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# Neural representations of Euclidean space

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology  
Faculty of Medicine  
Kavli Institute for Systems Neuroscience and  
Centre for the Biology of Memory

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## Nevrale representasjoner av sted

Moderne nevrovitenskap bygger på antagelsen om at kognitive fenomener som bevissthet, hukommelse, og stedsans oppstår fra den samlede aktiviteten av individuelle nerveceller. Hjerneområdene hippocampus og entorhinal cortex (EC) er kritiske for hukommelse og stedsans hos både mennesker og dyr. Hos rotter utgjør 'stedceller' i hippocampus egne kart for hvert miljø rotta utforsker mens 'gitterceller' i EC utgjør et koordinatsystem som passer til alle miljøer.

Både kart og koordinatsystem finnes i ulike skalaer i den øverste (dorsale) delen av hjerneområdene mens det hittil har vært uklart om dypere (ventrale) deler er involvert i stedsansen. Vi angrep spørsmålet ved å måle aktiviteten i enkeltceller langs hele lengden av begge hjerneområder hos rotter som løp frem og tilbake på en 18m spesialkonstruert løpebane, og fant stedceller og gitterceller langs hele lengden av begge hjerneområdene (Artikkel II og III). Skalaen til både stedcellene og gittercellene økte fra å representere steder på mindre enn 1m i den dorsale enden til opp mot 10 meter i den ventrale enden av hjerneområdene.

Videre utviklet vi en matematisk modell for *hvordan* minnekart i hippocampus kan være knyttet til stedskoordinater i EC (Artikkel I), og kom fram til et koblingskjema mellom gitterceller og stedceller som utnytter den systematiske økningen i skala fra dorsal til ventral. Modellen stemmer godt med de anatomiske koblingene mellom EC og hippocampus, og får støtte av nye eksperimentelle data.

Til slutt undersøkte vi hvordan stedskartene i hippocampus er knyttet til miljøets utforming. Tidligere matematiske beregninger har vist at kartenes geometriske forankring kan forklares hvis det finnes en tredje celletype som signaliserer rottas avstand og retning til ulike grenser i miljøet. Vi målte aktivitet i enkeltceller i EC mens rotter utforsket miljøer med ulike geometriske former (Artikkel IV). Blant de andre celletypene fant vi en liten gruppe "grenseceller" som bare er aktive når rotta løper i nærheten av en vegg eller bordkant.

Avhandlingen fremlegger ny evidens for at beregning av hierarkisk organisert stedsinformasjon er et grunnprinsipp for hvordan hippocampus og EC fungerer (f.eks. ved behandling av minner), påviser en hittil ukjent enhet for representasjon av geometri i EC, og antyder hvordan nevralt enheter kan samhandle for å støtte opp under kognitive funksjoner som stedsans og hukommelse.

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## Summary

As cognitive phenomena are believed to arise from neural activity, uncovering how neurons represent Euclidean one- and two-dimensional space provides a foundation for understanding how the brain organizes and processes information about terrestrial objects and events. Neurons in the hippocampus and medial entorhinal cortex (MEC) of rats exhibit discrete spatial receptive fields at a scale that increases with the neuron's distance from the dorsal pole of both structures. To find out whether spatial processing is a cardinal function of these structures, we recorded neural activity along the dorsal-most 85% of the CA3 area of the hippocampus (Paper II), and dorsal-most 75% of the MEC (Paper III) while rats explored an 18m linear track. Neurons at all dorsoventral levels of both structures displayed spatial receptive fields, implying functional homogeneity within the hippocampus and MEC. Spatial scale increased from dorsal to ventral in both CA3 and MEC. In hippocampus, field length ranged from less than 1m to more than 10m. In the MEC field length ranged from less than 50cm to approximately 3m, and inter-peak distance ranged from less than 1m to at least 8m. The parallel increase in spatial scale suggests a simple transformation from the repetitive spatial metric of grid cells to the unary place-cell representation of space. Developing a mathematical firing-rate model of place-cell activity to exploit this fact, we showed that place fields can be formed from converging grid-cell inputs that cover a range of spatial scales and orientations but have an overlapping firing peak in the place-field center (Paper I). Inferring metric relationships between entities in hippocampal association maps may therefore rely on interaction with the MEC coordinate system. Because metric information is in turn contingent on the geometric layout of the external environment, we initiated a search for neural representations of geometric features in the parahippocampus. A small proportion (< 10%) of cells that discharged close to environmental borders was found in all cellular layers of MEC as well as in pre- and parasubiculum (Paper IV). 'Border cells' typically had a firing field apposing one or more walls of the recording enclosure regardless of enclosure shape, size, or which room the rat was exploring, and responded to any wall, drop, or partition that impeded the rat's exploration. Taken together, this thesis demonstrates that hierarchically organized spatial processing is an integral property of the hippocampus and MEC, extends the evidence for a modular organization of spatial cognition, and suggests how such modules may interact to support behaviorally relevant functions like spatial memory and navigation.

## List of papers

- Paper I            **From grid cells to place cells: a mathematical model**  
Solstad T, Moser EI, and Einevoll GT (2006).  
*Hippocampus*, 16, 1026-1031.
- Paper II           **Finite scales of spatial representation in the hippocampus**  
Kjelstrup KB, Solstad T, Brun VH, Hafting T, Leutgeb S,  
Witter MP, Moser EI and Moser M-B (2008).  
*Science* 321, 140-143.
- Paper III          **Progressive increase in grid scale from dorsal to ventral medial entorhinal cortex**  
Brun VH, Solstad T, Kjelstrup KB, Fyhn M, Witter MP,  
Moser EI and Moser M-B (2008).  
*Hippocampus*, 18, 1200-1212.
- Paper IV          **Representation of geometric borders in the entorhinal cortex**  
Solstad T, Boccara CN, Kropff E, Moser M-B and Moser EI (2008).  
*Science*, 322, 1865-1868.

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Trygve Solstad

Trondheim, April 2009

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# 1 Introduction

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*There are two pure forms of sensible intuition, as principles of knowledge a priori, namely space and time*

Immanuel Kant, 1781

**Ruminations on the Promethean mind of man can be traced to our prime records of human writing. Ancient Egyptian texts (3000-2600 BC) mention the relationship between injuries to the head and cognitive impairment (Wilkins, 1964; Feldman and Goodrich, 1999). Since then, mental processes have been attributed both to the heart and a non-material soul, but after 600 medieval years of subjugation to ecclesiastical dogma the theory of mind prospered anew, culminating in a ravaging controversy over the preconditions for our mental experiences in the 18<sup>th</sup> century. On one side was John Locke's contention of a 'tabula rasa', alluding to the infant mind's indiscriminate aptitude for anything presented to it, which indicated that experience is the sole determinant of human cognition. On the other side Immanuel Kant maintained the notion of a transcendental aesthetic, the firm belief that space and time are congenital categories, preconditions for experience rather than products of the faculty of mind (Hergenhahn, 2001; Serck-Hanssen, 2005). Centuries later, experimental evidence points to a localized area in the human brain whose functioning is essential for conscious processing of events in space and time (Scoville and Milner, 1957). Neural activity in a primary network of this brain area in rodents has a single physical correlate –the animal's position in space (Hafting et al., 2005), indicating the presence of a prewired spatial framework for experiencing the external world. A tractable cellular model of spatial cognition, the brain's spatial maps bear promise of exposing the relationship between space and conscious experiences, and may hold the key to revealing general neural principles underlying human cognitive function. This thesis therefore seeks to advance our understanding about neural representations of Euclidean space.**

### **1.1.1 Localization of function**

Although the faculties of the mind were known to reside in the brain already by Hippocrates (460-360 BC) and Galen (AD 130-200), the brain was considered a homogeneous organ equably processing different mental faculties well into modern times (Finger, 1994). This holistic dogma was first challenged by the anatomist Franz Joseph Gall. After comparing the cognitive strengths and weaknesses of individual subjects to the shape of their skulls and brains, he concluded that the brain consists of multiple organs with separate functions and memory systems –a contention that would soon find experimental support. However, the size of a brain region was mistakenly conjectured to shape the overlying skull in a way that revealed an individual's corresponding mental ability, popularizing the erroneous science of phrenology (Marshall and Fink, 2003). In search of experimental support for Gall's functional localism, early 19<sup>th</sup> century scientists established the gross anatomical segregation of brain function by inducing controlled brain lesions in fowls. In particular, damage to the brainstem was found to invariably cause death, damage to the cerebellum specifically affected motor coordination, whereas extensive decerebration caused a global loss of perception and cognitive functions like will and judgment (Flourens, 1824) and left the animal in a sleep-like state (Rolando, 1809). However, lack of support for a finer functional segregation of memory and cognition within the cerebrum contested the localistic standpoint.

Turning the tables for cerebral localism, histological studies of frontal-parietal lobe patients revealed an anatomical prerequisite for normal linguistic function (Bouillaud, 1825; Auburtin, 1861) which was further segregated into separate areas contributing to the production (Broca, 1863) and comprehension (Wernicke, 1874) of speech. Subsequently, an increasing number of studies reported correlations between cortical lesions and specific functional deficits. Examples include linking visual recognition with the occipito-temporal cortex (Lissauer, 1890), and praxic abilities with the parietal cortex (Liepmann, 1900). Animal models also contributed to the mapping of brain functions, for instance by disclosing a primary role for the pre-central cortex in controlling motor behavior (Hitzig and Fritsch, 1870; Jackson, 1875). By the turn of the century, many sensory and motor-related brain areas were identified, and with the neural doctrine (Ramón y Cajal, 1911) the brain's information-processing unit was established. Still, more than 50 years would pass before there was identification of a biological basis for higher cognitive processing, relying on memory for conscious experiences.

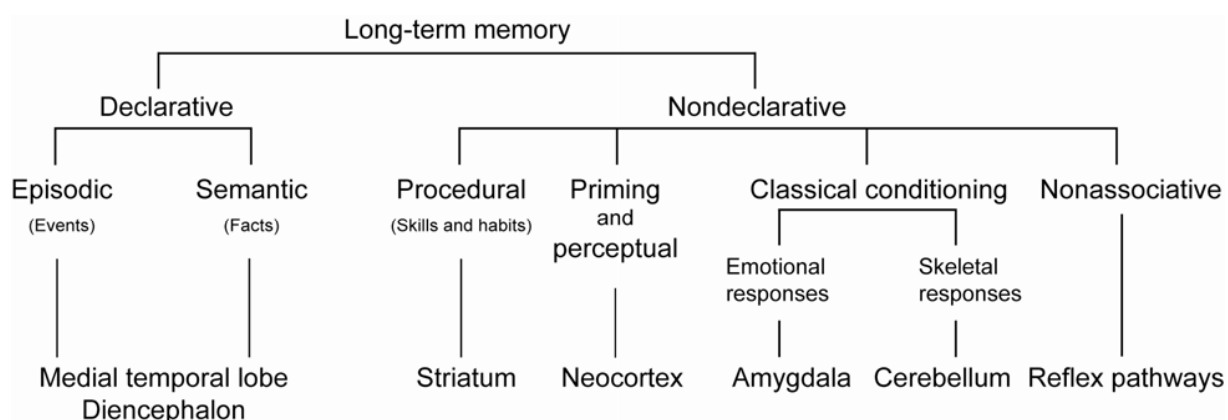
### **1.1.2 A theory of memory**

Memory can be defined as the ability to store information for later retrieval, and is a precondition for all forms of cognition and meaningful interaction with the external world. By the 1950s two main theories for the organization of memory prevailed. The first theory drew on Karl Lashley's failed quest for the 'engram', a hypothesized cortical patch containing the memory of a learned cognitive task (Lashley, 1929). After decades of making post-training lesions to different parts of the neocortex in cats, he framed the holistic concepts of 'equipotentiality', asserting that memories are dispersed across equable parts of the entire neocortex, and 'mass action' describing the observation that behavioral deficits correlated with the size rather than the locus of the lesion (Lashley, 1950).

Lashley's holistic view was opposed by an alternative theory originating with William James (James, 1890) that assumed two stages of memory-formation; a short-term system and a long-term system with a transfer function between the two. The most influential theory building on this idea is that of Donald Hebb (Hebb, 1949) which contains three main concepts. First, a group of neurons that is reliably activated by a certain external stimulus is termed a 'cell assembly' and constitutes the brain's internal representation of the stimulus. The perceived stimulus stays in short-term memory as long as activity flows through the cell assembly. Second, connections between repeatedly co-active neurons will strengthen through a physical growth process. Upon prolonged or repeated stimulus presentations this associative learning rule consolidates the internal representation into long-term memory. Subsequent presentation of an arbitrary part of the stimulus activates the entire cell assembly through the strengthened connections, effectively reinstating the original experience and defining a 'content addressable memory'. Third, Hebb speculated that activity flowing through a sequence of stored cell assemblies would correspond to a chain of thought (Hebb, 1949). Hebb's associative theory of memory formation inspired to continue the search for neural representations of external stimuli and events, and shaped a new tradition in computational theories for neural networks and representations.

The two-stage memory model implies that memories are gradually strengthened over time. Evidence that the strength of memories is temporally graded was reported already in the late 1800s after the observation that amnesic patients would more readily remember events from many years back than days-old episodes (Ribot, 1881), suggesting the gradual consolidation of

memories over time (McClelland et al., 1995; Squire and Alvarez, 1995; Meeter and Murre, 2004). Next, memory was suggested to be localized to the medial temporal lobe based on the bilateral degeneration of this structure in a severely amnesic patient (von Bechterew, 1900), followed by anecdotal reports of patients suffering temporally graded amnesia after vascular disease with appurtenant damage to the hippocampus and surrounding structures (Grunthal, 1947; Glees and Griffith, 1952; Zola-Morgan et al., 1986). The first amnesic to undergo rigorous psychophysical testing was the fatally epileptic patient H.M., who following bilateral ablation of his medial temporal lobes was relieved of seizures but at the same time entirely divested of access to subsequent conscious experiences more than a few seconds old (Scoville and Milner, 1957). H.M. learned complex motor tasks as quickly as age-matched controls, and his intelligence and short-term memory were normal, but in spite of years of routine testing, he expressed no recollection of having seen the tasks or his psychologist Brenda Milner before (Milner, 1965; Milner, 1972). Although H.M.'s lesions included the hippocampus, amygdale, and surrounding cortex (Corkin et al., 1997), his selective memory deficits are now considered characteristic of damage to the hippocampus (Zola-Morgan and Squire, 1986; Teng and Squire, 1999; Rosenbaum et al., 2000) and the parahippocampal area (Rempel-Clower et al., 1996; Bohbot et al., 1998). The study of amnesic patients confirmed William James' idea of distinct short-term and long-term memory systems, and meant a breakthrough for localism that has inspired the present taxonomy of memory systems (Figure 1).



**Figure 1.** Taxonomy of memory systems and their assumed anatomical origins (adapted from Squire, 2004).

Several independent or semi-independent memory systems have now been revealed, many of which we do not have conscious access to, like motor tasks, habit learning, and conditioned responses. Memory for information we cannot readily express verbally is termed ‘non-declarative memory’. Hippocampal damage selectively affects memory for information we have conscious access to, termed ‘declarative memory’. Declarative memory is again classified as either ‘semantic memory’ –memory for facts and lexical information, or ‘episodic memory’ – memory for events in space and time (Squire, 2004). In philosophical retrospect, the hippocampus seems to hold the key to processing information with a bearing on Kant’s pure forms of sensible intuition.

## 1.2 Spatial Cognition

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*...learning consists not in stimulus-response connections but in the building up in the nervous system of sets which function like cognitive maps*

Edward Tolman, 1948

Although hippocampal contribution to semantic memory has been debated (Vargha-Khadem et al., 1997; Squire and Zola, 1998; Tulving, 2002), functional brain imaging provides strong evidence for selective activation of the hippocampus and parahippocampus in encoding (Henke et al., 1997; Davachi and Wagner, 2002; Zeineh et al., 2003) and retrieval (Eldridge et al., 2000; Sperling et al., 2003) of multimodal associations, and hippocampal involvement in episodic memory is now indisputable. Finding good measures for episodic memory is problematic however, because even if people can report what they remember, what they don't remember is not easily surveyed (Knowlton and Fanselow, 1998). Decomposing episodic memory into 'what', 'where', and 'when' components (Tulving, 2002), the 'where' component is referred to as 'spatial memory'. Spatial memory is readily operationalized using navigational tasks due to its relation to a single physical variable (position), and is therefore a tractable model for episodic memory both in human and non-human subjects.

### 1.2.1 Spatial memory

Consistent with the view that space is an integral component of episodic memory (Tulving, 2002), damage to the human hippocampus also affects spatial memory (Teng and Squire, 1999). Brain imaging (MRI) of London taxi drivers has also revealed a significant correlation between hippocampal volume and professional experience (Maguire et al., 2000), and specific activation of the right hippocampus has been reported for London taxi drivers asked to recall complex routes from a virtual reality city during functional brain imaging (PET) (Maguire et al., 1997). Furthermore, given four alternatives, the location of a subject navigating a virtual reality arena could be accurately predicted on the basis of fMRI scanning of the subject's MTL (Hassabis et al., 2009). The predictive power of such coarse-scale functional brain imaging indicates that different positions are encoded in separate local neural circuits within the MTL. This notion

supplements reports of single hippocampal neurons recorded from epileptic patients waiting for brain surgery, that respond selectively to spatial locations in a virtual reality city irrespective of spatial view (Ekstrom et al., 2003).

In the absence of language, spatial memory is a particularly useful model for episodic memory in animals. Animals boast excellent spatial memory, exemplified by the ability of both birds and mammals to keep track of a large number (tens of thousands for some species) of food-caching sites over the course of weeks and months on the basis of distal cues and configurations of landmarks (Vander Wall, 1990; Jacobs and Liman, 1991; Jacobs, 1992; Sherry and Duff, 1996), proving animal navigation an attractive gateway to understanding spatial cognition.

### **1.2.2 Navigation**

Navigation can be defined as the ability to plan and execute a goal-directed path. Determining one's orientation and one's position relative to external reference points are essential prerequisites for this ability (Gallistel, 1990). To uniquely define orientation and position in an environment, at least three reference points in space are required. When given a constant start orientation as reference, animals can also be trained to find a goal positioned relative to one or two points in space, and if reward location is defined by two (or three) similar landmarks, gerbils will search at two (or three) locations if all but one landmark are removed (Collett et al., 1986). This illuminates the power of establishing a global reference frame to resolve situations in which position is underdetermined by local landmarks. When disoriented before performing a similar task, rats are unable to discern between rotationally equivalent positions even in the presence of a polarizing cue card (Biegler and Morris, 1993; Biegler and Morris, 1996), suggesting that the geometric layout of the environment is a prime determinant of the global reference frame.

### **1.2.3 Geometric determinants of orientation**

Already Watson (1907), Tolman (Tolman and Honzik, 1930) and Hebb (1949) noted that rats rely on distal cues to define their frame of reference, but the relation to geometry was first explored by Cheng (1986) who discovered that rats searching for a previously disclosed reward location in a rectangular enclosure made systematic rotational errors after rotating the enclosure relative to the featureless room, even in the presence of differentiating feature cues, like odors or textures in the corners or color of the enclosure walls. Similar results were obtained when rats were disorientated between each trial (Margules and Gallistel, 1988), effectively controlling for



the possibility that rats just follow a motor-sequence strategy. Subsequently, the ability to rely on both featural cues and surface geometry to define a reward location in a rectangular enclosure has been attested for a wide range of species, including fish (Sovrano et al., 2002), chicks (Vallortigara et al., 1990), pigeons (Kelly et al., 1998), rhesus monkeys (Gouteux et al., 2001), human children (Hermer and Spelke, 1994; Gouteux and Spelke, 2001), and human adults (Hermer-Vazquez et al., 1999).

Both rats (Benhamou and Poucet, 1998) and children (Gouteux and Spelke, 2001) are also able to extract geometry from the configuration of local landmarks to define a global reference frame. Rats would for instance ignore the distinctive features of local cues and make rotational errors when searching for a goal location uniquely defined by three distinct landmarks when they were arranged as an *equilateral* triangle, but unmistakably located the goal when the landmarks were rather arranged as an *isosceles* configuration, geometrically defining a reference orientation.

Although the geometry of boundaries (Cheng, 1986; Biegler and Morris, 1993; Biegler and Morris, 1996; Gouteux et al., 2001) or landmark configuration (Benhamou and Poucet, 1998) has frequently been shown to overshadow disambiguating features of visual and tactile cues, the dominating cue may also depend on prior experience when geometric and featural information is conflicting (Cheng and Newcombe, 2005). Nevertheless, the fact that animals are confused in geometrically ambiguous environments with disambiguating featural cues implies that the underlying representation of space must somehow be strongly tied to the geometric features of the environment. Thinking along these lines, Gallistel (1990) concluded that geometry may be used to extract the axes of the allocentric reference frame, defining the direction of heading, and hypothesized that processing of geometrical information constitutes a separate cognitive module.

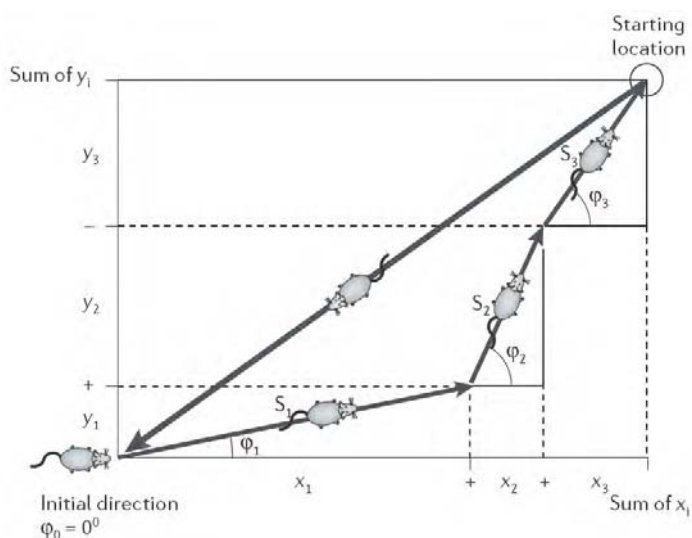
## **1.2.4 Measuring distance**

### ***1.2.4.1 Piloting***

In the presence of disambiguating landmarks an animal will normally infer its position from the perceived distance from these cues, which can be referred to as landmark-driven navigation or ‘piloting’ (Griffin, 1955). The capacity of chimpanzees to collect several pieces of food reward in random order after having passively observed an experimenter hide the food (Menzel, 1973), illustrates the use of piloting to encode reward locations.

### 1.2.4.2 Path Integration

Most species, from insects to humans, are also able to keep track of their own position relative to a reference point, like a nest, without the aid of landmarks (Etienne and Jeffery, 2004). Navigation based entirely on self-motion information is referred to as ‘dead reckoning’ (Griffin, 1955) or ‘path integration’ capturing the concept of calculating a homing vector by continuous summation of movement vectors (Figure 2; Mittelstaedt and Mittelstaedt, 1980), and may provide a mechanism to estimate position within an environment in the interim absence of external sensory input, for instance in darkness (Gallistel, 1990). An impressive expression of this navigational function is found in the desert ant, *Cataglyphis fortis*, which can return directly to its nest after travelling hundreds of meters through featureless terrain (Wehner and Srinivasan, 1981). Rodents also show high proficiency at path integration, demonstrated by secretly rotating a dark arena while animals randomly search for a hidden target. When the animal finds its goal, it can take a straight route home that deviates only by the angle of arena rotation, effectively controlling for the use of external cues (Etienne et al., 1996; Benhamou, 1997; Whishaw and Maaswinkel, 1998; Alyan and McNaughton, 1999; Maaswinkel et al., 1999). Path integration-based navigation is particularly error prone, and in the absence of external anchoring points animals make systematic errors in their homing-vector calculations that are remarkably similar across species (Muller and Wehner, 1988; Seguinot et al., 1993; Etienne et al., 1998; Seguinot et al., 1998). To counter the accumulation of error, animals therefore use landmarks to reset their path integrator (Etienne et al., 2004), and rely on external cues rather than self-motion information when the two distance estimates are conflicting (Etienne et al., 1998).



**Figure 2.** Path integration. In the absence of external landmarks, a rat can keep track of its position relative to a starting location by continuous addition of movement vectors ( $S_1$ ,  $S_2$ ,  $S_3$ ) derived from its own locomotion (McNaughton et al., 2006).

### **1.2.5 Defining position**

Distance information from both piloting and dead reckoning can be used to define position relative to an egocentric reference frame (taxon space) or an allocentric reference frame (locale space). In an egocentric reference frame an animal's position is defined relative to specific objects in the environment, yielding different coordinate systems for different objects. Navigation based on an egocentric reference frame includes following learned routes or performing learned sequences of motor actions between specific landmarks. In an allocentric reference frame the spatial relations between a rich set of cues define a global coordinate system in which the animal's position is uniquely determined independent of the position of specific objects. Navigation within an allocentric reference frame implies the use of a spatial map (O'Keefe and Nadel, 1978; Redish, 1999).

#### ***1.2.5.1 Egocentric reference frames and behaviorism***

When the distance between two defining landmarks in the experiment by Collett and colleagues (1986) was doubled, gerbils searched for the goal in two locations defined by the distance from either landmark, indicating an egocentric encoding of the goal location. Studies of route learning through simple mazes in the early 1900s provided abundant evidence that animals can use egocentric navigational strategies like making appropriate left or right responses to solve spatial problems (Small, 1901; Watson, 1907; Hunter, 1940). This encouraged John Watson to found the school of Behaviorism, claiming that all behavior can be explained by environmental events and redefining the goal of Psychology from the description and explanation of conscious phenomena to the prediction and control of behavior – ideas that dominated the field of animal cognition for the first half of the 20<sup>th</sup> century (Watson, 1913; Hergenhahn, 2001). In particular, behaviorist theory implied that rats rely exclusively on stimulus-response association pairs to find their way through a variety of mazes. Several anomalies in this theory were evident however. The observation that animals carry out spontaneous 'purposive behaviors' in the absence of environmental stimulation suggested that behaviorism omitted important aspects of animal behavior (McDougall, 1923). This omission from behaviorist theory was tried remedied by including intervening physiological variables between the stimulus and response (Hull, 1952), so that the probability of a response was contingent on the net effect of presented stimuli and intervening variables like habits and biological needs that caused a drive to obtain reinforcement. However, Hull's addendum to behaviorism could not alleviate the inability of rats to employ

egocentric strategies when solving problems when the egocentric reference frame conflicted with the allocentric bearing of surrounding landmarks (Watson, 1907; Hunter, 1920).

#### ***1.2.5.2 Allocentric reference frames and cognitive maps***

Shortcomings of behaviorist theory became prominent when animal behavior was analyzed in situations where the triggering stimulus could not easily be identified. For example, the long-range homing of migrating birds over distances far outreaching the range of their sensory systems (Watson and Lashley, 1915) seemed to require a ‘compass and map’-strategy (Kramer, 1953) rather than learned responses to particular stimuli. Furthermore, manipulating spatial properties like distal visual cues occasionally disrupted rats’ ability to locate a goal location in a previously learned maze (Watson, 1907; Tolman and Honzik, 1930), even if reward was only obtained by following a defined ‘temporal’ sequence of left and right turns (Hunter, 1920).

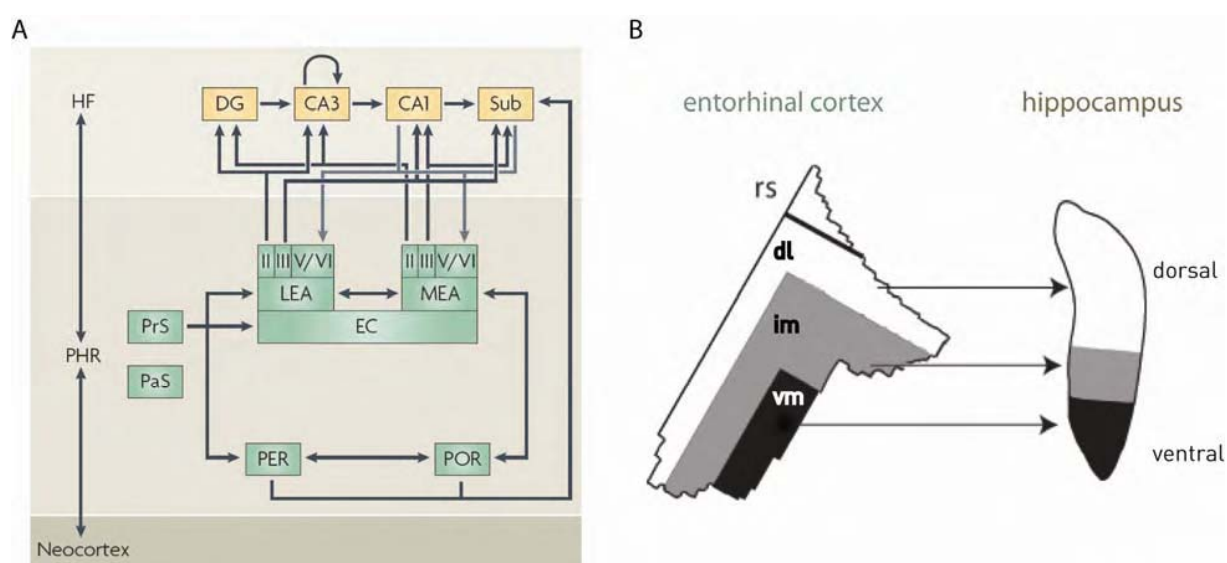
Eventually puncturing the contemporary view on animal learning, Edward Tolman demonstrated that rats would choose the shortest of several available routes in a previously visited maze and readily exploited novel shortcuts when available. Inferring the shortest of multiple unfamiliar routes is incompatible with the use of a behaviorist stimulus-response strategy, which would require the rat to traverse all available routes before deciding which one is shorter. Rather, Tolman argued that animals store a ‘cognitive map’ of their environment that they can later flexibly use to navigate (Tolman, 1948). The capacity of rats to infer novel shortcuts even in the absence of familiar external cues (Zanforlin and Poli, 1970) shows that an established cognitive map can guide both piloting and path integration-based navigation.

If animals solve spatial problems on the basis of a stored map of the environment, the map must be contained within some area of the brain. The disruption of access to episodic and spatial memory in humans following hippocampal damage posits a strong candidate for such a locus.

## 1.3 The hippocampus and surrounding cortices

### 1.3.1 Anatomical overview

A site of anatomical convergence seen nowhere else in the brain, the hippocampus is the first stage of neural processing with access to information from all sensory modalities, reflecting the characteristic multimodal cognitive deficits observed following hippocampal damage (Squire et al., 2004; Witter and Amaral, 2004). Hippocampus is Latin for ‘sea horse’, alluding to its curved and folded shape in the human brain (Amaral, 1987). The hippocampal formation is located in the gyrus hippocampi and consists of the dentate gyrus (DG), hippocampus proper, and the subiculum. Being a part of the allocortex, a phylogenetically old structure common to all mammals, the hippocampal formation is a three-layered structure distinguishing it from the surrounding neocortex which can generally be subdivided into six histologically identifiable layers (Amaral, 1987; Witter and Amaral, 2004).



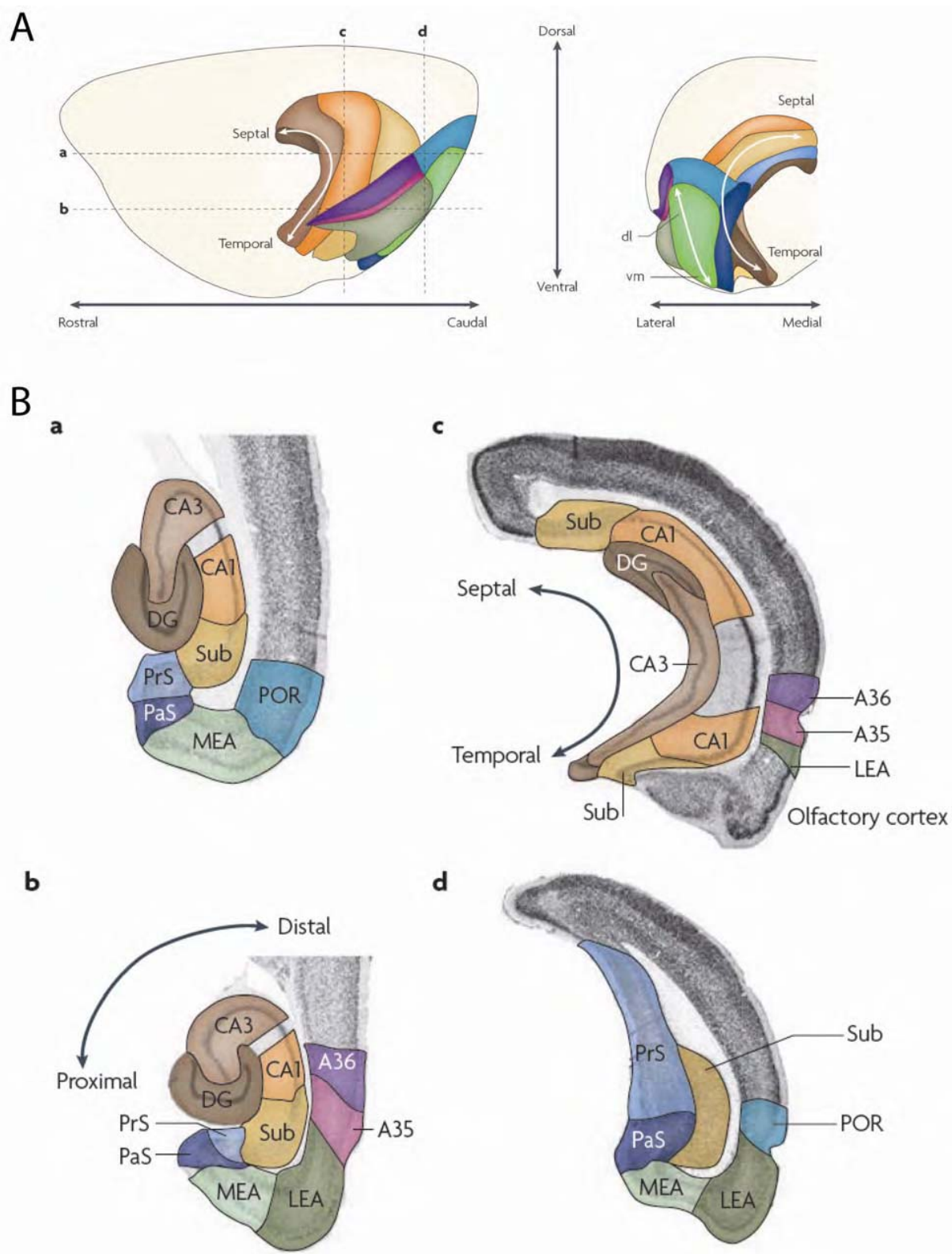
**Figure 3.** Hippocampal projections. **A.** Wiring diagram of the hippocampal formation (HF) and parahippocampal region (PHR). PER: perirhinal cortex. POR: postrhinal cortex. PaS: parasubiculum. PrS: presubiculum. EC: entorhinal cortex. LEA: lateral entorhinal area. MEA: medial entorhinal area. Roman numerals: cellular layers of the EC. DG: dentate gyrus. Sub: subiculum. (van Strien et al., 2009). **B.** Dorsoventral gradient of the perforant path projections from entorhinal cortex to hippocampus. rs: rhinal sulcus. dl: dorsolateral band. im: intermediate band. vm: ventromedial band. (Adapted from Dolorfo and Amaral, 1998).

The rat hippocampus has a stretched C-shape extending from the septal nuclei in the rostradorsal tip to the temporal cortex in the ventrocaudal end. This extension is referred to as the longitudinal, septotemporal, or dorsoventral axis of the hippocampus. The ‘transversal axis’ runs perpendicular to the dorsoventral axis. The hippocampal formation is organized as a unidirectional excitatory circuit laid out in the transversal plane (Andersen et al., 1971). The circuit starts in the superficial layers of the entorhinal cortex (EC), and runs sequentially through the DG, the CA3 and the CA1 areas of the hippocampus proper, to terminate in the subiculum. The subiculum mainly projects back to the deep layers of the entorhinal cortex, effectively closing an excitatory loop of information flow (Figure 3a). The tri-synaptic circuitry (DG-CA3-CA1-subiculum) characterizes the entire longitudinal axis of the hippocampal formation although longitudinal projections are also clearly present (Witter and Amaral, 2004).

In addition to the dorsal and ventral commissures that connect hippocampal areas between hemispheres, communication with the hippocampus is mainly routed through two fiber systems. Long believed to be the sole pathway for hippocampal output, the fimbria fibers assemble along the lateral surface of the dorsoventral axis. In the dorsal end they transition into the fornix that bidirectionally connects the hippocampus with the basal forebrain, hypothalamic and brain stem regions. Of special interest to our treatment of spatial cognition however, neocortical information is primarily conveyed through the angular bundle which connects the hippocampal formation to the entorhinal cortex, presubiculum and parasubiculum, and connects the entorhinal cortex to a variety of cortical and subcortical areas (Witter and Amaral, 2004; Amaral and Lavenex, 2007).

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**Figure 4** (opposite page). Anatomical organization of the hippocampal formation and the parahippocampal region. The hippocampal formation consists of the dentate gyrus (DG; dark brown), CA3 (medium brown), CA2 (not indicated), CA1 (orange) and the subiculum (Sub; yellow). The parahippocampal region comprises the presubiculum (PrS; medium blue), the parasubiculum (PaS; dark blue), the lateral (LEA; dark green) and the medial (MEA; light green) entorhinal cortex, the perirhinal cortex consisting of Brodmann areas (A) 35 (pink) and 36 (purple), and the postrhinal cortex (POR; blue-green). **A.** Sagittal view of the rat brain. **a** and **b** correspond to horizontal sections and **c** and **d** to coronal sections displayed below. **B.** Sections of the rat brain corresponding to the lettering on the sagittal illustration in the top pane. **a** and **b**: horizontal sections taken at different dorsoventral levels. **c** and **d**: coronal sections taken at different rostrocaudal levels.



All subfields of the hippocampal formation are directly targeted by the EC through the perforant path, a part of the angular bundle that perforates the subiculum. Especially prominent at dorsal levels, entorhinal projections also reach the hippocampus through the temporoammonic alvear pathway. Return projections to the entorhinal cortex exclusively originate in the CA1 and subiculum. Projections from the EC are topographically organized along the longitudinal axis, connecting any point on the long entorhinal axis to approximately one fourth of the long hippocampal axis, and leaving virtually no direct communication between the dorsoventral extremes (Figure 3b; Dolorfo and Amaral, 1998; Witter and Amaral, 2004). Entorhinal cortex directly or indirectly interfaces the hippocampal formation with most areas of the neocortex, and together with the perirhinal cortex, postrhinal cortex, and pre- and parasubiculum constitute the parahippocampal area (Burwell and Amaral, 1998b; Burwell, 2000; Witter et al., 2000). Also cytoarchitectonically the entorhinal cortex is a transition area between allocortex and neocortex. The structure has 6 identifiable layers like the neocortex, but they show a slightly different organization, the most prominent difference being a cell-free layer IV, termed 'lamina dissecans'. As layer I mostly consists of axonal fibers, the entorhinal cortex has four layers of principal neurons, the superficial layers II and III, and the deep layers V and VI (Witter and Amaral, 2004). Intrinsic entorhinal connections mainly originate in the deep layers and terminate in layer III (van Haeften et al., 2003).

The medial entorhinal cortex (MEC) can be distinguished from the lateral entorhinal cortex (LEC) on the basis of cytoarchitecture and extrinsic connections with neocortical areas (Witter and Amaral, 2004). The LEC is strongly innervated by the perirhinal cortex and, directly or indirectly, the frontal, piriform, insular, olfactory and temporal cortices (Deacon et al., 1983; Burwell and Amaral, 1998a), structures largely thought to convey non-spatial information about the surroundings (Hargreaves et al., 2005). In contrast, the MEC is innervated by the occipital, retrosplenial, and parietal cortices directly or through strong connections with the postrhinal cortex (Burwell, 2000), structures involved in processing visuospatial information. The MEC is also the main terminal of dense projections from the dorsal presubiculum and parasubiculum which communicate movement-related information from the retrosplenial cortex and anterior thalamus (van Groen and Wyss, 1990; Chen et al., 1994; Taube and Muller, 1998).



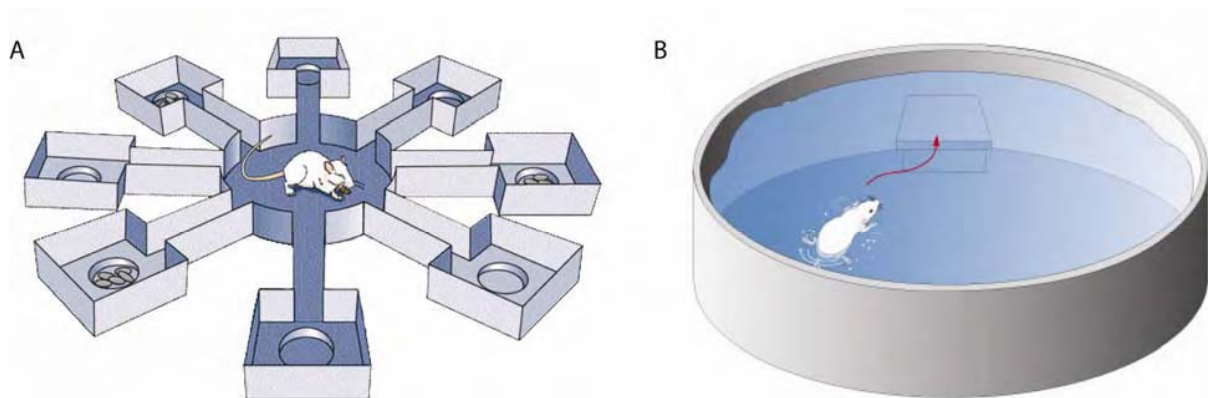
## 1.3.2 Hippocampal function

### 1.3.2.1 *Spatial tasks*

If the hippocampus contains allocentric spatial maps of the animal's environment, a primary prediction is that damage to the hippocampus leads to a disruption of navigational problems requiring an allocentric representation of space (O'Keefe and Nadel 1978). The effect of hippocampal lesions on maze learning in rats was already explored in the sixties (e.g. Hughes, 1965), but the first task designed to test the spatial map hypothesis was the radial arm maze in which the animal is required to collect food hidden at the end of several arms radiating from a central platform (Olton and Samuelson, 1976) (Figure 5a). Whereas normal rats quickly learn to visit each arm only once, rats with lesions to up- or down-stream structures of the hippocampus would persistently visit arbitrary arms without regard to their reward status (Olton, 1977). Long-term memory of spatial relations was tested in a version of the task where only a subset of the arms was associated with food reward. Rats that received fornix lesions after learning which arms were baited still revisited arms they had already collected the food from, but were able to avoid non-baited arms (Olton and Papas, 1979). This result was taken to indicate that the hippocampus is only involved in short-term "working" memory, keeping track of which arm had been visited within each trial, whereas the long-term storage of a cognitive map is encoded elsewhere since rats remembered which arms were not baited even with a disconnected hippocampus. However, although fornix-lesioned rats seemed to preserve long-term retention of the location of non-baited arms, the hippocampus was shown to be essential for the acquisition of the task (Jarrard, 1978; Jarrard et al., 1986). It is now clear that fornix lesions do not disconnect the hippocampus from relevant neocortical areas targeted through the angular bundle and entorhinal cortex (Witter and Amaral, 2004). There has also been thrown doubt on the necessity of relying on a spatial map to solve the radial arm maze, as memory of the allocentric orientation, not exact position, of the reward location is sufficient for high task performance (Brown, 1992; Brown et al., 1993), and controlling for the use of sequence strategies and intra-trial odor cues in this task is nontrivial.

Alleviating some of these issues, the water maze task was also designed to test the cognitive map hypothesis. On the basis of distal cues, a rat is trained to find a submerged platform in a circular pool filled with opaque water that masks local cues (Figure 5b). Normal rats rapidly learn to approach the platform in a straight trajectory regardless of starting position (Morris, 1981),

requiring a map-like strategy. With practice, rats can learn a new platform location in a familiar environment in a single trial (Morris et al., 1986), indicative of a snapshot-type memory (Gaffan, 1994). Complete hippocampal lesions render rats unable to learn the water maze task unless the platform position is visually revealed (Morris et al., 1982; Morris et al., 1990). Hippocampal lesions also disrupt retention of the platform location in rats that have already acquired the water maze task (Morris et al., 1982), even after extensive pretraining (Clark et al., 2005; Solstad, 2005). The inability to keep track of previously visited goal locations in the water maze and other allocentric spatial problems after hippocampal damage is consistent with the theory that the hippocampus stores spatial maps (O'Keefe and Nadel, 1978). However, lesions restricted to the medial entorhinal cortex have produced deficits comparable to those of hippocampal lesions both to acquisition (Schenk and Morris, 1985; Nagahara et al., 1995; Galani et al., 1997; Eijkenboom et al., 2000; Parron et al., 2004) and retrieval (Steffenach et al., 2005) of spatial memory tasks. Both structures therefore seem necessary for spatial memory.



**Figure 5.** Navigational tasks for investigating spatial cognition. **A.** A subset of the arms in the radial arm maze contains hidden food rewards. The rat is required to collect food from the baited arms. The number of re-entries to baited arms where food has been collected provides a measure of intra-trial “working” memory, whereas the number of entries to non-baited arms provides a measure of inter-trial “spatial reference” memory (Olton et al., 1979). Adapted from Pinel (2000). **B.** The water maze consists of a pool of opaque water with a submerged goal-platform. The rat is required to find the platform on the basis of distal visual cues, and its performance can be measured as latency to reach the platform, or time searching in the platform zone on retention trials where the platform has been removed (from Bear et al., 2007).

### **1.3.2.2 Memory vs Navigation**

To solve the water maze task, rats need both memory of the goal location and the ability to navigate towards that goal. The prominent spatial impairment seen in the water maze after damage to the hippocampus or parahippocampus might therefore be due to a disruption of navigational abilities rather than spatial memory (Whishaw et al., 1995). Path integration is significantly impaired after selective neurotoxic lesions of either the fimbria fornix, the hippocampus proper (Whishaw and Maaswinkel, 1998; Maaswinkel et al., 1999; Whishaw and Gorny, 1999), the entorhinal cortex, or the parietal cortex in rats (Parron et al., 2001; Parron and Save, 2004). Because the EC gates information to and from the hippocampus, the selective contribution of these structures to either memory or navigation is not easily determined. In some cases path integration is reported to be preserved after hippocampal damage (Alyan and McNaughton, 1999; Shrager et al., 2008). Moreover, the CA1 field of the hippocampus is necessary to recognize the goal location in an annular water maze task where navigation is not required (Hollup et al., 2001a; Brun et al., 2002), indicating that recognition memory is located in the hippocampus rather than the parahippocampus. Because the hippocampus is necessary to generalize a geometrically defined position across environments of different shapes (Tommasi and Save, 2005) and to define an allocentric reference based on the geometry of the enclosure (Jones et al., 2007), the hippocampus may be required to relate distance information to the surrounding cues, whereas navigational computations are of extra-hippocampal origin (O'Keefe, 1976; Redish, 1999).

### **1.3.2.3 Non-spatial tasks**

Human amnesia following hippocampal damage is characterized by the loss of episodic memories where spatial impairment is only a subcomponent, suggesting that hippocampal function extends past spatial mapping. Indeed, animals with selective neurotoxic lesions of the hippocampal formation are also impaired on a range of non-spatial tasks, like acquiring socially transmitted food preferences (Bunsey and Eichenbaum, 1995; Winocur et al., 2001), temporal trace conditioning (Takehara et al., 2002), and odor-sequence learning (Agster et al., 2002; Fortin et al., 2002; Kesner et al., 2002). In addition, rats with complete hippocampal lesions show markedly reduced fear-related responses, expressed as reduced food neophobia (Jarrard, 1968; Krane et al., 1976; Miller et al., 1986) and reduced freezing to the smell of a cat (Blanchard and Blanchard, 1972). The conjoint spatial and non-spatial impairments following

hippocampal damage supports a general role for the hippocampus in episodic-like memory, both in animals and humans (Lipton and Eichenbaum, 2008).

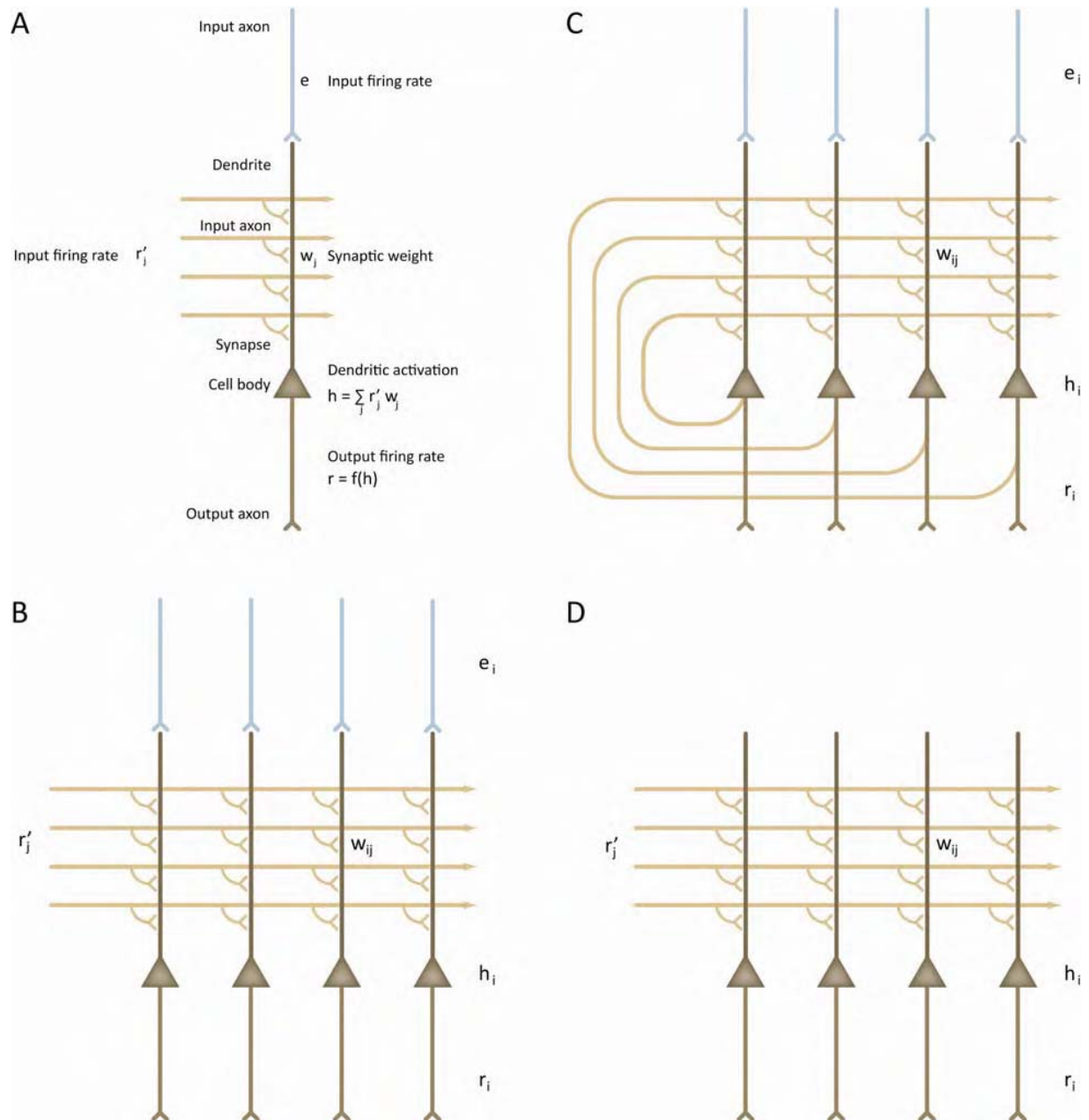
#### ***1.3.2.4 Functional segregation within the hippocampus***

Although hippocampal involvement in episodic memory is undisputed, there is also evidence that processing of the different components of episodic memory is segregated within the hippocampus. Most notably, damage to the dorsal, but not the ventral, hippocampus in rats has proven sufficient to induce amnesia for the route through a maze (Hughes, 1965; Sinnamon et al., 1978) or the goal location in the water maze (Moser et al., 1993; Moser et al., 1995). Selective lesions of the ventral hippocampus of rats block a variety of unconditioned fear reactions, including freezing behavior to cat odor or electric foot shock, avoidance of conspecifics in the social interaction test, open-arm avoidance in the elevated plus maze test, novel food avoidance in an unfamiliar environment, light-avoidance in a two-compartment light-dark box, and defecation in the open field test (Hock and Bunsey, 1998; Bannerman et al., 1999; Bannerman et al., 2002; Kjelstrup et al., 2002; Bannerman et al., 2003; McHugh et al., 2004; Pentowski et al., 2006). If there is a dorsoventral segregation of spatial and non-spatial processing, there must be an anatomical dividing line between the two regions. Indications that the dorsal-most two thirds of the hippocampus are indispensable for solving the water maze task (Moser and Moser, 1998b), while the ventral third is essential for the expression of emotional responses (Kjelstrup et al., 2002) are in agreement with the differential extrinsic anatomical connectivity of dorsal and ventral hippocampus (Chapter 1.3.1). A similar trend is seen for the entorhinal cortex, where dorsolateral lesions lead to inability to learn the water maze task, whereas ventromedial lesions do not affect performance in that task (Steffenach et al., 2005). It might therefore be that the ‘what’, ‘where’, and ‘when’ components of episodic memory (Tulving, 2002) are processed by different anatomical circuits within the hippocampus, somewhat at odds with the concept of episodic memory arising from multimodal cell-assembly-like associations within the hippocampus. In papers II and III we investigated whether spatial information is processed only in the dorsal parts or along the entire dorsoventral axis of both the hippocampus and MEC.

### **1.3.3 Computational network models of episodic memory**

#### ***1.3.3.1 Theoretical framework***

Building on hippocampal anatomy and Hebb's theory for associative learning, David Marr presented a pioneering network theory for the function of the hippocampus (Marr, 1971; Willshaw and Buckingham, 1990), in which he laid out the fundamental mathematics describing an implementation of associative memory in a network of hippocampal neurons. Theoretical analysis of binary networks with feed-forward (Willshaw et al., 1969) and recurrent (Kohonen, 1972; Gardner-Medwin, 1976; Hopfield, 1982) connections subsequently offered quantitative rigor to the proposed mechanisms behind memory for discrete associations (e.g. associations between objects), and have been developed into a computational framework for analyzing hippocampal operation with the extension to networks processing continuous (spatial) variables (Samsonovich and McNaughton, 1997; Rolls et al., 2002). The framework builds on the identification of three neural architectures that can be built from firing-rate neurons with associatively modifiable synapses and a local (Hebbian) learning rule (Figure 6; Rolls and Treves, 1998).



**Figure 6.** Network architectures implementing a local learning rule, inspired by the hippocampal subfields.  $e$ : firing rate of unconditioned input used during learning.  $r'_j$ : firing rate of the  $j^{\text{th}}$  conditioned input.  $w_{ij}$ : synaptic weight between input neuron  $j$  and output neuron  $i$ .  $h_i$ : somatic activation of  $i^{\text{th}}$  output neuron.  $f(\cdot)$ : non-linear or threshold-linear activation function.  $r_i$ : firing rate of  $i^{\text{th}}$  output neuron. **A.** Pattern associator with a single output neuron. **B.** CA1 pattern association network. **C.** CA3 autoassociation network. **D.** DG competitive network. Adapted from Rolls and Treves (1998).

### 1.3.3.2 CA1

Void of associational connections, the 400,000 pyramidal cells in CA1 (Amaral et al., 1990; Rapp and Gallagher, 1996) are organized as a one-layered feed-forward network. Although inhibitory interneurons are also present (Witter and Amaral, 2004), the CA1 essentially resembles a pattern association network (Rolls and Treves, 1998). Associations can be stored in the synaptic matrix arising from unidirectional projections from the CA3 and layer III of the entorhinal cortex that make connections on the apical and basal parts of the CA1 dendrites respectively. A possible functional role of the CA1 has been suggested to be retrieval of EC activity on the basis of a retrieved activity pattern from the CA3 (McClelland et al., 1995), although the architecture also supports learning of temporal relationships between patterns either from the CA3 or EC, important to the computation of prediction (Treves and Rolls, 1994; Rolls and Kesner, 2006). Behavioral evidence support that the CA1 but not the CA3 is required for rats to learn associations separated by a time interval for non-spatial tasks (Huerta et al., 2000; Kesner et al., 2005), but for spatial tasks both areas are required for sequence memory (Lee et al., 2005; Hoang and Kesner, 2008).

The computational capacity of a ‘pattern associator’ (Figure 6B) is limited to storing classical-conditioning-like associations between patterns of activity coming in from its afferent structures.

The firing rate of the  $j^{\text{th}}$  input neuron is denoted  $r'_j$ , and the firing rate of the  $i^{\text{th}}$  output neuron is denoted  $r_i$ . Synaptic weight,  $w_{ij}$ , denotes the strength of connection between input neuron  $j$  and output neuron  $i$ . Learning an association between unconditioned input-vector  $\mathbf{e}$  and conditioned input  $\mathbf{r}'$  is modeled as a change of synaptic weight,  $\delta w_{ij}$ , given the unconditioned response  $\mathbf{r} = g(\mathbf{e})$ , where  $g$  is the identity function or a linear function:

$$\delta w = k \mathbf{r} \mathbf{r}'; \quad \text{where } k \text{ denotes the learning rate}$$

Subsequent recall of the conditioned response,  $\mathbf{r} = g(\mathbf{e})$ , from the conditioned input  $\mathbf{r}'$ , is achieved through two steps. First, the somatic activity of each output neuron  $i$  is calculated:

$$h_i = \sum w_{ij} r'_j; \forall j$$

Second, the somatic activity is transferred to an output firing rate through a threshold-linear or non-linear (e.g. sigmoidal) activation function  $f$ :

$$r_i = f(h_i)$$

### **1.3.3.3 CA3 and pattern completion**

At the heart of the theoretical framework for the hippocampal function in episodic memory lies the CA3. Perfectly situated to receive both non-spatial ('what') and spatial ('where') information and sprouting with recurrent connections, comprising about 75% of the total number of CA3 synapses (Witter and Amaral, 2004), the 250.000 pyramidal neurons of the CA3 (Rapp and Gallagher, 1996) are thought to implement an autoassociation memory (McNaughton and Morris, 1987; Rolls and Treves, 1998) in which multimodal information can rapidly be associated to form episodic- or 'snapshot'-like memories through a Hebbian learning rule. The fact that mice are profoundly impaired in a one-trial spatial learning task after blockade of NMDA-dependent synaptic plasticity selective to the CA3 strongly supports the role of the recurrent collaterals in forming snapshot-like memories (Nakazawa et al., 2003).

Presented with an arbitrary part of a previously stored input pattern, the autoassociation memory can reproduce the original activity pattern in a process called 'pattern completion', an instantiation of content addressability. Such networks are said to display 'attractor dynamics' (Hopfield, 1982; Amit, 1989), meaning that fragmented or instable network activity will tend to be drawn towards a previously stored, stable pattern of activity, or a stable 'attractor state', alluding to a Hebbian cell-assembly representation of memories. The autoassociator (Figure 6C) works like the pattern associator, except that during learning  $\mathbf{r} = \mathbf{r}'$ , and during recall  $r_i = f(h_i + e_i)$ . Presented with a partial retrieval cue, pattern completion ( $\mathbf{r} = \mathbf{e}$ ) is usually achieved within 5-15 iterations.

In accordance with the proposition that the recurrent collaterals of the CA3 are necessary for pattern completion, mice with a knockout of the gene required for synaptic plasticity in the CA3 are still able to learn the location of a goal relative to allocentric cues, but when tested in the same task after a subset of the original cues are removed, performance drops significantly compared to controls (Nakazawa et al., 2002).

### **1.3.3.4 DG and pattern separation**

A primary hazard of associative networks is running into 'catastrophic interference' –the loss of previously stored information after storing a similar activity pattern on the same synapses. To minimize the risk of catastrophic interference, input patterns should be statistically uncorrelated or 'orthogonal'. The process of orthogonalizing patterns is called 'pattern separation' and can be



achieved though several mechanisms, some of which are implemented in a competitive network. Competitive networks are therefore attractive pre-processors for autoassociators. Due to its rich population of inhibitory interneurons, DG is suggested to serve competitive computations.

The dentate gyrus is the first structure in the unidirectional circuit of the hippocampal formation and hosts about 1.200.000 densely packed granule cells in a single 4-8 cells thick layer (West et al., 1991) in addition to a variety of inhibitory interneurons distributed among the molecular layer, the granule cell layer, and the polymorphic layer. The large population of interneurons and the sparsely activated population of cells (Jung and McNaughton, 1993; Leutgeb et al., 2007), make the competitive network an attractive model for the DG. Through the perforant path, layer II neurons from LEC and MEC project to the superficial and middle third of the molecular layer respectively, where they make contact with the same population of granule cells (Witter and Amaral, 2004; Amaral and Lavenex, 2007). The vastly greater number of granule cells compared to entorhinal afferents make the DG ideal for ‘expansion recoding’ or recoding input patterns to sparse non-overlapping patterns, a process adding to the pattern-separating capabilities of a competitive network (Rolls and Treves, 1998).

In competitive networks (Figure 6D), neurons compete for the privilege of representing a particular input pattern. Such networks learn to categorize input patterns, remove redundancy, orthogonalize similar input patterns, and produce sparse output patterns from redundant input.

Starting from a given set of synaptic weights,  $\mathbf{w}$ , output firing rate is calculated as before:

$\mathbf{u} = f(h_i)$ ; where  $h_i$  is somatic activation of output neuron  $i$

Neural competition is implemented as an “n winners take all” nonlinear operation,  $c$ , that determines the  $n$  number of neurons that will be active for each output pattern:

$$\mathbf{r} = c(\mathbf{u})$$

The hebbian learning rule is applied as before, after which the length of the synaptic weight vector is normalized to avoid saturation:

$$\Sigma(w_{ij})^2 = 1; \forall_j$$

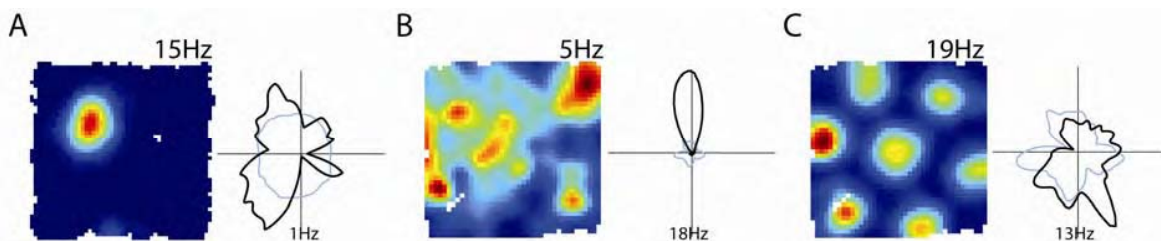
The process is repeated several times for all input patterns presented in random order.

## 1.4 Neural representations of spatial variables

*At a certain level of physiological analysis there  
is no reality but the firing of single neurons*

Donald O. Hebb, 1958

According to Hebb's theory that memory is represented by cell assemblies, it should be possible to recognize the internal representation of an external stimulus in the activity of single neurons. The computational framework for hippocampal function shows how such neural representations should ideally be organized in the different subregions of the hippocampus to support efficient processing of episodic memories. Three main functional classes of spatially tuned cells, place cells, head direction cells, and grid cells, have been described to reside within the hippocampus and parahippocampus (Figure 7). In addition, cells expressing conjunctive head-direction and grid-pattern responses exist in the deep layers of MEC. An extensive account for the properties of these neural representations of spatial variables is given in the following.



**Figure 7.** Known units of the spatial representation-circuit in the rat brain. Firing rate maps show average activity of a single neuron as the rat foraged in a 1m square arena. Dark blue color: no activity. Bright red color: maximal activity, denoted above each rate map. Polar plots show the neuron's preferred firing direction relative to the arena. Blue line: distribution of the animal's heading directions across the trial. Black line: Firing rate as a function of the animal's heading direction relative to the room. Maximal average firing rate denoted above each polar plot. **A.** Place cell recorded from the hippocampus. A single spatial receptive field and low directional selectivity is typical. **B.** Head direction cell recorded from MEC layer III. Strong directional preference and low spatial selectivity is characteristic. **C.** Grid cell recorded from MEC layer II, identifiable by its multiple firing fields arranged in a regular triangular pattern. Directional selectivity is rare in layer II but common in deep layers of the MEC.

## 1.4.1 Place cells

### 1.4.1.1 Basic phenomenon

Inspired by Edward Tolman's theory of cognitive maps, and equipped with newly developed technology for single-neuron recordings from behaving animals, O'Keefe and Dostrovsky (1971) aimed their electrodes at the CA1 area of the hippocampus of rats in search for Hebbian cell assemblies underlying spatial memory. Hippocampal principal neurons exhibited clearly delineated spatial receptive fields ('place fields'; Figure 7a), collectively forming an allocentric representation of the animal's local environment. The cells were termed 'place cells' and the rat hippocampus was taken to be a dedicated neural network for the representation and computation of spatial relationships, a neural substrate for Tolman's cognitive map (O'Keefe and Nadel, 1978 p.1-2):

"...there exists at least one neural system which provides the basis for an integrated model of the environment. This system underlies the notion of absolute, unitary space, which is a non-centred stationary ['allocentric'] framework through which the organism and its egocentric spaces move. We shall call the system which generates this absolute space a *cognitive map* and will identify it with the hippocampus."

The hippocampus consists of two main classes of cells, pyramidal cells and a heterogeneous collection of interneurons, that can be distinguished on the basis of anatomical, physiological and molecular properties (Freund and Buzsaki, 1996). Place cells are likely identified with the complex-spiking pyramidal cells (McNaughton et al., 1983; Henze et al., 2000), as inhibitory interneurons are rather characterized by narrow wave forms and high average firing activity that generally lacks spatial selectivity (Ranck, 1973; Fox and Ranck, 1981; but see Wilent and Nitz, 2007). The first-order firing correlate of hippocampal pyramidal cells is location, meaning that all pyramidal cells that are active in a given environment have at least one place field (Muller et al., 1987; Wilson and McNaughton, 1993) and that the location of firing is more reliable than the firing rate (McNaughton et al., 1983; Muller et al., 1994; Olypher et al., 2002). If the hippocampal representation is indeed a spatial map, it has to be updated by both self-motion information and external cues, related to the geometry of the environment, and structured in a way that is suitable for navigational computations.

### **1.4.1.2 Self-motion cues**

If place cells represent a spatial map that is used during navigation, the rat's position in the map should be updated by path integration to account for the behavioral data reviewed in Chapter 0. When rats are released from a movable start box on a linear track with a fixed goal at the end, place-field locations are initially determined by the distance from the start box (Gothard et al., 1996; Redish et al., 2000), taken to indicate that place-cell firing can be driven by self-motion information. The claim is supported by evidence that the firing rate of place cells is positively correlated with the speed of the animal (McNaughton et al., 1983; Wiener et al., 1989), especially evident when rats are running on a running wheel (Czurko et al., 1999), and that the hippocampal firing fields are spatially stable after removal of salient visual landmarks (O'Keefe and Conway, 1978; Pico et al., 1985; Muller and Kubie, 1987; O'Keefe and Speakman, 1987), and during periods of complete darkness (O'Keefe, 1976; Quirk et al., 1990; Markus et al., 1994). These experiments also demonstrate that place cells represent more than the rat's sensory input, and rather reflect the inner state of a stored association that can be maintained by partial cues, reminiscent of the concept of pattern completion.

### **1.4.1.3 External cues and geometry**

Consistent with the fact that animals primarily rely on external cues and the geometric layout of the environment to navigate (Chapter 1.2), the place-cell representation is anchored to external landmarks. Rotating salient visual cues, like a cue-card on the wall of the experimental arena, leads to a concurrent rotation of recorded place fields (Muller and Kubie, 1987; Jeffery et al., 1997), in line with the early behavioral observations of Watson (1907), Tolman (1930; 1948), and Hebb (1949).

The first evidence that the neural representation of space is influenced by the environment's geometrical layout came from the observation that place fields on the edge of a circular enclosure would occasionally be crescent shaped, in contrast to the circular symmetric place fields normally seen (Muller et al., 1987). Hippocampal place fields are also reported to cluster along the edges of an environment (Muller et al., 1987; Hetherington and Shapiro, 1997), suggesting that hippocampal input is especially strong along environmental borders. When stretching or compressing a recording enclosure in the absence of strong extra-maze cues, a subpopulation of place cells alter their firing patterns accordingly (O'Keefe and Burgess, 1996). Hippocampal place fields close to the enclosure walls are more strongly affected by the

deformation than fields close to the center of the arena. When a separate wall is inserted into the environment, most place fields show no additional response to the new wall, although some place fields acquire an additional ghost field at the same distance from the new wall as the original field from the bounding wall and fields intersected by the inserted wall might disappear entirely (Muller and Kubie, 1987). These geometric determinants of place-cell firing are consistent with the behavioral data concluding that the rat's spatial maps must be tied to local geometry (Chapter 1.2.3) and have been taken to support Gallistel's theory of a separate geometric module encoded directly upstream of the hippocampus (O'Keefe and Burgess, 1996). In paper IV we pursued the hypothesis that geometric surface-information is represented in the MEC.

#### ***1.4.1.4 Structure of the hippocampal map***

A spatial map can be implemented in several different ways, and need not resemble topographic maps. To guide navigational computations, the hippocampal map has for instance been suggested to have a graph-like structure, where place cells correspond to nodes and the synaptic strengths between place cells correspond to the inverse distance between place fields of the connected nodes of the directed graph. Such a weighted graph can be searched for the optimal path between already visited nodes, and solve the shortcut problem (Muller et al., 1996).

Although the place-field size increases systematically from dorsal to ventral parts of the dorsal hippocampus (Jung et al., 1994; Maurer et al., 2005), the hippocampal map is non-topographic in the sense that anatomically neighboring place cells have place fields in unrelated positions within an environment, such that any local ensemble of place cells will cover large parts of an environment (O'Keefe and Speakman, 1987; Wilson and McNaughton, 1993). Place-cell maps for different environments are also unrelated in the sense that the relative positions of place fields are not preserved across environments (see Chapter 1.4.1.6) (O'Keefe and Conway, 1978; Quirk et al., 1990; Leutgeb et al., 2005b). This non-topography does not easily lend itself to navigational computations for several reasons. First, because there is no consistent relation between the anatomical distance between two place cells and the metric distance between their place fields, the synaptically encoded distance information will be subject to catastrophic interference and utterly fragile unless a separate metric map is used for each environment (Samsonovich and McNaughton, 1997). Although storing multiple maps with separate metrics is

not impossible, it will be inefficient use of storage capacity. Second, although a typical CA1 or CA3 place cell has a single place field in an environment, some cells show multiple fields in the same environment (Muller et al., 1987; Wiener et al., 1989) and in the dentate gyrus multi-field place cells are predominant (Jung and McNaughton, 1993; Leutgeb et al., 2007). Distance-information represented as synaptic strength between place cells with multiple fields will be ambiguous or corrupted. Third, a neural implementation of the proposed graph-searching algorithms is not easily accomplished. Encoding an anatomically separate metric or path integrator would therefore be a more efficient way of organizing the spatial mapping (Redish, 1999).

#### ***1.4.1.5 Non-spatial correlates of place-cell activity***

That the hippocampal map is not well-suited for metric computations is in accordance with the view that the hippocampal representations embrace multiple sensory modalities collectively defining an associational map in which space is a particularly prominent component, at least in rodents (Leutgeb et al., 2005b; Lipton and Eichenbaum, 2008). The non-spatial functions of the hippocampus inferred from amnesic patients and hippocampectomized animals (Chapter 1.3.2.3) are reflected in second-order correlates of place-cell responses. Different place cells are linked to different sets of cues (Shapiro et al., 1997; Tanila et al., 1997; Rivard et al., 2004; Yoganarasimha and Knierim, 2005). In particular, place cells cluster around reward locations (Eichenbaum et al., 1987; Breese et al., 1989; Kobayashi et al., 1997) or in the platform zone of an annular water maze (Hollup et al., 2001b; Brun et al., 2002). A subpopulation of these cells follows such landmarks when moved, whereas other cells seem unaffected by displacement of local landmarks (Muller and Kubie, 1987; O'Keefe and Speakman, 1987; Markus et al., 1994; Knierim et al., 1995; Cressant et al., 1997; Rivard et al., 2004). This dichotomy can be interpreted as reflecting a representation of the independent positions of several distinct objects, including the animal itself, within the same allocentric map. Furthermore, place-cell responses are reported to be contingent on odor cues (Eichenbaum et al., 1987; Eichenbaum et al., 1988; Otto and Eichenbaum, 1992), behavioral task (pattern of running in an open field; (Markus et al., 1995), and stage of task (Eichenbaum et al., 1987; Otto and Eichenbaum, 1992; Hampson et al., 1993), supporting the computational theory presented in Chapter 1.3.3 which assigns a primary role for the hippocampus in processing episodic memory.

#### ***1.4.1.6 Hippocampal remapping and memory***

The fact that place cells maintain a stable representation across repeated presentations to the same environment over several days (Muller et al., 1987; Wilson and McNaughton, 1993) makes place-cell maps attractive models for the neural representation of spatial memories. As discussed in Chapter 1.3.3, optimal memory-performance is achieved when the representation of different memories are statistically uncorrelated, obtainable through a pattern-separation process (Rolls and Treves, 1998). The effect of neuronal pattern separation is observed in the hippocampus as a substantial and consistent alteration of the activity pattern of place cells in response to sensory or motivational changes (O'Keefe and Conway, 1978; Kubie and Ranck, 1983), referred to as 'remapping' (Muller and Kubie, 1987; Quirk et al., 1990). Two distinct types of hippocampal remapping can be identified. 'Rate remapping' refers to substantial changes in firing rates without significantly affecting the location of firing fields in the active place-cell ensemble. 'Global remapping' refers to arbitrary changes in both location and firing-rate of individual place fields, including partial substitution of the active subpopulation of neurons (Leutgeb et al., 2005b). Rate remapping occurs whenever noticeable changes are made to non-spatial features of the environment, like a transition from black to white walls (Leutgeb et al., 2005b; Fyhn et al., 2007; Leutgeb et al., 2007). Global remapping is most easily induced by changing the location of the animal's environment (Leutgeb et al., 2005b), but can also be triggered by substantial changes to the configuration of salient landmarks (Bostock et al., 1991; Hayman et al., 2003; Fyhn et al., 2007) or the behavioral task (Quirk et al., 1990; Markus et al., 1995; Wood et al., 2000; Wills et al., 2005) without changing the location of the recording arena but likely disrupting essential anchoring points for the established allocentric reference frame.

The different hippocampal dynamics during global and rate remapping indicates that spatial and non-spatial information are treated semi-independently in the hippocampus, as changes to non-spatial aspects of the environment are reflected in a dynamic rate code anchored to a stable spatial code. The apparent independence of spatial and non-spatial information encoding agrees with the notion of separate neural origins of the two categories of information (Hargreaves et al., 2005), and is consistent with theoretical work verifying the capacity of attractor networks to encode both continuous (spatial) and discrete (non-spatial) variables in a reciprocally associative manner, an essential feature of episodic memory (Rolls et al., 2002).

#### ***1.4.1.7 Place cells support CA3 attractor dynamics***

The computational network theory for episodic memory hinges on the autoassociative CA3 field functioning as an attractor network. A main characteristic of attractor networks is the ability to perform pattern completion, crucial for content-addressability. Place fields both in CA1 and CA3 exhibit signs of pattern completion, demonstrated by retained place-field locations after removing salient visual cues (O'Keefe and Conway, 1978; Pico et al., 1985; Muller and Kubie, 1987; O'Keefe and Speakman, 1987), running in complete darkness (O'Keefe, 1976; McNaughton et al., 1989; Quirk et al., 1990; Markus et al., 1994), or changing contextual features like the color of the enclosure walls (Leutgeb et al., 2005b). Consistent with computational theory, the CA3 shows a stronger reproduction of the original pattern than the feed-forward network of CA1 (Lee et al., 2004; Vazdarjanova and Guzowski, 2004; Leutgeb et al., 2005a), and when discordance between local and distal cues is created by rotating each set of cues by 90 degrees in opposite directions, the CA3 place cells retain strong internal coherence, meaning that place fields of all cells follow either the local or the distal cues, whereas CA1 place cells show a heterogeneous response, different cells following either of the two set of cues (Lee et al., 2004).

Pattern completion and internal coherence offer indirect evidence of attractor dynamics. More direct support for the existence of attractor states within the CA3 network comes from a study in which rats were familiarized with a circular and a square environment in which they displayed independent CA3 representations. Upon a gradual morph of one shape to the other, the representation would stay highly correlated to the original shape up to a certain point in the morph sequence, at which point global remapping to the other environment occurred and was maintained for the rest of the morph sequence (Wills et al., 2005). The lack of distinct representations for shapes intermediate between square and circle is indicative of independent attractor states for the square and circular environments.



## **1.4.2 Head direction cells**

Place cells convey the animal's position within an allocentric reference frame. However, the observation leading to the cognitive map theory in the first place was the animal's ability to rely on external cues to define the allocentric bearing of the environment (Tolman, 1948). Although some place cells are reported to be sensitive to the animal's direction of movement (McNaughton et al., 1983), a neural implementation of the prominent sense of direction finds upstream origins.

### **1.4.2.1 Basic phenomenon**

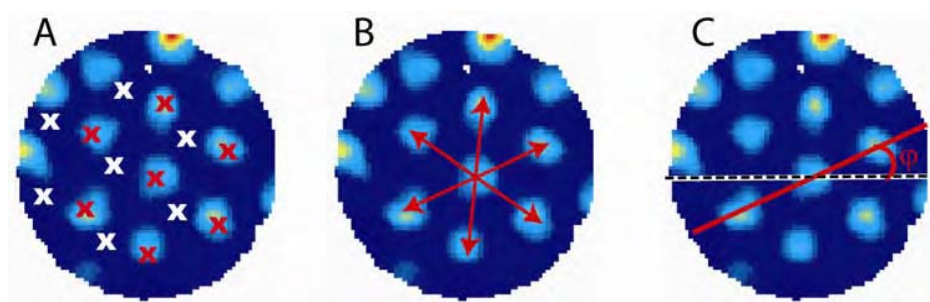
In 1984 another unit of the brain's spatial representation was revealed (Taube et al., 1990a). Single neurons in the dorsal presubiculum, immediately upstream of the medial entorhinal cortex, were preferentially active when the animal pointed its head in a certain direction of the environment, and the cells were termed 'head direction cells' accordingly (Figure 7b). The directional tuning curve of head-direction cells is typically triangular or Gaussian (Blair and Sharp, 1995; Taube, 1995), with a directional firing range varying between 60 to 150 degrees, averaging at 90 degrees. The firing rate is virtually unaffected by the head's pitch or roll, and whether the animal is moving or not (Taube and Muller, 1998). Analogous to the hippocampal representation of position, neighboring head-direction cells display unrelated directional preferences, and all heading directions are equally represented within a local ensemble of head direction cells (Taube et al., 1990b). In contrast to place cells however, the preferred direction of firing relative to an external reference frame is retained across days and controlled by external cues, as demonstrated by rotation of a salient visual cue-card (Goodridge et al., 1998). The preferred direction of firing relative to neighboring cells is also preserved across environments (Taube et al., 1990b). Head-direction cells therefore encode what can be referred to as a 'cognitive compass'.

### **1.4.2.2 Anatomical loci**

Head-direction cells have been found in a vast number of brain areas in addition to the dorsal presubiculum (Taube, 2007). Most notably in the anterior dorsal thalamic nucleus where head-direction cells have small but significant secondary correlates with linear and angular head velocity (Taube et al., 1990a; Taube, 1995; Sharp et al., 2001). Also noteworthy is the significant number of head-direction cells reported in retrosplenial cortex (Chen et al., 1994; Cho and Sharp, 2001), and the medial entorhinal cortex (Sargolini et al., 2006).

### 1.4.3 Grid cells

To guide navigation based on spatial maps, the direction signal from presubicular head-direction cells must enter the hippocampus through the entorhinal cortex. Early recordings from the entorhinal cortex reported only weak spatial modulation in entorhinal neurons (Barnes et al., 1990; Quirk et al., 1992; Frank et al., 2000; Frank et al., 2001). However, the navigational deficits following dorsolateral, but not ventromedial, entorhinal cortex lesions (Steffenach et al., 2005), the highly specific topography of anatomical connections with the dorsal hippocampus (Dolorfo and Amaral, 1998; Witter and Amaral, 2004), and the fact that CA1 place fields prevail in the absence of CA3 output (Brun et al., 2002) encouraged investigation of neural activity confined to the dorsolateral part of the medial entorhinal cortex. Approximately one third of the neurons recorded from the dorsolateral MEC were found to exhibit stable place-specific firing fields, reminiscent of hippocampal place cells save the omnipresent expression of multiple place fields in entorhinal neurons (Fyhn et al., 2004). Increasing the size of the recording enclosure, the entorhinal neurons revealed a strikingly regular triangular pattern of firing fields, tessellating any environment the animal traversed, which gave rise to the name ‘grid cells’ (Figure 7c; Hafting et al., 2005).



**Figure 8.** Grid cells are defined by three variables. **A.** Spatial phase, denoting the position of the firing fields relative to the center of the arena. **B.** Spacing, denoting the average distance between neighboring firing fields. **C.** Orientation, denoting the positive angle between a defined horizontal line and the first of the three grid axes when moving in the anti-clockwise direction. From (Moser and Moser, 2008).

### **1.4.3.1 Basic phenomenon**

A grid cell can be defined by three parameters: The orientation of the triangular grid pattern relative to the environment, the spacing denoting the shortest distance between neighboring fields in a grid pattern, and the spatial phase denoting the position of grid fields relative to the environment (Figure 8).

Whereas orientation and spacing of anatomically neighboring grid cells are similar, their spatial phases are randomly distributed, and the position of the rat can be reconstructed (predicted) from a local group of recorded neurons as accurately as in the hippocampus (Fyhn et al., 2004). As for the dorsal hippocampus, spatial scale of MEC grid cells increases systematically from dorsal to ventral MEC, and non-neighboring grid-cells can have different orientations, at least between hemispheres (Hafting et al., 2005), but whether orientations are constant within a hemisphere (Barry et al., 2007) or vary systematically with anatomical location awaits clarification. Grid cells in layer II of the MEC are typically non-responsive to the animal's head direction, whereas the other cellular layers (layers III, V, and VI) of MEC contain both pure head-direction cells and 'conjunctive cells' expressing joint grid- and head-directional properties, in addition to a population of cells seemingly non-selective for spatial properties of the environment (Sargolini et al., 2006).

As for the head-direction system, all grid cells are active in all environments, and the relative phase-difference between neighboring grid cells is preserved across environments (Fyhn et al., 2007). That neighboring cells always encode the same relative distance, opens for simple ways of calculating distances smaller than the grid spacing and means that distance information is only stored once in a 'universal spatial metric' which can be used for all subsequently generated hippocampal maps (Redish, 1999; Hafting et al., 2005).

### **1.4.3.2 Self-motion cues**

In the absence of visual cues, grid cells preserve their spatially stable firing pattern for an extended period of time although the firing fields are slightly less confined during periods of complete darkness (Hafting et al., 2005), suggestive of attractor dynamics that are updated by a path integration mechanism. Grid cells are also immediately active and exhibit a spatially stable firing pattern when entering a completely dark environment for the first time, indicating that the firing pattern can be generated entirely on the basis of path integration.

### ***1.4.3.3 External cues and geometric determinants***

Grid cells are anchored to the external environment, as they follow salient visual cues upon rotation (Hafting et al., 2005). In accordance with behavioral experiments (Chapter 1.2.3), surface geometry of the enclosure exerts strong control over the grid-cell firing pattern when the enclosure is stretched or compressed (Barry et al., 2007). This avoids ambiguous positional representations by preserving the allocentric representation of the original shape in the manipulated shapes, and means that the enclosure geometry either influences the animal's perceived speed of movement or directly calibrates the path-integration mechanism.

### ***1.4.3.4 Grid cells and hippocampal remapping***

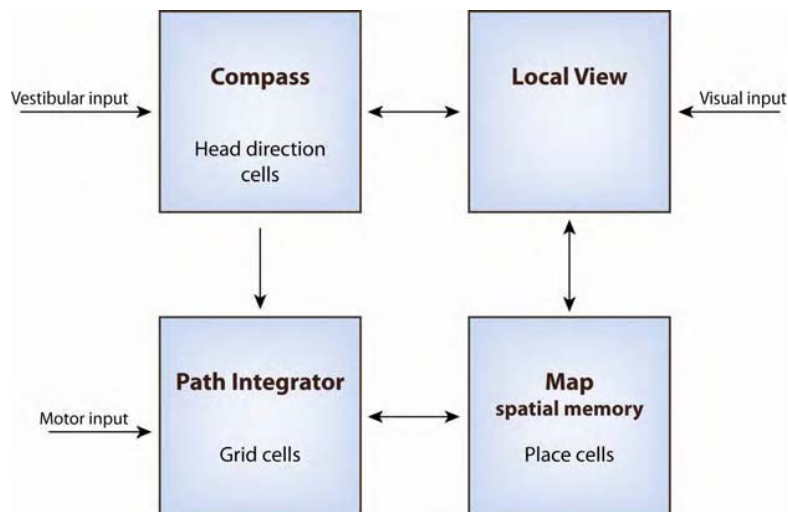
Grid cells have not been reported to respond to non-spatial aspects of the environment (Fyhn et al., 2007), strengthening the view that the MEC encodes an allocentric spatial metric (Hafting et al., 2005). As a consequence, no systematic change is observable in the grid-cell ensemble when rate remapping is observed in the CA3, neither in position nor rate of the grid-cell subfields. When global remapping is observed in the CA3, however, a coherent shift in spatial phase relative to the local geometry of all simultaneously recorded grid cells is also observed. The grid-cell translation is under some circumstances accompanied by rotation, expansion, or contraction of the grid fields (Fyhn et al., 2007). This phenomenon has several important implications. First, spatial and non-spatial signals entering the hippocampus are likely mediated by separate neural populations, since both grid cells and place cells are associated with spatial transformations of the environment, while only place cells respond to non-spatial transformations (Leutgeb et al., 2005b; Leutgeb et al., 2007). LEC represents a candidate origin of non-spatial information arriving to the hippocampus (Naber et al., 1997; Hargreaves et al., 2005). Second, the coherent entorhinal dynamics observed during stochastic reorganization of the spatial representation in CA3 supports the view that spatial pattern separation occurs at the entrance to the hippocampal formation (Leutgeb et al., 2007), consistent with the idea that the DG acts as a pattern separating pre-processor for the CA3 (Rolls and Treves, 1998). Third, as a model of memory, the predictive power of the MEC in differentiating between global and rate remapping in the hippocampus accentuates the spatial component of episodic memory and cognition. However, as the CA3 is thought to be a content-addressable memory, the spatial component of a memory should not only work as a retrieval cue, but also be imposed by hippocampal recall from non-spatial inputs.

#### ***1.4.3.5 Dependency on the hippocampus***

Indeed, the entorhinal firing patterns lose both their spatial stability and the regular triangular firing pattern when the hippocampus is lesioned (Fyhn et al., 2004), supporting the role of the hippocampus in both the long-term storage of associating a certain spatial map with a certain environment or context and in the anchoring of grid-cell responses to external cues. However, the grid-cell pattern is maintained for several minutes after sudden inactivation of the hippocampus by the GABA-agonist muscimol (Hafting et al., 2008), defending MEC independency in representing navigational computations. In agreement with the lesion studies, the grid-cell pattern gradually vanishes upon protracted hippocampal inactivation, possibly reflecting the gradual accumulation of error in the path-integration system without access to anchoring landmarks for resetting the path integrator (Bonnevie et al., 2006).

## 1.5 Theoretical models of navigation and spatial representations

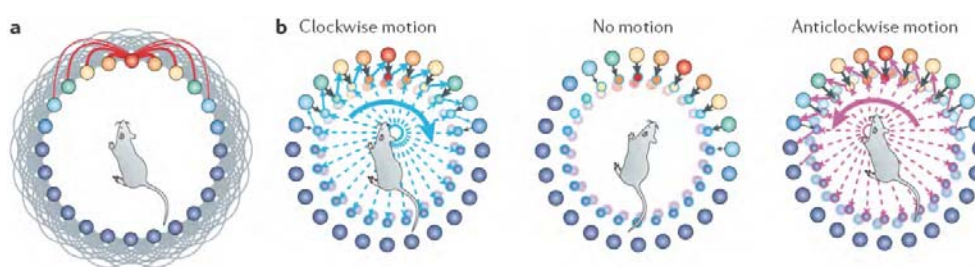
Identifying the properties necessary to perform map-based navigation, Touretzky and Redish (1996) proposed a systems level model of the hippocampal navigation system in which they attempted to identify the critical anatomical structures involved in each navigational subfunction (Figure 9). In their model, the head-direction system integrates angular velocity information from the vestibular system or optic flow, and serves as a compass sense. A local view system, consisting of egocentric representations of the local features of an environment like visual landmarks and geometric surfaces, is hypothesized to reside in the parietal cortex or the deep layers of EC. The representation of separate spatial maps for each environment is projected on the hippocampal place cells, but for an allocentric mapping to arise from the animal's first-person perceptions of an environment, local views and features must be transferred from egocentric anchoring points to allocentric coordinates. Part of this transfer operation is thought to rely on a path integrator external to the hippocampus, now concordant with the metric representation of the MEC grid-cell system (Touretzky and Redish, 1996; Redish, 1999). The systems-level framework provides a good starting point for investigating how the different spatial representation-networks of the hippocampus and parahippocampus may work together on the network level to solve navigational tasks.



**Figure 9.** Systems-level model for how spatial representations interact to perform navigation. Adapted from Touretzky and Redish, 1996.

### 1.5.1.1 Head-direction cell model

Animals' remarkable sense of direction is thought to arise from the network of head-direction cells. The most common model of head-direction cell firing activity is that of seeing the population of head-direction cells as a 'ring attractor' network, in which cells are circularly arranged according to preferred direction of firing (Skaggs et al., 1995; but see Song and Wang, 2005). With local excitation among neurons with similar directional tuning and global inhibition of neurons with different directional tuning, a stable activity state of the network will spontaneously appear as a local 'activity bump' on the neural ring which represents the animal's current heading direction (Figure 10). To shift the bump of active neurons anticlockwise or clockwise as the animal turns its head to the left or the right, head-direction cells project to a hidden layer of 'rotation cells' that are asymmetrically projecting back to the head-direction cell layer. A rotation cell is only activated by joint input from a head-direction cell and a cell tuned to the animal's angular head velocity (Stackman and Taube, 1998; Bassett and Taube, 2001; Sharp et al., 2001). An activated rotation cell will shift the active head-direction cell population in the ring attractor in the direction of angular velocity through the asymmetrical connections. The model provides head-direction cell responses closely matching neurophysiological data in simulations (Redish et al., 1996; Zhang, 1996). For example, the current head direction can drift in face of random noise to the system, and if rotating the rat at a velocity below the animal's vestibular threshold the rat will be disoriented, but neighbouring head-direction cells will always retain their relative head-direction preference (McNaughton et al., 2006).



**Figure\_10.** Attractor model for the network of head direction cells, originally proposed by Skaggs et al. (1995). **a.** Neurons are conceptually arranged in a ring according to their relative direction of preferred firing. Warm colors indicate high activity, cold colors indicate low activity. The strength of excitatory connections between neurons decreases with distance on the ring. With global inhibition, a bump of activity appears spontaneously, effectively defining the rat's current directional heading. **b.** An inner layer of asymmetrically connected neurons tuned to the animal's angular velocity is responsible for appropriately shifting the bump of activity around the ring of head direction cells as the animal turns its head. Adapted from McNaughton et al., 2006.

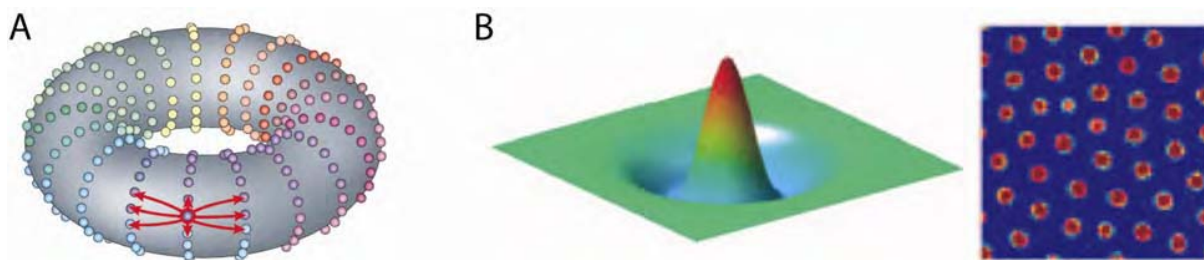
### **1.5.1.2 Grid-cell models**

Several models have been proposed to account for the formation of grid cells. Most of these models are inspired by the idea that the spatially stable activity pattern arises from path integration, producing hexagonal firing patterns from an incoming velocity signal, possibly mediated by the vestibular system or visual optic flow. Another class of models assumes a pre-existing spatial representation, defined by distal cues or local landmarks, which is transformed to allocentric coordinates in the MEC grid-cell system. The models can also be classified according to network architecture, and as the intrinsic connections of the MEC remain elusive, the anatomical grounds for implementing attractor dynamics are still debated (Witter and Moser, 2006).

#### **1.5.1.2.1 Attractor network models**

Mechanisms underlying regular triangular pattern formation have been described for a variety of physical systems ranging from chemical substances to animal coats and neural tissue (McNaughton et al., 2006). In a neural population where units are connected through short-range excitation and global inhibition, a single confined ‘bump’ of activity forms spontaneously, representing the set of co-active cells (cell assembly) sharing a spatial phase. The activity bump can move smoothly around the neural sheet in response to velocity-modulated input, effectively performing path integration, or make discrete jumps to other stable states, as when entering a new environment (Samsonovich and McNaughton, 1997). Repetitive firing patterns can emerge either by imposing periodic boundary conditions (toroidal network topology, see Figure 11a; McNaughton et al., 2006), or by using long-range rather than global inhibition (Mexican hat connectivity, see Figure 11b; Fuhs and Touretzky, 2006) which produces multiple activity bumps that move coherently across the neural population. In both network instantiations, hexagonal symmetry arises as a result of the radial symmetric connections between grid cells of different spatial phases, and spatial frequency is determined by the network’s sensitivity to the incoming linear speed signal (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Welinder et al., 2008).





**Figure 11.** Attractor network models for grid-cell firing. **A.** A toroidal network topology ensures periodic firing in neurons conceptually arranged according to their relative spatial phase of firing (McNaughton et al., 2006). **B.** A non-periodic network topology (right) gives rise to hexagonally repeating firing patterns assuming that each neuron expresses a mexican hat-type connectivity structure (left) (Fuhs et al., 2005; McNaughton et al., 2006).

Although it is not clear whether the MEC possesses the required degree of excitatory recurrent connections to implement an attractor network (Witter and Moser, 2006), several factors indicate that attractor dynamics are at play in the grid-cell population. First, the firing patterns of neighbouring grid cells maintain internal spatial coherency between environments. Second, grid cells are robust to “contextual noise”, as the grid-cell activity pattern is largely resistant to the removal of visual cues (Hafting et al., 2005) and modulation of contextual characteristics like the color of the walls (Fyhn et al., 2004), and enclosure shape (Leutgeb et al., 2007). Third, a population of ‘conjunctive cells’ that represent joint grid- and head-direction cell properties is found in layers III, V and VI of the MEC (Sargolini et al., 2006), as required to shift the activity bump around the neural population of grid cells in analogy to the rotation cells in the head-direction cell model (McNaughton et al., 2006).

#### 1.5.1.2.2 Feed-forward models

The regular triangular grid-cell pattern has also been proposed to arise from mechanisms not related to network architecture. Interference between temporal neural oscillations can produce a spatially stable firing pattern given that the difference in oscillation frequencies is proportional to the rat’s running speed (O’Keefe and Recce, 1993). A spatially stable hexagonal firing-pattern can be achieved from such oscillatory interference if three conditions are met. First, a grid cell must receive input from three or more head-direction cells with relative angular differences of multiples of 60 degrees. Second, the grid cell must have an intrinsic oscillation frequency that differs from the incoming head-direction signals by an amount proportional to the animal’s running speed. And third, the head-direction cell inputs must be synchronized at some point for

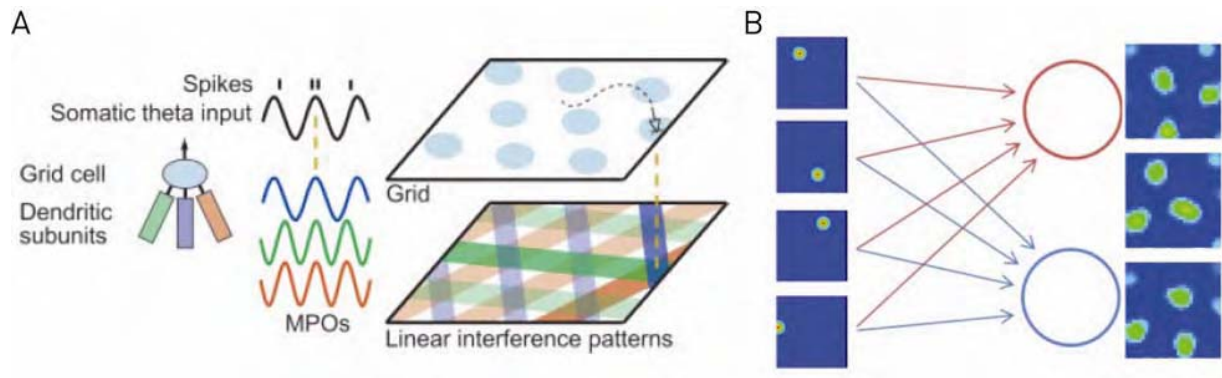
their maximal spatial amplitudes to coincide (Figure 12a; Burgess et al., 2007; Giocomo et al., 2007; Hasselmo et al., 2007). Spatial scale of the grid pattern is determined by the temporal oscillatory difference, theorized to be reflected in the intrinsic oscillations of stellate cells, varying systematically along the dorsoventral axis of the MEC (Giocomo et al., 2007).

Because the nature (acceleration, velocity, distance, position or other) of the primary input to the grid-cell network is yet to be identified, it is not given that the grid-cell network's primary function is path integration. Rather, the spatially stable activity pattern may arise from some form of slowly varying, spatially modulated, incoming signals. For instance, each grid cell may be seeking an optimal equilibrium between maximizing the amount of space it represents and minimizing the metabolic cost of firing spikes (through firing-rate adaptation). With Hebbian learning and arbitrary spatial inputs, such a network will settle into a stable state with neurons that exhibit hexagonal firing patterns in the open field, but may produce different sets of patterns in environments not allowing for the same degree of behavioural homogeneity (Figure 12b; Kropff and Treves, 2008).

Alternatively, spatially selective neurons have been suggested to arise from a hierarchy of slow feature analysis-computations, optimizing a compromise between representing the slowest varying features of arbitrary sensory inputs while preserving high information content through a competitive (sparsifying) mechanism (Franzius et al., 2007). Such a principle for the formation of spatially selective neurons produces a whole range of activity phenomenology, resembling head-direction cells, spatial view cells, place cells, edge-selective cells, and to some extent grid cells. Also in this model, the firing pattern is highly dependent on the movement pattern of the animal, and thus on the shape of the environment, i.e. yielding different firing pattern symmetry for a circular and square enclosure.

Whereas the attractor model cannot easily explain the apparent non-topography of spatial phases within a local ensemble of grid cells, general problems for grid-cell models that do not implement attractor network dynamics include synchronizing the grid-cell orientations of neighboring grid cells, and preserving the relative difference in spatial phase and orientation between neighboring grid cells between different environments where the movement statistics of the animal may be very different. Disclosing the determinants of grid-cell firing will be a prime undertaking for differentiating between theoretical models of grid-cell formation and for

determining whether the MEC is specifically designed to perform path integration or plays a more general function in spatial cognition and sequence encoding.



**Figure 12.** Feed forward models of grid-cell firing. **A.** Oscillatory interference model. The soma of a grid cell (blue) oscillates at a frequency slightly lower than that of its three or more dendrites (green, purple, brown) that receive direction-modulated input from head-direction cells oriented  $60^\circ$  apart. Because the difference in oscillation frequency between the soma and dendrites varies linearly with the rat's running speed (phase precession), a hexagonal grid-cell pattern emerges from the underlying grating functions (Burgess et al., 2007). **B.** Firing-rate adaptation in a feed-forward network results in hexagonal firing patterns (rate-map column to the right) in grid cells (red and blue circles) provided spatially tuned inputs (rate-map column to the left; e.g. from hippocampus or cortical structures). Adapted from Kropff and Treves (2008).

### **1.5.1.3 Place-cell models**

Chapter 1.4.1.7 reviewed evidence that hippocampal place fields are under the influence of CA3 attractor dynamics. Attractor dynamics is an attractive feature for stabilizing neural representations in the face of noise and can produce localized place fields as a result of path integration (Samsonovich and McNaughton, 1997). However, because CA1 is sufficient for spatial learning (Nakazawa et al., 2002) and CA1 cells still exhibit place fields both in the absence of CA3 output in rats (Mizumori et al., 1989a; Mizumori et al., 1989b; Brun et al., 2002) and in the absence of NMDA-dependent synaptic plasticity in the CA3 of mice (McHugh et al., 1996), the generation of place fields does not require the CA3 attractor network but likely depends on an extrahippocampal spatial signal.

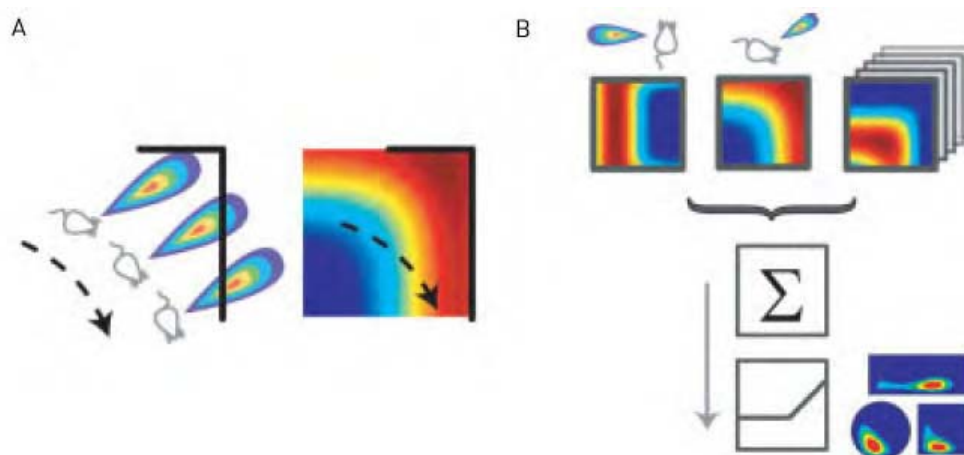
Several models have investigated how place fields can arise from integrating spatial signals mediated by cortical or parahippocampal structures (Best et al., 2001). The first place-field model considered a hard-wired feed-forward network where the activity of each place cell corresponded to a thresholded sum of input from a set of feature detectors (Zipser, 1985). Each feature detector signaled a location parameter, e.g. retinal angle between two landmarks which scales with environmental size or distance from certain landmarks that is scale-invariant (Burgess, 2007). The model can account for the changes in place-cell firing observed upon enclosure manipulation (Muller and Kubie, 1987).

Investigating the role of learning to form place-cell activity, Sharp (1991) assumed a set of cortical neurons, tuned to the rat's distance from and orientation relative to a certain distal cue, that projected to a competitive layer of hypothesized entorhinal neurons. The entorhinal neurons in turn projected to another competitive layer of hippocampal neurons that turn out to exhibit spatially confined firing fields that are robust to partial cue removal and mimic hippocampal place fields during enclosure expansion (Sharp, 1991).

To account for the distribution of place-cell responses during manipulations of enclosure shape and size, O'Keefe and Burgess (1996) proposed a feed-forward model in which place cells received input from hypothesized boundary vector cells that are tuned to the rat's allocentric distance from and bearing to environmental boundaries (Figure 13). After fitting boundary vector cells to a certain place field, the model predicts the place-field shape in a novel enclosure shape (Hartley et al., 2000), accounts for the crescent-shaped place fields close to the edges of a

circular enclosure (Muller et al., 1987) and for the observation that the strength of place-field sensitivity to geometric manipulations decreases with distance from the enclosure boundaries (O'Keefe and Burgess, 1996).

With the discovery of grid cells, a main source of metric input to place cells was likely revealed. It has been suggested that place cells may arise from a thresholded sum of grid-cell input with different spatial scales that have an overlapping firing field (O'Keefe and Burgess, 2005). In the tradition of the feed-forward models beginning with Zipser (1985), we analyzed a mathematical firing-rate model to investigate the biological plausibility and phenomenological consequences of place cells performing such 'metric coordinate read-out' from entorhinal grid cells in paper I.



**Figure 13.** Boundary vector cell model of place-cell firing. **A.** A hypothesized boundary vector cell fires as a function of the rat's distance from, and allocentric orientation to, a wall. **B.** Place-cell activity is modeled as the threshold-linear sum of input from a set of boundary vector cells, yielding a place field which is primarily responsive to the geometric boundaries of the enclosure (Barry and Burgess, 2007).

## 2 Objectives

### 2.1 Relationship between grid cells and place cells

Anatomical connectivity and fundamental differences in network dynamics between the entorhinal and hippocampal spatial codes indicate that grid cells in the dorsolateral band of the medial entorhinal cortex provide pristine spatial input to hippocampal place cells (Witter & Amaral, 2004; Hafting et al., 2005; Fyhn et al., 2007). Although causality is difficult to infer from available data, the hypothesis that multimodal associations in the hippocampus are supplied with allocentric spatial coordinates from the MEC can be explored through computational modeling. In Paper I we developed an analytical firing rate model to investigate whether and how the place-specific activity of hippocampal place cells can be explained as a coordinate-readout from the spatially repetitive firing patterns of entorhinal grid cells.

### 2.2 Representation of spatial scales

The acclaimed functional dissociation between spatial and non-spatial processing between dorsal and ventral hippocampus conflicts with the view that hippocampal function is that of associating multimodal information into episodic memories. Mainly due to the relative inaccessibility of the ventral hippocampus, the neural basis for the functional dissociation is under-investigated. Single-unit recordings have until now been confined to the dorsal half of the hippocampus. Within this region however, spatial maps are represented at gradually increasing scales from dorsal to ventral (Poucet et al., 1994; Jung et al., 1994; Maurer et al., 2005). Despite the incongruous connectivity of ventral hippocampus and MEC, this topography raises the possibility that space is represented throughout both structures at increasing spatial scales, reaching scales in ventral areas that are too large to be detected by standard test arenas like the open field and water maze. In Papers II and III we investigated this hypothesis using an 18m linear track as an extended environment.

### 2.3 Representation of geometry

The brain's ability to establish an allocentric reference frame on the basis of geometrical features of the environment has been demonstrated by behavioral studies showing that a wide range of species from humans (Hermer & Spelke, 1994; Doeller and Burgess, 2008) to rats (Cheng, 1986;

Jones et al., 2007) and fish (Sovrano et al., 2002) confuse geometrically equivalent positions, even in the presence of disambiguating cues like colors or textures on the walls. This geometric influence on navigational behaviour finds its neurophysiological reflection in the spatial maps of place cells and grid cells in the hippocampus and medial entorhinal cortex. When stretching or compressing a rat's recording enclosure in the absence of salient extramaze cues, a subpopulation of place cells and all grid cells alter their spatial firing patterns accordingly (O'Keefe and Burgess, 1996; Barry et al., 2007). Hippocampal place fields close to the enclosure walls are more strongly affected by the deformation than fields close to the center of the arena, and a subset of place cells is systematically modulated by the insertion of additional walls.

Mathematical modeling has indicated that the phenomenology of boundary-modulated place cells can be accounted for by assuming that place-cell firing is determined by input from boundary vector cells, neurons hypothesized to carry information about the animal's distance from the different boundaries in the environment (Hartley et al., 2000). These models predict the existence of a neural network encoding geometric features of the environment one synapse upstream of the hippocampus. As virtually all information targeting the hippocampus is interfaced by the entorhinal cortex, we set out to determine whether cells that encode the geometric layout of an environment exist in the spatial representation-circuit of MEC (Paper IV).

### 3 Synopsis of results

#### Paper I: From grid cells to place cells: a mathematical model

Earlier models of place-field firing have assumed that hippocampal input consists of either pure velocity information (Samsonovich and McNaughton, 1997) or spatial information tuned to arbitrary features of the environment mediated by hypothesized cortical neurons (Zipser, 1985; Sharp, 1991; O'Keefe and Burgess, 1996). The discovery of grid cells in the MEC that express allocentric spatial information one synapse upstream of the hippocampus offers a likely primary source of spatial information to hippocampal place cells (Hafting et al., 2005; O'Keefe and Burgess, 2005). We therefore developed an analytical firing-rate model of hippocampal place cells to investigate how grid-cell input can underlie place-field formation.

Grid cells  $g_{\mathbf{w}}(x,y)$  of different spacings and orientations (denoted  $\mathbf{w}$ ) were modeled as a linear sum of three 2D sinusoids. Place fields  $f(x,y)$  were then formed as a sum of grid cells and stabilized by a spatially unspecific inhibitory term  $C_{inh}$ :

$$f(x, y) = \sum_{\mathbf{w}} A_{\mathbf{w}} g_{\mathbf{w}}(x, y) - C_{inh}$$

Because the grid-cell function  $g_{\mathbf{w}}(x,y)$  is made up of sinusoids, the coefficients  $A_{\mathbf{w}}$  could be derived from Fourier theory assuming  $f(x,y)$  to be Gaussian, although the exact form of the coefficients were not crucial for generating a localized place field.

The main result from the model is that single place fields form when summing input from a modest number ( $\sim 10$ ) of grid cells with a coincident firing peak, random orientations, and random spacings within a biologically plausible interval (28cm-73cm; Hafting et al., 2005). Multiple fields arise, however, when the spatial phase variation is high, or when the place cell is connected to two or more grid cell populations of different spatial phase. Variation in the contributing grid orientations and spacings ensures precise non-repeating place fields. The assumption of a systematic variation in the furnishing grid spacings can be experimentally tested by inactivating the dorsal or ventral MEC, as the model predicts a subsequent increase or decrease in hippocampal place-field size, respectively.



## Paper II: Finite scales of spatial representation in the hippocampus

The anatomical projections to the dorsal two-thirds and ventral one-third of the hippocampus are segregated and mediate different types of information (Witter et al., 1989). Consistent with this scheme, behavioural studies indicate that whereas dorsal hippocampus is crucial to performing navigational tasks, the ventral third of the structure is strongly implicated in the expression of non-spatial behaviours such as fear (Bannerman et al., 2002; Kjelstrup et al., 2002). Neurophysiological experiments have identified place cells in the dorsal and intermediate parts of the hippocampus that collectively encode context-specific spatial maps. Although the maps are spatially non-topographical, the scale at which a neuron represents space increases systematically along the dorsal-to-ventral axis (Jung et al., 1994; Maurer et al., 2005). However, it remains to be established whether the ventral pole, with its unique external connections, is part of the same graded spatial map. To address this question, we recorded spike activity from individual CA3 pyramidal cells in the dorsal (25 – 33% of d-v axis), middle (52 – 67%) and ventral (67 – 85%) portions of the hippocampus while rats explored small and large environments (1 and 2 m wide boxes and an 18 m long linear track). In the dorsal CA3, active pyramidal cells had sharp and stable place fields in all environments. Most cells had a single place field or one field in each direction on the linear track, with a diameter of about 50 cm. In the middle CA3, active cells had single place fields, but fields were broader, often covering almost half of the area of the 2 m box and approximately 3 m of the linear track. In the ventral third of CA3, active cells showed negligible spatial modulation in the small two-dimensional environments, but discriminated between different small environments as well as the dorsal CA3 on the population level. On the 18 m track a subset of the ventral cells had confined and broadly tuned place fields, extending more than 10 m in some cases. Place fields on the linear track were directionally modulated at all dorsoventral recording levels. These results suggest that, despite the unique involvement of the ventral hippocampus in fear-related behaviour, space is represented throughout the hippocampus, with the scale of representation increasing systematically from the dorsal to the ventral pole.

### Paper III: Progressive increase in spatial scale from dorsal to ventral MEC

Grid cells in layer II of the dorsal-most 25 % of medial entorhinal cortex (MEC) are topographically organized in the sense that the inter-peak distance of the grid increases systematically with anatomical distance from the postrhinal border along the dorsal-to-ventral axis (Hafting et al., 2005). Based on extrinsic connectivity, the MEC can be divided into a dorsolateral, an intermediate, and a ventromedial area (Witter et al., 1989; Burwell et al., 1998). Spatial modulation is apparent also in the intermediate area (Quirk et al., 1992; Fyhn et al., 2004), but cells with multiple periodic firing fields have only been observed at the dorsal end. However, conventional recording environments may be too small to detect grid-like firing patterns at such large spatial scales. To determine whether a periodic representation of space is present throughout the dorsoventral axis of MEC, we recorded layer II neurons at dorsal, intermediate and ventral levels while rats explored a 2×2 m box and an 18 m linear track. The exact recording positions were estimated using histological reconstructions and ranged from 640 to 4000  $\mu\text{m}$  from the postrhinal border. Cells from all dorsoventral levels had distinct firing fields in the box and on the linear track. In the box, cells with more than three firing locations showed clear regular spacing, as in grid cells in the dorsal MEC (Hafting et al., 2005). On the track, the inter-peak distance and the field size were regular in some animals but variable in others. The spatial scale increased significantly from dorsal through middle to ventral MEC. The range of median inter-peak distance between fields in single cells ranged from less than 1m in the dorsal MEC to  $\sim 8\text{m}$  in some ventral recordings. Mean field length ranged from less than 50cm in the dorsal pole to more than 2m in some ventrally located cells. The inter-peak distance was similar for both running directions on the linear track, but the location of the fields shifted between directions. The results suggest that (i) the MEC encodes grid patterns throughout the dorsal-to-ventral extent of the structure and (ii) the spatial scale of the representation increases systematically from dorsal to ventral levels, following the pattern of hippocampal place cells (Paper II).

## Paper IV: Representation of geometric borders in the entorhinal cortex

The existence of a separate brain network representing geometric features of the environment has been anticipated by studies demonstrating that both navigational behavior (Gallistel, 1990) and neural representations of spatial relationships (Muller & Kubie, 1987; O'Keefe & Burgess, 1996; Barry et al., 2007) are contingent on the local geometrical layout of an animal's surroundings. In order to investigate whether a neural representation of geometric features exists within the spatial representation-circuit of the MEC, we recorded neural activity from all layers of the MEC while rats explored environments of different sizes and shapes. A small proportion (< 10%) of neurons was selectively active when the animal was close to one or more geometric borders of the environment. Border cells were observed in all cellular layers of the MEC as well as in pre- and parasubiculum. In a 1 x 1 m recording enclosure, border cells fired along the entire extent of one or several walls. This activity was maintained when the enclosure was stretched to 2m in the x or y directions. The cells also retained their firing pattern across days, in enclosures of different sizes and shapes, in different rooms, and on an elevated table without walls. An additional field appeared along a barrier that was placed parallel but not perpendicular to the original firing field. Evidence that the rat's running direction does not correlate with a border field's orientation tuning speaks to the fact that border cells do not simply code for the restriction of movement in a certain direction, but rather respond to the presence of a border.

Between environments, border cells retained their orientation tuning relative to both head direction cells and other border cells recorded at the same time, although the relation to a polarizing cue card was not predictable from one room to the next. A shift in the border cells preferred wall of firing between experimental conditions was always associated with a concurrent shift in the spatial phase and orientation of simultaneously recorded grid cells, a marker of global remapping in the hippocampus (Fyhn et al., 2007).

These results suggest that, in addition to grid cells and head direction-responsive cells, the parahippocampus contains neurons that encode the borders of the local environment. These cells may be instrumental in anchoring grid fields and place fields to a geometric reference frame.

## 4 Discussion

For three decades, the field of spatial cognition has been dominated by the theory that navigation is guided by a cognitive map, residing in the hippocampus (O'Keefe and Nadel, 1978). Because loss of memories for conscious experiences is the most obvious consequence of damage to the human hippocampus (Squire et al., 2004), uncovering the relation between spatial variables and episodic memory is essential. Pertinent questions in this context are how the hippocampus organizes spatial information, and whether spatial mapping is integral to hippocampal processing or confined to a separate intrahippocampal circuit. The discovery of grid cells in the immediately upstream structure medial entorhinal cortex (MEC) suggests that spatial computations are not the primary pursuit of the hippocampus. Rather, the spatial map encoded in hippocampal place cells (O'Keefe and Dostrovsky, 1971) may be derived from the MEC. Because both navigational behavior and neural maps can be controlled by manipulating the geometric layout of the external environment, an additional functional unit in the spatial representation circuit might also exist to provide geometric anchoring of the spatial maps (Gallistel, 1990; O'Keefe and Burgess, 1996).

Five main contributions to the field of spatial cognition can be identified from the papers contained in this thesis. First, because hippocampal place cells were found to constitute a cardinal feature of the entire dorsoventral extent of hippocampal CA3 region (Paper II), the theory that space is an integral component of hippocampus-dependent episodic memory (Tulving, 2002) is strongly supported. Second, the spatial scale of the hippocampal representation was found to increase systematically from dorsal to ventral regions of the structure, suggesting that data advancing a principal segregation of hippocampal function should be reinvestigated from the perspective that ventral hippocampal circuits might be involved in coarse-scale spatial cognition. Third, the increasing spatial scale of hippocampal place fields along the dorsoventral axis is mirrored by the increasing spatial scale of grid cells along the corresponding axis (Paper III), substantiating the tight functional coupling between the two structures. Fourth, a mathematical model was developed to show that hippocampal place cells can efficiently acquire spatial coordinates from the entorhinal spatial map through a simple wiring principle in which grid cells with coincident firing peaks but diverging scales and orientations contribute to a single place field (Paper I). The model provides an analytical

framework for investigating interactions between grid cells and place cells, and gives some intuition about how episodic memories might be associated with spatial variables. Finally, the report of entorhinal neurons exhibiting orientation-specific responses to the animal's proximity to borders in the environment (Paper IV) supports the notion of a dedicated brain network for the representation of geometrical features. Such features likely play a key role in establishing an allocentric reference frame. In the following, an account for the significance of each contribution is given in the context of present theory and literature. The thesis concludes with a discussion of how multimodal representations may come together in the hippocampus to guide navigation and spatial cognition in general.

## 4.1 On the structure of spatial maps

### 4.1.1 Functional differentiation

Behavioral data and anatomical connectivity suggest a double dissociation between the functional relevance of dorsal and ventral parts of the hippocampus. Whereas high-precision navigation depends critically and selectively on the dorsal two thirds of the hippocampus (Moser et al., 1993; Moser et al., 1995; Moser and Moser, 1998a) which afferent anatomical regions are primarily associated with visuospatial information (Witter and Amaral, 2004), the ventral third of the hippocampus is rather implicated in the expression of fear-related behavior (Kjelstrup et al., 2002) and is associated with afferent structures processing non-spatial sensory and emotional information (Witter and Amaral, 2004). Recent behavioral studies have given additional support to the unique role of dorsal hippocampus in spatial processing compared to the exclusive involvement of ventral hippocampus in olfactory (Hunsaker et al., 2008) and fear-related (Hunsaker and Kesner, 2008; Czerniawski et al., 2009) tasks. Conflicting with a dichotomy between spatial and non-spatial processing as an explanation for the functional dissociation between dorsal and ventral intra-hippocampal processing, fear-related memory is disrupted by inactivation of the dorsal hippocampus when the fear-related stimulus is defined by a fine-scale spatial location within a recording enclosure rather than defined by the overall “context” of the environment (Pastalkova et al., 2006), implicating the dorsal end of the structure in associating fear-related information with fine-scale spatial positions. If fear itself was uniquely represented in the ventral hippocampus, one would expect the fear-related response to generalize to the overall context rather than to disappear upon damage to the dorsal hippocampus. Also

contrasting the notion of a fundamental dissociation between the modalities of dorsal and ventral information processing, paper II demonstrates that spatial information is indeed represented throughout the entire hippocampus at a spatial scale increasing from less than a meter in the dorsal pole to more than 10 meters in the ventral pole.

The acclaimed dichotomy of information processing implies an anatomical transition point between processing of spatial and a rather vaguely defined collection of non-spatial behaviors. Based on extrinsic connectivity, it has been hypothesized that this transition point occurs about two thirds down from the dorsal tip of the hippocampus, whereas functional lesion studies indicate a transition point somewhere between the midpoint and the ventral third (Moser and Moser, 1998a). Re-evaluating the lesion data in light of the gradually increasing spatial representation of the hippocampus, such a functional transition point likely varies with the spatial layout of the task, begging revision of the paradigmatic double dissociation between spatial and non-spatial functions of the dorsal and ventral hippocampus. Studies claiming the exclusive involvement of ventral hippocampus in emotional tasks typically employ spatially unspecific tasks like contextual fear-conditioning where the animal must only differentiate between two environments. Associating large place fields or visual stimuli with fear-related information probably suffices to solve this task. The abolished fear-response to open arms in a plus maze and reduced neophobia after selective damage to the ventral hippocampus is not as easily explained on the other hand, as these are general behavioral responses not necessarily contingent on episodic memory (Kjelstrup et al., 2002). Indeed, the ventral third of the hippocampus uniquely receives information from structures involved in emotional and non-visual sensory processing (Witter and Amaral, 2004). However, regardless of the hippocampal contribution to fear-related behaviors, be it novelty detection or regulation of emotional responses, the deficit may be caused by detaching the hippocampus from structures processing emotional information rather than reflecting a fundamental difference in intrahippocampal processing of this information. It is therefore still unclear whether the ventral hippocampus is in some way unique for processing information with emotional content.

To settle the question of whether dorsal hippocampus is unique for spatial processing, or just unique for processing space at small scales, studies of large-scale behavioral tasks should be conducted. Interestingly, a recent study also suggests a functional differentiation between dorsal

and ventral hippocampus in coding for spatial and temporal relationships (Czerniawski et al., 2009). Although vulnerable to the same criticism as other studies establishing functional dissociations between dorsal and ventral hippocampus, the result draws attention to the question of whether also temporal relationships are represented at an increasing or decreasing (temporal) scale from dorsal to ventral hippocampus.

#### **4.1.2 Spatial context**

Although ‘context’ is an ill-defined concept frequently encountered in the hippocampal literature (e.g. Eichenbaum, 2004) which exhaustive treatment is beyond the scope of this thesis, it is interesting to notice that within the limits of conventional recording arenas, ventral neurons provide an efficient population code for defining an environment or ‘spatial context’. In fact, ventral hippocampal place cells were first thought to be ‘context cells’, which they in practical terms may well be. Their large spatial receptive fields would on the population level represent entire environments with a single cell assembly, or ‘static code’, rather than unrelated positions within an environment. This allows for immediate determination of which environment the rat is presently in, avoiding the need to sample most of space to compare population-level representations of similar environments required if the only representation was that of fine-scale spatial maps seen in the dorsal hippocampus. This is a very useful feature for retrieval of the relevant spatial map during global remapping.

#### **4.1.3 Number of place fields**

The attractor model of Samsonovich and McNaughton (1997) and the discovery of grid cells displaying multiple firing fields in the upstream MEC raised the question of whether also hippocampal place cells exhibit repeating firing patterns in large environments. We did not find a tendency of an increased number of firing fields for dorsal CA3 place cells on the long linear track compared to conventional recording arenas (mean number of place fields on the 18m track (overestimation):  $1.5 \pm 0.1$ ; Jung et al. (1994) report 1.22 place fields per hippocampal cell in a 1m square arena; Wiener et al. (1989) report that 54% of their recorded hippocampal place cells had multiple subfields in a square arena, averaging at 1.8 fields per place cell which is also an overestimation due to the inclusion of very small subfield sizes). However, since the environment used in our study is approximately one dimensional, it is possible that the number of cells needed to represent a linear track is much smaller than for a two-dimensional arena.

Place-cell recordings in large two-dimensional arenas must therefore be conducted to achieve large-environment data comparable to earlier studies. One study reports that multiple place fields arise in extended two-dimensional arenas (Fenton et al., 2008). However, the extended environment used was an especially enriched arena with objects and staircases, and location-specific food- and water-rewards. Non-spatial, object-related, and task-dependent factors may therefore have influenced the number of place fields observed in the Fenton study, as discussed in chapter 1.4.1.5.

#### **4.1.4 Environment-dependent place-field size**

In the dorsal pole of the CA3 we found the mean place-field size to be approximately 1m on the long linear track. This is very large compared to the field-sizes of the same neurons recorded in two-dimensional arenas (mean of  $628\text{cm}^2$ , corresponding to a diameter of 28.3cm), and indicates that rather than exhibiting more fields, place fields scale up in large environments. A similar environment-dependent field expansion has been reported for grid cells (Fyhn et al., 2007). However, in proportion to the size of the environment, mean field size of dorsal place cells was remarkably similar across environments in our hands ( $6.19 \pm 1.16\%$  in square arena vs  $5.94 \pm 0.18\%$  on linear track), indicating the stabilization of both number of fields and field size, e.g. through a competitive network mechanism, when initializing new spatial maps. Maurer et al. (2005) found no significant difference in place-field size across a large and small linear track, however. Dorsal place fields covered on average 6.4% of the large (382cm) and 14.6% of the small (167.5cm) track. Possibly, the rats may relate field size to the overall size of the room, as Maurer and colleagues used the same room and same extra-maze cues for both the large and the small linear track, while in paper II the square and linear environments were in two different rooms. Alternatively, the fact that Maurer et al compared two one-dimensional tracks might be the most relevant difference from our comparison. To further the understanding of the network dynamics underlying hippocampal distribution of place fields among active place cells, comparing field size, number of fields, and number of active cells in small and large arenas within and across rooms for the same cell samples will be insightful.

#### **4.1.5 Implications for entorhinal cortex**

Acknowledging the large-scale spatial representation of ventral hippocampus gives rise to two competing hypothesis concerning the origin of the spatial signal. Either temporal differences in

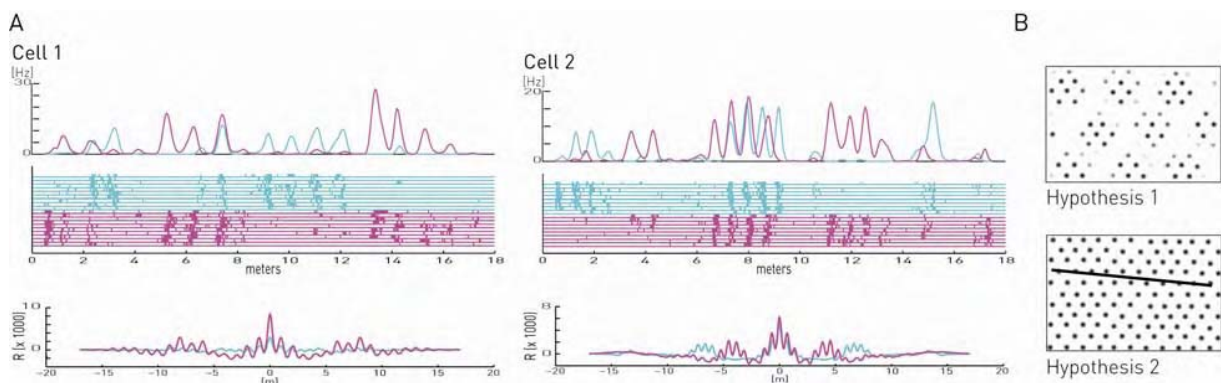


the intra-hippocampal network dynamics gives rise to the spectrum of spatial scales on the basis of the differential quality of incoming signals, or the hippocampal network receives pre-filtered spatial information directly from immediately afferent structures. Previous studies have reported neurons with single place fields or weak spatial modulation with low information content in parahippocampal areas (Quirk et al., 1992; Frank et al., 2000; Frank et al., 2001; Hargreaves et al., 2005). In analogy to the hippocampal data, these early studies may have used too small recording arenas to detect an underlying spatial structure in the firing activity. Taking the perspective that spatial information is primarily provided by the MEC as modeled in paper I, the large place fields observed in ventral hippocampus implicates the existence of large-scale grid cells in the ventral MEC. Using an 18m long linear track similar to the one used in paper II, we revealed neurons with a repeating pattern of firing fields were observed for the dorsalmost 70% of the MEC (paper III). Some cells exhibited only one or two large firing fields, possibly reflecting grid cells with too large scale to be measured on our large but limited experimental track. This result shows that the hippocampal and entorhinal representations of space are organized as parallel spatial maps of increasing spatial scale from dorsal to ventral as indicated by the anatomical connectivity between the two structures (Dolorfo and Amaral, 1998), consolidating the place-field model of paper I.

#### **4.1.6 Representing one- versus two-dimensional environments**

Loss of regularity is one of the most striking changes in the repetitive firing-pattern of grid cells from the two-dimensional arena to the long linear track. Two main hypotheses were put forward to explain this phenomenon. Either grid cells define a one-dimensional representation of the linear track in which visual stimuli override path-integration input and define a non-regular or ‘discontinuously regular’ pattern across the large environment, or grid cells always take a regular two-dimensional representation in which a linear environment cuts through at an arbitrary angle, predicting a firing pattern containing two spatial frequencies. Although some cases of dual oscillatory tendencies were observed (Figure 14), the linear activity pattern could not be superimposed on the two-dimensional pattern regardless of trajectory angle (unpublished observations). However, grid-field size on the linear track was significantly larger than in the open field, as for the hippocampal place-field recordings in paper II. Therefore, a simple mapping between the two-dimensional and one-dimensional environments is not to be expected.

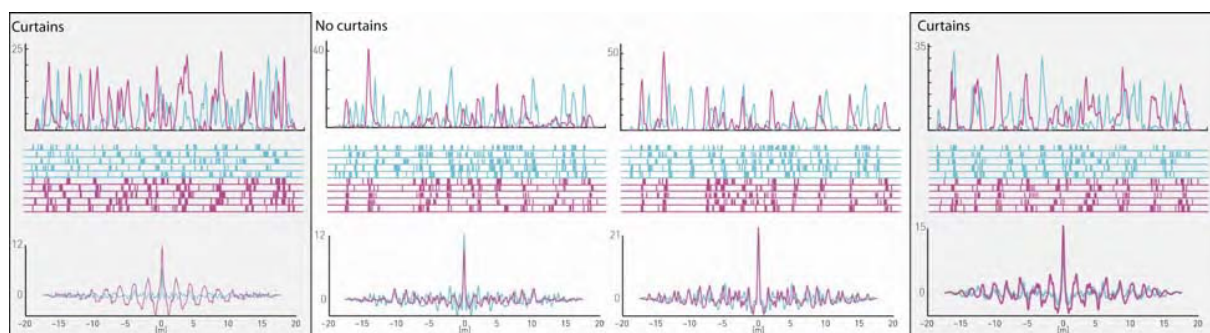
In the absence of salient landmarks, rats may rely more on path-integration based mechanisms. Homogenizing the environment by adding black curtains along both sides of the track resulted in more regularly spaced grid fields (unpublished observations; Figure 15), meaning that either the grid pattern is anchored to visual cues along the track that reset the grid pattern at arbitrary positions, defending the first hypothesis, or the cue-deprived environment caused the orientation of a two-dimensional grid pattern to align with the track, defending the second hypothesis.



**Figure 14.** Are grid-cell activity patterns fundamentally two-dimensional? **A.** Some grid cells exhibit nested spatial oscillations on the 18m linear track. Cyan: left-to-right running direction. Magenta: right-to-left running direction. Top: Firing rate maps for each running direction. Middle: each horizontal line corresponds to one lap, and each vertical bar to one spike elicited by the neuron. Bottom: autocorrelation of the rate map indicates two spatial frequencies. **B.** Two possible explanations for the dual spatial oscillations. Top: Grid cells are modulated by two or more spatial frequencies both in one- and two-dimensional space. Bottom: The grid cell represents two-dimensional space, and the linear track cuts through the two-dimensional grid-cell pattern at an arbitrary angle.

In a further attempt to tear the two possibilities apart, the two-dimensional arena can be linearized into a ‘hairpin maze’. Grid cells display fundamentally distinct representations of these two different compartmentalized versions of the same physical space, and a general mapping is not easily defined between them. The hairpin experiment is also consistent with the use of path integration to define location from fixed reset points defined at the end of each corridor in the maze (Derdikman, 2008). The evidence thus favors independent grid-cell representations of one- and two-dimensional space, but what determines individual grid-field anchorage and regulates grid spacing remain unresolved issues. Isolating the self-motion component by recording grid cells in animals running along the extended linear environment in complete darkness would yield

valuable clues to the impact of visual cues on the regularity of grid-cell firing. Such experiments were not technically feasible in our study.



**Figure 15.** The firing pattern of grid cells is more regular when black curtains mask salient visual cues alongside the 18m linear track, as evident from the autocorrelations (bottom). Colors and symbols are as in Figure 14.

#### 4.1.7 Nature of the increasing spatial scale

Still controversial, the increase in grid scale along the dorsoventral axis can be either step-wise or gradual. This issue is intimately related to the question of which mechanism underlies grid-cell formation. A single-cell phenomenon like oscillatory interference (Giocomo et al., 2007) or firing-rate adaptation (Kropff and Treves, 2008) could produce a continuum of spatial scales along the dorsoventral axis reflecting the intrinsic resonance frequency of MEC layer II stellate cells which decreases from dorsal to ventral. An attractor network process (Fuhs and Touretzky, 2006; McNaughton et al., 2006) on the other hand, would require a modular organization with a single spatial scale for each module, giving rise to a stepwise increase in grid scale owing to differential sensitivity to an incoming velocity signal or to differences in the particular architecture of the module. Barry and colleagues have argued for a stepwise increase in grid scale on the basis that neurons separated by dorso-ventral recording distances of  $50\mu\text{m}$  displayed a constant difference in spacing even across animals, supporting a modular organization of the grid-cell network (Barry et al., 2007). Although the entorhinal cortex layer V of rats shows columnar packing of neurons, a similar structure is not evident in layer II (Witter and Amaral, 2004) where the most symmetric and direction-invariant grid cells are found (Hafting et al., 2005; Sargolini et al., 2006). However, increasing the recording depth by a constant distance could also yield a constant scale increase if scale is linearly represented along the dorsoventral axis in a continuous fashion.

#### **4.1.8 Hierarchical theories of spatial processing**

The fact that both the entorhinal cortex and the hippocampus process spatial variables at multiple scales in parallel is also interesting in the context of behavioral evidence that humans seem to process spatial relationships in a hierarchical manner, underestimating distances between locations within a region while overestimating distances between locations belonging to different regions, suggesting that human spatial memory is organized with nested levels of detail (Stevens and Coupe, 1978; Hirtle and Jonides, 1985; McNamara, 1986). In a typical experiment, subjects tend to misjudge the relative position of two cities located in two different American states, as the super-ordinate spatial relation of the states overshadows the intercity relationship (Stevens and Coupe, 1978). Furthermore, distances between two locations are exaggerated if they belong to different regions compared to locations within regions (Kosslyn et al., 1974; Cohen et al., 1978; Thorndyke, 1981; Newcombe and Liben, 1982), and determining the direction between two locations is performed faster if the two locations are in different super-ordinate regions than within the same region (Wilton, 1979). Determining whether a location name belonged to a learned environment is also performed faster if the preceding name belongs to the same region than if it belongs to a different region of the environment (McNamara, 1986).

Hierarchical organization of spatial memory is ideal for parallel processing of spatial maps at multiple scales, providing fast, cost-efficient algorithms for solving route-planning problems in which finding the optimal solution is not critical. Inspired by the human navigation data, one algorithm proposed to perform this function is the fine-to-coarse planning heuristic (Wiener and Mallot, 2003), in which the route is generated as the animal moves through space. For each movement decision the algorithm will execute the small-scale movement that minimizes the large-scale distance between current location and goal location. Although an optimal route is not guaranteed, the algorithm minimizes memory load, as the animal doesn't have to remember the entire route as it traverses it, only its current location and the goal location.

Evidence that humans employ hierarchical route planning heuristics comes from experiments where people are navigating environments divided into regions and sub-regions. Rather than choosing the shortest route measured as total distance to the goal, subjects tend to take the shortest route out of the region containing the start location (Bailenson et al., 1998), and in the face of several equidistant routes, subjects prefer the route beginning with the longest straight

segment (Bailenson et al., 2000). Although corresponding data is not available for rats, the results of papers II and III strongly support the capacity for hierarchical processing in navigation and path planning in rats, and suggest a neural basis for hierarchical representations and route planning heuristics in humans.

## 4.2 A representation of geometry

Gallistel (1990) theorized that animals use geometric features of their environment to define the major axes of an allocentric reference frame, and that they encode a separate geometric module to perform this function. Although a wide range of species from fish to humans can navigate on the basis of geometric cues (Cheng, 1986; Hermer and Spelke, 1994; Sovrano et al., 2002; Jones et al., 2007; Doeller and Burgess, 2008; Doeller et al., 2008) and the spatial representations in hippocampus and MEC are influenced by local geometry (O'Keefe and Burgess, 1996; Barry et al., 2007), evidence of a separate locus or network for geometric computations has been lacking. The boundary vector cell model (O'Keefe and Burgess, 1996) advances the possibility of a separate network of geometrically tuned neurons, but in principle distortions of the spatial maps corresponding to geometric manipulations of the environment could also be due to direct sensory influences, like the perceived reduction of velocity in the elongated axis of the arena which would produce elongated grid fields in an attractor network-implementation of grid cell formation (McNaughton et al., 2006). In paper IV we reveal a network of neurons representing the borders of the surroundings regardless of the specifics of the environmental characteristics. The network is a likely source of geometric influence on grid cells and place cells, and may underlie the ability to use geometric cues as a navigational aid in establishing an allocentric reference frame from egocentric cues or local views.

### 4.2.1 Separate functional MEC cell types

To establish that the border cell is a separate functional cell type in spatial representation circuit, the fact that it is not just a subpopulation of another cell type must be beyond doubt. In particular, it is important to be assured that border cells are not just large-scale grid cells, or head-direction cells recorded from animals with particular behavioral biases. The activity pattern of border cells differ from that of grid cells in at least five major respects. First, border cells have firing fields exclusively along the edges of an open field in multiple environments. Since grid cells take an arbitrary spatial phase in each new environment (Hafting et al., 2005; Fyhn et al.,

2007), firing fields of grid cells are as likely to be found in the center of the arena as in the periphery. This was also found to be the case for grid cells reported in paper IV. Second, all border cells active along a single wall also responded to an additional wall inset at an angle parallel to the originally preferred wall of firing. None of the 41 analyzed grid cells altered their firing pattern in response to the inset wall. If a grid field was intersected by the new barrier, the cell would still fire at the original position not directly occupied by the barrier. Third, in a circular arena, border cells would show crescent-shaped firing fields similar to what has been observed for a subpopulation of hippocampal place fields (Muller et al., 1987), whereas grid fields maintained the circular perimeter regardless of boundary shape (Hafting et al., 2005; paper IV). Fourth, given the activity of simultaneously recorded head-direction cells, the spatial component of a border cell's firing field could be estimated from its activity in other environments (paper IV, Figure 3b). Because the spatial phase of a grid cell is arbitrary between environments, grid-cell responses cannot be predicted on the basis of other cell types. Fifth, a subpopulation of border cells fired along several walls of a rectangular enclosure. This is not consistent with a triangular pattern of separate grid-cell firing fields.

The fact that border-cell responses can be predicted on the basis of head-direction cells is due to the orientation-selectivity of border cells and does not implicate that the two cell types come from the same class of cells. We showed that for head-direction modulated border cells, the border-related activity could not be explained by behavioral factors like an overrepresentation of the preferred head direction along the wall associated with a firing field (paper IV, Sup.Fig.12). However, a peculiar phenomenon was evident when analyzing some border cells with firing fields along all four walls of the enclosure. The border cells did not show direction selectivity for a single direction, but fired exclusively when the rat ran along the wall in either the clockwise or anticlockwise direction, e.g. only when the border was at the animal's right-paw side. Although a purely qualitative observation, this phenomenon might give important clues to how border cells might be formed, and suggests that brain areas like the parietal cortex involved with encoding left-right distinctions (Nitz, 2006; Whitlock et al., 2008) might contribute to the process.

#### **4.2.2 Is MEC the locus of a geometric module?**

The cells reported in paper IV were recorded from all layers of the MEC, parasubiculum, and presubiculum. Previously, a small number of cells with similar characteristics have been

observed in the subiculum (Sharp, 1999; Barry et al., 2006). Unless these boundary-related cells are recorded from the immediately adjacent presubiculum or afferent/passing perforant path fibers from the MEC (Witter and Amaral, 2004), fine-tuned boundary-related information must be encoded in a distinct part of the subiculum, as other studies of spatial firing patterns in subicular neurons have not reported cells reminiscent of the border cells we recorded from MEC (Barnes et al., 1990; Henriksen et al., 2007). Because histological traces, cellular waveforms, and cluster isolations for boundary vector cells are not available, final conclusions must be deferred, but the presence of a subicular locus for border-related information would be analogous to the discovery of grid cells in a part of the entorhinal cortex not previously investigated (Fyhn et al., 2004).

Because neurons both in CA1 (Muller and Kubie, 1987; O'Keefe and Burgess, 1996) and subiculum (Sharp, 1999; Barry et al., 2006) are found to be modulated by geometric borders, and direct projections from subiculum to CA1 and CA3 are scarce at best (Witter and Amaral, 2004), two possible routes of border-related information flow exist. Either the source of border-related information is in the MEC, rendering both CA1 place cells and subicular cells directly receptive to border-related information, or border-related activity originating from the subiculum influences hippocampal place cells through the MEC, paralleling the route of head-direction information originating in the presubiculum. Although an extensive account for the subicular boundary-related cells is not yet available, present data cannot distinguish between the two possibilities. Recording border-cell activity in the MEC during subicular inactivation would yield valuable insights for resolving this issue in the future.

Consistent with the data presented in paper IV, a recent study of grid cells in rats running in a small square environment reported a single case of an additional class of neurons selectively active along the enclosure walls. Upon sudden expansion of the square, grid cells unpredictably shifted their spatial phase in the new environment, while the border-related neurons remained selectively active along the entire length of the corresponding wall in both enclosures (Savelli et al., 2008).

Although the origin of geometric information is still undetermined, border-related information in the MEC is ideally situated to influence the entorhinal and hippocampal spatial maps. What is the evidence that border cells actually influence downstream spatial maps?

### **4.2.3 Causality**

The representation of geometric borders in the MEC does not itself provide an explanation for how geometric information is used to navigate in an environment. The experiments documenting coherent dynamics between simultaneously recorded border cells, grid cells, and head-direction cells during rotation of salient cues and between environments show that either the three cell types are influenced by the same source of information, or exert influence on each other (Figure 3 in paper IV). Given the contrasting network dynamics during hippocampal remapping, the possibility that border cells reflect the output of place-cell processing is unlikely, an assertion strengthened by the observation that only a subset of recorded place cells respond to geometric manipulations (Muller and Kubie, 1987; O'Keefe and Burgess, 1996), whereas all single-wall border cells acquired twin firing-fields in response to the inset wall, and the vast majority of border cells discharged along their preferred walls of firing in the extended enclosure. Similarly, grid cells in some, but not all, animals stretched with the expanded recording arena, and not a single grid cell reacted to the inset wall, suggesting that grid cells and border cells are decoupled sources of spatial information interacting either directly or through the hippocampus. The latter point is consistent with reports of gradual disappearance of the grid-cell pattern after temporal inactivation of the hippocampus, as if anchoring to landmarks and environmental borders is no longer available without the hippocampus (Bonnievie et al., 2006). Information about geometric borders may therefore be mediated to cortical structures through the hippocampus, consistent with Gallistel's proposed axes-defining function of the geometric module (Gallistel, 1990). Specific inactivation of the border-cell network is required to establish the functional role of the border-cell network however.

### **4.2.4 What drives border cells?**

Because border cells respond to a variety of different borders, the activity does not seem to be tied to a specific modality, like visual, tactile, or olfactory stimuli. In particular, we tried to passively stimulate the rat's whiskers while recording from a border cell, but no rate modulation of the neuron was found (unpublished observations). When a 5cm high table was inserted in the middle of the arena, the same border cell discharged along the westward-facing side of the table when the rat ran on the arena floor, but was inactive when the rat ran atop the table along the corresponding westward-facing drop. When the table was turned upside down, resembling a 5cm high fence, the cell was active along the westward-facing walls both inside and outside the fence



(Figure S6 in paper IV). Behaviorally, the rat had a harder time climbing up on the table than down from the table, suggesting that the border-cell response is contingent on the perceived effort needed to traverse an obstacle. Consistent with this view, border cells did not respond to a 1cm high inset barrier that the rat could easily step over (unpublished observations). In the sense that the border-cell response depends on whether the rat ‘considers’ a border to impede its path, border cells might be conceptually more abstract units of cognitive processing than head-direction cells, grid cells and place cells that have clear physical determinants, being direction and position in allocentric space.

#### **4.2.5 Identity-independent object representation**

Any object acknowledged as an obstacle by the rat would probably elicit a response from the population of border cells. This allows for encoding of obstacles or objects in the spatial map of the environment without regard to the identity of the different objects, useful for navigational tasks like path planning and object avoidance. In a recent study, novelty for object identity and the spatial position of an object were shown to be dissociable functions (Hunsaker et al., 2007). Since grid cells were shown to be ignorant to individual objects like the inset wall in paper IV, border cells could form the neural basis for encoding identity-independent object representations, mediated by NMDA-dependent plasticity from the MEC, while non-spatial object identity is mediated by other pathways, like the lateral perforant path from LEC as suggested by Hunsaker and colleagues. The low-rate “shadow activity fields” remaining in some border cells after removal of the inset barrier (Figure S5 in Paper IV) indicates a role for plasticity in the border-cell network, possibly reflecting a difference in expected and experienced sensory input.

#### **4.2.6 Interaction between border cells and hippocampal spatial maps**

The boundary vector cell model of place-cell firing asserts that place fields are formed by dendritic summation of input from boundary vector cells (O'Keefe and Burgess, 1996; Hartley et al., 2000). The observed border cells differ from the predicted boundary vector cells in two important respects. First, very few neurons were found to be dislocated from the wall that their activity was tuned to, with the notable exception of some neurons with a narrow stripe of inactivity between the wall and the firing field (Paper IV, fig 1). Second, a subpopulation of border cells showed no direction-selectivity, but was rather active along all walls of the environment. In other words, recorded cells did not display a joint distance and directional tuning

to single walls required for a ‘vector’ representation of boundaries. The fact that few if any border cells represent areas significantly away from the borders suggests that border cells are not sufficient to define position away from the edges of a recording, implicating the need for grid-cell input to define position in areas void of boundaries. This view is consistent with the observation that place cells are overrepresented close to environmental borders, that place cells on the edge of the arena are more affected by geometric cues than cells close to the middle of the arena, that some place cells have crescent-shaped fields along the edge of a circular enclosure (Muller et al., 1987; O’Keefe and Burgess, 1996), and that the barrier-induced place-field (O’Keefe and Burgess, 1996) and border-field doubling is not observed in grid cells (paper IV).

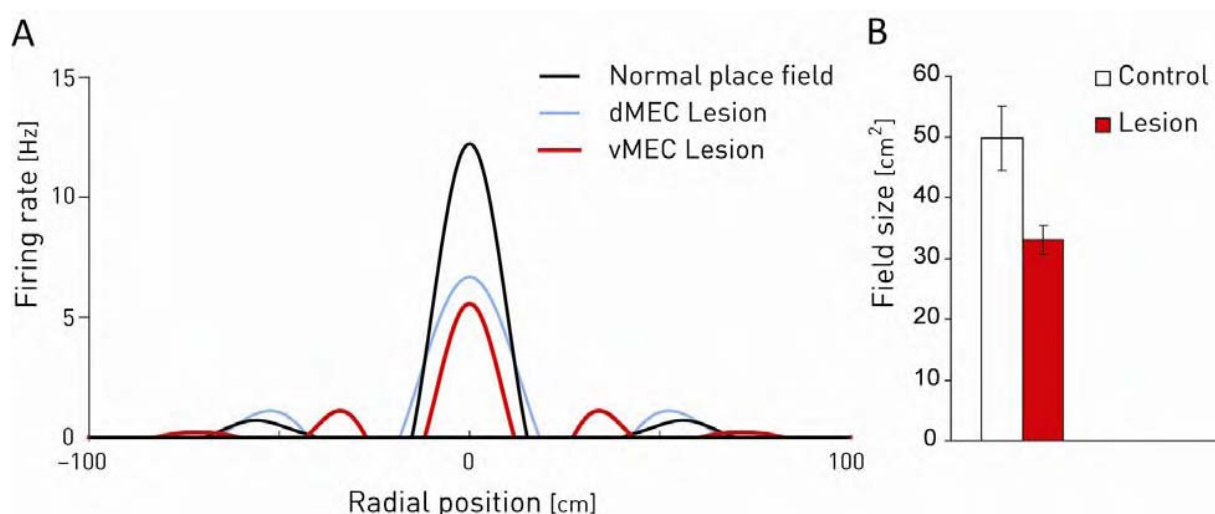
However, other cell types are likely to contribute to the spatial firing properties of place cells. Whether border cells belong to a broader class of multimodal ‘feature detectors’ (Zipser, 1985) remain for future work to elaborate on, but in line with this idea is the existence of cells intermingled with the other entorhinal cell types that are highly active for the center of the environment and progressively less active as the rat approaches the borders (Paper IV fig 1), and cells that are predominantly active in the corners of an environment (unpublished observations). In addition, as the firing rates of MEC neurons vary significantly between sessions (Fyhn et al., 2004), whereas hippocampal firing rates are relatively stable between sessions and rather vary systematically with contextual modulations of the environment (Quirk et al., 1990; Leutgeb et al., 2005a; Leutgeb et al., 2005b), cells encoding non-spatial information likely contribute to the place-cell code as well.

### 4.3 Towards a mechanism for place-field formation

In paper I we showed that any positional coordinate within the allocentrically defined environment can be extracted as place-specific responses in hippocampal pyramidal cells from dendritic summation of grid-cell inputs, and specified the constraints imposed on the contributing set of grid cells to produce realistic place fields. The main message from the model is that single place fields can emerge in a place cell with input from a small number of grid cells sampling a range of spacings, random orientations, and a coincident grid-field peak at the place-field location. In the following we will look at each of the constraints and discuss the biological plausibility and implications of such a wiring scheme.

### 4.3.1 Spatial scales

Modeled place cells receiving input from grid cells with large spatial scales would have larger place fields than place cells receiving input from grid cells with small spatial scales. This property comes with the corollary that damage to the ventral MEC should decrease hippocampal place-field size and damage to dorsal MEC should increase hippocampal place-field size. This prediction was recently confirmed in an experiment where CA1 place cells were recorded from animals with large lesions to the MEC, sparing only the dorsal-most tip (Van Cauter et al., 2008). Hippocampal place fields in these animals were significantly smaller than sham-lesioned animals (Figure 16). This provides strong evidence that CA1 place cells integrate spatial information from a range of grid cells along the dorsoventral axis of MEC, in accordance with anatomical connectivity and model assumptions (Dolorfo and Amaral, 1998; Witter and Amaral, 2004). Similarly, the parallel increase in spatial scale in grid cells and place cells along the entire dorsoventral axis (papers II and III) consolidates the view that a place field can reflect read-out of an allocentric coordinate from the spatial metric of MEC.



**Figure 16.** Accordance between model prediction from paper I and experimental data. **A.** Because place fields are constructed from grid cells of multiple spatial scales, the firing rate model from paper I predicts that damage to grid cells with large or small spatial scale leads to a decrease or increase of hippocampal place-field size respectively. **B.** Experimental data from Van Cauter et al. (2008) shows that place-field size is significantly reduced in animals with MEC lesions sparing only the dorsal-most end that contains grid cells with small spatial scales.

### **4.3.2 Existence of multiple grid orientations**

The model also assumes that contributing grid cells express a variety of different orientations, which helps to reduce symmetric ‘noise’ outside of the place field. The attractor model approach to creating grid cells does not easily comply with the existence of multiple grid orientations, unless the grid-cell network is modular so that different orientations are realized in independent networks and co-vary with spacing along the dorsoventral axis of MEC (McNaughton et al., 2006). A study by Barry and colleagues (2007) casts further doubt on the existence of multiple grid orientations, as the grid orientation of simultaneously recorded grid cells was not evenly distributed over the full 60 degree range of relative orientation-difference, even for grid cells of different spatial scales. Although strong non-linear thresholding might partially substitute for the increased signal to noise ratio achieved by including multiple orientations (McNaughton et al., 2006), the original study of grid cells also leaves room for the interpretation that grid-cell orientation is not homogenous throughout MEC. In particular, it was demonstrated that grid cells recorded simultaneously from opposite hemispheres could have different grid orientations (Hafting et al., 2005). Recording sites in these bilateral recordings varied both along the mediolateral and the dorsoventral axis, and it could not be established whether the orientations were topographically distributed along either axis or just differed between the two hemispheres as a whole. In any case, at least two concurrent grid orientations can be assumed to contribute to the positional code, and 16 degrees of maximal spread in relative grid-orientation over a dorsoventral range of  $\sim 100\mu\text{m}$  within a hemisphere was observed in the data by Barry et al. (2007), already likely to significantly increase the least common multiple of the spacings of superimposed grid-cell patterns.

### **4.3.3 Hippocampal cells with multiple place fields**

In the model of paper I we primarily investigated how grid-cell inputs must be wired to hippocampal pyramidal neurons to produce single-field place cells. The model shows that even in quite extended environments, the available grid-cell inputs do not impose constraints on the firing pattern of place cells. That is, with input from more than 10 grid cells, place cells can display a single place field in environments 100 times larger than the conventional  $1\text{m}^2$  recording arena. In principle, any number of place fields can be produced in a place cell without interfering with each other. It is therefore interesting to note that place cells with multiple place fields are commonly encountered in enriched and extended environments (e.g. Fenton et al., 2008), which

suggests that a single-field place-cell encoding is not viable when a large amount of environmental features are to be embedded in the map. However, the grid-cell inputs for each individual field of multi-field place cells are under the same constraints as single-field place cells in the proposed model. Since path planning would prove much more difficult in a representation with positional ambiguities, the existence of multi-field place cells further advances the view that the hippocampal map is used for memory representations rather than navigational computations. If the spatial coordinates used for navigational computations are not encoded by the hippocampal map itself, but rather defined by the concurrently active MEC grid cells, multi-field hippocampal place cells do not impose problems for disambiguation within the hippocampal map.

#### **4.3.4 Grid phases and remapping**

Although the model only considered the static case of place-cell activity in a single environment after the assumed stabilization of place-cell firing, we speculated that to comply with the phenomenon of global remapping, place cells active in a second environment must receive input from a second set of co-active grid cells defining the new position of activity for each place cell in the new environment. Falling out of the assumption of circular symmetric place fields, only grid cells with an overlapping firing-field center are required to produce a confined place field. In fact, if contributing grid cells have random grid phases, random CA1 rate-map patterns are produced (paper I), leading us to encourage the search for a biological mechanism to select grid cells with overlapping firing-rate peaks as an algorithm to perform a “coordinate readout” from the grid-cell system.

A dynamic pattern-separating process has been suggested to be responsible for the global remapping of hippocampal cell ensembles during coherent spatial-phase shifts in the grid-cell network observed upon entering a new environment, possibly realized through a competitive network in DG (Rolls and Treves, 1998). However, a competitive network with associative learning, simulating a population of DG granule cells receiving input from a set of grid cells with random spacings, orientations, and spatial phases (Rolls et al., 2006), could not easily reproduce experimentally observed dentate fields (Leutgeb et al., 2007), neither in terms of field size nor the number of fields in each cell. In the perspective of the modeling results from paper I, the competitive function was not sufficient to select grid-cells with coincident firing peaks from the

random input activity, likely due to the low variation in activity in these patterns which is inversely related to the number of inputs.

An elegant solution to the problem of coincident grid-peak detection is to exploit the phenomenon that grid cells express ‘phase precession’; as a rat runs through the firing field of a place field or grid field, the cell discharges progressively earlier relative to the ongoing 6-12Hz local field-potential oscillation (‘theta rhythm’) (O’Keefe and Recce, 1993; papers II and III; Hafting et al., 2005). Owing to the phase-precession phenomenon, grid cells with firing-field peaks that coincide in space also discharge in the same phase of the theta rhythm around this peak, regardless of spatial scale differences between the cells. Modeling place cells selective for input occurring on a certain phase of the theta rhythm, realistic place fields can be produced in a competitive spiking neural network with phase-precessing grid-cell inputs (Molter and Yamaguchi, 2008). The resulting weight function of individual place fields in this model is similar to the weight function proposed in paper I, and theta-phase selectivity therefore posits a candidate mechanism for acquiring the spatial-phase selectivity necessary to extract the animal’s current coordinates from the grid-cell network.

The strict distinction between rate and global hippocampal remapping is based on experiments revealing a segregation of network dynamics between changes to spatial location and changes to contextual features like color or shape of the enclosure (Leutgeb et al., 2005a; Leutgeb et al., 2005b). However, systematically varying two non-spatial sensory modalities, Anderson and Jeffery (2003) reported incidents of ‘partial remapping’, in which on the population level, hippocampal place cells showed responses intermittent between rate and global remapping even though spatial location was preserved between trials. To account for partial remapping, Hayman and Jeffery (2008) built on the idea that projections from the MEC and LEC convey spatial and non-spatial (‘contextual’) information respectively (Leutgeb et al., 2005b; Knierim et al., 2006), and terminate on the same granule-cell dendrites in the subiculum (Witter and Amaral, 2004). Proposing that the LEC inputs serve the function of gating MEC inputs, rate remapping could occur from mild rate changes in the LEC activity patterns, e.g. when changing the intensity of a modality like color or shape, asserting only weak modulation of incoming grid-cell patterns, whereas global remapping could occur from presenting a completely orthogonal contextual activity pattern from the LEC, e.g. when exchanging one odor for another, effectively selecting

new sets of grid-cell inputs for the new context through ‘dendritic gating’. Depending on the strength of contextual modulation by the LEC, different shades of remapping can be produced in the DG population without changes in the grid-cell population. Although simulations and a detailed account for how the specific wiring required should arise is lacking, the gating mechanism proposes that partial remapping should be manifested through a substantial change in the LEC representation without changes in the grid-cell representation, which can be experimentally tested by multi unit recordings.

#### **4.3.5 Representations of external entities**

A representation of self-location is meaningless without defined relations to external entities. The models we have investigated mainly account for the spatial aspect of place-cell firing. The hippocampus also contains conjoint representations of location and non-spatial stimuli like geometric features (Muller et al., 1987; O’Keefe and Burgess, 1996), objects (Rivard et al., 2004; Ho et al., 2008), and other contextual features of the environment (Lipton and Eichenbaum, 2008) even though the recognition of object identity is not dependent on the hippocampus (Brown and Aggleton, 2001). Because spatial location, at least self-location, finds an anatomically localized neural representation in the MEC, a neural representation of spatially uncoupled feature identities might also find an anatomical basis immediately upstream of the hippocampus. This would correspond to a model of spatial memory involving three processing components: processing of object identities likely involving the LEC and perirhinal cortex (Murray et al., 2007), processing of spatial location involving the MEC, and the binding of objects to locations contingent on the hippocampus (Postma et al., 2008). Consistent with this model, preliminary observations of object-related firing correlates have been reported in the LEC (Knierim et al., 2006; Deshmukh and Knierim, 2008) one synapse upstream of the hippocampus, and in perirhinal neurons (Uprety et al., 2008) immediately upstream of the LEC (Witter and Amaral, 2004).

The function of binding objects to spatial locations is in agreement with theories of the hippocampus as an episodic memory, as theoretical studies indicate that the associative memory network can represent discrete (non-spatial) variables on top of the representation of a continuous (spatial) variable without compromising either encoding (Rolls et al., 2002). In paper I we show that grid cells of different scales may collectively provide the hippocampus with

unambiguous metric coordinates. Spatially uncoupled features like odors or multimodal object identities represented in the perirhinal and lateral entorhinal cortices may therefore be associated with distinctive coordinates in an allocentric reference frame defined by contextual, distal and local geometric cues, effectively forming content-addressable episodic-like memories and spatial maps that comply with environmental geometry. Previously learned grid-cell metrics can be rapidly reinstated when revisiting a familiar environment through backprojections from the CA1 after CA3 memory retrieval based on geometric or contextual cues, in line with the findings that grid cells (Fyhn et al., 2004; Bonnevie et al., 2006) lose their long-term stability relative to external cues after hippocampal inactivation, indicating that the association between non-spatial external cues, geometric anchoring points, and the allocentric coordinate system is lost.

#### 4.4 Spatial maps and navigation

Five distinct spatial representations have been suggested to be required to perform allocentric navigation. These include the representation of a local view, consisting of a representations of local landmarks, a path integrator for the accommodation of vector arithmetic, an allocentric orientation in space, a place code for binding local views and egocentric cues to allocentric coordinates, and a goal memory accommodating trajectory planning (Redish, 1999). Following Hebb's statement that it is necessary to understand how information is represented in order to reveal how it is stored and processed, we now have candidate neural correlates of many behaviorally identified prerequisites for animal navigation. These are represented by the head-direction system functioning as a neural compass that defines the allocentric bearing, the border-cell system representing local boundary orientation, the grid-cell system functioning as a metric coordinate system, and the place-cell system functioning as a storage site for multimodal associations, content-addressable memories, or cognitive maps. Through the grid-cell network, coordinates for an arbitrarily chosen goal location within the cognitive map may be dynamically allocated, although there is some evidence to suggest that goal-encoding is present within the CA1 (Fyhn et al., 2004). Lesion studies have provided indirect evidence of a relationship between the neural representations and behavior, but are the spatial maps driving actual cognitive processes like navigation and path planning?

Rats that are trained to collect a reward by alternating between left and right turns in a T-maze occasionally make mistakes or get confused (Tolman, 1939; Johnson and Redish, 2007). On such



occasions, Tolman noticed that an animal would sit at the crossroads and turn its head to both sides before making a decision, a behavior he termed ‘vicarious trial and error’ (VTA). Exploiting this phenomenon, Johnson and colleagues provided indirect evidence that the hippocampal map is actually used during path planning. Recording hippocampal place cells during periods of VTA, high-resolution temporal firing-patterns of place cells during high-frequency population oscillations (ripples) revealed ‘sweeps’ of activity running through place cells coding for consecutive locations along either of the two available paths at the junction (Johnson and Redish, 2007). Immediately following events when the rat realized it had made a wrong turn, sweeps going in the direction the rat should have chosen were observed. Although this is still not causal evidence, hippocampal sweeps may reflect the neural underpinnings of cognitive processing, either as a spatial map read-out by other structures involved in task planning like the prefrontal, posterior parietal and retrosplenial cortices (Shrager et al., 2008; Whitlock et al., 2008) or as performing the actual computation. This encourages further investigation into hippocampal involvement in navigation, path planning and decision making which brings us to the question of how navigational processes are computed.

The suggestion that the hippocampus is a cognitive or spatial map of the environment spurred a debate over the structural implementation of this map. Storing a full metric map of the entire environment implicates the possibly wasteful storage of positions the animal might never visit, and storage capacity would be greatly attenuated by storing separate maps for each different environment, necessary to account for the global remapping phenomenon. In familiar terrain, insects like the desert ant (Collett et al., 1992) and the honeybee (Wehner et al., 1996; Menzel et al., 1998) seem to navigate by splitting their routes into separate segments between pairs of visual landmarks, analogous to tracing a graph with directed edges representing local movement vectors connecting consecutive landmark nodes (Schlkopf and Mallot, 1995; Collett et al., 1998; Collett et al., 2001; Collett and Collett, 2002). There is also evidence to support that humans rely on graph-like representations of space for route-navigation under certain circumstances (Gillner and Mallot, 1998; Mallot and Gillner, 2000). Although corresponding behavioral data are not available for rats, it has been suggested that the hippocampal representation of space fulfills the requirements for encoding a ‘cognitive graph’ (Muller et al. 1996), sufficient for performing navigational computations like searching for the shortest path or inferring a novel route. The theory assumes that place-field position represent nodes in the graph and synaptic resistance

between place cells represent directed edges. However, due to the orthogonal place-field locations between environments (Muller and Kubie, 1987; Leutgeb et al., 2005b) and occurrence of multi-field place cells (Muller et al., 1987; Fenton et al., 2008), distance vectors encoded in synaptic weights between place cells would be lost after visits to several environments.

The grid-cell network in MEC provides an elegant solution to these problems, as an exhaustive metric map can be provided at the same cost for small and large environments due to its repetitive structure and multiple spatial scales. If nodes in the hippocampal network are given coordinates in the MEC coordinate system, the distance between arbitrary entities stored in the hippocampal memory network can be calculated on demand, requiring only short-term working memory, instead of being explicitly encoded in hippocampal synapses. This would allow both route following and, in the spirit of Tolman's rats, the deduction of novel shortcuts. How movement vectors between two grid-cell coordinates could be calculated awaits elucidation, but it is interesting to note that, contrasting the hippocampal map, temporal differences between neural responses in the grid-cell network should translate directly to metric distance between locations in a way similar to what was initially proposed for the hippocampal representation by Muller et al. (1996). This hypothesis can be made from the observations that directional synaptic weights between neighboring grid cells of the same spatial scale are probably of equal strength to ensure a spatially stable firing pattern across running directions (Fuhs and Touretzky 2005; McNaughton et al. 2006), and that the topology of synaptic connections between grid cells is likely to be hardwired because inter-grid relationships are preserved across environments (Hafting et al. 2005).

## 5 Conclusions

This thesis provides evidence that spatial correlates of principal-cell firing can be found throughout the dorsoventral axis of the CA3 and MEC, implicating the entire hippocampus in spatial and episodic memory. This conclusion is contrary to the previously held notion of a functional segregation between dorsal and ventral parts of these structures in processing spatial and nonspatial information respectively. It is further established that the scale of the neural representation of space increases from dorsal to ventral, allowing for a simple mechanism of mapping grid-cell coordinates to location-specific place fields in the hippocampus. Finally, validating predictions from computational models, a new class of neurons that encode environmental borders was revealed to intermingle with grid- and head-direction cells in the parahippocampal areas.

Demonstrating a strikingly modularized organization of spatial cognition, the neural representations necessary to perform navigational tasks can be broken down into atomic functional networks of cells whose computations are brought together in downstream structures. We have made the case that border cells, head-direction cells, grid cells and place cells are sufficient to define an allocentric reference frame based on geometric cues, define a spatial metric anchored to the allocentric reference frame, and embed objects, landmarks, and events within grid-cell coordinates in an associational cognitive map in the hippocampus that may underlie episodic-like memories. Navigation can be achieved through calculating movement vectors between nodes encoded in the hippocampal map, where coordinates are given through the association to grid cells. Where and how this computation is actually performed is still an open question, representing an important avenue for future research.

In historical perspective, the localistic tradition of identifying functional units of the brain starting in the 1900s represents a continued successful approach to understanding mental phenomena. Although the medial temporal lobe is not the seat of consciousness itself, as amnesic patients are consciously aware, only not of their past (Scoville and Milner, 1957), the uncovering neural representations of Euclidean space inspires faith in 21<sup>st</sup> century neuroscience to unveil a network-level understanding of cognitive processes, and may well constitute a biological basis for Kant's transcendental aesthetic – the a priori ability to perceive space and time.

## Legal and ethical aspects

All animal experiments in this thesis were conducted according to the Norwegian Animal Welfare Act (Lov om dyrevern, no. 73 av 20. desember 1974) and the European Convention for the Protection of Vertebrate Animals used for Experimentation and Other Scientific Purposes.

The research laboratory is licensed by the national authority for animal research, and satisfies the requirements for rodent units as recommended by the European Convention. The previous inspection of the animal facility was conducted January 1<sup>st</sup>, 2005 and is valid through March 29<sup>th</sup>, 2011.

All experimenters involved in the experimental studies were certified through a compulsory course in laboratory animal science for researchers (NEVR8003).

All experiments were designed to minimize the number of experimental animals used and maximize the animals' wellbeing through continual inspection by the researchers, qualified animal caretakers, and the laboratory vet.

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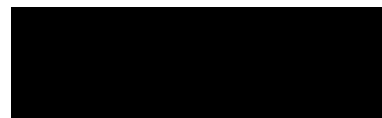




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