Evaluating the role of hippocampal processing in encoding and storing reward relevant information for goal-directed behavior

DISSERTATION

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Abstract

The neural basis of goal-directed action in decision-making is theorized to incorporate the cognitive representations of external stimuli; the representations of future possibilities and the individual value assigned to each prospective outcome. In complex multimodal scenarios the same set of external stimuli may be represented in multiple ways, some of which more efficient for achieving the goal than others. For example, in spatial navigation, there are numerous ways by which space may be represented. It is believed that both the cognitive representation of space and of future possibilities are implemented in the hippocampus as a cognitive map. And yet, factors that determine which of the myriad possible representations will be learned and implemented by the hippocampus in a cognitive map to guide behavior are still unknown. Therefore, we devised two tasks in which the reward rule was manipulated to require the representation of different sets of stimuli:

In the first manipulation, we recorded the activity of CA1 neurons of rats performing a spatial navigation task where olfactory cues and spatial dimensions were selectively altered to predict rewarding outcomes. We found that when an olfactory rule governed reward, neuronal activity gradually shifted to represent olfactory coordinates. In contrast, when the reward rule was a spatial one, a gradual shift in neuronal representation occured towards better encoding of spatial coordinates. This reorganization of representation in CA1 preceded marked behavioral improvement, suggesting that the critical step in learning is downstream of CA1 rearrangement. These findings reveal that as learning progresses, CA1 place cell activity rearranges to encode those aspects of experience that are most relevant for goal-directed behavior.

In the second manipulation, we trained mice in a complex odor discrimination task in a four- armed maze with an attentinal set-shifting paradigm. In this task, the reward rule was associated with one of two odors, which were presented in random positions in the maze. The correct arm choice in the maze was irrespective of the spatial dimensions of the task. After initial learning was completed, we introduced an interdimensional shift (ID) by using novel pairs of reward-relevant odors. We compared the learning performance of two mouse lines expressing different levels of the kainate receptor subunit, GluK2. GluK2 is a kainate type glutamate receptor with metabotrophic characterictics, whose

disfunction has been implicated in humans with cognitive disabilities (Motazacker et al., 2007). The GluK2 wildtype mice successfully learned to associate a particular odor with the rewarding outcome and reached asymptomatic levels after 10 days of training. Moreover, they applied the reward rule to a different set of odors (ID shift) and reached asymptomatic levels after 5 days of training. In contrast, GluK2 knockout mice could only perform at chance levels. These data show that, mice are capable of associating olfactory information with rewarding outcomes. Furthermore, they can learn a rule and apply it to similar settings by forming an attentional set shift. These findings show that intact cortico-hippocampal processing as well as unimpaired Kainate receptor function in those structures are crucial in storing and recalling reward relevant information for goal-directed behavior.

Zusammenfassung

Kognitive Repräsentationen externer Reize, insbesondere die Repräsentation zukünftiger Möglichkeiten und der jeweilige Wert, der jedem möglichen Ergebnis zugewiesen wird, werden als Bestandteil der neuralen Grundlage zielgerichteten Handelns bei der Entscheidungsfindung diskutiert. In komplexen, multimodalen Szenarien kann dieselbe Reihe externer Stimuli auf verschiedene Arten repräsentiert werden, wobei einige davon effizienter zum Erreichen des Ziels sind als andere. Beispielsweise gibt es in der räumlichen Navigation zahlreiche Möglichkeiten, wie der Raum repräsentiert werden kann. Es wird angenommen, dass sowohl die kognitive Repräsentation des Raums als auch die der zukünftigen Möglichkeiten im Hippocampus als kognitive Karte implementiert sind. Die Faktoren, die bestimmen, welche dieser unzähligen möglichen Repräsentationen vom Hippocampus in einer kognitiven Karte als Orientierungshilfe für das Verhalten gelernt und implementiert werden, sind jedwoch noch weitestgehend unbekannt. Aus diesem Grund haben wir zwei Aufgaben entwickelt, bei denen die jeweilige Belohnungsregel manipuliert wurde, um Repräsentationen unterschiedlicher Stimuli erforderlich zu triggern:

Bei der ersten Manipulation zeichneten wir die Aktivität von CA1-Neuronen in Ratten auf, die eine räumliche Navigationsaufgabe ausführt haben. Olfaktorische Hinweise und räumliche Dimensionen, die dazu dienten, belohnende Ergebnisse vorherzusagen, wurden dabei selektiv geändert. Wir fanden heraus, dass, lag eine olfaktorische Regel der Belohnung zugrunde, die neuronale Aktivität sich graduell in Richtung der Repräsentation olfaktorischer Koordinaten verschoben hat. War die Belohnungsregel dagegen eine räumliche, kam es zu einer allmählichen Verschiebung der neuronalen Repräsentation zu einer verbesserten Kodierung der räumlichen Koordinaten. Diese Neuorganisation der Repräsentation in CA1 ging einer deutlichen Verhaltensverbesserung voraus, was darauf schließen lässt, dass der entscheidende Lernschritt der CA1-Reorganisation nachgeschaltet ist. Diese Ergebnisse zeigen, dass CA1 im Laufe des Lernprozesses die Zellaktivität umgestaltet, um die Aspekte der Erfahrung zu codieren, die für das zielgerichtete Verhalten am relevantesten sind.

Bei der zweiten Manipulation trainierten wir Mäuse in einer komplexen Geruchsunterscheidungsaufgabe in einem vierarmigen Labyrinth und einem

attentional set-shifting Paradigma. In dieser Aufgabe war die Belohnungsregel mit einem von zwei Gerüchen assoziiert, die in zufälligen Positionen im Labyrinth präsentiert wurden. Die Wahl des richtigen Armes im Labyrinth war unabhängig von den räumlichen Dimensionen der Aufgabe. Nachdem das anfängliche Lernen abgeschlossen war, führten wir eine interdimensionale Verschiebung (ID Shift) ein, indem wir neuartige Paare von belohnungsrelevanten Gerüchen verwendeten. Wir verglichen die Lernleistung von zwei Mauslinien mit unterschiedlichen Expressionsniveaus der Kainat-Rezeptor-Untereinheit GluK2. GluK2 ist ein Kainat-Glutamat-Rezeptor mit metabotrophen Eigenschaften, deren Störung bei Menschen mit kognitiven Behinderungen eine Rolle spielt (Motazacker et al., 2007). Die GluK2-Wildtyp-Mäuse lernten erfolgreich, einen bestimmten Geruch mit dem belohnenden Ergebnis in Verbindung zu bringen, und erreichten nach 10 Tagen Training ein asymptomatisches Niveau. Darüber hinaus wandten sie diese Belohnungsregel auf einen anderen Geruchssatz an (ID-Shift) und erreichten nach 5 Tagen Training ein asymptomatisches Niveau. Im Gegensatz dazu konnten GluK2-Knockout-Mäuse nur zufällige Ergebnisse erzielen. Diese Daten zeigen, dass Mäuse in der Lage sind, olfaktorische Informationen mit belohnenden Ergebnissen zu assoziieren. Darüber hinaus können sie eine Regel lernen und mit Hilfe eines attentional set shift auf ähnliche Situationen übertragen. Diese Ergebnisse zeigen, dass intakte cortico-hippokampale Verarbeitung sowie unbeeinträchtigte Funktion des Kainat-Rezeptors in diesen Strukturen von entscheidender Bedeutung für das Speichern und Abrufen von belohnungsrelevanten Informationen für zielgerichtetes Verhalten sind.

Contents

“ All life is problem solving”

Karl Popper

Introduction

Decision making and goal-directed behavior

From surviving in a jungle to maneuvering on a busy highway, animals and humans are often required to respond to complex inputs from their environment. While they are continuously interacting with the world, different neural mechanisms in the brain perceive and integrate multisensory input to select actions as a behavioral outcome. Decision-making may be viewed as the cognitive process of *action-selection*, which entails interaction between multiple neural systems with individual neuronal and computational properties (Cisek and Kalaska, 2010). These actions can be quick responses like reflexes; predictive responses in Pavlovian conditioning (Dayan et al., 2006); learned responses like habits (Sutton, 1998) or deliberate responses, which require making distinct choices (goal-directed action/behavior)(van der Meer et al., 2012; Niv et al., 2006). The latter responses are supported and shaped by additional neural processes, which include the sensory system for perception and interpretation of sensory stimuli, the motivational system for updating the value assigned to each choice and the motor system for selecting a physical action.

Decision-making has been extensively studied to decipher how neuronal signals from different brain structures are integrated to provide a behavioral outcome (Cisek and Kalaska, 2010; Gold and Shadlen, 2007; Kable and Glimcher, 2009; Mysore and Knudsen, 2011; Padoa-Schioppa, 2011; Wallis and Kennerley, 2010). Accumulating evidence has pointed at two main classifications in decision-making: perceptual decision-making and value-based decision-making (Cisek, 2012; Platt, 2002; Sugrue et al., 2005). Perceptual decision-making is the process of perception and integration of sensory information to select an action from a set of alternative actions. Frequently devised experimental approaches use sensory discrimination tasks where researchers control the nature and quality of sensory information and reward the subjects for specific sensorimotor responses (Andersen and Buneo, 2002; Dorris and Glimcher, 2004; Gold and Shadlen, 2001; Leon and Shadlen, 1998; Parker and Newsome, 1998; Rizzolatti and Luppino, 2001). Studies in perceptual decision-making have been successful in defining cortical circuitry in sensori-motor control for action-selection. However, not every correct choice can be immediately derived from a sensory input. Value-based decision making processes incorporate

information about reward and motivation, where the individual selects an action based on the subjective value it assigns to a choice (Rolls et al., 1996; Schall, 2001; Sugrue et al., 2004, 2005b; Tremblay and Schultz, 1999, 2000; Watanabe, 1996). Common experimental paradigms make use of qualitative and quantitative reward manipulations to study neural basis of value-based decisions (Holt and Laury, 2002; Kennerley and Walton, 2011; Padoa-Schioppa, 2011).

Although traditional cognitive psychology compartmentalizes executive functions in the frontal lobe for value-based decisions, and separates them from sensorimotor processing in perceptual decisions, it is hard to assume that these processes work separately or only consecutively in many real-life situations, where the sensory-motor control and value representations of choices are everchanging (Cisek, 2012). For instance, in natural foraging behavior, animals experience multisensory input, including possible risks, while they are presented with new valuable choices as they are already engaged in action of a previous decision in a specific spatial setting. This scenario would require the animals to manage their sensorimotor processing in parallel to resetting their valuation of different outcomes. Furthermore, the spatial attributes of their environment and their geographic proximity to a choice would have significant effects on their decisions. Therefore, theoretically, a neural mechanism should carry out a set of operations to correctly perform a decision-making process:

1.The representation of the goal. Any neural representational system and decision-making process which guide behavior needs to incorporate what the goal is and the goal location to use strategies to achieve it. Both prefrontal cortex (PFC) and the hippocampus have been shown to encode past and future goals and goal locations (Falcone et al., 2016; Hok et al., 2005; Hollup et al., 2001; Save et al., 2008).

2. A comprehensive representation of the current problem depending on the specifics of the decision. Sensory, value, action and spatial representations in cortical and subcortical structures make up the neural correlates of external input and processes for information processing. (Hok et al., 2007; Pleger et al., 2006; Preuschhof et al., 2006; Seamans et al., 2008; Shadlen et al., 1996; Wang and Burkhalter, 2007).

3. Association of certain representations with correct actions, which make "good" decisions and learning of such actions. Habitual learning, motivation and reward

processing in basal ganglia provide a functional hub for action-selection processes (Mink, 1996).

4. Activate a feedback mechanism, which notifies the decision-making circuit of a good or a bad decision. The neurotransmitter dopamine has been shown to play a key role in this step (Korotkova et al., 2006; Morris et al., 2004, 2006)

5. Enable flexibility in the current representation of the problem in (1) to better serve the needs of the problem. The hippocampus has been shown to be able to form multiple internal representations of the environment (cognitive maps), which are encoded in the firing patterns of its principal neurons. Furthermore, the hippocampus has been shown to map both the past experiences and future possibilities and implement changes in its representations when needed (Tolman, 1948; O'Keefe and Dostrovsky, 1971).

The following sections will introduce the neural structures involved in decision making processes for adaptive goal-directed behavior with a focus on the rodent cognition (murines: rats and mice) since it is predominantly involved in both the conceptual and the experimental work presented in this study.

Elements of Goal-directed Behavior are represented in the Frontal cortex

Neuranatomy of Prefrontal Cortex

Convergent evidence from anatomy, phsysiology and lesion studies have shown several distinct regions of rodent prefrontal cortex (Dalley et al., 2004; Uylings and van Eden, 1990) (Figure i1). The rodent prefrontal cortex is divided into 3 subregions: First one is a medial frontal division, whose dorsal and ventral regions include precentral (PrC) and anterior cingulate (ACC) cortices; a ventral region with prelimbic (PrL), infralimbic (IL) and medial orbital (MO) cortices. Second one is a lateral region, which includes the dorsal and ventral agranular insular (AID, AIV) and lateral orbital (LO) cortices. The third region is a ventral region with ventral orbital region (VO) and ventral lateral orbital (VLO). The prefrontal cortex receives higly organized inputs from the thalamus and sends direct projections to the lateral septum, mesencephalon and autonomic regions of the brainstem (Groenewegen et al., 1997). Moreover, PFC receives reciprocal inputs from sensory cortical areas and posterior parietal cortex, as well as from subcortical suctures such as the substantia nigra, ventral tegmental area, amygdala, lateral hypothalamus and hippocampus and it projects back to them (Groenewegen et al., 1997; Kolb, 1984).

PFC also targets the main nuclei of the forebrain cholinergic and monoaminergic neurotransmitter systems including noradrenaline (NA) containing neurons in the locus coeruleus, dopamine (DA) neurons in the ventral tegmental area, serotonin (5-HT) neurons in the raphe' nuclei and acetylcholine (ACh) neurons in the basal forebrain. These neural connections influence inhibitory and excitatory synaptic transmission and neuromodulate cortical processes. Rats with lesions to the prelimbic cortex of the medial PFC show reduced sensitivity to contingency degradation (Balleine and Dickinson, 1998; Corbit and Balleine, 2003) and this loss in experimental action –outcome contingencies result in a decrease in ACh efflux in the prelimbic cortex (PrL) and a substantial increase in NA efflux; there is an increase in 5-HT and DA levels in the PrL during the delay period before obtaining reward (Dalley et al., 2002)

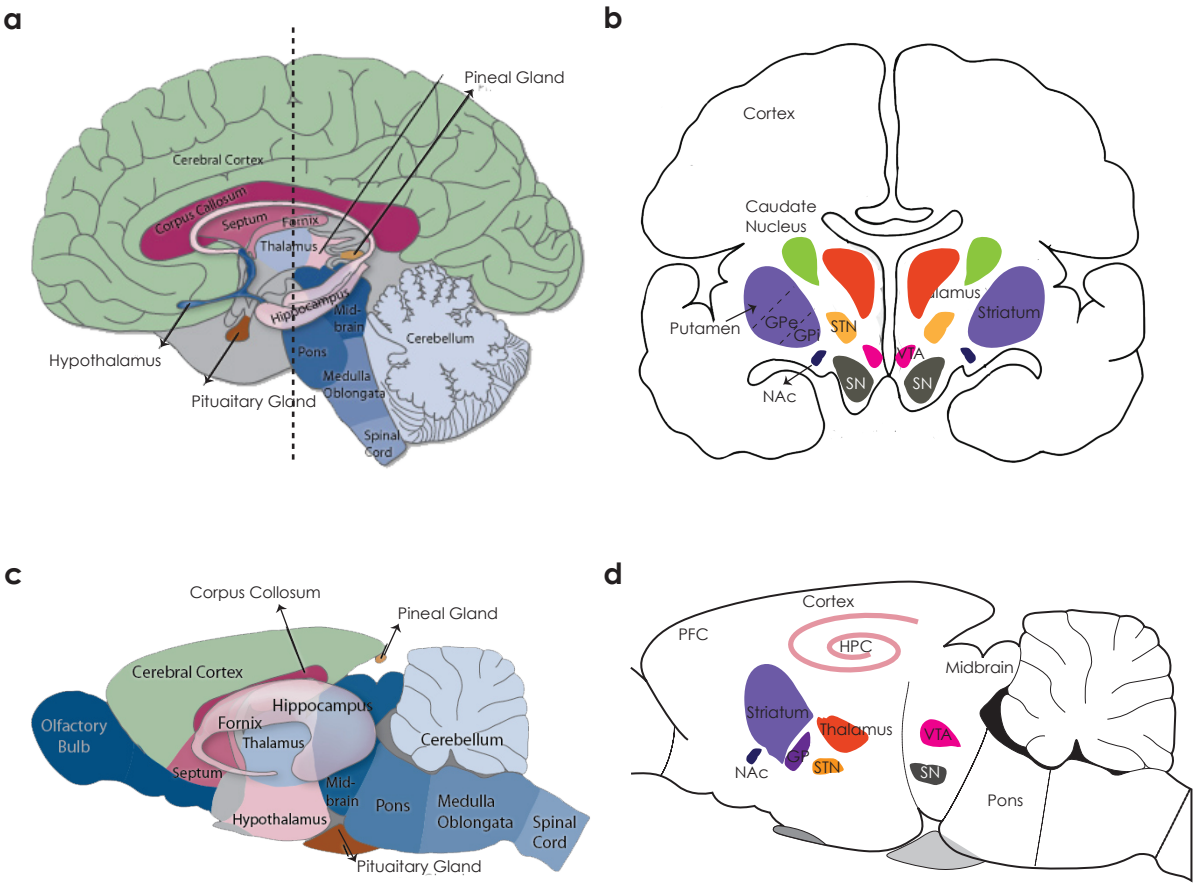

Figure i1 Comparative Illustration of Human and Rat Brain
a Top Left Schematic drawing of human brain, sagittal view. Neural structures are separated by different colors. Dashed line indicates the coronal section in b. **b** Main components of human basal ganglia, coronal section, as indicated by the dashed line in a, : the striatum(dorsal striatum: caudate nucleus, in green, and putamen, in purple; ventral striatum: nucleus accumbens (NAc) and globus pallidus external and internal (GPe and GPi repectively); thalamus in orange; subthalamic nuclei (STN); substantia nigra (SN) in grey; ventral tegmental area (VTA) in pink. **c** Schematic drawing of the rat brain, sagittal view. **d** Illustrative drawing of basal ganglia nuclei and other neural structures in the rat. The prefrontal cortex (PFC), the cortex , the hippocampus (HPC). The other neural structures are abbreviated as in b. Note that there is no caudate nucleus in the rat.

Neural Representations in the Cortex

Multiple areas in rodent sensorimotor and frontal cortex are involved in high order cognitive functions such as planning, problem solving and decision-making. The sensorimotor cortex receives sensory information from all sensory modalities and it is involved in somatosensory, olfactory, auditory and visual processing as well as movement planning. Large portions of the cortex are modulated by inputs from sensory modalities. For the visual modality, multiple cortical areas present tuning curves for light intensity and spatial orientations and represent visual space in the rodent brain (Marshel et al., 2011). However, vision is not their primary sense during navigation and rodents rely heavily on olfactory and somatosensory information. Thus, they devote a large part of their thalamus and cortex to their whiskers, and they have large olfactory bulb. A substantial part of the rodent somatosensory cortex, the barrel cortex, is composed of neurons that tune their activity to specific whisker stimulations, and whisker organization on the snout can be mapped somatotopically onto coloumns in the barrel cortex (Woolsey, 2016). Rodents use their whiskers as a large sensory organ to interact with their environment and the barrel cortex has been used as a reliable model in neuroplasticity studies. Olfactory perception starts in the nasal sensory epithelia neurons whose activities are mapped onto the activity of olfactory sensory neurons in the olfactory bulb and further processed in the piriform cortex (PIR), circumventing the thalamus, in contrast to other modalities (Stettler and Axel, 2009). The rodent piriform cortex can filter out incidental olfactory stimuli and detect novel stimuli (Wilson, 2000a, 2000b); it is capable of converging multiple odor sensations into single perceptual odor-objects (Wilson and Stevenson, 2003a, 2003b) and provide the orbitofrontal cortex (OFC) and hippocampus with information on odor-identity. It has been documented that in complex olfactory-discrimination learning paradigms, there are changes in the intrinsic excitability of neurons in the piriform cortex (Saar et al., 1998, 2001) and the hippocampal CA1 area (Zelcer et al., 2006). The principal projection neurons in the piriform cortex, the pyramidal neurons, typically display a post-burst slow after-hyperpolarization (sAHP) and the post-burst sAHP amplitude in piriform cortex pyramidal neurons is reduced after learning. This initial increase in the intrinsic excitability and reduced post-burst sAHP amplitude has also been reported for hippocampal CA1 pyramidal neurons (Moyer et al., 1996; Saar et al., 1998). These changes are thought to be one of the underlying mechanisms in *metaplasticity*,

defined as the global modulation of plasticity, (Abraham, 2008; Abraham and Bear, 1996; Hulme et al., 2013) which facilitates complex learning.

Together with the prefrontal cortex and the hippocampus, PIR is involved in odor associative and contextual memory (Litaudon et al., 1997; Saar et al., 1999; Schoenbaum and Eichenbaum, 1995).

Over the past decade many functional and anatomical homologies have been described between primate and rodent prefrontal cortex (PFC) (Brown and Bowman, 2002; Kolb, 1984; Seamans et al., 2008). Functionally, the primate dorsolateral prefrontal cortex (dlPFC) is involved in working memory tasks representing goal-related information for planning and problem solving; anterior cingulate cortex (ACC) neurons are active during action-selection and are also associated with attention in action-selection. Furthermore, primate ACC represents value of actions accumulated over time and lesions in this region decrease the ability to form long-term representations of values of certain choices (Hanks and Summerfield, 2017; Seamans et al., 2008). Accumulating evidence from single unit recordings in rodents show that rodent medial prefrontal cortex (mPFC) combines the activity of primate ACC and dlPFC on a basic level. The rodent mPFC is suggested to represent and maintain a particular rule or a strategy. Studies involving inactivation or lesions in the mPFC have shown working memory deficits and decreased ability in switching task rules. The ability to rapidly adjust behavior according to changing rules is therefore considered a function of the PFC, and neuropsychiatric disorders including autism, schizophrenia, addiction and degenerative disorders often affect cognitive flexibility (Braver et al., 2003; Clarke et al., 2007; Shad et al., 2006; Thoma et al., 2007; Verdejo-García et al., 2006). An effective way of measuring the flexibility of PFC in learning is by using attentional set-shifting paradigms, where subjects are presented with changing sets of stimuli and rules to solve a task. In attentional set-shifting, subjects are trained to develop a bias toward a particular dimension of the task (shape or color of an object, odor, light, floor texture, etc.) and after they learn the stimulus-correct choice responses, 3 different discrimination abilities are monitored: (i) different exemplars of stimuli in the same stimulus dimension as the previus trials are introduced (intradimensional shift, ID, for instance a new odor); (ii) a switch is made and a different stimulus dimension now guides correct choices (it is presented along with the previously relevant dimension- extradimensional shift, ED; light instead of odor); (iii) stimulus-reward association is reversed (reversal shift, for instance blue

✔/pink ✖ is switched to blue ✖ /pink ✔). Wisconsin card sorting test (WCST) and it variations have been frequently used in humans and primates, and it has been shown that rodents can achieve formation of an attentional set-shift in odor tasks (Berg, 1948; Birrell and Brown, 2000; Bissonette et al., 2008; Floresco et al., 2006; Garner et al., 2006; Nelson, 1976; Papaleo et al., 2008). Concordantly, frontal lobe lesions or mutations that effect executive cognition in rodents hinder the formation of an attentional set as observed in humans and primates (Kolb, 1984; Schoenbaum et al., 2003a; Uylings et al., 2003; Schoenbaum et al., 2003b). In the case of a reversal shift, where the stimulus-reinforcement pairing is swapped but the test stimuli and the relevant stimulus dimension are unchanged, the reversal learning of the opposite stimuli-reinforcement value pairing is suggested to be mediated by OFC (McAlonan and Brown, 2003; Schoenbaum and Roesch, 2005). Furthermore, OFC, whose activity is correlated with outcome predictions, value of choices, control of impulsive choices and confidence in perceptual decisions in primates (Bechara et al., 2000; Thorpe et al., 1983), exhibit similar neuronal coding properties in rodent OFC. Moreover, through reciprocal connections with piriform cortex, OFC neurons provide contextual information based on past experiences. Thus, OFC can help the system recognize a particular odor more quickly in olfactory learning and facilitate adaptation in goal-directed behavior in rodents (Feierstein et al., 2006; Furuyashiki et al., 2008; Roesch et al., 2006). Another cortical area, which receives input from auditory, visual and somatosensory cortex, is posterior parietal cortex (PPC), carrying navigation and working-memory related signals. During decision-making tasks PPC neurons gradually increase their activity in case of accumulating sensory information, for instance, PPC neurons are active when a mouse holds a decision in mind. Both anatomical, lesion and physiological data obtained from the rodents show that PFC serves as a supervisory hub for maintaining attention and detection of action-outcome contingencies, providing a base for goal-directed behavior in decision-making (Balleine and Dickinson, 1998; Bussey et al., 1997).

In addition to the representations in sensory and frontal cortices, the entorhinal cortex (EC), which is located in the caudal end of the temporal lobe, provides the system with metric representations of space (Hafting et al., 2005; Moser et al., 2014) and also participates in mnemonic coding (Boccara et al., 2019). These representations are encoded in the activity of its grid cells, and EC neuronal activity correlates with the current perception of space as well as directon of movement

and speed of the animal (Chen et al., 2019; Kropff et al., 2015). Importantly, the EC is the primary input structure of the hippocampus, which plays an essential role in declarative memory and formation of flexible context-dependent representations of space (cognitive maps), combines general spatial properties and unique features of the environment in a neural map (Aronov and Tank, 2014; Aronov et al., 2017; Eichenbaum, 2017; Jeffery, 2007a; O'Keefe, 1978; Shapiro et al., 1997; Tolman, 1948).

Additionally, PFC projects directly to EC (Vertes, 2004) and indirectly via the nucleus reuniens of thalamus (Cassel et al., 2013; Hoover and Vertes, 2012; Varela et al., 2014). It has been discussed that these projections might relay information from PFC to hippocampus. Concordantly, lesioning and pharmacological inactivation of PFC affect hippocampal place fields (Hok et al., 2013; Kyd and Bilkey, 2005). Therefore, PFC –hippocampal interactions could be a crucial part of navigational and goal-directed planning in decision-making.

Hippocampal representations and goal-directed behavior

Neuroanatomy of the hippocampus

The hippocampus is located in the temporal lobe of the mammalian brain (Figure i2). Although the size and the shape of the hippocampus vary across mammalian species, its functions are highly conserved. At the circuit level, the hippocampus is divided into 4 fields: Dentate gyrus (DG), CA1, CA2, CA3 (Figurei2), and unlike most cortical structures, the connectivity between these fields is mostly feed-forward. The main cortical input structure of hippocampus is entorhinal cortex (EC). Both the lateral and medial subdivisions of EC provide input to the HPC formation, with layer II of medial entorhinal cortex (MEC) projecting to the DG, CA3 and CA2, and layer III of MEC projecting to CA1 and the subiculum. CA1 and the subiculum provide output to layer V of EC (Amaral and Witter, 1989; Andersen et al., 2006, 2004). Two pathways, starting in MEC and lateral entorhinal cortex (LEC), converge onto single neurons in the DG, CA3 and CA2, but target different neurons in CA1 and the subiculum (Figure i2). Projections from MEC target proximal neurons CA1 (close to CA2) but distal neurons in the subiculum (close to the PrS). Layer II of LEC and MEC project to the granule cells of DG, whose axons make synapses with the pyramidal cells of CA3. The CA3 pyramidal cells provide the main input to the CA1 pyramidal cells. CA1 also receives direct input from both LEC and MEC; and it projects to subiculum and deep layers of EC. Besides EC, another major projection from hippocampus goes to the lateral septal area via the fornix and to the mammillary body of the hypothalamus. CA1 and subiculum send direct connections to prelimbic cortex (van Groen and Wyss, 1990; Jay et al., 1989; Swanson and Cowan, 1977; Tierney et al., 2004; Verwer et al., 1997), and CA1 sends also indirect projections to the prelimbix cortex via the anterior thalamic nuclei (Cenquizca and Swanson, 2007; Prasad and Chudasama, 2013; Varela et al., 2014). Direct projections from hippocampal pyramidal cells synapse onto both the pyramidal neurons (Carr and Sesack, 1996) and local inhibitory interneurons in the PFC (Gabbott et al., 2002).

The hippocampus also receives modulatory dopaminergic projections from VTA and SNc; strong choligernic projections from medial septum (MS); noradrenergic projections from locus corelous (LC); which regulate the physiological state of hippocampal theta rhythm and formation of memory (Cobb and Davies, 2005; Gomperts et al., 2015; Hopkins and Johnston, 1984; Rossato et al., 2009).

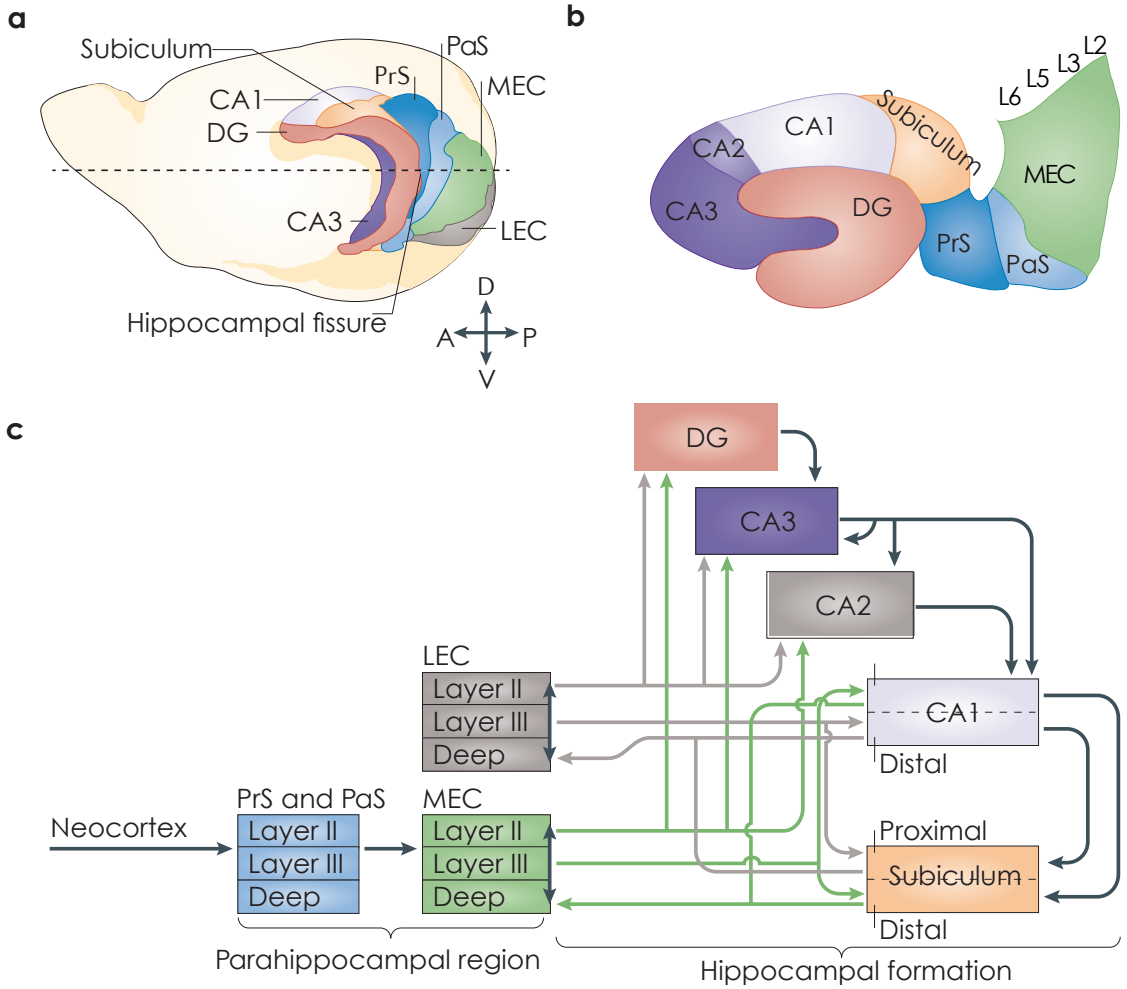

Figure i2 Hippocampal formation and its Circuitry in the rodent brain **a** Illustrative drawing of the right hemisphere of a rat brain, with a focus on the hippocampal formation and the parahippocampal region. (A, anterior; D, dorsal; P, posterior; V, ventral). **b** horizontal section through the right hemisphere; The dorsoventral position of the section is indicated by the dashed line in a. Together, the images in a and b illustrate the positions of hippocampal and parahippocampal areas: the dentate gyrus (DG), CA1–CA3, the subiculum, the medial entorhinal cortex (MEC)with 4 layers (L2-6), the lateral entorhinal cortex (LEC), the PrS and the PaS. The borders and the extent of individual subregions are colour-coded **c** The connectivity model of the hippocampal formation and parahippocampal region. Reciprocal connections are indicated by double-headed arrows. (Adapted from Moser 2014)

Neural representations in the hippocampus

The hippocampus is undoubtedly the most studied neural structure in experimental neuroscience. This interest has stemmed from two independent lines of consideration. On one hand, the relatively easy approach, the distinctively structured anatomy and the considerable size in rodents have all contributed to the study of the hippocampus as a model system for basic principles in neuroscience. Thus, such diverse phenomena as long term synaptic plasticity (Bliss and Lomo, 1973), intrinsic plasticity (Coulter et al., 1989; de Jonge et al., 1990), state related network oscillations (Harper, 1971) and spike timing dependent plasticity (Bi and Poo, 1999) have all been described and studied in the hippocampus, but have been shown to apply to other brain regions as well. On the other hand, specific studies of hippocampal function were inspired by two robust findings: First, the severe amnesia induced by lesions of the hippocampal formation (Konkel and Cohen, 2009; Scoville and Milner, 2000; Zola-Morgan et al., 1986). Second, the fact that when recorded in moving rats, hippocampal primary neurons tend to fire in specific locations in the environment (O'Keefe and Dostrovsky, 1971b). These cells, which carry the activity patterns of hippocampal pyramidal neurons, are termed as "*place cells*", and the location at which they selectively fire is called a place cell's "*place field*". The seminal discovery of places cells has made the hippocampus the locus of forming spatial representations of the environment (O'Keefe, 1978) and it was recognized as the site for construction of cognitive maps in the brain.

Declarative Memory and Navigation

Both patients and model animals with lesions in the hippocampal regions are primarily impaired in tasks involving declarative memory (memory for facts and events). A prevailing theory of hippocampal function is that it is involved in the creation of declarative memories (Squire, 2004; Squire and Zola, 1996; Squire and Zola-Morgan, 1988). While the declarative memory theory has been very influential, its operational predictions are hard to investigate. However, a number of features believed to be unique to declarative memory have yielded more specific models of hippocampal memory. Declarative memory is almost synonymous with explicit memory: memory based on explicit recollection of prior learning episodes. Therefore, some groups have assigned the hippocampus with the role of explicit recollection (Aggleton and Brown, 2006; Gilboa et al., 2006). In an attempt to precisely locate the

anatomical substructures, cellular and molecular mechanisms involved in the various processes of declarative memory, a number of memory tests have been devised for use with rodents. The most famous one, now the first of every battery of behavioral testing conducted with genetically modified animals, is the Morris water maze (Morris, 1984). Indeed, animals with hippocampal lesions are impaired in this task (Moser et al., 1995; Riedel et al., 1999), as are rats with disabled NMDA receptor functioning (Davis et al., 1992).

In the Morris Water maze, a mouse/rat must navigate in a water reservoir using visual cues from the environment to safely reach a hidden or a visible platform. In the Morris water maze task, navigational strategies that are used by the rodents can be easily separated and manipulated. The animals can follow 5 different navigational strategies to find the platform (Gerstner and Abbott, 1997; O'Keefe, 1978; Sutherland et al., 1983; Whishaw and Mittleman, 1986):

Random navigation: The animal has no prior knowledge of information about the platform's location and it randomly explores the pool (Archer, 1983; Renner, 1990) .

Taxon navigation: The animal can use a cue, which will serve as a beacon for orientation. For instance, if the platform is visible, the animal can swim *towards* it. Concordantly, if the platform is in close proximity to another cue, the animal will orient itself towards that cue (Gallistel, 1990; Schone , 1985).

Praxic navigation: if the location of the platform is constant, the animal can use a series of motor movements, which will lead it to the platform. The animal starts swimming at the same location using the same orientation and it finally reaches the platform (Eichenbaum et al., 1990; Moghaddam and Bures, 1996; Save and Moghaddam, 1996)

Route navigation: Animals use combinations of taxon and praxic strategies to navigate and learn to associate direction with available cues. Early studies on navigation used sequences of T-junctions in complex mazes, in which animals used sequences of taxon and praxic navigation strategies, to create route strategies (O'Keefe and Nadel, 1978)

Place navigation: The animals learn to use cue patterns to construct a map of their environment and relate the location of the platform to the map. Moreover, the

animals can identify its own location in one coordinate system and learn to relate the platform's location to it and plan their route (Tolman, 1948).

There are other classifications that have been proposed in rodent navigation. Some researchers further divided different orientations, such as chemotaxes (orientation to odors), phototaxes (orientation to light) (Schone , 1985; Russell, 1941). Kuiper's and Trullier proposed a hierarchical organization in navigation where first level is based on simple stimulus-response abilities but higher level strategies involve using combinations of topographical and geographical information as well as determining self-location and goal finding(Lee, 1996; Trullier et al., 1997) which could all be classified as place navigation.

Besides the study of declarative memory in the hippocampus, another line of thought has focused on the nature of declarative representations, *relational representation theory*, particularly on their flexibility and ability to generate generalization and inferences (Konkel and Cohen, 2009; Reber et al., 1996). It is claimed that this type of memory centers on the ability to store the relations between the various ingredients in the memory. Such relations may be temporal (Kumaran and Maguire, 2006), spatial (Spiers and Maguire, 2006) or associative (Konkel et al., 2008; Ranganath et al., 2004). During place navigation, animals can store declarative representation including both spatial and non-spatial features of the external space and express them in an internal representation system. Such internal, neural representations are called cognitive maps, and animals are thought to be capable of creating and using multiple cognitive maps (Tolman, 1948).

Cognitive Map theory

Cognitive map theory dates backs to 20th century psychologist Edward Tolman who opposed to the behavioristic notion that all behavior was stimulus-response conditioning. He carried out maze learning experiments for rats, in which they freely explored differently structured mazes to find food pellets. After learning, the number of errors (walking blind alleys) as well as the latency to reward was reported to have decreased. Interestingly, when the food pellets were introduced later into the training, rats avoided the blind alleys and reached the reward port in a shorter time compared to non-rewarding trials (Tolman and Honzik, 1930). These data suggested that the animals had mapped their environment earlier, even in non-rewarding trials.

Thus, Tolman suggested that, incoming stimuli are worked over in the brain in a tentative map, where routes and paths and environmental relationships are represented and, when needed, a stripped map is utilized to aid goal-directed behavior. He also designed a remarkable two-step food foraging task for rats (Tolman et al., 1946), where in the training step (first step), rats learned to through a corridor with a number of turns to reach the reward retrieval point. In the second step of training, the apparatus had changed such that the same route was no longer possible, but the reward was still at the same location, which was now at the end of one of the arms of a sun-burst maze. Rats chose mostly the arm that pointed towards the 'place' where the reward had been in step 1. The second most-visited arm was one of the apparatus compartments, which led to reward in step 1. These experiments suggested that rats were capable of forming and using a comprehensive map, which included a sense of direction as well as a manual to run along a certain path to retrieve reward. Tolman proposed that goal-directed planning is processed by using internal models of learnt environments (Tolman, 1948) where each model represents the connections between different inputs through actions in a "cognitive map", which collects, encodes, stores, recalls and decodes information about the relative locations and attributes of an actual or a symbolic spatial environment. Cognitive maps enable animals to construct spatial knowledge, and help them combine navigational strategies to move towards a goal. Among the navigational strategies rodents use, the place navigation strategy stands out because it utilizes one or multiple cognitive maps. In the rodent navigation system, several spatial parameters have been shown to be represented and used by the animals, as outlined below:

Local view: The local view theory deals with relational representations of landmarks (Kesner and Olton, 1990). The term implies having a particular sight from a particular viewing position. However, the local view includes not only the visual and but also the non-visual cues (auditory, olfactory and somatosensory cues), the spatial and non-spatial features of landmarks (brightness of a light cue) (Bostock et al., 1991).

In the primates, the evidence suggests that there are two representational pathways for local view: the dorsal visual stream which passes through parietal cortex carrying spatial aspects of local view, and the ventral visual stream, which passes through

inferotemporal cortex and represents identity aspects of local view. There is evidence to support a similar distinction in rodents (Kolb et al., 1994).

Path integration relates to metric representations of position. It has been shown that animals are able to return to a reference point from any location in an environment. Over the past two decades a number of structures has been implicated to be involved in path integration in the rodent brain. Both hippocampal (Samsonovich and McNaughton, 1997)and subicular lesions (Sharp, 1997) disrupt path integration, and it has been hypothesized that the subiculum-parasubiculum-superficial entorhinal cortex loop plays the crucial role in path integration, updating the hippocampal place code in rodents (Redish and Touretzky, 1997).

Head direction is related to orientation. A number of structures in the rodent brain have been shown to have cells that tune their firing to head direction. These include post-subiculum (Taube et al., 1990), the anterior thalamic nuclei (ATN) (Blair and Sharp, 1995; Knierim et al., 1995; Taube et al., 1990), the lateral mammillary nuclei (LMN) (leonard, stackman and taube 1996), the lateral dorsal nucleus of the thalamus (LDN) (Mizumori and Williams, 1993) and to a lesser extent the posterial, parietal and cingulate cortices (PPC and PCC) (Chen et al., 1994a, 1994b)

Goal memory: Although head direction and path integration help animals with their spatial orientation, it is not enough to find a goal from any coordinate system. Therefore, it is essential to compute a path in the coordinate system that is useful for the current goal. Goal memory is a representation that incorporates motivational and spatial inputs and contains trajectory planning to reach the goal. Rodents are capable of learning complex routes in mazes by integrating information on current location and their needs. Posterior cingulate cortex receives input from subiculum (Brent A. Vogt, 1993; Wyss and Van Groen, 1992), which provides information on location of the animal; anterior thalamic nuclei (Sripanidkulchai and Wyss, 1986; Wyass and Groen, 1992) and the postsubiculum (Finch, 1993), which are components of head direction system. Lesions of the PCC result in impairment of navigation in the water maze (Sutherland and Hoesing, 1993). Therefore, PPC has been suggested to play a role in the long term storage of routes (Redish and Touretzky, 1997; Sutherland and Hoesing, 1993).

Grid cells: The metric representation for local space is encoded in the activity of *grid cells* of the medial entorhinal cortex (MEC). Grid cells tune their firing to multiple discrete and regularly spaced locations (Hafting et al., 2005). Their firing locations form a hexagonal pattern. Positional relationship between grid cell ensembles are maintained from one environment to another. Therefore the changes in the surrounding environment does not affect the spatial relationship between their firing fields (Fyhn et al., 2007). The activity of grid cells is dynamic and strongly dependent on motion cues (proprioceptive inputs and optic flow), which suggests that their representations are based on path integration. Since the EC projects strongly onto the hippocampus (Figure i2) and their activity is synchronized through 4Hz oscillations, it is believed that EC provides the hippocampus with general metric information about the environment, and the hippocampus creates representations which are specific to an individual environment (context dependent representations for place code).

Place code: Place code refers to the distributed representation of position, which connects landmarks to the metric representations of the environment. For animals to navigate within a familiar environment, they need to use a consistent representation of position from trial to trial. Cognitive map theory proposes that the hippocampus serves as an internal model of the environment. In their famous experiment, O' Keefe and Dostoevsky implanted single electrodes and wire bundles into the CA1 region of the hippocampus and allowed the rat to freely explore a square arena. They recorded extracellular single unit activity and realized that different cells tuned their firing to different locations and to different tactile stimuli in the arena. (O'Keefe and Dostrovsky, 1971). Ever since their discovery, many studies of the hippocampus have focused on the activity and properties of place cells and a large body of evidence has shown that single neurons of the hippocampus, recorded during awake, intact behavior fire in specific locations in the environment (O'Keefe and Dostrovsky, 1971;Mehta et al., 2000;Junge et al., 1998;Knierim and McNaughton, 2001;Nakazawa et al., 2004;Battaglia et al., 2004;Leutgeb et al., 2005;Dragoi and Buzsaki, 2006;Johnson and Redish, 2007;Jeffery, 2007;Kjelstrup et al., 2008).

Properties of Place cells in the hippocampus

A place cell will mostly (but not always) have a single place field in standard experimental environments, but it will have more place fields in larger environments.

Remarkably, when an animal is reintroduced to a familiar environment the place fields of neurons remain unchanged. Moreover, they continue to have their place fields in the dark (Quirk et al., 1990; Save et al., 1998; Zhang et al., 2014). Place cells are mainly inactive outside of their place fields, and their firing patterns can be modulated by both distal and proximal cues in the environment (Carman and Mactutus, 2002; Renaudineau et al., 2007; Save et al., 1998). The firing patterns of hippocampal place cells have shown to change with more than the location of the animal, like with change in contextual specificity, including colors and odors (Hayman et al., 2003); stage of a task of match/non-match of samples, and even with a change in problem solving strategies (Yeshenko et al., 2004), allowing for a multimodal internal representation (Poucet et al., 2000; Takahashi and Sakurai, 2009).

Place cells fire non-topographically. Thus, place fields of neighboring place cells are not necessarily close to each other (Redish et al., 2001), however the location of the animal can be decoded by studying the ensemble activity of place cells (Wilson and McNaughton, 1993).

The size and shape of place fields are affected by the size and geometry of the rats' environment (Kjelstrup et al., 2008; Muller and Kubie, 1987a; O'Keefe and Burgess, 1996). Place cells in the dorsal hippocampus tend to have more confined place fields, whereas in the intermediate and ventral regions they have more sparse place fields (Jung et al., 1994; Maurer et al., 2005; Muller and Kubie, 1987b).

Besides their constancy in their representation in familiar environments, place cells are also very dynamic in their representations. When animals are transferred to a new environment, or when the attributes of the environment change, cells change their place fields in a seemingly unpredictable manner (random remapping/orthogonalization) (Anderson and Jeffery, 2003; Cressant et al., 2002; Jeffery et al., 2003; Leutgeb et al., 2005; Wilson and McNaughton, 1993). This phenomenon is termed remapping.

Hippocampal states and remapping

When looking at the local field potential (LFP) of the hippocampus, representing large scale population activity, it is composed of consequtieve states of neuronal population activity, which is a reliable indicator hippocampal information processing (Kemere et al., 2013). When animals are actively exploring, hippocampal oscillations

are recorded between 7-10 Hz freuquency band, called the theta oscillations (Buzsáki, 2002; Hasselmo and Stern, 2014) . Each place cell of the hippocampus fires at a particular phase on the theta cycle during exploration, but they gradually shift their firing to an earlier time, thus allowing for rapid information encoding (theta phase-precession) (O'Keefe and Recce, 1993; Skaggs et al., 1996).

When animals are resting or are not exploring, a distinct hippocampal state shows brief high frequency oscillations between 150-250 Hz. These oscillarions are termed sharp-wave ripples (SWRs), which originate from the CA3 region and propagate to the CA1 (Buzsáki, 1986; Csicsvari et al., 2000). Neuronal ensembles, which were active during exploration, become reactivated in a temporally preserved manner, providing a rapid replay of past experiences. SWRs can be observed during sleep, inactivity, as well as during awake states, especially when reward locations change frequently and animals need to form and retrieve memory traces to efficiently obtain reward. Together with theta phase precession, SWR form a functional framework for forming and maintenance of hippocampal representations in a outcome-relevant manner (Davidson et al., 2009; Diba and Buzsáki, 2007; Dupret et al., 2010a; Foster and Wilson, 2006; Jackson et al., 2006; Kudrimoti et al., 1999; Singer and Frank, 2009).

If indeed the brain uses the hippocampus as its cognitive map for goal-directed behavior, its output, the CA1 pyramidal neurons, should represent behaviorally relevant properties of the environment in a preferential manner. As mentioned earlier, CA1 pyramidal cells respond to different modalities (Jeffery, 2007) and are sensitive to changes in metrics (O'Keefe and Burgess, 1996) and environmental contexts (Komorowski et al., 2009) and task requirements (Markus et al., 1995) allowing for flexible representations of complex inputs. In a fixed environment, the representation of these cells has been shown to be remarkably stable. However, in new or sufficiently changed environments, these cells remap by adjusting and altering their place-fields (Leutgeb et al., 2005; Muller and Kubie, 1987). Detecting this remapping phenomenon may be utilized as a marker for the behavioral relevance of the different environmental feature sets.

Reinforcement learning and goal-directed behavior

Neuroanatomy of Basal Ganglia

The basal ganglia consist of a group of nuclei (the basal nuclei) in the brain of vertebrates, which is situated at the base of the forebrain (Figure i1). The basal ganglia are interconnected with cerebral cortex, thalamus and the brain stem and its function has been implicated in execution of movement, cognition, motivational learning and emotional processing (Haber et al., 2000).

The main components of basal ganglia are the striatum (dorsal striatum: caudate nucleus and putamen; ventral striatum: nucleus accumbens and olfactory tubercle), globus pallidus, substantia nigra, subthalamic nucleus (Figure i1). The size and composition of basal nuclei vary between primates (including humans) and rats but their connectivity and functions exhibit very similar properties. The primary input structure of basal ganglia is the striatum and it receives excitatory glutamergic input from cortex, amygdala and the hippocampus and additional input arrives via thalamus; dopaminergic input from substantia nigra pars compacta (SNc) and sends inhibitory projections to output nuclei of basal ganglia, which are the internal segment of globus pallidus (GPi); substantia nigra pars reticulara (Snr) and the ventral pallidum. The output nuclei, then, exert GABAergic inhibitory effect on their target thalamic nuclei, which projects back to globus pallidus (Alexander and Crutcher, 1990; Gerfen, 1992)

Neural Correlates of Reinforcement Learning

As animals respond to sensory stimuli, typically, the chosen responses are those yielding favorable outcomes or *reinforcement*. In reinforced behavior, animals learn to adapt their choices of action to discover which actions will maximize rewarding outcomes. Theoretical and behavioral principles underlying reinforcement learning of these adaptive choices have been well studied since the foundation of behavioral psychology (Pavlov, 1927; Skinner, 1974; Thorndike, 1911) and are best known as 'the law of effect' (Thorndike, 1911). Edward Lee Thorndike, the famous 19th century psychologist, designed puzzle boxes for cats, dogs and chicks in which they learned to press a lever or pull a string to escape the box to retrieve food. After the learning phase, animals adopted the rewarding responses, and decreased the useless responses (e.g., scratching the floor and the bars). Thorndike coined the term

'law of effect', which argues that if an association between a stimuli and a response in a state leads to a satisfying state, those responses are likely to be strengthened, and if the association leads to an unsatisfying state then those responses are likely to be weakened. Therefore, action selection requires the correct identification of the stimuli-set and learning what aspects of a complex environment are relevant for each task. It is believed that learning of action selection is carried out through *reinforcement learning* and accumulating anatomical, physiological and pathophysiological evidence has shown basal ganglia as the main neural structure for the action selection processes(Mink, 1996).

For learning of the action selection to occur, there should be a discrepancy between expected and actual outcomes and this difference should be represented in the neuronal activity. Computational reinforcement learning models have theorized that dopamine neurons in basal ganglia carry a *reward prediction error signal* to their targets (Montague et al., 1996; Schultz et al., 1997a) which contains the difference between the value of an expected outcome and the one actually received (Montague, 1999; Niv and Schoenbaum, 2008). Concordantly, data from both primates and rats show that responses of dopamine neurons convey the reward prediction error signal (Morris et al., 2004, 2006; Roesch et al., 2007; Tobler et al., 2005). The main source of dopamine in the midbrain are dopaminergic neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) (Andén et al., 1964). Axonal projections from these neurons provide dopaminergic (DA) innervation of the striatal complex (dorsal striatum) and nucleus accumbens (ventral striatum) and, to a lesser amount, innervation of subthalamic nucleus and globus palllidus. Dopaminergic innervation of the striatum facilitates LTP in the striatum and the reinforcement learning of sensori-motor actions takes place. Moreover, most of the glutamergic cortico-striatal synapses are adjacent to dopaminergic terminals (Moss and Bolam, 2008) and thus, dopaminergic signals are in a prime position to modulate plasticity in the cortico-striatal pathways and learning in the basal ganglia. DA input from VTA and Snc, as well as a separate projection from VTA reaches the hippocampus, amygdala and prefrontal cortex, which are partially connected back to the striatum (Nestler et al., 2015).

Dopaminergic input onto the hippocampus

Hippocampus receives topographically preserved input from VTA and SNc, and like in the striatum these projections facilitate LTP in the hippocampus (Gasbarri et al., 1994). It has been suggested that VTA and hippocampus form a functional loop for novelty detection. It has been suggested that, VTA projections to hippocampus control the entry of behaviorally significant information into the hippocampus and monitor the formation of long-term memory (Lisman and Grace, 2005). It has been shown that dopamine nuclei and VTA activation modifies hippocampal encoding and generalization (Shohamy and Wagner, 2008; Wittmann et al., 2005), VTA and HPC synchronize through 4 Hz oscillations (Fujisawa and Buzsáki, 2011) and lesions in VTA result in spatial working memory deficits (Gasbarri et al., 1996). In addition blocking of D1/D5 receptors in the hippocampus disturbs spatial learning (O'Carroll et al., 2006).

Working Hypothesis

In many learning scenarios, adequate input identification is crucial. To actually implement the "law of effect" in the real world, it should be essential to learn about the relevant parameters in the initial state and decide which attributes of the state are crucial for the current state for adaptive goal-directed behavior. Choices in real-life situations always involve cues that are of a multidimensional, often of multimodal nature, and thus, are extremely difficult to categorize. In particular, planned goal-directed behavior requires sampling of complex combinations of stimuli from several different senses. This plethora of information gives rise to numerous, equally possible ways to categorize stimuli; thus, emphasizing the need to single out the most relevant cues for deciding the best course of action.

We hypothesize that rodents use cortico-hippocampal interactions and dopaminergic modulation of these structures for navigational decisions by planning and evaluating prospective routes and adjust their hippocampal representations along significant aspects of a setting by dynamically tracking reward contingencies.

In this work we propose that the hippocampal representations of the environment is organized in an outcome relevant map, which will represent only a subset of dimensions that will be efficient in retaining useful information to allow for practical planning and allow generalization. Furthermore, we hypothesize that construction of multiple cognitive maps is a dynamic learning process, which tracks the record of relevant information and is contingent upon reward. To test this hypothesis we trained animals to solve two types of problems:
1. A spatial problem, which requires learning to represent space according to one of two spatial rules. We recorded the activity of CA1 neurons of rats performing a spatial navigation task, where different subsets of spatial dimensions were manipulated to predict rewarding outcomes independently of other dimensions. We recorded the activity of hippocampal CA1 place cells during the course of learning, and analysed changes in their place fields to see if there is a gradual shift towards encoding stimuli that are predictive of goal-related outcomes.

2. A rule-based attentional shifting multidimensional-discrimination problem, which requires learning of an olfactory rule. We trained mice to learn an odor discrimination task to associate a particular odor with reward. We, later, implemented an

intradimensional shift and trained the mice with a new set of odors to see if the previous learning of correct choices guided the animals to apply the olfactory rule to a new setting.

Methods

Ethics statement and animals

All experimental procedures were conducted in strict accordance with the Institutional Animal Care and Use Committee of the Haifa University, Berlin State, as well as the EU rules and regulations for the use of animals in science research.

Rats

Seven male Long-Evans rats (Charles-River, 12-18 weeks old at beginning of experiments) were used in the rotatable olfactory ring track task. The first Long-Evans rat was bred by Dr Long And Dr Evans by crossing an albino female in Wistar Institute (later known as Wistar rat) and a wild male rat (rattus norvegicus). The Long-Evans strain is an outbred laboratory rat, which is considered as the golden standard in behavioral studies among other fields of study such as ageing, nutrition, metabolism and toxicology. They are also frequently used in behavioral electrophysiology due to their rapid learning skills (Gökçek-Saraç et al., 2015; Harker and Whishaw, 2002; Turner and Burne, 2014)

The rats were maintained in a 12 h light/12 h dark cycle with unlimited access to food and water prior to the start of the experiments. Food restriction is a commonly used protocol to increase motivation of animals in behavioral experiments. However, we chose to restrict rats' water consumption to eliminate the electrical noise that chewing introduces to electrophysiological recordings. The animals' water consumption was restricted to 1/2 hour every 24 hours and their body weight was maintained at 90% of their baseline measure.

Mice

14 genetically modified C57Bl6 mice (GluK2 wildtype =9 and GluK2 knockout =5) were trained in the olfactory plus maze. 57Bl6 mice are documented to be fast learners, display relatively low anxiety levels and are also frequently used in transgenic studies. The mice were maintained in a 12 h light/12 h dark cycle with unlimited access to food and water prior to the start of the experiments. Experiments were designed for an apparatus, which delivered liquid reward. We restricted the mice's water consumption to increase learning motivation, and mice were restricted

to 1/2 hour of water consumption every 24 hours to maintain 85% of their baseline body weight. Due to time limitations, mice were only subjected to behavioral training. No electrophysiological recordings were carried out.

Apparatus and Behavioral Task

The laboratory space was divided into two compartments. The first compartment consisted of the recording system (Neuralynx, US or Axona LTD, UK) and a computer, which were located outside the recording area. The second compartment consisted of the behavioral equipment for training, a camera for tracking animal positions and recording cables for electrophysiological acquisition. The recording area, was surrounded by a custom made faraday cage and covered by opaque black curtains. A faraday cage (Michael Faraday, 1836), commonly used to shield the area of electrophysiological recordings from external noise, built with conductive metal mesh and connected to an earth-outlet to ground the accumulated electrical charges on the mesh.

Rotatable Olfactory Ring Track

The apparatus used for the spatial set navigation task was a 60 cm diameter (outer), 10 cm wide annular shaped black wooden running track . It was situated 1 m above the floor on a rotating stand. The track was lined with twelve 3 mm wide holes, through which a unique set of four odors was delivered in four equally spaced odor delivery points (Figure M1a). The odors used were commercial scents regularly used in the cosmetics and food industry, diluted 1:1000 from concentrated liquid. All experiments were conducted in the dark to prevent interference of visual cues.

On each trial, the rats were placed in a constant position in the maze (in lab coordinates) and were allowed to explore the maze for 2 minutes and locate their liquid reward (0.3 ml water). Following each trial, the rats were removed from the arena and the arena was rotated to a new angle in a pseudo-random fashion. Reward location depended on the experimental condition. For one group of animals (RR condition), reward was delivered at a constant position between 2 odors (Figure M1a), and for the other group (CR) at a constant position in lab coordinates (Figure M1b). Animals underwent 10 daily trials for 20 days. The animals' position and neuronal activity were recorded continuously throughout the experiments.

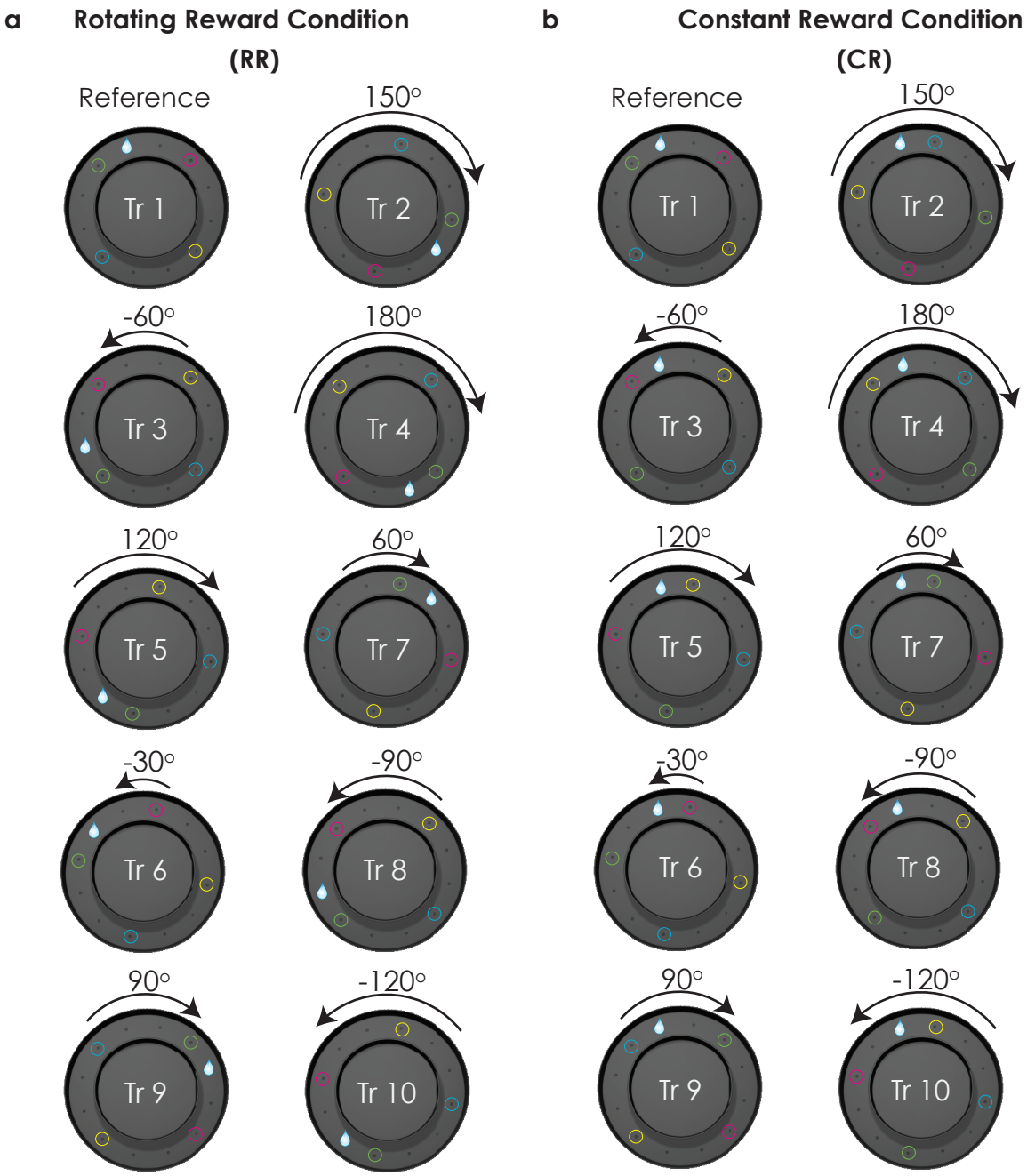

Figure M1 Rotatable olfactory ring track task
a Behavioral setup in the Rotatable Reward (RR) configuration. A rotatable ring track with four equally spaced odor delivery ports (colored circles) was rotated for 10 daily trials (Tr 1-10). The angle and the direction of each rotation is showed by curved arrows above each scheme. Liquid reward (water, in blue) was delivered in a predefined position between two particular odors (between green and pink circles) **b** Behavioral setup in the Constant Reward configuration (CR). The ring track with four equally spaced odor delivery ports was rotated for 10 daily trials. The angle and the direction of each rotation is showed by the curved arrows above each scheme. Liquid reward (water, in blue) was delivered in a predefined position in lab coordinates.

Olfactory Plus Maze

The apparatus used for the olfactory set-learning task was a black Plexiglas elevated plus maze with four 10x30 cm arms and a 15x15 central hub (Figure M7a and Figure M7c). The entrances to the arms were blocked by guillotine doors (Figure M7). Infrared (IR) sensors at both ends of the arms marked arm entry and track completion. The central hub was equipped with four nose pokes located on the floor, 2 cm away from each door. The nose pokes had IR sensors to detect nose entry, yellow colored light emitting diodes (LEDs) and two tubes through which odorized air was delivered and pumped out. Each odor delivery tube could deliver 2 different odors. The odors used were commercial odors that are regularly used in the cosmetics and food industry, diluted 1:1000 from commercially concentrated liquid. Experiments were conducted in dim light. Each trial started with mice located in the central hub of the maze. After a variable inter-trial interval, 2 pseudo-randomly chosen nose pokes were illuminated by LEDs. Two different odors were delivered to these nose pokes. Upon LED activation in the 2 nose pokes, the doors of the corresponding arms were manually opened and access to the arms was allowed. Mice chose an arm to enter. If the correct arm was entered and traversed, the mice were rewarded by 0.1 ml of water delivered at a reward port at the end of the arm. The reward was delivered in the arm associated with a specific odor. Mice were trained for 20 daily trials until they reached a criterion performance of 75% correctly performed trials. Following the first odor phase, an intradimensional shift was performed, whereby a different pair of odors was used and the animals had to associate one of the new odors with the reward. Mice were again trained for 20 daily trials until they reached a criterion performance of 75% correctly performed trials.

Tetrode and Microdrive Preparation

Tetrode recordings are a commonly used method for single unit recordings in *in-vivo* electrophysiology (O'Keefe and Recce, 1993; Wilson and McNaughton, 1993; Gray et al., 1995). A tetrode is comprised of 4 fine insulated wires twisted around each other. Typically, a 12-20 cm piece of fine insulated wire (Platinum %10 Iridium/ Tungsten, California Fine Wire, CA) is cut and the tips of the wire are merged using a piece of silk tape. The shape of figure eight is formed and the eight-shaped wire is placed on an elevated rod on its circular ends. A magnetic bar is hung to the waist of the eight-shaped wire, creating slight tension to keep the wire on the metal rod. A

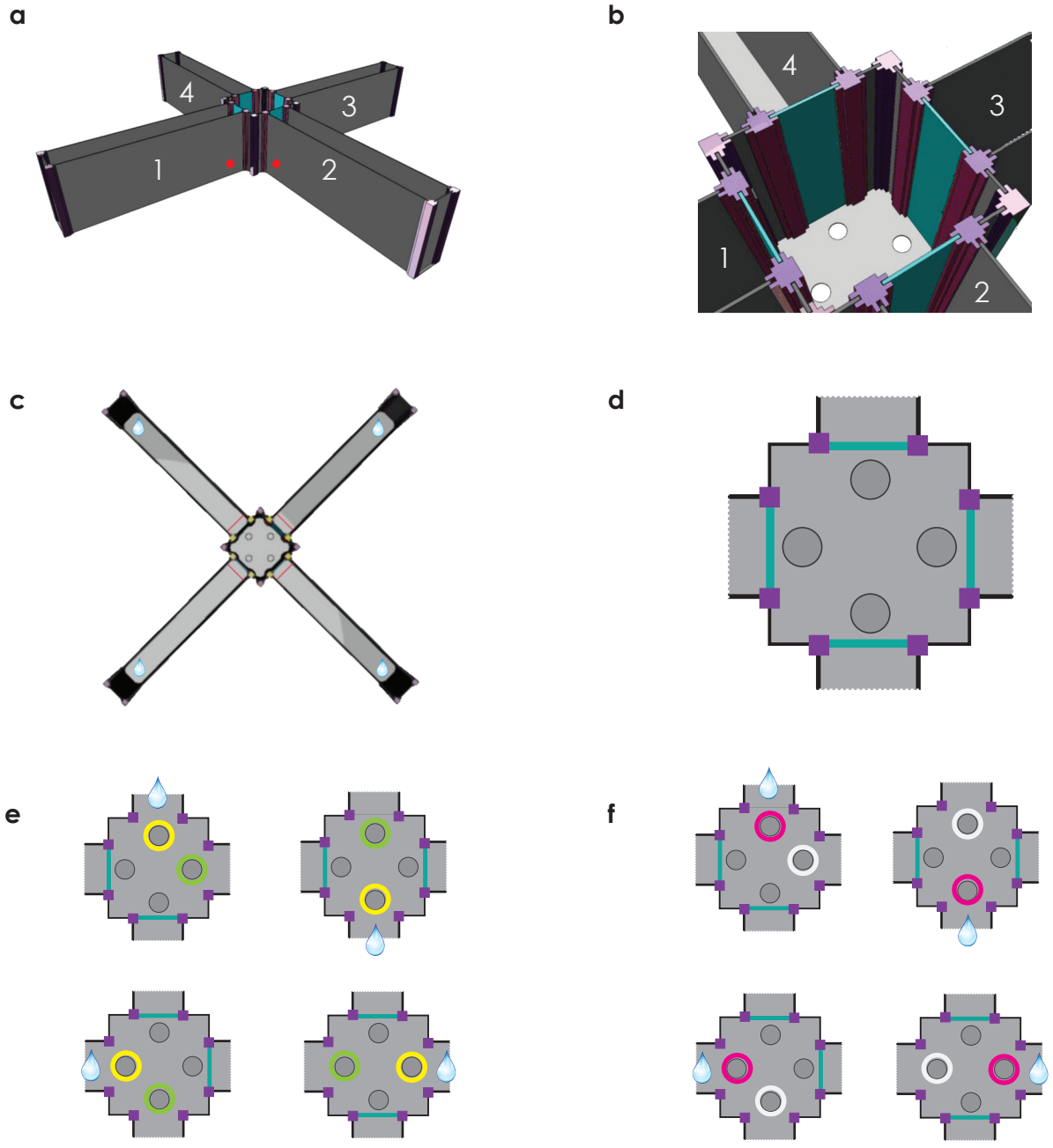

Figure M7 Olfactory Plus maze task (Olfactory discrimination task)
a Sideview of the illustrative 2d-model of olfactory plus maze. Arm doors are in blue, IR (infrared) motion sensors are depicted as red dots. **b** Zoomed view of the maze's central hub. Arm doors in blue, holes at the base represent odor pokes. **c** Top-down view of the olfactory plus maze. Red lines indicate IR motion sensor positions, water ports at the end of each arm are represented by blue water drops. **d** Simplified drawing of model in panel b, top-down view. Doors are illustrated in blue, dark grey circles represent odor pokes **e-f** Olfactory set learning task. Panels show 4 example trials. A set of 2 odors is given at a different arm entry in each trial, for 20 trials a day (odors are depicted by yellow and green circles in panel e and pink and white circles in panel f) Liquid reward is represented by the blue water drop in each trial. The yellow odor is associated with water reward in panel e and pink odor is associated with water reward in f.

magnetic stirrer, whose center is aligned to the middle point of the magnetic bar, is placed under the magnetic bar and approximately 12 counter-clockwise twists are applied at 60 rpm. After the 4 legs of the wire are twisted together, the magnetic stirrer is turned off. The twisted tetrode wires are further fused together by means of a heating gun at 420 degrees at a 2-3 cm distance to the wires. This step helps the insulation on each leg to merge together to form a more robust wire bundle. Next, the heating gun is removed and the magnetic bar is cut loose. The tetrode is released from the rod by making two fine cuts on top, which forms 4 non-bonded strands of wire on the top end of the tetrode (4 channels of the tetrode). The tetrode is carefully removed and placed in a dust-free box and the procedure is repeated to manufacture more tetrodes for the microdrive.

A microdrive is a general name given to devices, which carry a number of receptacles, wires or cannulae, which receive and pass current, or release chemical substances. In this study we used 2 different microdrives loaded with tetrodes. The first one was a custom made 16-tetrode Microdrive (fully loaded: 4 grams, Figures M2-M4), and the second one was a 4-tetrode Microdrive (Figure M5) (fully loaded: 2.6 grams, Axona limited). The preparation of the microdrives is explained in methods figures M2 - M5.

16-Tetrode Microdrive:

The main components of the microdrive are the base, the enclosure and the cap (FigureM2b). The base is placed on the rat's head, by support of dental acrylic, just above the craniotomy, which allows the tetrodes passage into the brain. The tetrodes and portions of guide tubes exit holes in the bottom of the base and can be gradually and separately lowered into the brain by turning the drive screws. The enclosure surrounds and protects the moveable parts of the microdrive. The cap also strengthens the microdrive but its main functions are providing access to the drive screws and forming a connector between the tetrodes and grounds and the recording cable.

The first step of making the 16-tetrode microdrive is to prepare the tetrode carriers (shuttle and cannula), each of which advances a tetrode into the brain from its initial implanted position. The guide cannula is inserted to the shuttles. A small amount of glue (5-minute epoxy) is applied to the top of the shuttle at the guide cannula hole

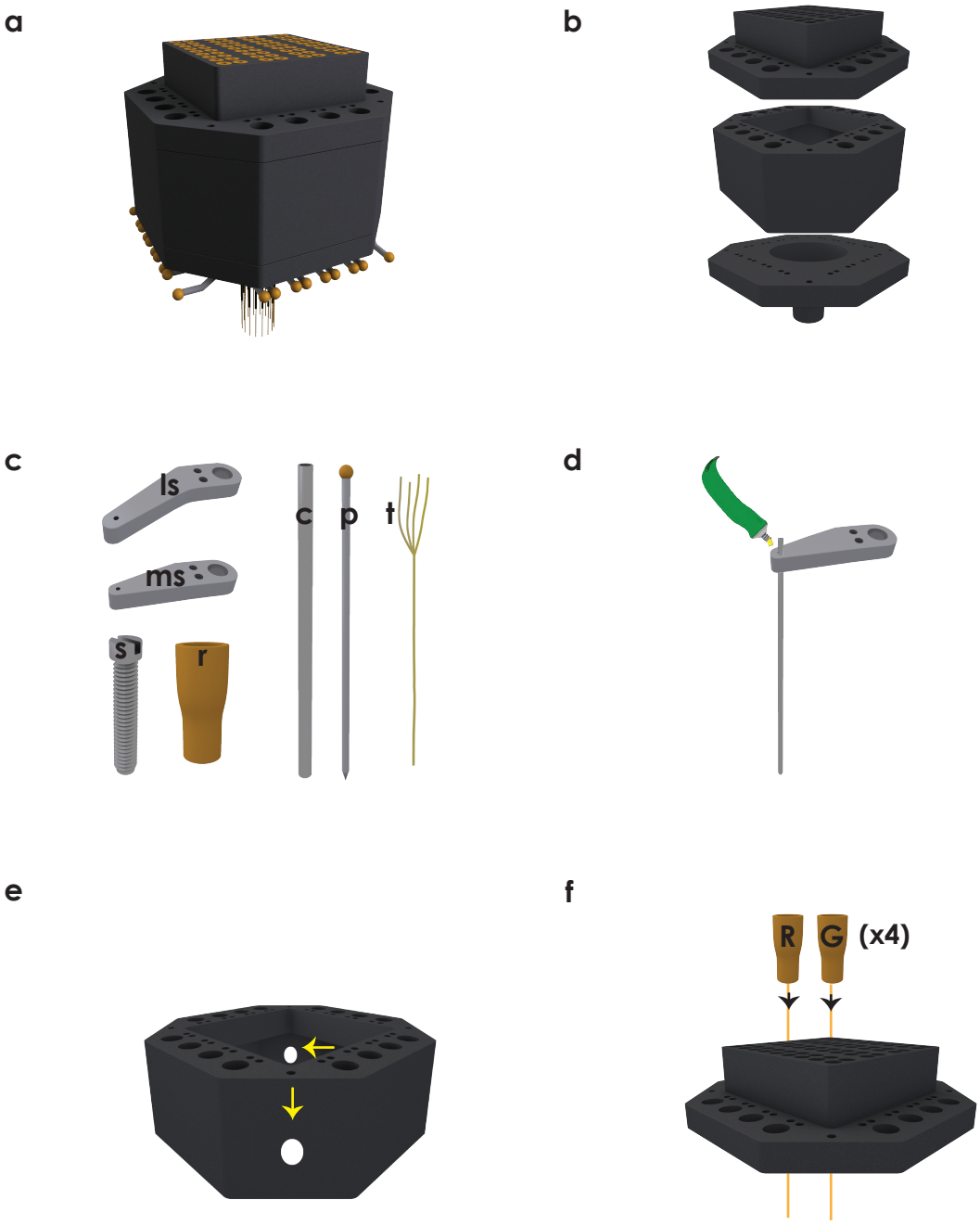

Figure M2 16-Tetrode Microdrive Preparation Parts

a Illustrated 2d model of a fully loaded microdrive. **b-c** Microdrive assembly components; in b top to bottom: the cap, the enclosure and the base; in c ls and ms (lateral and medial shuttles), s (screw), r (receptacle), c (cannula), p (drive pin), t (tetrode) **d** microdrive with the guide cannula inserted and glued on top **e** the enclosure with 2 drilled holes, indicated by the yellow arrows **f** Reference (R) and ground wire(G) receptacles are being inserted in the cap (black arrows indicate the direction)

(Figure M2d). The length of the guide cannulae can vary depending on the target brain structure. For this study, 13-15 mm long cannulae were used, which is the standard cannula length for dorsal hippocampus recordings.

Secondly, two small holes are drilled on two sides of the enclosure to create an outlet for reference and ground wires of the microdrive (Figure M2e). Next, 8 insulated wires are soldered to 8 receptacles and they are inserted into the cap in the reference and ground channel holes in the middle (Figure M2f). Later when the cap is lowered onto the microdrive, the reference and ground wires exit the microdrive from the holes drilled on two sides of the enclosure.

The base is loaded with the metal pins and the shuttles are connected to the base by threading them into the metal pins (Figure M3a-3d), letting the tips of the cannulae exit from designated holes in the base bottom. The enclosure is put through the pins and lowered until it meets the base (FigureM3e). The drive screws uplift the shuttles to their initial position (Figure M3f-FigureM4a).

Next, the tetrodes are carefully loaded into the cannulae (Figure M4a-M4b). Then, with the reference and ground receptacles in place, the cap is lowered onto the enclosure (leaving 1 cm space between the enclosure and the cap to provide access for sending tetrode channels receptacle holes in the cap). Next, wires from each tetrode are carefully sent through the right hole in the cap. The procedure is repeated for 16 tetrodes and the top is lowered carefully until it meets the enclosure (Figure M4c). Next step is to insert the receptacles into each hole on the cap (Figure M4d). This step strips the insulation on the wire, establishes electrical contact between the receptacle and the tetrode wire and captures the wire in the hole. The wires are trimmed by using spring scissors as close to the top of the receptacles as possible (FigureM4d) and a motorized mini saw is used to clip the excess length of the pins on the base (Figure M4e). Application of epoxy (Figure M4e) and dental acrylic (Figure4f) on the enclosure and pin exit holes strengthens the microdrive. Finally, the tips of the tetrodes are trimmed by spring scissors to give them a uniform length (3-5mm).

4-Tetrode Microdrive

The unloaded 4-tetrode microdrive (Axona LTD, UK; Minidrive, Biosignal Group) consists of a male connector with 17 channels (16 recording channels and 1 ground

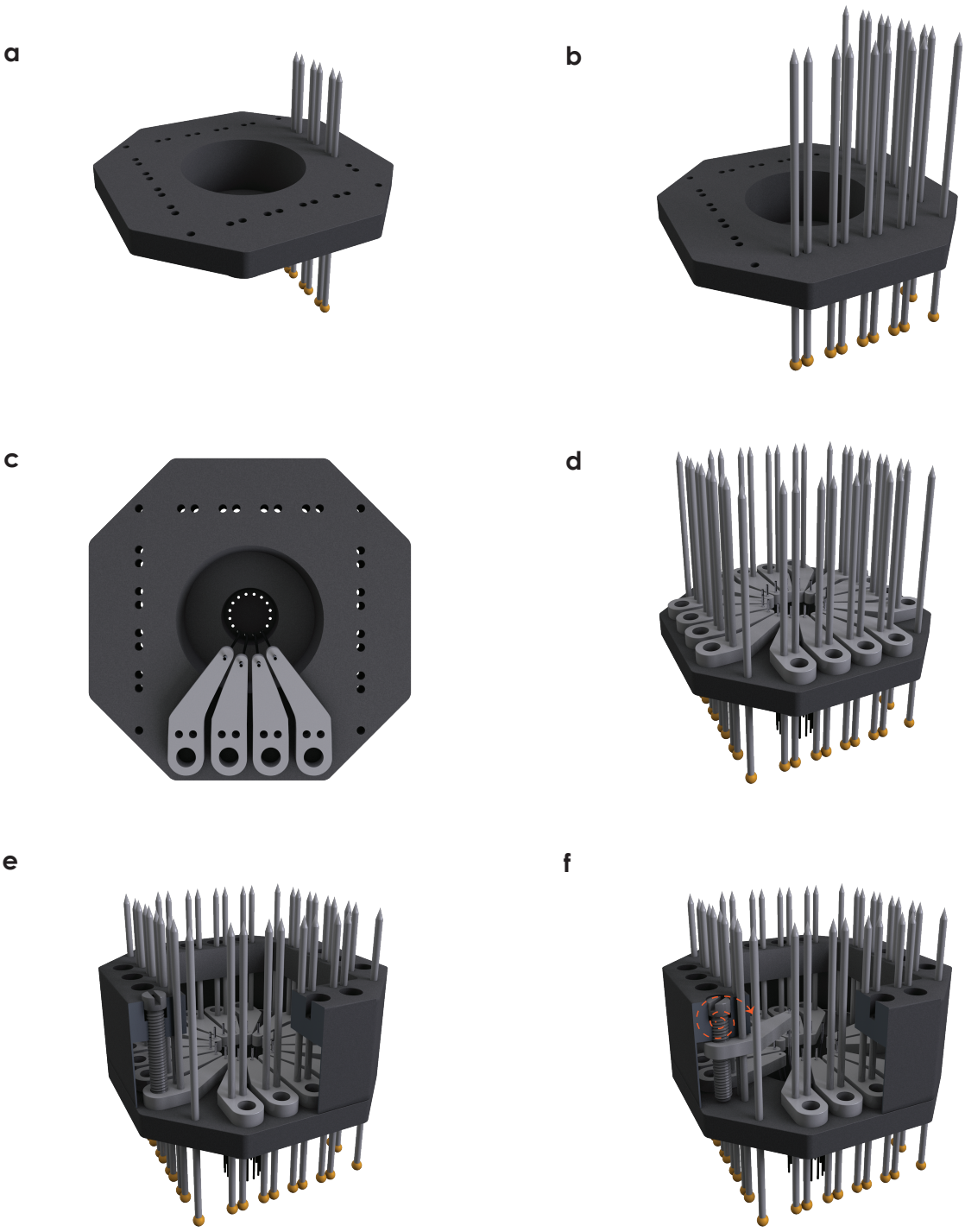

Figure M3 Preparation of 16-tetrode Microdrive

a-b Illustrative model of the microdrive base and insertion of drive pins into the drive holes in the base **c-d** Illustrative model shows tetrode carriers are placed onto their drive pins on the base and the cannulae exit the designated holes in the base bottom **e** Model depicts the microdrive with the enclosure placed onto the pins and a drive screw inserted which connects the enclosure and the shuttle. **f** Model depicts the microdrive with the enclosure placed onto the pins and a tetrode carrier in the process of being raised by its drive screw into its upper position (indicated by orange spiral).

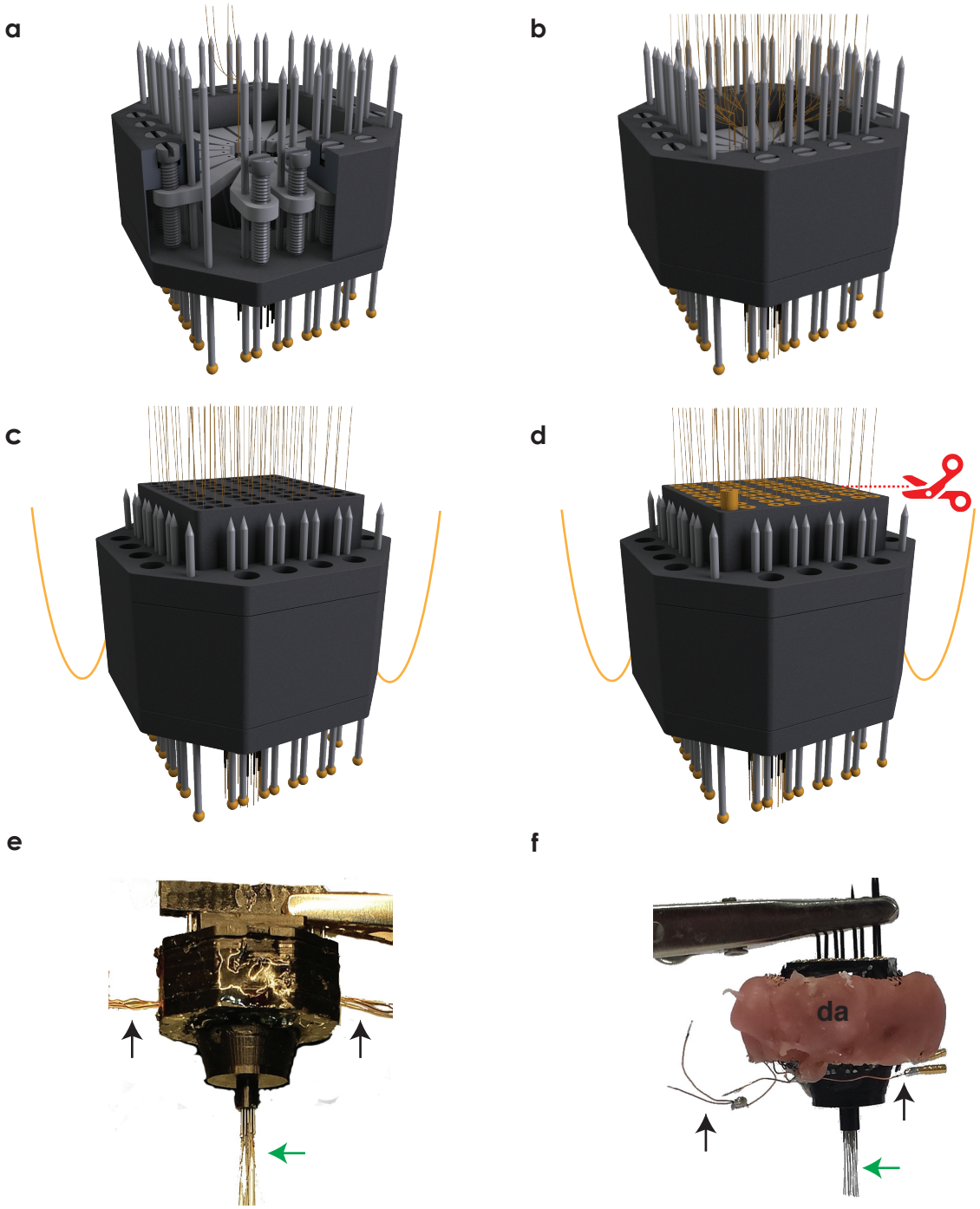

Figure M4 Preparation of 16-tetrode Microdrive

a Illustrative model shows all tetrodes carriers raised to their highest positions **b** 16 tetrodes are inserted into the cannulae which are on the shuttles **c** The model depicts the drive cap placed on the enclosure and the 4 wires from each tetrode exit the receptacle holes on the drive cap. Yellow arches represent reference and ground wires **d** The model shows the receptacles placed in the cap holes and the tetrode wires located between the receptacles and the cap holes. The schematized red scissors and the dashed line indicate the cutting position. Yellow arches represent reference and ground wires **e-f** Photos of a fully loaded16-tetrode microdrive, black arrows indicate reference and ground wires and green arrows indicate tetrode tips. da stands for dental acrylic in panel f

channel) and it is anchored to two metal stands by dental acrylic (Figure 5a). One of the metal stands serves as a drive screw, which allows the microdrive to be lowered after implantation.

First step to prepare the 4-tetrode microdrive is to build a guide cannula for tetrode loading. Typically a metal cannula (270µm-outer diameter) is anchored to the microdrive, on the front side of the screw, with dental acrylic. Next, a shorter and wider outer cannula (300µm-outer diameter) is temporarily attached to the microdrive by rubber gum (Figure M5b). Outer cannula is released after the implantation to protect the part of the tetrodes, which is between the cannula tip and the skull. Next, the ground channel and the microdrive channels are partly stripped of their isolation coat at the tips (Figure M5b). Tetrodes are inserted into the cannula and tetrode wires are coiled around uncoated tips of microdrive channels (Figure M5c). Then, each channel tip is coated with silver paint to increase connectivity between the tetrode wire and the channel wire. Note that silver paint must be applied carefully and separately on each channel tip to prevent shorting between channels. Next step is to apply many layers of varnish to isolate channels from external electrical noise and protect them from damage (Figure M5d). Spring scissors are used to trim tetrode tips to an equal length of 3-5 mm (Figure M5f).

The last 2 steps in microdrive preparation are measuring the channel impedance values and plating the tetrode tips. The impedance of each channel is first measured in saline, noted down, and the tips of the tetrodes are then lowered into a plating solution (gold or platinum). Channels with impedance values between 150 and 300 are not plated. To plate the channels with impedance values higher than 300 megaohms, the ground wire is connected to the plating solution through an additional wire and tetrode tips are dipped into the plating solution. The microdrive is connected to a current generator and -1µA current pulses are applied. Then, the tetrode tips are removed from the plating solution and they are placed back in saline to measure resulting impedances. These two steps are repeated until each channel has an impedance value lower than 300 kΩ.

Surgical Procedures

Rats were handled for one week prior to the surgery and initiation of the training on the spatial set navigation task. Rats were anesthetized using isoflurane-oxygen

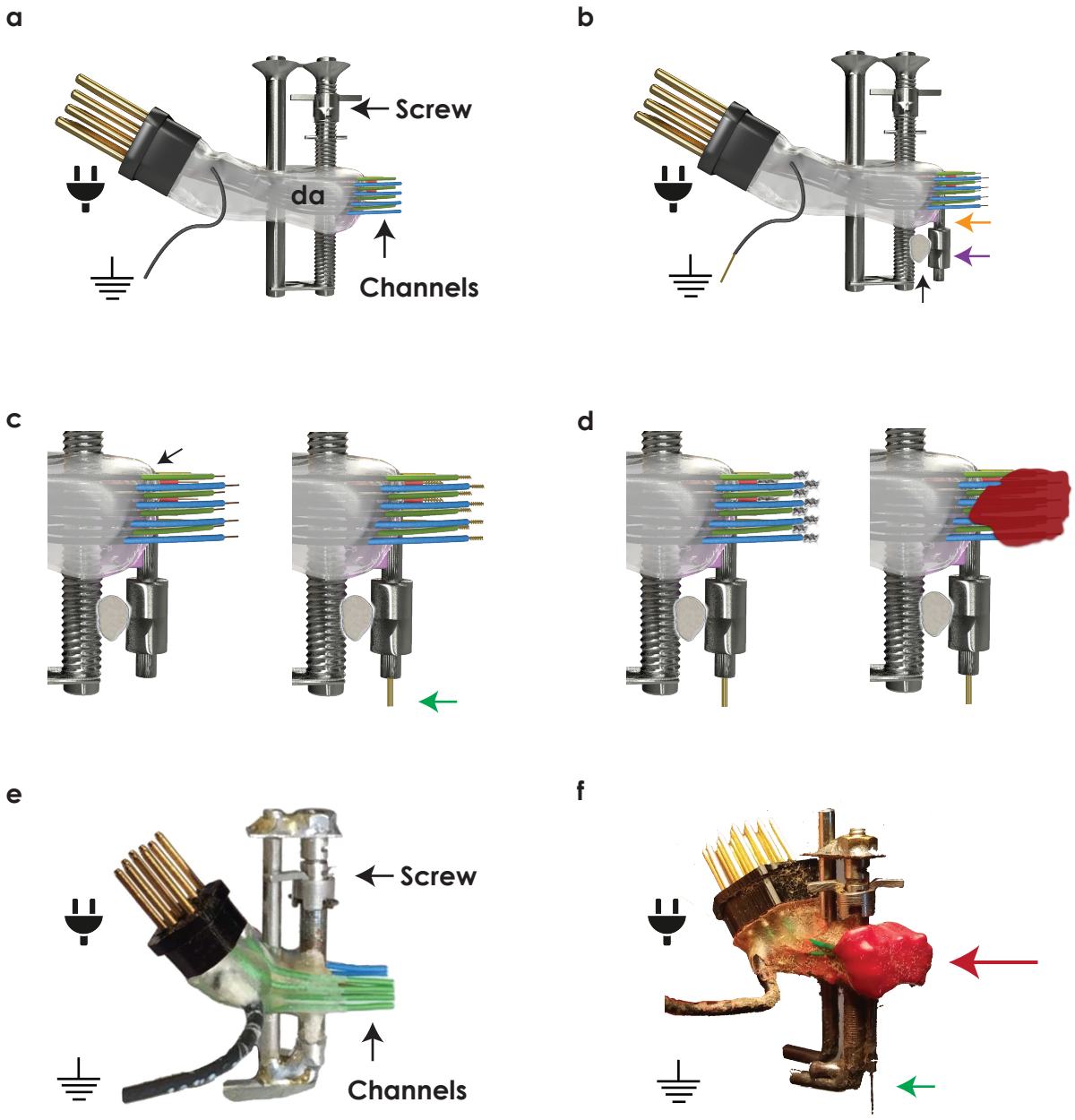

Figure M5 4-Tetrode Microdrive Preparation

a Illustrative model of the microdrive. The Male connector is indicated by the plug sign, ground wire by the earthing sign, the channels and the screw by arrows. da stands for dental acrylic. **b** The model shows the tips of the ground wire and 16 channels party stripped of their isolation, tetrode guide cannula (yellow arrow)anchored; outer cannula(purple arrow) attached to the microdrive by a piece of rubber clay(black arrow). **c** Zoomed view of the model front profile, **Left** tetrode loading port indicated by the black arrow **Right** Tetrode channels are coiled onto the channel tips and tetrode tips exit the tetrode cannula (green arrow) **d Left** Channel tips are covered in silver paint **Right** Channels covered in varnish **e** Photo of an unloaded microdrive **f** Photo of a fully loaded microdrive.

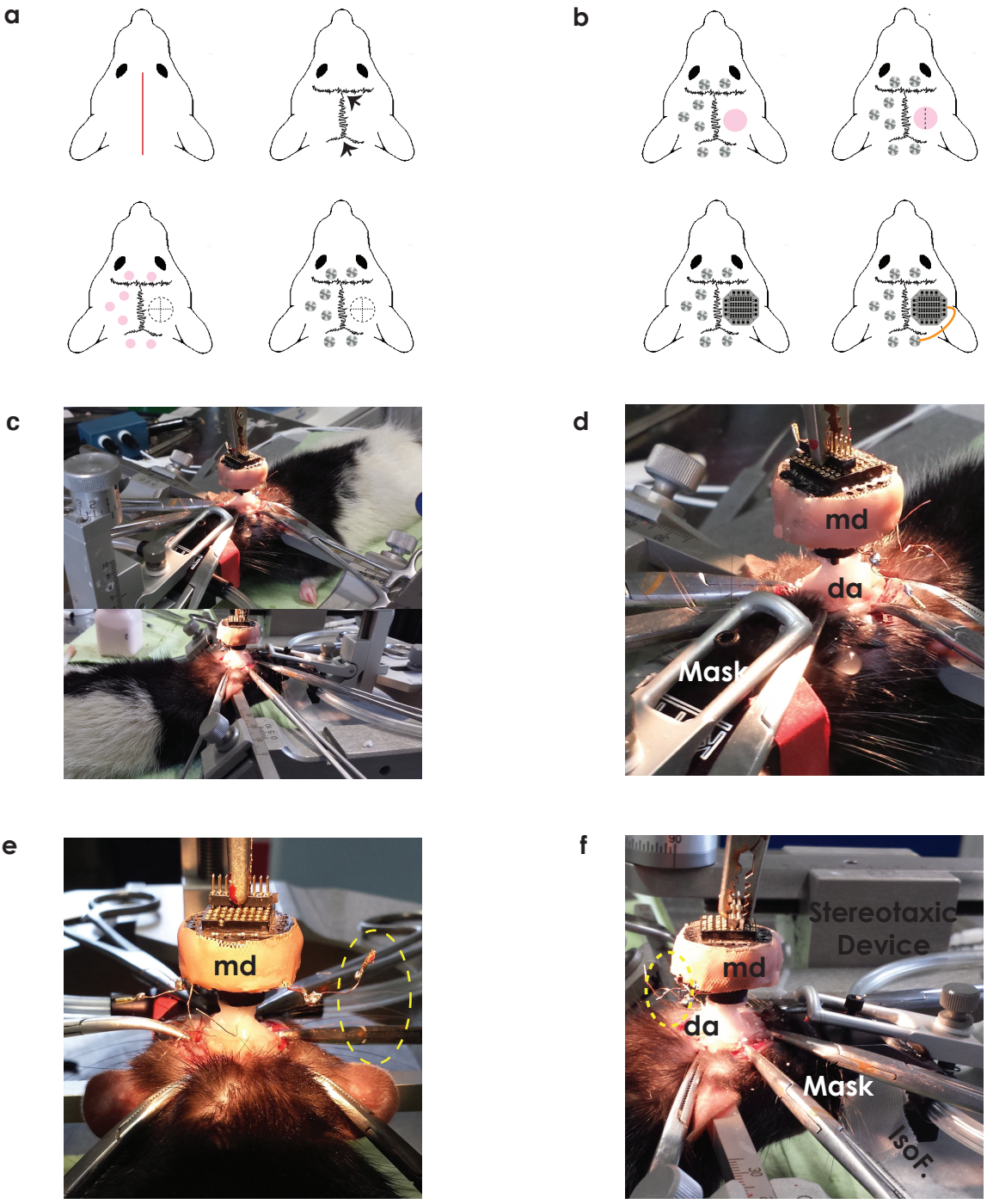

Figure M6 Microdrive Implantation Surgery

a-b Illustrations of a rat's head during microdrive implantation surgery, top-down view. **a** The red line represents sagittial incision; arrowheads indicate bregma and lambda respectively; small pink circles represent drilled screw holes and dashed circle represents the marked craniotomy site (-3.8mm posterior and 2.5mm lateral to Bregma); Bottom Right, screws are driven into the skull **b** Top, trephine hole (pink circle), dashed line represents dura incision. Bottom, microdrive is represented by the grey structure, yellow line represents the ground wire **c-f** Photos of microdrive implantation surgery: md (microdrive); da (dental acylic); mask (surgery mask); IsoF. (tube for isoflourane-O_2 mixture); yellow dashed oval indicates unconnected microdrive ground wires in e and f .

mixture (0.5-2%), the scalp was shaved with a mini-shaver and they were placed on a stereotaxic device (Kopf Inst.). The scalp was disinfected with alcohol and Betadine. Following a 2 cm sagittal incision (Figure M6a, top left), skin, connective tissue and part of temporal head muscles are scraped. Craniotomy coordinates are marked using Bregma (Figure M6a top right and Figure M6a bottom left) as the reference point (3.8 anteroposterior and 2.5mm lateral (Paxinos and Watson, 2006)). Using a micro-drill (Fine Science Tools) 9-11 screw holes were drilled in the skull for mini bone screws (jewelers' screws) (FigureM6a bottom left). Next, jewelers' screws were driven into the holes (FigureM6a bottom right). Following a 1.5 mm craniotomy (FigureM6b top left), dura mater was incised to allow easy passage for tetrodes into the brain (Figure M6b). Next step was to lower the 4-tetrode or 16-tetrode microdrive into the trephine hole and implant above dorsal hippocampus (1.5-1.6 mm ventral from dura surface) (Figure M6b bottom left, Figure M6c-d). The ground screw, which was soldered to an insulated wire prior to surgery, was connected to the ground microdrive wire. The mini bone screws as well as the stationary parts of the micro-drive were secured to the skull by dental acrylic (Figure M6c-d).

Electrophysiological Recordings

Following one week of recovery, the tetrodes were advanced to their target position in the CA1 pyramidal cell layer, as indicated by stereotaxic depth estimates and electrophysiological characteristics of local field potential and unitary activity (Csicsvari et al., 1999). In particular, theta activity in the local field potential (LFP) during motion and neuronal firing that is spatially tuned were required to start experimental recordings.

Continuously recorded extracellular traces of unit activity were collected at 48 KHz or 30 KHz (Axona dacqUSB, UK and Neuralynx ERP-27, Bozeman MT USA, respectively), filtered at 500-6000 Hz and sorted off-line to isolate extracellular action potentials emitted from single units by using various features of action potential waveforms (Figure R2c).

Head position and direction were monitored using a 6 mm lens infrared camera that was positioned in the center of the recording chamber ceiling and detected the IR LED signals emitted from the animal's headstage. The video signal was sampled at 50 or 25 frames/sec and digitized by Axona data acquisition system (UK)/ Neuralynx

(USA). All behavioral data was synchronized with the neuronal data (Axona and Neuralynx).

Data Analysis

Data inclusion criteria for *in-vivo* data set:

Standard analysis methods were employed to study the coding of spatial and stimuli by the recorded neurons. For each neuron, a rate map was computed separately for each trial. Only cells and trials with a mean firing rate of 0.1-20 Hz, peak firing rate of at least 0.8 Hz (Navratilova et al., 2012) and spatial information content (Skaggs and McNaughton, 1998) of over 0.5 bits/spike on at least 5 trials were subject to subsequent analysis. Out of the 596 neurons recorded in the RR group and 1828 neurons recorded in the CR group, 222 and 587, respectively, were used for further analysis.

Statistical analysis:

Data are presented as mean ± S.E.M., or explicitly stated. Results of statistical tests are considered significant at $P<0.01$, unless specified otherwise. Comparisons between distributions were conducted using a Kolmogorov-Smirnov test. OSI was compared between groups and days using a two-way Friedman test with post-hoc comparisons (with Bonferroni correction). For comparison of latencies to reward between training days we used repeated measures ANOVA.

Place angle calculation:

For each rate map, we calculated the best angle of the neuron as follows: We determined place fields in the rate map by locating the positions with elevated firing, clustering them to fields and finding the largest one. This was achieved by first delineating contours of >20% of peak firing rate in the session (Huxter et al., 2003). The corresponding pixels were clustered using a K-means algorithm and using silhouette analysis to determine the best number of clusters. Finally, place field coordinates were defined as the centroid of the largest pixel cluster.

Odor Space Index calculation:

To calculate the relation between maze orientation and place field angle, we expressed the series of place field positions in unwrapped polar coordinates θ_i and

the corresponding series of maze orientations in polar coordinates φ_i. These allowed us to calculate the Spatial Dispersion of the series: SpD= $\sum_i(\theta_i - \bar{\theta})^2$, where: $\bar{\theta}$ is mean θ over all trials. SpD is residual sum of squares (RSS) from a model in which all firing fields of a single neuron reflect a single value.

Similarly, Odor Dispersion was defined as: $OdD = \sum_i((\theta_i - \theta_0) - (\varphi_i - \varphi_0))^2$, where θ_0 and φ_0 are used to align all angles in a series to a single reference point (θ_0 =106° and φ_0 = 45.1° for the example cell in Figure R7a). OdD is the respective RSS for a model in which all firing fields of a single neuron reflect a single point in odor coordinates.

Odor space index was then calculated by $OSI = \frac{SpD-OdD}{SpD+OdD}$. Thus, OSI ranges from -1 for neurons that encode space in lab coordinates, and +1 for neurons encoding olfactory coordinates.

Change points of OSI and behavioral performance were analyzed using a regression to hinge type change point model and accepted for P < 0.01 for the maximum likelihood model (Fong et al., 2016).

All analysis was conducted using custom written functions in MATLAB (Mathworks MA) and R statistical software.

Histology

At the completion of the training and recording, the animals were deeply anesthetized with isoflourane and a 40μA current was passed through tetrodes to create micro-lesions for electrode track visualization. Subsequently, the animals were perfused with Paraformaldehyde (PFA 4%). The brains were removed and stored at 4° in a 4% formaldehyde/sucrose solution. Frozen brains were cut to 40-100 μm thick brain slices and were stained Glial Fibrillary Acidic protein (GFAP)/ Cresyl Violet. Images of the sections were acquired with an Olympus BX 61 microscope. Sections where impressions of tetrodes could be seen were used to determine the location of recorded cells (Figure R2a).

Results

Rats learn the appropriate coordinate system for navigation

To examine how goal-directed navigation may affect the type of spatial mapping in the hippocampus, we designed a dual dimension setup comprised of a rotatable ring track with four equally spaced, fixed odor delivery points. Liquid reward was delivered in one of 12 equidistant positions located around the ring (Figure M1). Reward position was determined according to the lab coordinates or odor coordinates (Figure M1), depending on the experimental condition (see below). Seven liquid-restricted rats were trained to navigate in darkness for 10 trials in each recording session for a total of 20 days. In each trial, rats were placed on the track in a constant position (in the lab coordinates) (Figure R1a bottom panel) and were allowed 2 minutes to locate and consume a single drop of water in the predefined position. The location of the rats in the arena was recorded using the infrared LED signal on the headstage (Figure R1a top panel). Following each trial, the arena was rotated in a pseudo-random fashion, shifting the odors correspondingly. Rats were divided into two groups: In the rotating reward group (RR), reward position was fixed with regards to odor coordinates (placed 2/3 of the path between two pre-defined odors) but shifted in each trial with relation to lab coordinates (Figure M1a). Conversely, in the constant reward group (CR), reward always remained at a fixed location with relation to the lab, but shifted at each trial with regards to odor locations (Figure M1b). The latencies to reward of animals from both groups were logged and analyzed. Although rats in the CR groups were initially faster, rats in both groups successfully learned to obtain the reward (Figure R1b), showing decreasing latencies to reward and reaching asymptotic performance after 10-12 days (2-way ANOVA with interaction, group effect $F_{(1)}=14.68$, $P_{group}<0.001$, $F_{(19)}=11.89$ $P_{days} < 0.001$, $F_{(19)}=1.03$ $P_{daysXgroup} > 0.4$). These data show that rats successfully learn to use the appropriate spatial set for navigation and for reward collection.

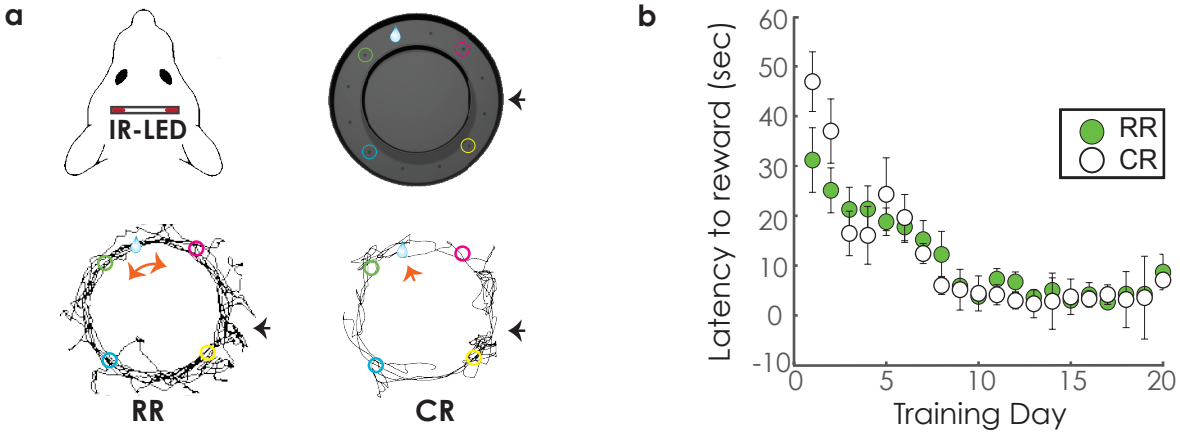

Figure R1 Rats learn to navigate in the spatial set navigation task
a Top Left Illustration of a rat's head and infrared LED lamps (IR-LED) on the preamplifier which is connected to the implanted microdrive. **Top Right** Rotatable ring track with four equally spaced odor delivery ports (colored circles) Reward is depicted as a water drop (blue), black arrow indicates the entry point to the track for the rats. **Bottom Left** Example trajectory of a rat in the RR group (in black), odors shown in colored circles. Note that in RR group reward position rotates with every track rotation (orange arrows) **Bottom Right** Example trajectory of a rat in the CR group (in black), odors shown in colored circles. Note that in CR group reward position is predefined in lab coordinates (orange arrow) **b** Learning curves in CR and RR configurations. Latency to reach reward port of rats in the RR group (green) (N = 4) and CR group (black) (N = 3). Asymptotic performance is reached after 10-12 days in both groups (2-way ANOVA with interaction, group effect F_{1}=14.68, P_{group} < 0.001,day effect F_{19} = 11.89; P_{days} < 0.001, interaction F_{19} = 1.03; $P_{days\ X\ group}$ > 0.4)

Encoding of space by CA1 neurons is determined by reward regularity

Neurons Recorded in the spatial set navigation task

We next tested whether the improvement in performance was mirrored by changes in neural activity in the hippocampus. We used tetrodes to record CA1 neurons (Figure R2a,b) throughout the learning period. CA1 neurons were sorted to single units according to spike shape features (Figure R2c) and spatial ratemaps for each recorded neuron were calculated for the 2-minute trials (Figure R2d). Out of the 596 recorded neurons in the RR group and 1828 recorded neurons in the CR group, 222 and 587, respectively, displayed spatially selective firing properties and were used for analysis (see Materials and Methods for inclusion criteria).

Neurons Recorded in the spatial set navigation set display similar firing properties

Neurons from both animal groups displayed similar firing properties. Spatial ratemaps of each 2-minute trial generated for neurons from the RR (Figure R3a) and CR (Figure R3b) group showed typical spatial firing fields which did not differ in peak firing rates (Figure R3c, Kolmogorov-Smirnov Test, $D_{581,1618} = 0.071$, $P > 0.2$) or size of place fields (Figure R3d, Kolmogorov-Smirnov Test, $D_{581,1618} = 0.068$, $P > 0.2$). These calculations show that neurons recorded in RR and CR configurations exhibit similar firing characteristics during navigation in the olfactory ring track.

Calculation of maze and place field orientation angles

Despite the similarity between the two experimental groups in both the behavioral and the neuronal patterns, successful performance in each of the two tasks requires navigation strategies that rely on different sensory modalities: rats in the RR group had to rely on olfaction, whereas rats in the CR groups likely relied on self-motion cues. We therefore tested the underlying hippocampal maps for differences reflecting the two strategies. To determine the spatial feature sets that were encoded by the neurons, we investigated the relation between the maze orientation and the place-field of the neuron in each trial. Figure R4 depicts examples for calculation of maze orientation angle and place field orientation angle, which include the following computations:

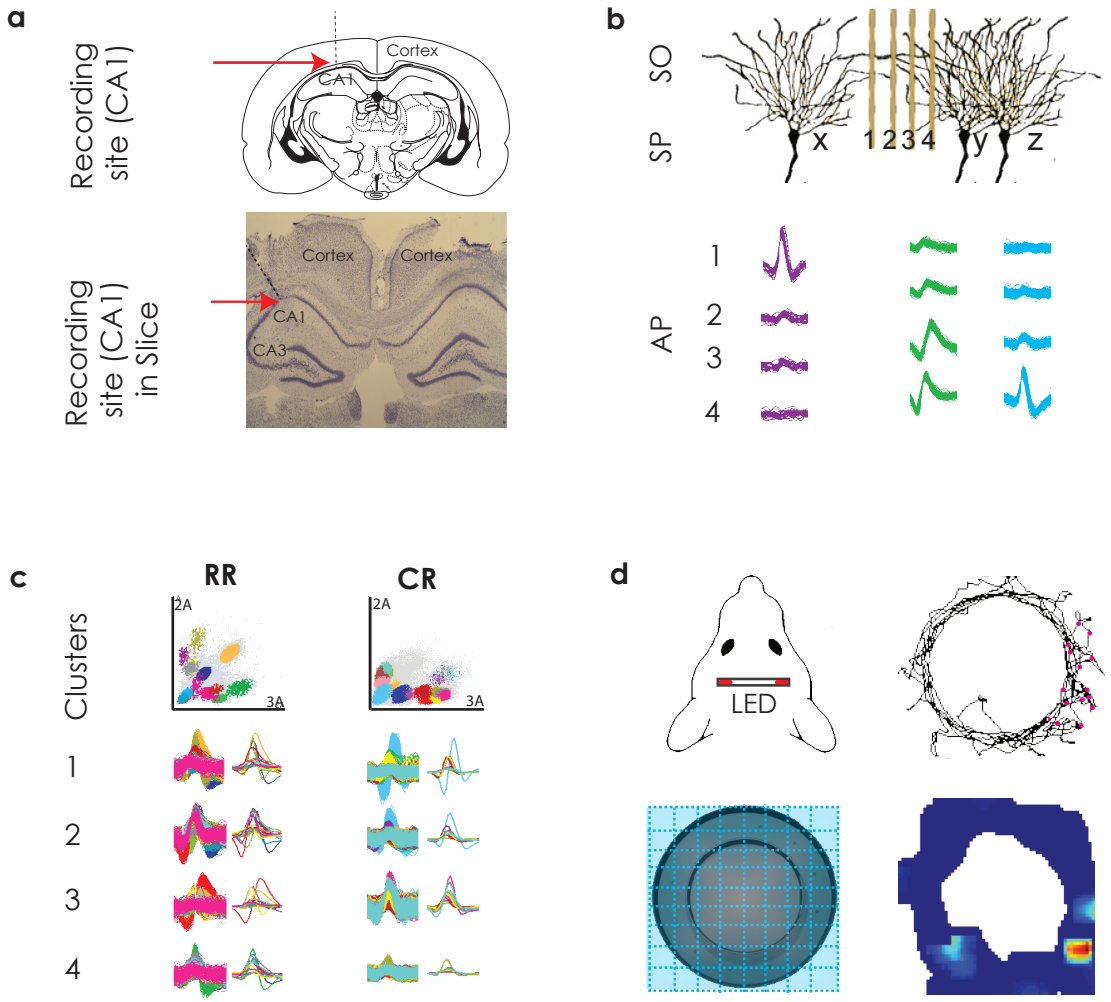

Figure R2 Neurons recorded in the spatial set navigation task
a Recording coordinates. **Top:** Schematic coronal section of the rat brain at target coordinates (Red arrow: -3.8 mm posterior, 2.5 mm lateral to Bregma, modified from Paxinos and Watson, 2006). **Bottom:** Coronal section and electrode tracks in the CA1 pyramidal layer of the dorsal hippocampus after micro-lesioning, indicated by the red arrow. **b Top** Illustrations of 3 CA1 pyramidal neurons (x,y,z) and their two anatomical layers; Stratum Oriens(SO), Stratum pyramidale (SP). Golden bars represent 4 channels of a tetrode wire. Note that sizes of the wires and the neurons are not proportional for illustrative reasons. **Bottom**: AP(Action Potentials), Simultaneous recordings of neurons x (purple APs),y (green APs) and z (red APs). Numbers 1-4 stand for the tetrode channels. **c** Example clusters and waveforms (all traces and average traces) of neurons which were recorded and spike sorted for 1 day. Left panel shows RR group and right panel shows CR group. Channel numbers of the tetrode are1-4. **d Top Left** Illustration of a rat's head and video tracking infrared LED lamps (IR-LED). **Bottom left** Rotatable olfactory ring track is computationally divided into pixel grids (semi transparent blue mesh) **Top right** Trajectory of a rat on the rotatable olfactory ring track (in black) and spikes fired by a place cell (pink dots). **Bottom Right** Spatial Ratemap of the place cell in top right (pink dots), peak firing rate is 5.3 Hz.

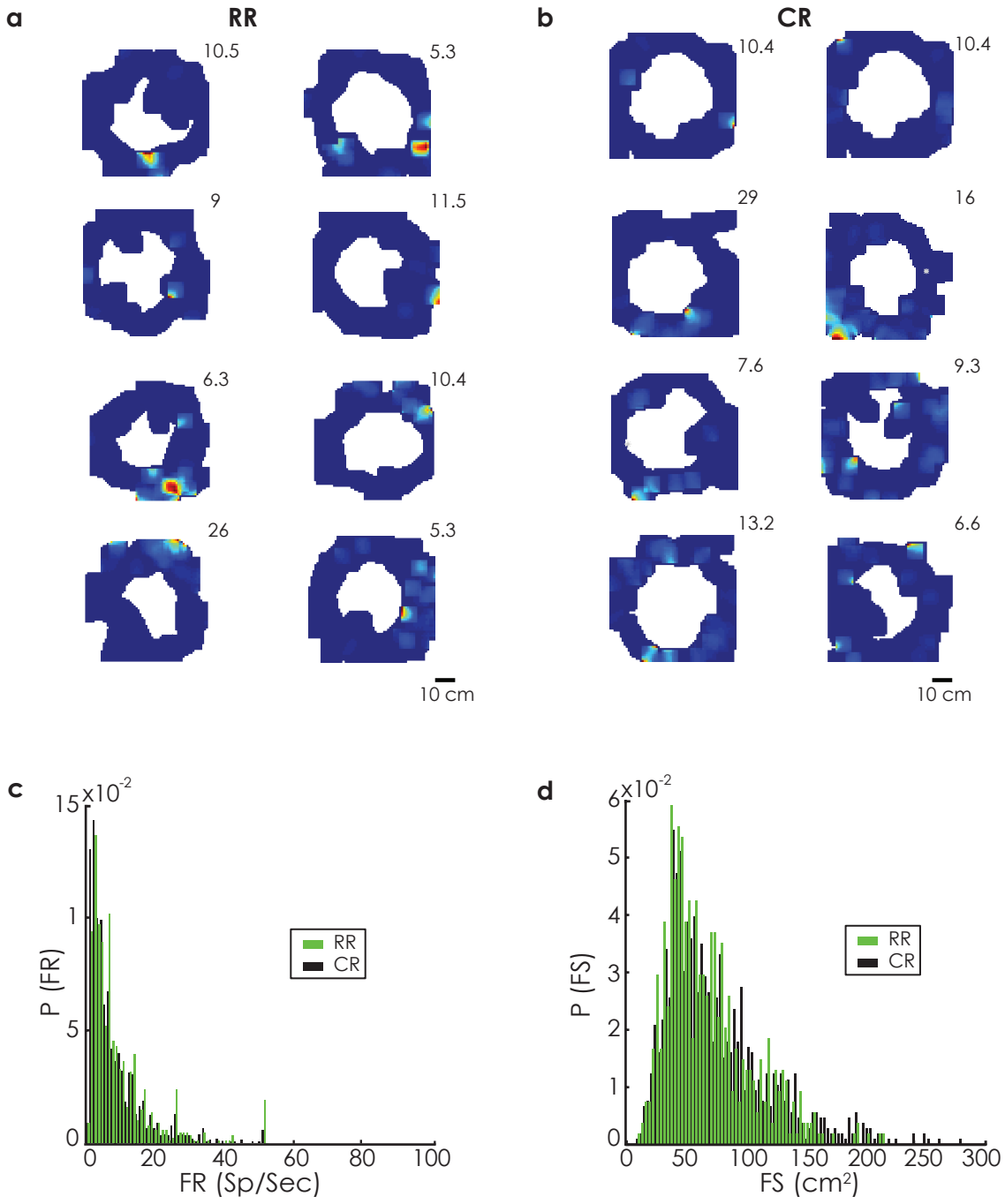

Figure R3 Properties Neurons recorded in the Rotatable olfactory set navigation task
a 8 spatial ratemap examples from 8 individual cells recorded in the RR group **b** 8 spatial ratemap examples from 8 individual cells recorded in the CR group
c Peak firing rates (FR) of analyzed neurons in both behavioral configurations. Probability density function of peak firing rates (P(FR)) in the center of place fields. Green: cells recorded in the RR configuration. Black: cells recorded in the CR configuration. Peak firing rates do not differ between groups (Kolmogorov-Smirnov Test, $D_{581,1618}$ = 0.071, $P > 0.2$ **d** Field sizes (FS). Probability density function of neuronal field size (P(FS)). Green: cells recorded in the RR configuration. Black: cells recorded in the CR configuration. Field sizes do not differ between groups (Kolmogorov-Smirnov Test, $D_{581,1618}$ = 0.068, $P > 0.2$).

1. φ_0: A reference orientation for the recording arena was defined by taking the angular position of one particular odor port (e.g., apple). Then, we calculated angular position of that odor port in each trial (φ_i) after each rotation (depicted by a yellow circle in Figure R4a, R4b top row).

2. θ_0: A reference orientation for the place field of each place cell was calculated (Figure R4a and R4b, bottom row). Then, we calculated the angular position of that place field in each trial (θ_i) after each rotation (Figure R4a, R4b top row). After the maze and place field orientation angles were calculated, the spatial and odor dispersion for all firing fields of each neuron was defined (see methods odor space index calculation).

Mapping of space by CA1 neurons depends on reward configuration

Figure R5a depicts the spatial rate maps of a typical neuron recorded in the RR configuration for 10 trials, along with the corresponding maze positions. In this example, the reward is shifted in accordance with the spatial configuration of the odors within the maze, and the cell's place-fields follow the maze rotation angles. Calculation of the correlation between maze orientation and neuronal field orientation for this example cell (Figure R5c) revealed a positive linear relationship between the two ($R^2 = 0.94$, $P < 0.001$). Importantly, the slope of the regression line is close to 1, indicating that this neuron accurately reflects a single position in odor coordinates. In marked contrast, the place fields of a neuron recorded in the CR condition (Figure R5b, R5d), where reward location remained fixed with relation to the external lab, and did not track maze coordinates, but rather persisted to represent a fixed location with relation to lab coordinates ($R^2 = 0.19$, $P > 0.2$). Since maze orientation was defined relative to the lab coordinates, the fixed place-field orientation across rotating maze positions indicates that this neuron indeed accurately reflects a single position in lab coordinates.

Correlation of place field orientations with maze orientations

Activity at the population level was assessed by calculating the correlation between maze orientation and neuronal field orientation in all training days (see methods section). We found that 56.3% of cells recorded in the RR configuration showed a significant correlation with maze rotation ($P < 0.01$, green violin plot in FigureR6a). In contrast, only a small fraction of the cells recorded in the CR configuration were

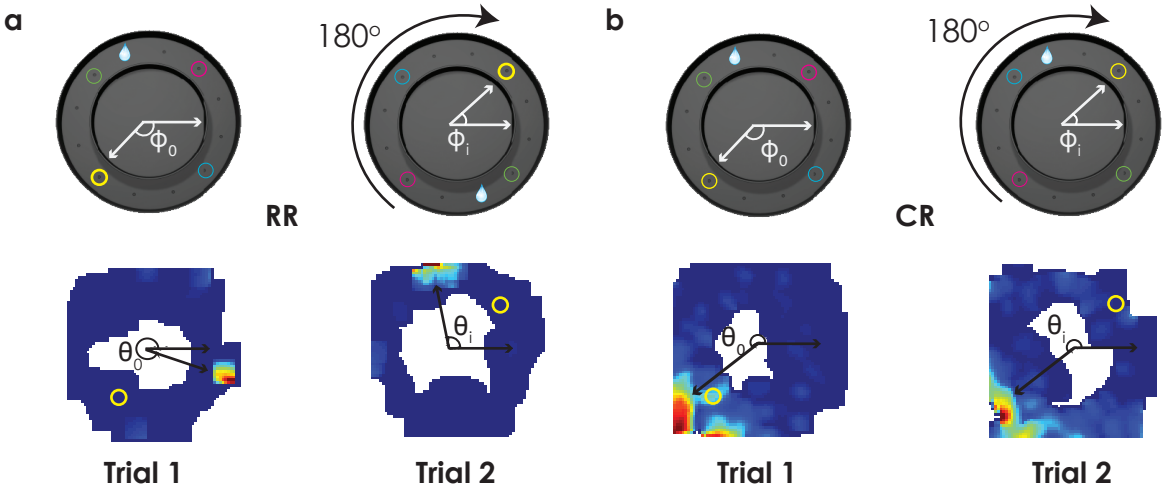

Figure R4 Calculation of maze and place field orientation angles

a Calculation in the RR group. **Top Row** Rotatable ring track (maze) with four equally spaced odor delivery ports (colored circles) for 2 trials. . **Bottom Row** Corresponding spatial ratemap of an example place cell for 2 trials. **Top Left** Odor represented by color yellow is highlighted and serves as reference position for the rotatable ring track orientation (ϕ_0). **Top Right** Ring track is rotated by 180 degrees in Trial 2, the new ring track orientation is ϕ_i . **Bottom Left** Spatial ratemap of the place cell in Trial1 . Place field orientation is θ_0 . **Bottom Right** Spatial ratemap of the same place cell in Trial2, after ring track rotation. The new place field orientation is θ_i. **b** Calculation in the CR group. **Top Row** Rotatable ring track with four equally spaced odor delivery ports (colored circles) for 2 trials. **Top Left** Odor represented by color yellow is highlighted and serves as reference position for the rotatable ring track orientation (ϕ_0). **Top Right** Ring track is rotated by 180 degrees in Trial 2 , the new ring track orientation is ϕ_i . **Bottom Left** Spatial ratemap of a place cell in Trial 1. Place field orientation is θ_0. **Bottom Right** Spatial ratemap of the same place cell in Trial 2, after ring track rotation. The new place field orientation is θ_i.

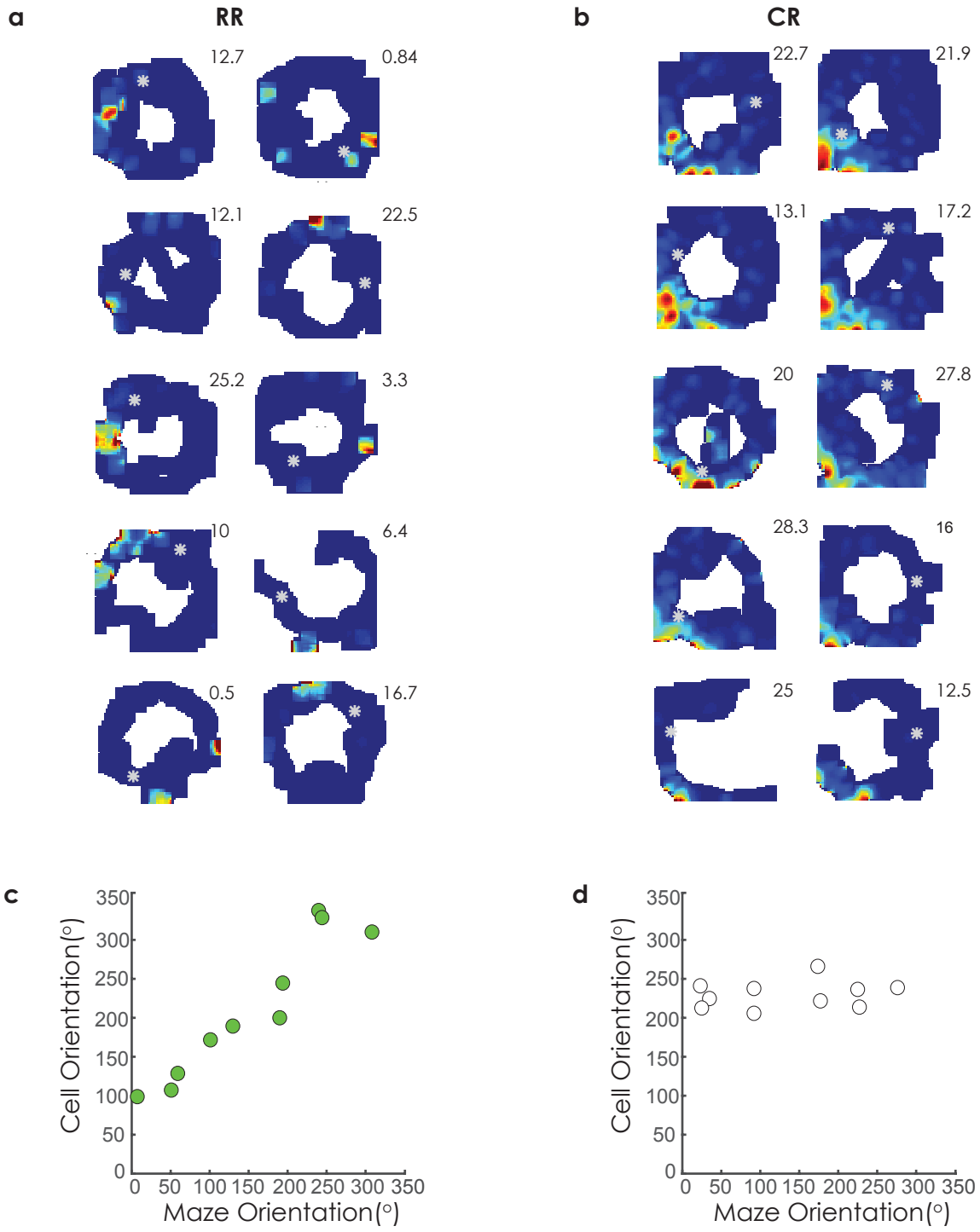

Figure R5 Mapping of space by CA1 neurons depends on reward configuration
a Spatial ratemaps of an example cell recorded in the RR configuration across 10 trials. White asterisks marks the orientation of the arena (maze orientation). Peak firing rates are noted on top right corner of each spatial ratemap. **b** Spatial ratemap of an example cell recorded in the CR configuration across 10 trials. Same conventions as in a. **c** Correlation between the orientation of the recording arena (maze orientation) and orientation of the center of the place field of the cell in a ($r^2 = 0.94$, $P < 0.001$). **d** Correlation between the orientation of the recording arena (maze orientation) and orientation of the center of the place field of the cell in b ($r^2 = 0.19$, $P > 0.2$).

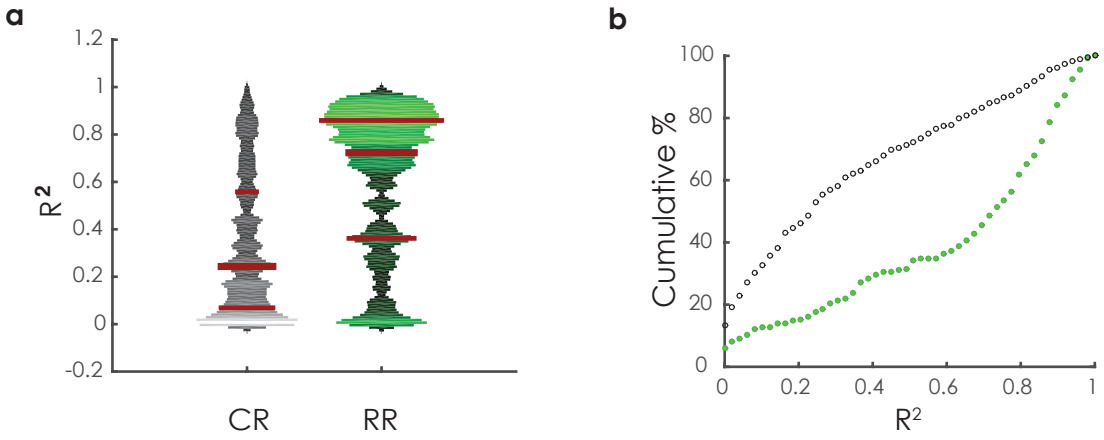

Figure R6 Correlation of place field orientations with maze orientations
a Violin plot, distribution of R^2 values of the Pearson correlation between the orientation of the recording arena and the orientation of all recorded cells. Horizontal red lines indicate quantiles and divide the number of observations into 4 equal parts. Median is depicted with a red line between two quantiles. Wider sections of the violin plot represent a higher probability that members of the population will take on the given value; the narrower sections represent a lower probability. In Green: Cells recorded in the RR configuration, 56.3% of cells recorded in the RR configuration show a significant correlation with maze rotation ($P < 0.01$). In black: Cells recorded in the CR configuration, only 16% of cells show a significant correlation with maze rotation ($P < 0.01$). **b** Cumulative distribution of R^2 values of the Pearson correlation between the orientation of the recording arena and place field orientation of all recorded cells (calculated as in Fig. R4 and R5). Green circles: cells recorded in the RR configuration. Black circles: cells recorded in the CR configuration.

significantly correlated with maze rotations (16% of cells showing a significant correlation (*P* < 0.01*)*, grey violin plot in Fig R6a). Figure R6b shows the difference in cumulative distribution of correlation coefficients for RR (green circles) and CR (black circles) groups.

Together, these data suggest that CA1 place cells differentially encode cognitive maps according to the dimensions that are relevant to the current goal.

Learning is paralleled by CA1 remapping to encode reward-relevant dimensions

CA1 neurons shift to represent reward-relevant coordinates

We observed that reward regularity causes differential encoding of space by the neurons. To determine the feature set encoded by CA1 cells, we devised an Odor-Space Index (OSI) that quantifies the extent to which each neuron follows spatial (lab) coordinates vs. olfactory (maze) coordinates (see Materials and Methods and Figure R7a, b). For each recorded neuron we used the calculated relationship between place field orientation and maze rotation (see examples in Figure R5c, R5d) to define two dispersion measures: The spatial dispersion (SpD) was defined as the deviation of the neuron's place-fields across maze rotations from their mean in lab coordinates. Similarly, the odor dispersion (OdD) was defined as the deviation of each neuron's place fields from their position according to odor rotation (see Materials and Methods). We then calculated the Odor Space Index $OSI = \frac{SpD-OdD}{SpD+OdD}$, where OSI values range from -1 for neurons with place-fields perfectly reflecting spatial coordinates, to +1 for neurons perfectly reflecting olfactory coordinates. Figure R7c shows the evolvement over time of the OSI values for both experimental groups during the training period. Both groups exhibit similar initial OSI, with negative values of (-0.26 ± 0.11 and -0.39 ± 0.12 on day 1 for the CR and RR groups, respectively), until they diverge after 12 days (Two-way ANOVA with interaction, day effect $F_{(19)} = 2.26$, $P_{days} < 0.01$; group effect $F_{(1)} = 212.5$ $P_{groups} < 0.0001$, interaction $F_{(19)} = 6.74$ $P_{interaction} < 0.0001$). While neurons of the CR rats decrease their OSI, exhibiting a shift of the population towards better encoding of space in lab coordinates, neurons of the RR rats show an increase in their OSI, indicating a shift towards encoding space in olfactory coordinates.

CA1 neurons shift with learning to represent reward-relevant coordinates

Note that the shift in encoding properties of the neurons parallels the time course of the behavioral learning curve (compare Figure R1b and Figure R7c). The deviation of the OSI values from their baseline seems to precede the marked improvement in performance. To quantify this effect, we applied separate change point analyses to detect the deviation of the OSIs from their baseline value, as well as the point at which performance reached plateau. The OSI curve deviated from its default

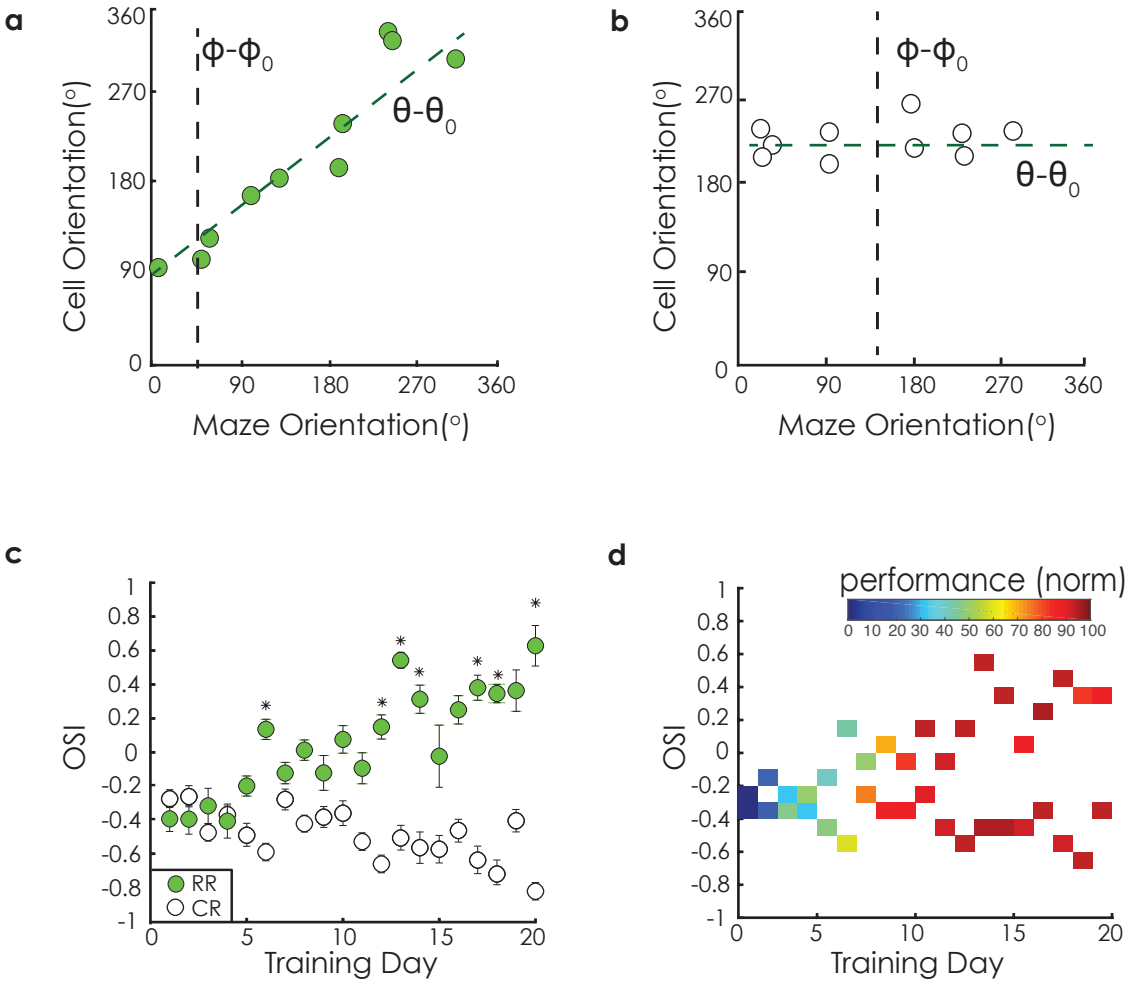

Figure R7 CA1 neurons shift to represent space in reward-relevant coordinates

a Correlation between the orientation of the recording arena and orientation of the center of the place field of an example cell recorded in the RR group. Green dashed line represents the difference between θ and θ_0. Place field orientation is 106°. Black dashed line represents the difference between φ and φ_0. Maze orientation is 45.1°. **b** Correlation between maze orientation and orientation of the place field of an example cell recorded in the CR group. Same conventions as in a. Place field orientation is 200°; maze orientation is 145°. **c** Odor Space Index values (OSI) as a function of training days of cells in the RR (green) and CR (black) groups (mean ± SEM). (2-way ANOVA with interaction, day effect $F_{(19)} = 2.26$, $P_{(days)} < 0.01$; group effect $F_{(1)} = 212.5$ $P_{(groups)} < 0.0001$, interaction $F_{(19)} = 6.74$ $P_{(interaction)} < 0.0001$). Asterisks denote differences at post hoc comparisons with Bonferroni correction at $P < 0.01$). **d** OSI values for both RR and CR group as a function of training days and performance. The shift in OSI values is paralleled by behavioral improvement after day 9 (color coded, warm colors).

baseline value after 7.45 days, $P < 0.001$, while learning flattened on day 10 ($P < 0.001$). Indeed, when OSI is examined as a function of performance level, OSIs change abruptly and cluster according to the experimental groups prior to significant improvement in performance (Figure R7d). Change point analysis of OSI to performance revealed a general shift of the OSIs when the animals reached 45.8% of their maximum performance level. After this point, the OSIs of the two groups differed significantly (mean (CR)=-0.472, mean (RR)=0.0254), 2 tailed Welch two sample t-test, $t_{43.69} = 7.04$, $P < 0.001$), whereas before they did not differ (mean (CR)=-0.358, mean (RR)=-0.335), $t_{6.5} = 0.32$, $P = 0.75$). These data show that, in a spatial task, CA1 neurons arrange their representations to better encode the reward-relevant coordinate dimension and their spatial representations are shaped to represent the spatial reward rule most efficiently. However, these data do not conclude if a similar process takes place for learning non-spatial reward rules.

Mice successfully learn to use the correct olfactory response strategy for obtaining reward

To examine the types of information that may be maintained in the rodent brain while learning different feature sets, which are important for reward, we designed an olfactory discrimination task (olfactory set learning), in which the spatial dimension of the task was irrelevant for goal obtainment. In this task, we manipulated the reward rule in a multidimensional olfactory discrimination task (see Methods). Briefly, water restricted mice were placed in an elevated plus maze. The central hub of the maze contained 4 nose pokes and 2 different odors were presented in each trial to two randomly chosen nosepokes, signifying two arms. A predefined odor was associated with liquid reward (water), and the second odor was not rewarded. Reward was delivered at the end of the correctly chosen arm (Figure R8a). After sampling both odors, the mice chose an arm to enter. Fourteen liquid-restricted mice (GluK2 wildtype ($GluK2^{+/+}$), N=9; GluK2 knockout ($GluK2^{-/-}$), N=5) were trained to sample odors and choose an arm for 20 trials a day. GluK2 wildtype mice successfully learned to associate a certain odor with reward and reached asymptomatic levels in 10 days (blue circles in Figure R8b) These data show that, mice can perform successfully in a multidimensional task by associating the relevant stimuli with correct responses and by ignoring the spatial features of the task, when non-spatial rules are relevant for goal attaintment.

We next wanted to see if mice could also form an attentional shift rather than making simple stimulus-response associations. Therefore, after they learned to obtain reward with the first odor set, we introduced an intradimensional shift and presented the mice with a novel pair of odors. This paradigm revealed successful set-shifting ability; the mice applied the rule successfully and associated the rewarding odor with the correct arm in a shorter time period in comparison to the first encounter with the rule. (blue circles in days 15-20 in Figure R8b). These data show that mice can successfully learn to use the correct olfactory response to obtain reward. Furthermore, when they are challenged by a switch in the relevant dimension of the odor discrimination task, they successfully form an attentional shift and apply the previously learned rule to new settings.

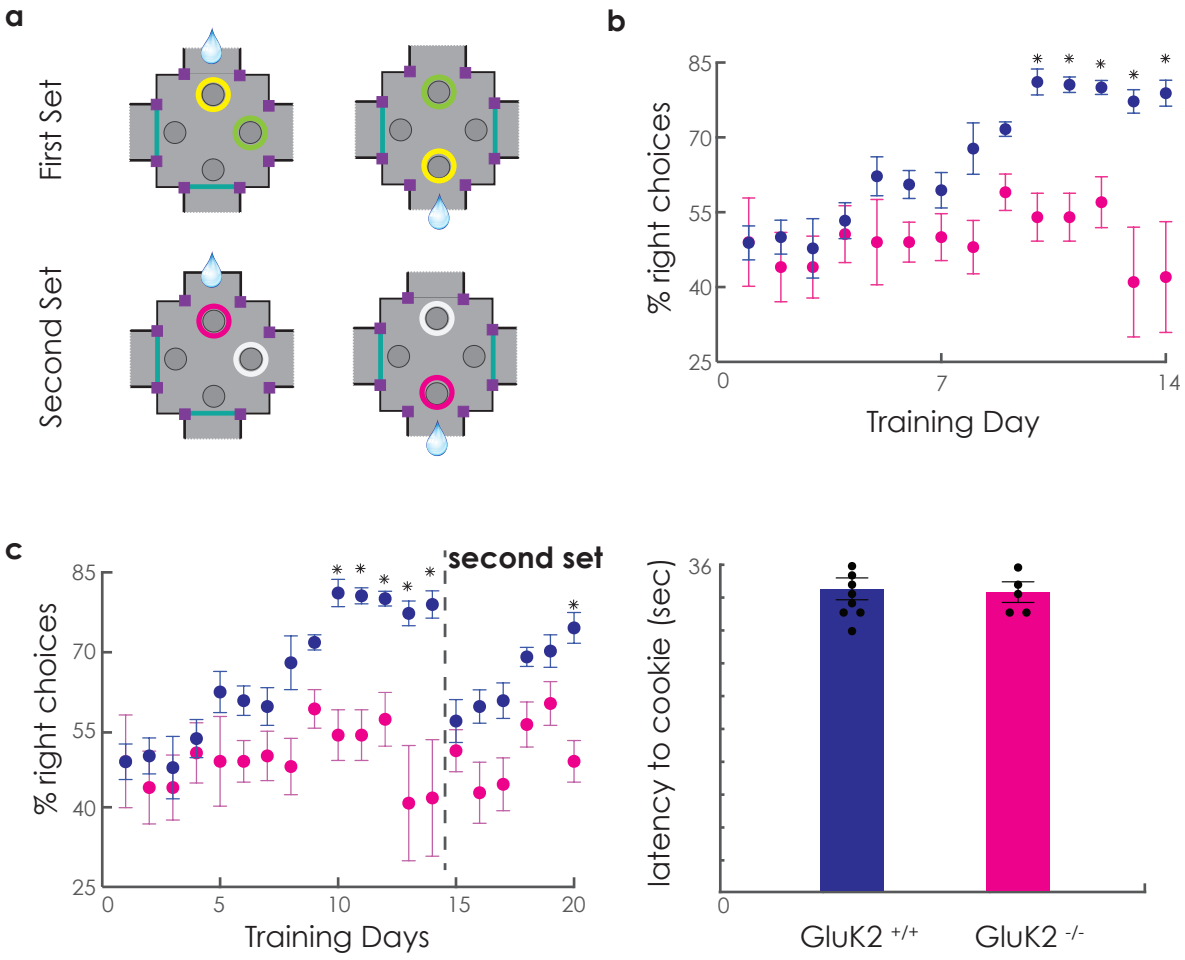

Figure R8 Mice learn the correct olfactory response strategy for reward
a Top view of the illustrative description of olfactory discrimination task **b** A set of 2 odors is given at a different arm entry in each trial, for 20 trials a day (depicted by yellow and green circles in top row and pink and white circles in bottom row).The yellow odor is associated with water reward in the 1.set and pink odor is associated with water reward in the 2. set. **b** Learning curve of mice in the olfactory plus maze. The performance is depicted as percentage of right choices as a function of training days. GluK2$^{+/+}$ mice (in blue, N=9) and GluK2$^{-/-}$ mice (in pink, N=5)are represented by color blue and pink respectively. (mean ± SEM). Asymptotic performance is reached after 9 days by GluK2$^{+/+}$ mice. GluK2$^{-/-}$ mice perform only at chance levels (2-way ANOVA with interaction, day effect $F_{(13,156)} = 5.37$, $P_{(days)} < 0.0001$; group effect $F_{(1,12)} = 45.31$ $P_{(groups)} < 0.0001$, interaction $F_{(13,156)} = 3.38$ $P_{(interaction)} < 0.001$) Asterisks denote differences at post hoc comparisons with Bonferroni correction at $P < 0.01$). **c** Learning curve of mice in the olfactory plus maze with second odor set. Same conventions as in b. The grey dashed line indicates the training day (day 15) when the second odor set was introduced. GluK2$^{+/+}$ mice reach asymptotic performance after 5 days. GluK2$^{-/-}$ mice perform only at chance levels (2-way ANOVA with interaction, day effect $F_{(3.7,44.2)} = 5.39$, $P_{(days)} < 0.01$; group effect $F_{(1,12)} = 25.92$ $P_{(groups)} < 0.001$, interaction $F_{(5,60)} = 1.75$, ns, $P_{(interaction)} = 0.14$) **d** Latency to cookie retrievel in seconds (sec). Individual data points are indicated by black dots. Both the GluK2$^{+/+}$ mice (blue bar, mean: 32,6 sec) and GluK2$^{-/-}$ mice (pink bar, mean: 32,2 sec) found the cookie and displayed no significant difference in their latencies (t-test, P=0.85), errors bars in SEM.

Kainate receptor dysfunction impairs complex-learning skills

After establishing the learning protocol in wildtype mice (GluK2 wildtype), we next wanted to know whether this task could be leveraged as an assay to test complex-learning skills in genetically modified mice. Complex learning tasks require long-term modulation of intrinsic neuronal excitability in multiple brain areas and learning induced neuronal excibility is a phenomenon in multiple brain regions (Moyer et al., 1996; Oh et al., 2003; Saar et al., 2001; Zelcer et al., 2006). This increase has been also reported in hippocampus and is induced by reducing the conductance of a slow potassium current in CA1 neurons. In the hippocampus, activity dependent AHP reduction is GluK2 dependent (Fisahn et al., 2005), and GluK2 kainite receptor disfunction has been implicated in cognitive disabilities (Lanore et al., 2012; Micheau et al., 2014). Therefore, we tried to compare learning performance of GluK2 wildtype and GluK2 knockout mice in the olfactory discrimination task. In contrast to their wildtype littermates, the GluK2 knockout mice could not learn the task and could only perform at chance level (2-way ANOVA with interaction: day effect $F_{(13,156)}$ = 5.37, $P_{(days)}$ < 0.0001; group effect $F_{(1,12)}$ = 45.31 $P_{(groups)}$ <0.0001, interaction $F_{(13,156)}$ = 3.38 $P_{(interaction)}$ < 0.001) (Figure R8b).

Similarly, GluK2 knockout mice were also unable to show successful performance when presented with the second set of odors, whereas their wildtype littermates successfully formed an attentional shift (2-way ANOVA with interaction: group effect $F_{(1,12)}$=25.92, P_{group}<0.001, day effect $F_{(3.69, 44.23)}$=5.39; P_{days} <0.001, interaction $F_{(5,60)}$=1.75; $P_{daysXgroup}$ > 0.05 (Figure R8c)

We next tested the mice in a commonly used cookie test (Yang and Crawley, 2009) to see if GluK2 depletion had an effect on their odor sensation, on motor skills or on their motivation. In this test, mice were firstly habituated to flavored food pellets and are allowed to explore a clean cage containing a food pellet buried in its bedding. GluK2 wildtype and GluK2 knockout mice spent similar amount of time exploring the new cage, they were able to find the food pellet buried in the bedding and showed no significant difference in their statistics ($GluK2^{+/+}$ mean: 32,6 sec) and $GluK2^{-/-}$ mice (pink bar, mean: 32,2 sec) found the cookie and displayed no significant difference in their latencies (t-test, *P*=0.85), errors bars in SEM. (Figure R8d). These data indicate that the decreased performance displayed by GluK2 knockout

mice in the olfactory discrimination task is not related to an olfactory impairment, a motor disfunction or to lack of motivation.

These data suggest that mice with unimpaired hippocampal processing can successfully identify the crucial components of their environment and, importantly, map strategies. Moreover, they can apply these strategies to similar scenarios with improved learning performance.

Discussion

The current experiments provide evidence that the construction of cognitive maps in the hippocampus is determined by the environmental dimensions, which are relevant to goal-attainment. We have shown that successful task performance depended on a particular subset of input dimensions and hippocampal place cell activity can form distinct reduced representations of space that are dictated only by the reward-relevant dimension. During learning, a shift occurs in the spatial dimensions represented by the place cells, and this representational shift parallels the time course of learning. In addition, similar representational shifts may take place during rule learning, assisting implementation of rules to novel settings by using previously learned strategies. A possible neural mechanism subserving formation of reduced representations could be unimpired hippocampal processing.

Optimal performance in both tasks used in this study relies olfactory-discrimination, memory, spatial navigation and reinforcement learning, and hence involve primarily three brain circuits: cortical, hippocampal and basal ganglia circuits.

The first cortical structure is the olfactory cortex, which can be broadly divided into the piriform cortex and orbitofrontal cortex. Principle neurons of the piriform cortex receive direct input from the primary sensory organ, the olfactory bulb and electrophysiological single unit recordings from these neurons show that they tune their activity to different odors (Illig and Haberly, 2003; Rennaker et al., 2007; Schoenbaum and Eichenbaum, 1995). Therefore, the activity of single neurons and neuronal ensembles in the piriform cortex are expected to reflect the animals' discrimination ability. In our experiments with rats, we assume that, initially, the cortical representation of idiothehic and presented odors would improve and as animals learn to associate reward with the presented odors, only the neurons encoding reward-relevant odors would increase the modulation in their tuning curves. In our experiments in mice, it is possible that before formation of the attentional-shift, the cortical representation of the presented odors would improve. By contrast, within the attentional-shift period, we assume that the same neurons would increase the modulation in their tuning curves, such that neuronal ensembles will better code all (already presented and new exemplars) odors. It has been shown that intrinsic neuronal excitability cannot be induced by synaptic activation in

piriform brain slices of GluK2 knockout mice and viral-induced overexpression of Gluk2 in piriform cortex pyramidal neurons results in remarkable enhancement of complex olfactory discirmination learning (Chandra et al., 2019). However, since both the hippocampus and the piriform cortex receive primary olfactory inputs, and the behavior in both odor discrimination tasks is heavily hippocampus dependent and require the formation of an episodic memory trace (Christian and Thompson, 2003; McEchron and Disterhoft, 1999; Shors, 2004; Thompson and Kim, 1996), it could be speculated that all of the learning related changes (in case of both tasks) occur only in the hippocampus, which encodes odors within a context. Simultaneous recordings from the hippocampus and the pirifrom cortex and checking whether the coding of the same odors improves in a differently designed task could provide more insight into hippocampal encoding of context.

Correct performance of an odor discrimination task requires accurate odor discrimination, which supposedly occurs in the piriform cortex. However, it also requires correct formation of an episodic memory trace from the odor to the reward (Thompson and Kim, 1996; McEchron and Disterhoft, 1999; Christian and Thompson, 2003; Shors, 2004; Bangasser et al., 2006). Since the versions of olfactory-discrimination tasks presented in this thesis are of spatial nature, this episodic memory should be represented in the activity hippocampal CA1 and CA3 place cells (O'Keefe and Dostrovsky, 1971b; Dragoi et al., 1999; McNaughton et al., 2006; Sugar and Moser, 2019). It is possible that, initially, animals plot multiple cognitive maps and employ different strategies to obtain reward. In principle, our tasks' design (the pseudorandom presentation of 2 odors among 4 different ports in rule-based olfactory discrimination task and pseudorandom rotations of the olfactory dimension in spatial olfactory discrimination task) discourage the animals from associating tactile intra-maze cues and proprioceptive cues to reward contingency. Yet, it is possible that animals map these incidental details in the beginning of training days. It is likely, however, that later, they make use of a stripped map, which carries only specific odor-reward associations. This is likely to occur by strengthening the appropriate cortico-striatal (Haber, 2016)and reciprocal HPC-PFC projections (Shastri, 2002; Cooper and Ritchey, 2019). This work provides behavioral evidence for this hypothesis, since the previously learned strategy in the plus maze was implemented in solving the task with the second set of odors.

The performance in the both odor discrimination tasks also involves reinforcement learning, which occurs in the cortico - basal ganglia circuits (Barto, 1995; Bar-Gad et al., 2003). The basal ganglia is considered the seat of the action-selection and decision-making processes, by tuning the strength of connections of different actions according to their outcome (a good or a bad decision). The input nucleus of the basal ganglia, the striatum, recieves massive innervation from all cortical (sensory and other) areas (Selemon and Goldman-Rakic, 1985; Brown and Feldman, 1993; Brown and Sharp, 1995; Richards and Taylor, 1982; Hintiryan et al., 2016). In addition, it receives heavy neuro-modulatory innervation by dopamine, acetylcholine and serotonin which have been identified with teaching elements developed in the computational world of reinforcement learning (Schultz et al., 1997b; Daw et al., 2002; Morris et al., 2004b, 2006c). This combination of inputs allows striatal neurons to code the value of upcoming actions (Samejima et al., 2005), compounded on the task related responses seen in the striatal projection neurons (Barnes et al., 2005). In addition, collaterals of dopaminergic input to the striatum, which project to the cortex or to the hippocampus, may tune the acvitiy of cortical and hippocampal neurons to more appropriately accord with 'good' decisions (Retailleau and Morris, 2018).

Our experiments in rats were conducted in darkness to avoid anchoring to recent visual cues (Quirk et al., 1990). Nevertheless, rats in the CR group succeeded in navigating to a goal, which was fixed at lab coordinates. Since their entry point into the maze was constant throughout their trials, and trials were relatively short, it is likely that animals used self-motion cues for path integration to correctly locate the reward (McNaughton et al., 1996). It is more surprising that the initial OSI of rats from both groups was close to -0.5, and remained so for many days. This implies that the default mode of spatial encoding in the hippocampus of adult rats relates to global space coordinates, even in the absence of visual feedback, and that hippocampus constructs maps using the remaining available information. However, we cannot rule out the possibility that it is precisely this absence of visual cues that induced this state, as it has been shown that such conditions favor the reliance on response rather than space strategies (Restle, 1957). It is therefore possible that the rats' inability to use visual cues imposed striatum-dependent responses for task performance, and that the resulting low OSI is a product of this strategy. Our experiments in mice were carried out in dim light; however, goal-related cues did not include any extra-maze

visual information. Since there were no correlations with the animal's changing geographic orientation and the reward, mice also had to learn not to depend on a spatial strategy but construct an olfactory map, which informed them about correct entry arm, regardless of their position.

Studies of the impact of reward on place cell activity have shown that paths toward reward location is preferentially represented by place cells (Pfeiffer and Foster, 2013), that learning new goal locations is accompanied by rearrangement of CA1 neurons, such that more neurons encode the new goal locations, either by shifting their place fields (Dupret et al., 2010) or by extra-field firing (Pfeiffer and Foster, 2013), and that spatial coding is more reliable under these conditions as evidenced by lower over-dispersion measures (Fenton et al., 2010). Since a concentration of cells with partially overlapping place fields in proximity to the goal implies spatial encoding with a higher resolution, such rearrangement may serve to optimize routes towards the goal, zooming in on the fine detail of the destination (Boccara et al., 2019). However, note that this solution requires re-tailoring to each change of the environment. By contrast, we show, that when a general reward rule can be extracted, the whole map rearranges to best capture the rule. The newly formed map is more efficient and useful for a whole family of similar problems. As in other forms of rule learning, learning of space-related tasks may be regarded as a two-tiered process. In the first stage of fast learning, animals learn the specific parameters of the given environment, improving their ability to infer their position in the existing map. This is implemented by transiently enhancing the representation of important locations by increasing the number of neurons that encode them (Dupret et al., 2010; Pfeiffer and Foster, 2013). A second, slower learning phase, involves the formation of a different type of map. This map may enable efficient representation in the most relevant dimension for future learning of similar tasks. This is reminiscent of the acquisition of learning sets (Harlow and Settlage, 1948), where repeated exposure to problems of similar form presents with the opportunity to form an abstract representation of a set of problems for which a general strategy can be established. In our tasks, repeated exposure of the animals to track configurations, which co-vary with reward along a single dimension, which is the olfactory dimension, present with the opportunity to form a reduced map highlighting this dimension. We specifically check and confirm this hypothesis in our mice study. Our data in mice demonstrate the ability of forming learning sets, as demonstrated by the ease of performing intradimensional

attentional shifts, allowing the mice to learn rules and apply them to future dicriminations in a time-efficient manner.

Previous studies showed that activity of CA1 neurons is organized in multiple reference frames. It was further shown that activity is more stable in a task-relevant frame, suggesting that purposeful behavior affects hippocampal place cell activity (Zinyuk et al., 2000). Several studies also describe hierarchies in determining representations that favor either distal (Shapiro et al., 1997) or, in other conditions, proximal cues (Renaudineau et al., 2007b; Siegel et al., 2008). However, we show in electrophysiological results, that the hierarchy is set by relevance to goal-directed behavior, rather than a hard-wired hierarchy based on physical attributes of the actual reference frames. Concordantly, our experiments in mice display supporting behavioural evidence. Therefore, we can expect that during learning of set-shifting paradigms (Robbins, 1996) hippocampal representation will shift gradually to represent the dimensions relevant to the different sets. Conversely, after acquisition, representation may immediately switch between different reference-frames according to the currently relevant dimension, as reported for visual stimuli in decision related regions of the primate parietal cortex (Toth and Assad, 2002).

One of the advantages of our behavioral paradigms is the relatively slow learning of the animals. This enabled us to track the dynamics learning in both tasks. Mice required 10 days to learn odor-reward association but showed a faster dynamic (5 days) in implementing the strategy to a new set. Concordantly, the dynamics of of the neural representation throughout the considerable time period of the learning process in rats showed that, the improved representation of CA1 neurons accurately mirrored the behavioral improvement that depended on positive reinforcement. In fact, it seems that the OSI shift slightly preceded the behavioral improvement, suggesting that the representational shift is a critical step of learning. One possible explanation for this correlation is that both processes depend upon a common reinforcement mechanism. As we showed, the hippocampal cognitive map is shaped by relevance for reward collection. Thus, there should be a neuronal signal conveying reward information to the hippocampus (Shohamy and Adcock, 2010). A natural candidate is a projection from the ventral tegmental area (VTA), a midbrain nucleus containing dopaminergic neurons, which is commonly implicated in reinforcement learning (Morris et al., 2006c; Schultz et al., 1997c; Sutton, 1998; Waelti

et al., 2001). Dopaminergic neurons within the VTA project to the hippocampus, where dopamine receptors are expressed on various types of cells (Gangarossa et al., 2012; Gasbarri et al., 1994b; Rosen et al., 2015). Recent studies demonstrated the impact of this projection on synaptic plasticity in CA1 (Rosen et al., 2015), as well as on hippocampal reactivation and spatial learning (McNamara et al., 2014). It has been also recently shown that, neuronal ensemble configurations that consistently co-vary with the dopaminergic input will undergo stabilizing plasticity processes (Retailleau and Morris, 2018). This information transfer between the two regions may take place during the recently identified synchronization of VTA neurons with hippocampal sharp wave-ripple events (Gomperts et al., 2015) or during slower network oscillations (Fujisawa and Buzsáki, 2011).

Overall, we show a critical reward dependence of the hippocampal cognitive map for goal directed behavior. We propose that reward dependence of hippocampal encoding is a two-step process. In the first phase, reward related modifications occur in the existing map to facilitate navigation towards a goal. However, such tailored maps are only useful for ad-hoc navigation problems. They cannot be generalized to extract an efficient rule for behavior. The second phase requires the formation of a different type of map, which requires improved modulation of tuning curves of cortical representations, accurate representation of correct action in the striatum and of the trajectory of movement (spatial mapping) in the hippocampus. This improvement will be reflected in increased functional connectivity between hippocampal-striatal projections, which result in an increased coherence in the local field potentials and increased correlation in the firing of single neurons, that participate in the task (Figure D1).

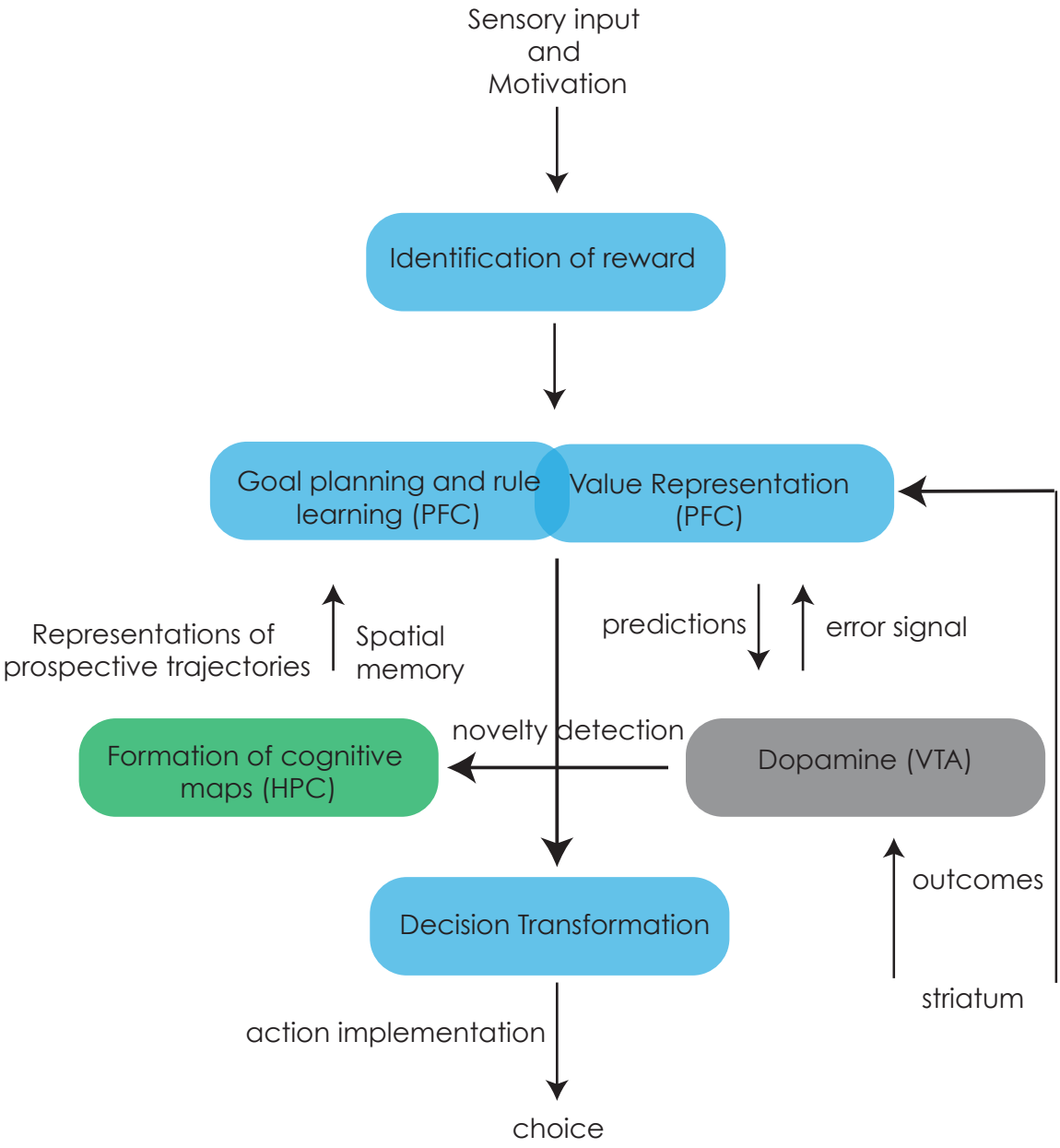

Figure D1 Conceptual framework for goal-directed action selection

Multimodal sensory stimuli is integrated and interact with the physiological needs of the animal to correctly identify reward. Next, a value is assigned to the reward and at this stage neurotransmitter dopamine carries a prediction-error signal to inform the system of any discrepancy between the expected outcome and the received outcome. In parallel, HPC aids the PFC in working memory, goal planning and rule learning by providing spatial memory as well as representations of future trajectories. This could help ensure PFC that a learned rule is correctly performed in the current trajectory. The HPC receives from VTA dopaminergic nuclei which carry novelty signal. This updates the HPC representations to rearrange in a reward-relevant manner. After dopaminergic input, the new value representation in the PFC drives decision transformation and a choice is made.

Experimental Outlook

Both of our experimental paradigms can be very useful in further examining the time coarse of creating and modulation of neural representations with a focus on two main considerations:

1. What are the dynamics of cortico-hippocampal connections and striatal projections in construction of cognitive maps and rule learning in goal-directed decision-making?

Single unit recordings from rodent cortical and down stream structures (striatum and hippocampus) during manipulation of task parameters (odor vs tactile; vs sound in the plus maze) and change in task rules can provide insight into cortical and hippocampal processes that create generalizations over learning episodes. Furthermore, simultaneous recordings of local field potentials in the cortex, striatum and the hippocampus could show the changes in functional connectivity between these structures. In addition, future studies combing optogenetic activation of the VTA terminals along with pharmacological manipulations of the dopamine receptors in the hippocampus may yield further insight into the reward dependence of the formation of the hippocampal cognitive map.

2. What are the intrinsic properties of neuronal plasticity, which takes place during hippocampal representations and rule learning in goal-directed decision-making?

The neurophysiological mechanisms underlying learning is thought to be long term plasticity (LTP and LTD), which regulate synaptic efficacies of specific connections. Intrinsic properties of neurons, which participate in a particular learning process, undergo long-term changes after learning, however in order for flexible representations to form, their activity must be protected from saturation or extinction of their synapses. Therefore, metaplasticity mechanisms, which regulate long-term changes and increase the information storage capacity of synapses, can be used to gain further insight into neuronal plasticity in cortical and hippocampal representations as well as in rule learning.

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Author Contributions

Genela Morris and Tuğba Özdoğan designed the study and the experiments. Tuğba Özdoğan performed the experiments. Genela Morris and Tuğba Özdoğan analyzed the data. Susanne Rieckmann prepared the histological slices and optimized the cutting and staining procedures.

Appendix

Besides the experimental work and data analysis presented in this thesis, I also contributed to the following scientific research articles.

Publication 1: GluK1 inhibits calcium dependent and independent transmitter release at associational/commissural synapses in area CA3 of the hippocampus.

Contribution: 3rd Author, *In Vitro* recordings of extracellular field potentials in mouse hippocampal slices

Abstract

CA3 pyramidal cells receive three main excitatory inputs: the first one is the mossy fiber input, synapsing mainly on the proximal apical dendrites. Second, entorhinal cortex cells form excitatory connections with CA3 pyramidal cells via the perforant path in the stratum lacunosum moleculare. The third input involves the ipsi-and contralateral connections, termed the associational/commissural (A/C) pathway terminating in the stratum radiatum of CA3, thus forming a feedback loop within this region. Since this excitatory recurrent synapse makes the CA3 region extremely prone to seizure development, understanding the regulation of synaptic strength of this connection is of crucial interest. Several studies suggest that kainate receptors (KAR) play a role in the regulation of synaptic strength. Our aim was to characterize the influence of KAR on A/C synaptic transmission: application of ATPA, a selective agonist of the GluK1 KAR, depressed the amplitude fEPSP without affecting the size of the fiber volley. Blockade of GABA receptors had no influence on this effect, arguing against the influence of interneuronal KARs. Pharmacological and genetic deletion studies could show that this effect was selectively due to GluK1 receptor activation. Several lines of evidence, such as PPF changes, coefficient of variance–analysis and glutamate uncaging experiments strongly argue for a presynaptic locus of suppression. This is accompanied by an ATPA-mediated reduction in Ca^{2+} influx at excitatory synaptic terminals, which is most likely mediated by a G-Protein dependent mechanism, as suggested by application of pertussis toxin. Finally, analysis of miniature EPSCs in the presence and absence of extracellular Ca^{2+} suggest that presynaptic KAR can also reduce transmitter release downstream and therefore independent of Ca^{2+} influx.

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Publication 2: Cannabinoid Type 2 Receptors Mediate a Cell Type-Specific Plasticity in the Hippocampus.

Contribution: 2nd Author, Hippocampal *in vivo* recordings in freely moving mice, analysis of data, micro-lesioning of the brain for histology

Abstract

Endocannabinoids (eCBs) exert major control over neuronal activity by activating cannabinoid receptors (CBRs). The functionality of the eCB system is primarily ascribed to the well-documented retrograde activation of presynaptic CB1Rs. We find that action potential-driven eCB release leads to a long-lasting membrane potential hyperpolarization in hippocampal principal cells that is independent of CB1Rs. The hyperpolarization, which is specific to CA3 and CA2 pyramidal cells (PCs), depends on the activation of neuronal CB2Rs, as shown by a combined pharmacogenetic and immunohistochemical approach. Upon activation, they modulate the activity of the sodium-bicarbonate co-transporter, leading to a hyperpolarization of the neuron. CB2R activation occurred in a purely self-regulatory manner, robustly altered the input/output function of CA3 PCs, and modulated gamma oscillations in vivo. To conclude, we describe a cell type-specific plasticity mechanism in the hippocampus that provides evidence for the neuronal expression of CB2Rs and emphasizes their importance in basic neuronal transmission.

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Publication 3: A Cellular Mechanism Underlying Enhanced Capability for Complex Olfactory Discrimination Learning.

Contribution: 3rd Author, Behavioural training of mice in olfactory discrimination task for rule learning

Abstract

The biological mechanisms underlying complex forms of learning requiring the understanding of rules based on previous experience are not yet known. Previous studies have raised the intriguing possibility that improvement in complex learning tasks requires the long-term modulation of intrinsic neuronal excitability, induced by reducing the conductance of the slow calcium-dependent potassium current (sI_{AHP}) simultaneously in most neurons in the relevant neuronal networks in several key brain areas. Such sI_{AHP}reduction is expressed in attenuation of the postburst afterhyperpolarization (AHP) potential, and thus in enhanced repetitive action potential firing. Using complex olfactory discrimination (OD) learning as a model for complex learning, we show that brief activation of the GluK2 subtype glutamate receptor results in long-lasting enhancement of neuronal excitability in neurons from controls, but not from trained rats. Such an effect can be obtained by a brief tetanic synaptic stimulation or by direct application of kainate, both of which reduce the postburst AHP in pyramidal neurons. Induction of long-lasting enhancement of neuronal excitability is mediated via a metabotropic process that requires PKC and ERK activation. Intrinsic neuronal excitability cannot be modulated by synaptic activation in neurons from GluK2 knock-out mice. Accordingly, these mice are incapable of learning the complex OD task. Moreover, viral-induced overexpression of Gluk2 in piriform cortex pyramidal neurons results in remarkable enhancement of complex OD learning. Thus, signaling via kainate receptors has a central functional role in higher cognitive abilities.

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Erklärung an Eides statt

Ich, Tuğba Özdoğan, versichere an Eides statt, dass ich die vorgelegte Dissertation mit dem Thema: „Evaluating the role of hippocampal processing in encoding and storing reward relevant information for goal-directed behavior " selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.

Berlin, den 26. September 2019