, 1980). As such, self-motion

700 information is generally concerned with cues internally generated, which makes it a relatively

701 simpler form of information. However, given the vast number of possible internal cues that these

702 cells may encode and the fact that, as we saw earlier, many encode a conjunction of stimuli,

703 these representations can be difficult to recognise or examine. Nevertheless, a number of brain

704 structures and cells have been identified that reliably encode such features.

705   As mentioned above, early studies found that place cells conjunctively encode velocity

706   as well as place (McNaughton et al., 1983), and studies of head direction cells have similarly

707   found modulation by movements including angular head velocity (Chen et al., 1994; Sharp,

708   1996). Additionally, head direction cells in some regions show anticipatory firing that was

709   originally suggested to reflect a motor efference signal (Blair et al., 1997; Blair and Sharp,

710   1995); however, it still occurs during passive movements (Bassett et al., 2005), and may reflect

711   vestibular information about predicted head direction instead. Movement sensitivity is found in

712   many other regions however. One such structure is the striatum, the activity of which is often

713   compared and contrasted to that of the hippocampus. Whereas the hippocampus is thought to

714   underlie the encoding of flexible, perhaps rare or unlikely experiences (Eichenbaum, 2004), the

715   striatum appears to be more closely involved with repetitive experiences (Berke, 2009). In

716   evidence of this, when animals are trained on a task that allows only the use of body-referenced

717   (egocentric) or world-referenced (allocentric) information, inactivation of the striatum tends to

718   increase the use of a hippocampal-dependent 'place' strategy, whereas inactivation of the

719   hippocampus tends to increase the use of a striatum-dependent 'response' strategy (Packard

720   and McGaugh, 1996). This makes the striatum an important structure for processing task-

721   relevant action information which is often similar if not identical in repetitive tasks; it also

722   implicates the striatum in the formation of automated responses or habits (Jog et al., 1999; for a

723   review see Yin and Knowlton, 2006). Consistent with this, many studies reveal that the activity

724   of striatal neurons is related to specific body movements in both primates (Alexander and

725   DeLong, 1985; Schultz and Romo, 1988) and rats (Gardiner and Kitai, 1992; West et al., 1990).

726   In behavioural tasks, striatal neurons also seem to encode task-relevant information such as

727   rewards (van der Meer et al., 2010; van der Meer and Redish, 2009), task phase (Barnes et al.,

728   2005; Kermadi and Joseph, 1995) or response sequences (Berke et al., 2009; Jin and Costa,

729   2010).

730   Strikingly, many striatal cells fire preferentially when the animal is making a particular

731   movement at a particular location in an environment, such as turning left in a T-maze (Thorn et

732   al., 2010). This is a pattern that has been seen elsewhere too: neurons which respond to

733   specific response sequences can also be found in the posterior parietal cortex (PPC)

734   (McNaughton et al., 1989; McNaughton et al., 1989; Chen et al. 1994). Neurons here are often

735   modulated by head direction (Chen et al., 1994; Whitlock et al., 2008), but cells are also

736   modulated by other factors, perhaps related to the time since the last response was made,

737   distance to a goal or the animal's allocentric spatial location (Nitz, 2006; Nitz, 2012). More

738   recent research suggests that these cells may represent a phase in the process required to

739   transform egocentric information into an allocentric reference frame. By this view, they actually

740   encode the egocentric position of a cue (Wilber et al., 2014). In support of this, previous studies

741   identified that rats with posterior parietal cortex lesions suffered a strange inability to orient

742   themselves towards a cue (Kolb et al., 1994) and rats are generally impaired in spatial tasks

743   after lesions to this area - especially if those tasks require using proximal visual cues (Kolb et

744   al., 1994, 1987; Save et al., 1992). A similar integrative process has been suggested to take

745   place in retrosplenial cortex (RSC), where neurons can be found that encode both response

746   sequence and spatial location (Alexander and Nitz, 2015). These cells were recorded in a

747   stereotyped maze environment meaning that the location specificity may be due to similar visual

748   scenes rather than location, however, in open field experiments conjunctive representations of

749   spatial location and head direction have also been observed (Jacob et al., 2016) making this

750   less likely. Recent reports also suggest that cells may reside in the retrosplenial cortex (Jacob et

751   al., 2016, 2014) and nearby subiculum (Olson et al., 2016) that encode a conjunction of visual

752 and head direction information (Fig 7), in the case of the subiculum these cells have been

753 suggested to represent an animal's allocentric direction of travel.

754 ## Conclusion

755 The study of the neural encoding of space began with the discovery (albeit spread

756 across 30 years) of a triumvirate of spatially modulated neurons: the place cells, head direction

757 cells and grid cells. Studies of the network in which these neurons are embedded has revealed

758 many more cells that have firing properties relevant to spatial encoding (See Fig. 8 for a

759 summary "wiring diagram"). Some of the response profiles are conjunctive, making activity

760 sometimes difficult to decipher, and it seems likely that the "big three" cell types represent

761 nodes of unusually decipherable (by scientists at least) representatives of a diverse array of cell

762 types, many of which will only be understood using complex analytical methods.

763 We have seen that spatial tuning outside of the hippocampus and medial entorhinal

764 cortex is not particularly unusual. Why might these spatial representations exist in structures

765 outside the hippocampus at all? Do they receive their spatial inputs from place cells in the

766 hippocampus? Or are these representations independent of that signal? The answers to these

767 questions are probably complex. We do know that the hippocampus represents a melting pot of

768 spatial and non-spatial inputs, which in themselves must come from outside the structure. We

769 know this because where other spatial signals such as that carried by the head direction system

770 and grid cell system can be easily disrupted by lesions, the spatial representation of the

771 hippocampus continues almost perpetually, even in the absence of both of these signals. This

772 suggests that activity in the hippocampus is the result of multiple inputs and can adapt to a loss

773 of a substantial amount before degrading. However, this fine-tuned spatial signal is likely also

774   exported to other structures that are either associated with spatial navigation processes or

775   involved in integrating it with other information. To compound the matter, many of these

776   projections are likely to be reciprocal, so that the output of these structures will also be found in

777   the hippocampus. Untangling this dense web of interconnections and shared spatial responses

778   is a slow process that began almost forty years ago and will require still a great deal of

779   sophisticated electrophysiology and concomitant behavioural investigation.

780   # Future research

781   We have covered many different cell types so far discovered in a variety of different

782   brain regions, but the question of how spatial cognition is supported is far from resolved. For

783   instance, interneurons are spread throughout the brain and as we have seen here, may

784   contribute significantly to the spatial modulation of many other cell types (Hangya, Muller and

785   Czurko, 2010). Neural network models, deep learning projects and major collaborative research

786   such as the Human Brain Project all require data concerning the activity profiles of neurons in

787   different brain regions. Yet, electrophysiology research has yet to tackle this large population of

788   diverse neurons found throughout the brain, in part because it is often hard to find real-world

789   correlates of neuronal activity, and we do not yet have a full suite of analytic tools with which to

790   describe and interpret more complex firing patterns. Advanced brain research will require a

791   fuller understanding of these neurons and the role they fulfil (Sik et al., 1997).

792   Even for cells that do have discernible real-world correlates, it is often unclear what

793   inputs many spatial neurons are sensitive to. For instance, what constitutes an object, and why

794   do object sensitive cells fire at or around certain items in the environment but not others? What

795   makes these items different to walls or textures on the floor? For a better understanding of brain

796 networks and how neurons process information we must know in greater detail what specific

797 features these cells are attending to or if they represent a model of a more complex

798 representation.

799 It is similarly unclear what constitutes a boundary. Are boundary sensitive neurons

800 representing a physical barrier? Research suggests that they respond to vertical drops (Lever et

801 al., 2009), which is an absence of support rather than the presence of a barrier, so perhaps

802 boundary cells instead represent simple linear features of an environment? However the cells

803 do not seem to be sensitive to patterns, textured flooring or changes in ground colour,

804 suggesting that they instead represent something more meaningful to the animal such as

805 impediments to locomotion (Stewart, 2014). Are boundary cells also sensitive to virtual or

806 otherwise non-physical barriers, such as a purely acoustic boundary (e.g., Hayman et al 2008)?

807 Future research will be needed to clarify these relationships. It is also unknown whether the

808 boundary cells found in the subiculum (Lever et al., 2009), mEC (Bjerknes et al., 2014), anterior

809 claustrum (Jankowski and O'Mara, 2015), rostral thalamus (Jankowski et al., 2015) and anterior

810 cingulate cortex (ACC)(Weible et al., 2012) are related or if they represent divergent features.

811 Perimeter cells in some of these regions, which fire along all boundaries, and their 'boundary off'

812 counterpart which fire away from all boundaries, certainly seem to satisfy a different function

813 and perhaps precede the formation of traditional boundary cells, but this is unknown.

814 Another major, unsolved question concerns the representation of spatial goals in the

815 brain. Research shows that in many cases animals plan what they want to do in terms of

816 trajectories (Grieves et al., 2016a) and continuously recall entire trajectories through space

817 (Pfeiffer and Foster, 2013). However, there is evidence of goal encoding in the prefrontal cortex

818 (Hok et al., 2005) and the circuit this forms with the hippocampus (Ito et al., 2015). Recent data

819   also suggest that some animals may possess a constantly updating goal vector that can be

820   observed in the activity of single neurons (Sarel et al., 2015) or in the activity of whole brain

821   regions (Howard et al., 2014). Finding out how goals are stored and retrieved, and the steps

822   that lead to action planning, will be a major task for the coming period and will need to include

823   areas of the brain outside the hippocampus, in addition to hippocampus itself. Indeed, one

824   conclusion that should be drawn from the examples described in this review is that many

825   fascinating functions of the brain and of brain networks reside outside the most widely

826   researched brain regions. The next generation of behaviourists and neuroscientists will certainly

827   work together to better elucidate the form and function of different brain structures and the

828   diverse neural specificity that awaits there.

829

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831   ---
832   Insert Fig. 8 [summary diagram] near here
833   ---
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1584 # Figure legends

1585 **Figure 1** Recording of the three first-discovered spatial cell types. ***A,*** A typical

1586 experimental setup for recording single neurons from freely exploring rats implanted with

1587 chronically indwelling electrodes. ***B,*** Data from a single hippocampal place cell in a single, 4-min

1588 recording trial. The left plot shows the action potentials ("spikes" - red squares) superimposed

1589 on the cumulative path of the rat across the 4 mins. Note that the spikes mostly occurred in the

1590 northeast part of the environment. The right plot shows the same data depicted, as it commonly

1591 is, as a heat plot of dwell-time-adjusted firing rate (see colour bar) between peak (100%) and

1592 20% (peak). Action potentials and dwell time are binned, smoothed and divided to give a spatial

1593 map of the cell's firing rate as a function of spatial location. The patch of spatially localised firing

1594 is known as a place field, or firing field. ***C,*** Two trials recorded from a post-subicular head

1595 direction cell, in a symmetrical apparatus having a single polarising landmark. Each polar plot

1596 shows firing rate as a function of head direction. In the left plot, when the landmark is to the

1597 north, the cell fires maximally when the rat's head faces south. In the right plot, the landmark

1598 was rotated to the east when the rat was not in the compartment - now, when the rat returns,

1599 the cell fires to the west, maintaining the same relationship to the landmark. This shows that the

1600 cells are influenced by local cues and not by geocentric ones such as the Earth's magnetic field.

1601 ***D,*** Recording of an entorhinal grid cell, firing depicted as in ***A***. Note that instead of a single

1602 region of spiking, the cell spikes in multiple places that form a close-packed hexagonal array,

1603 like the one shown in the inset. The constant spacing between firing fields is characteristic of a

1604 given cell and is relatively constant in different environments, leading to suggestions that these

1605 cells function to encode distances.

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1607   **Figure 2** Example cells and a graphic representation of their anatomical distribution in

1608   the rat brain. *A, left*, the firing rate heat map of a place cell (adapted from Grieves et al., 2016a)

1609   recorded as a rat explored a circular arena. **Middle**, an example head direction cell firing rate

1610   plot (adapted from Bjerknes et al., 2015). These 'polar' plots show the action potentials emitted

1611   by a cell, binned in terms of the animal's head direction at the time and divided by the amount of

1612   time spent facing that direction overall. This cell fires at a high rate when the animal is facing to

1613   the north east of the environment: this direction is the cell's 'preferred firing direction'. **Right**, an

1614   example firing rate map of a grid cell (Casali and Jeffery, 2015), this is produced using the same

1615   method as for the place cell. Multiple firing fields can be observed which form a triangular or

1616   hexagonal grid that spans the environment. *B,* a graphic representation of the location these

1617   cells occupy in the rat brain (white outline). Black lines highlight the region where each cell was

1618   discovered but they may be found in multiple regions. Brain regions are denoted by

1619   abbreviations, these are: HPC = hippocampus; Sub = subiculum, RSC = retrosplenial cortex;

1620   PrS = presubiculum; PaS = parasubiculum; mEC = medial entorhinal cortex; lEC = lateral

1621   entorhinal cortex; PFC = prefrontal cortex; OFC = orbitofrontal cortex.

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1627 **Figure 3** Place cells outside the hippocampus. The plots show heatmaps, similar to the ones in

1628 Figure 1, from various studies demonstrating the existence of highly spatially tuned cells outwith

1629 the hippocampus. **Top row:** Sharp et al. (2006 adapted from figure 3) reported observing cells

1630 with spatial characteristics very similar to hippocampal place cells in the subiculum, place cells

1631 have perhaps also been observed in the medial entorhinal cortex (Quirk et al., 1992 adapted

1632 from figure 2) and anterior claustrum (Jankowski and O'Mara, 2015 adapted from figure 1).

1633 **Middle row:** Jankowski and O'Mara (2015 adapted from figure 1) found evidence for spatially

1634 selective cells throughout the rostral thalamus (Jankowski et al., 2015 adapted from figure 2).

1635 **Bottom row:** Spatially selective cells have also been observed in the lateral septum (Leutgeb

1636 and Mizumori, 2002 adapted from figure 3; Zhou et al., 1999 adapted from figure 4).

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1645   **Figure 4** Border/boundary cells. The plots show heatmaps, similar to the ones in Figure

1646   1, from various studies showing firing of cells concentrated near boundaries in the environment,

1647   irrespective of other contextual cues and of spatial location. **Top row:** boundary cells recorded

1648   in the subiculum by Lever et al. (2009 adapted from figure 2) and more recently by Stewart et al.

1649   (2014 adapted from figure 2). It is clear that cells in this region respond to boundaries, firing

1650   along them. This is best demonstrated using the classical 'barrier' test, as shown in the

1651   righthand plots. These cells can also fire at a distance to boundaries, as can be seen in the

1652   second plot from the left. **Second row:** border cells recorded in the medial entorhinal cortex by

1653   Savelli et al. (2008 adapted from figure 4), Solstad et al. (2008 adapted from figure 1) and more

1654   recently by Bjerknes et al. (2014 adapted from figure 1). As in the subiculum, these cells

1655   respond to boundaries, but few respond at a distance to them. **Third row:** boundary cells

1656   recorded by Jankowski and O'Mara (2015 adapted from figure 3) in the anterior claustrum.

1657   Unlike the more classical boundary cells, these seem to respond to all boundaries in the

1658   environment. **Bottom row:** Weible et al. (2012 adapted from figure 3) demonstrated that similar

1659   'all-boundary' responses can be observed in the anterior cingulate cortex, they termed these

1660   cells 'annulus' or 'bulls-eye' depending on whether they fired along boundaries or away from

1661   them. Jankowski et al. (2015 adapted from figure 4) also observed annulus cells in the nucleus

1662   reuniens of the thalamus.

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1667   **Figure 5** Object cells. These plots show heatmaps, similar to the ones in Figure 1, from

1668   various studies showing the firing of cells related to objects in the environment. **Top row:** object

1669   sensitive cells recorded in the lateral entorhinal cortex by Deshmukh and Knierim (2011 adapted

1670   from figure 3) and Tsao et al. (2013 adapted from figure 1). These cells fire near to objects

1671   placed in the environment, regardless of their identity. As can be seen in the right example,

1672   these cells do not typically show spatially selectivity in the absence of objects. **Middle row:** two

1673   example cells recorded by Jankowski and O'Mara (2015 adapted from figure 4) in the anterior

1674   claustrum. In the absence of objects these cells are somewhat spatially modulated, but when

1675   objects are added these cells show very specific firing around them. **Bottom row:** two cells

1676   recorded by Weible et al. (2012 adapted from figure 5) in the mouse anterior cingulate cortex.

1677   Cells in this brain region are also sensitive to the presence of objects, firing around them.

1678   However, some cells, as in the left example, instead fire in an area marking the *absence* of a

1679   previous object.

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1686   **Figure 6** Goal cells. These plots show heatmaps, similar to the ones in Figure 1 but with

1687   a slightly different colormap that ranges from orange (no firing) to purple (maximum firing).

1688   These four medial prefrontal cortex cells were recorded by Hok et al. (2005 adapted from figure

1689   3) and demonstrate a clear field of activity surrounding the goal zone. This zone was where rats

1690   had to wait to trigger the release of food and is thus dissociated from the location of actual food

1691   consumption.

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1702   **Figure 7** Conjunctive cells. These plots show heatmaps, similar to the ones in Figure 1,

1703   from various studies showing the multi-modal or conjunctive firing of different cells. Next to

1704   these are shown directional 'polar' plots as described in Figure 1. **Top row:** conjunctive cells in

1705   the medial entorhinal cortex (mEC); Tang et al. (2015 adapted from figure S3) report that the

1706   activity of boundary cells may also be directional, like that of head direction cells. Latuske et al.

1707   (2015 adapted from figure 5) similarly report that some head direction cells can show a strong

1708   spatial modulation, much like place cells. Sargolini et al. (2006 adapted from figure 3 and S7)

1709   also demonstrated that many grid cells also show directional modulation similarly to head

1710   direction cells, further strengthening the view that these cells may be involved in processing

1711   self-motion information. **Bottom row:** spatially responsive cells can be observed in the

1712   retrosplenial cortex (RSC) and these cells often also have directional correlates (Cho and

1713   Sharp, 2001; adapted from Jacob et al., 2016). Cacucci et al. (2004 adapted from figure 2)

1714   observed cells in the pre- and parasubiculum that were sensitive to the heading direction of the

1715   animal but which also showed strong spatial selectivity.

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1721   **Figure 8** Schematic diagram concentrating on the brain regions and cell types discussed

1722   in this review. Place cells can be found in the hippocampus, nucleus reuniens (NRe),

1723   parataenial nucleus (PT), anteromedial nucleus (AM), claustrum, medial entorhinal cortex and

1724   subiculum. Place correlates (i.e. weak spatial activity) can be found in the orbitofrontal cortex

1725   (OFC), postrhinal cortex, lateral entorhinal cortex and lateral septum. Grid cells can be found in

1726   the medial entorhinal cortex, pre- and parasubiculum. Head direction cells can be found in the

1727   lateral mamillary nuclei (LMN), anterodorsal nuclei (ADN), laterodorsal nuclei (LDN),

1728   retrosplenial cortex (RSC), postsubiculum, nucleus reuniens and anteromedial nucleus (AM).

1729   Boundary cells can be found in the parasubiculum, claustrum, subiculum, anterior cingulate

1730   cortex, pre- and parasubiculum and medial entorhinal cortex. Object sensitive cells can be

1731   found in the lateral entorhinal cortex, postrhinal cortex, orbitofrontal cortex (OFC) and the lateral

1732   septum. Goal cells can be found in the medial prefrontal cortex (mPFC) and prelimbic and

1733   infralimbic regions of the prefrontal cortex. Self-motion or egocentric cells such as those

1734   encoding running speed or angular head velocity can be found in the mEC, striatum, RSC, PPC,

1735   LMN and DTN. For a more in depth review of the connectivity of the anterior thalamic nuclei see

1736   Jankowski et al. (2013) or Aggleton and Nelson (2015). For the mammillary bodies see

1737   Dillingham, Frizzati, Nelson and Vann (2015). For the circuit between hippocampus, mPFC and

1738   NRe see Vertes, Hoover, Szigeti-Buck and Leranth (2007) or Griffin (2015). For the entorhinal

1739   cortex see Canto, Wouterlood and Witter (2008). For hippocampal, subicular pre- and

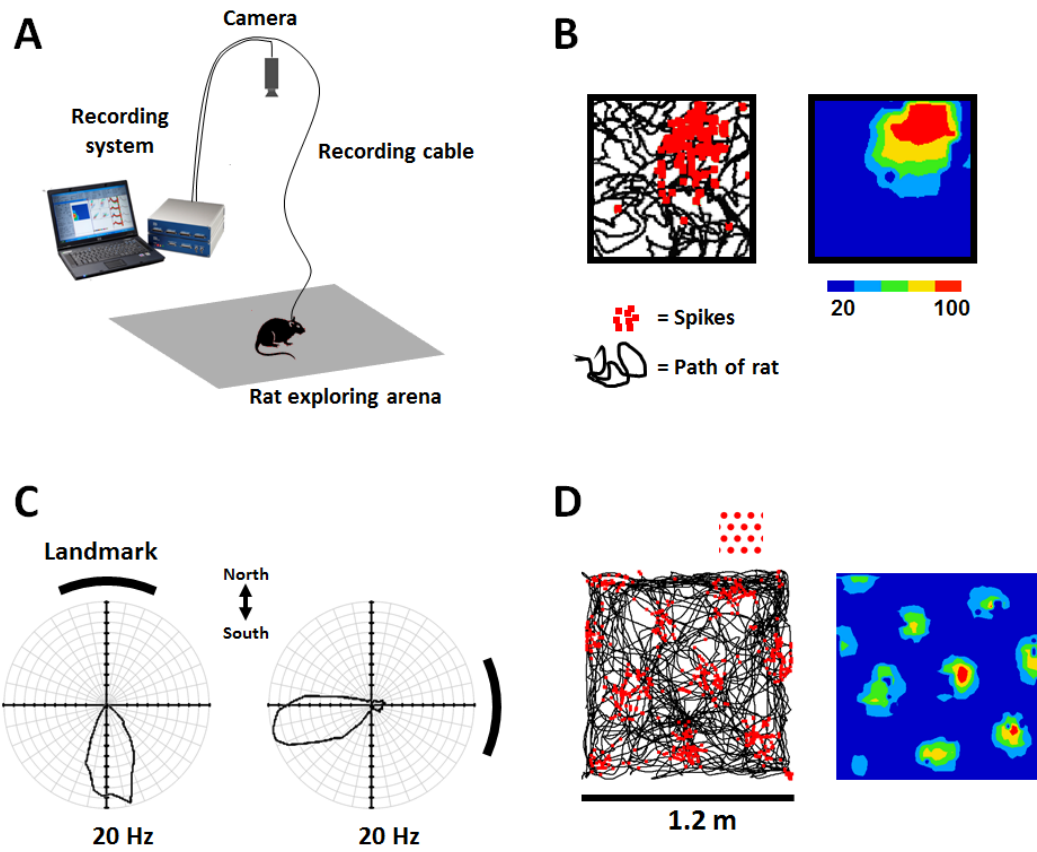1740   parasubicular connectivity see van Strien, Cappaert and Witter (2009).
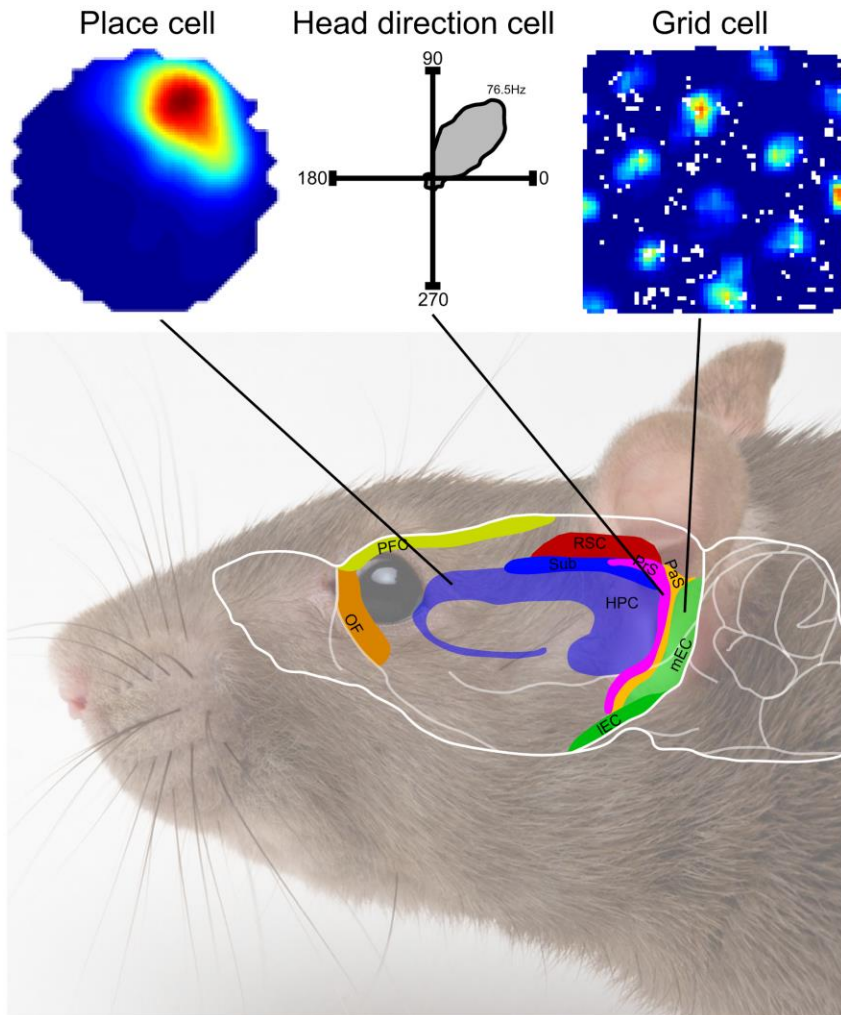
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1744   # Figures

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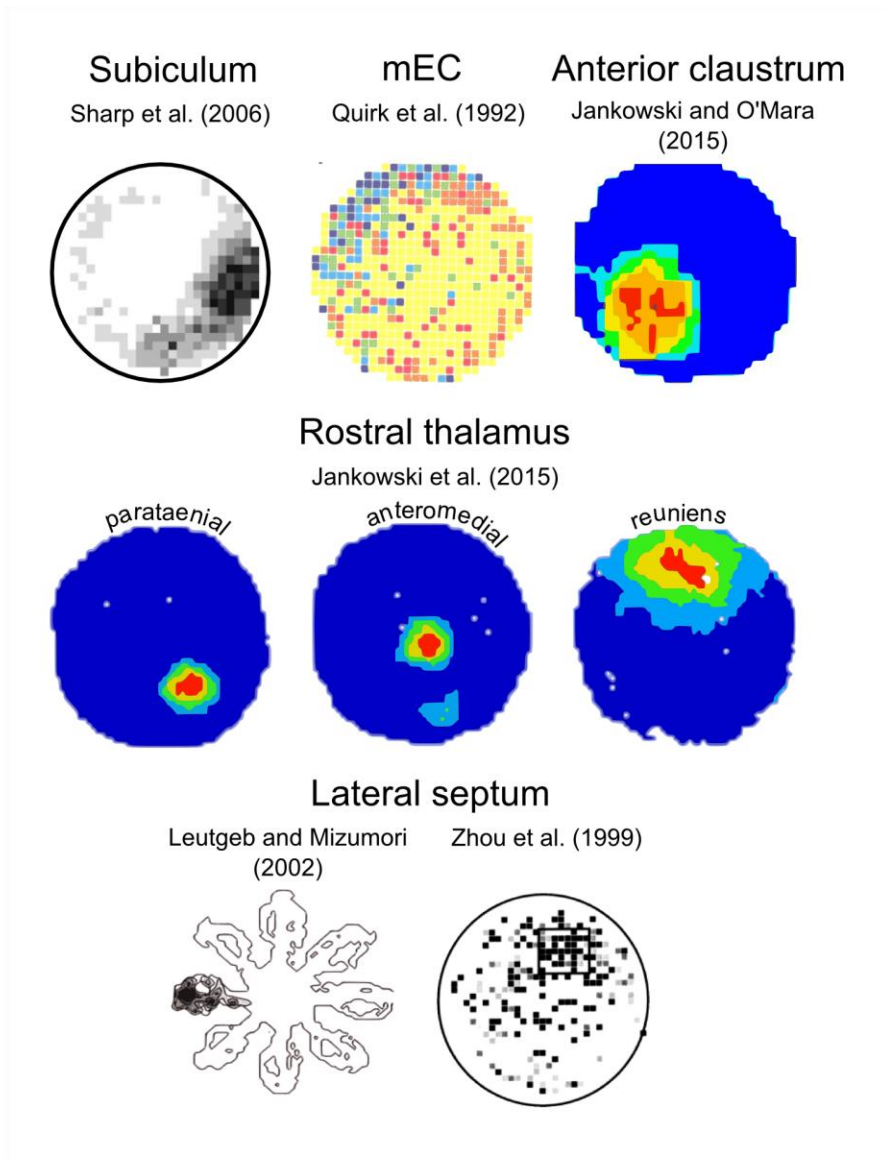1746   Figure 1
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Figure 2

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Figure 3

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Figure 5

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Medial prefrontal cortex
Hok et al. (2005)

◯ = spatial goal zone

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1764   Figure 6
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Figure 7

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1773   Figure 8
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