Hippocampal Representation Of Touch and Sound Guided Behavior.

PhD Candidate:

Pavel M. Itskov

Supervisor:

Prof. Mathew E. Diamond

Trieste, September 30, 2009
Cognitive Neuroscience Sector, International School
for Advanced Studies (SISSA), via Beirut 2–4, 34014 Trieste, Italy;
and Italian Institute of Technology – SISSA unit

Acknowledgements

I would like to thank Mathew E. Diamond.
Without his constant support and great ideas this work would have never been done.
His supervision made these 4 years an unforgettable and exciting experience.

I am thankful to Ekaterina Vinnik
for her ideas, criticism and encouragement as well as substantial contribution to the data analysis.

I am grateful to Armin Lak, Arash Fassihi, Natalia Grion and John Nicholls
for valuable comments of the work and fruitful discussions.

I'm grateful to Stefano Panzeri for his numerous advices on data analysis.

Jan Schnupp and Christian Honey
Helped in designing and setting up the auditory categorization task.

Erik Zorzin, Rudy Boz, Fabrizio Manzino Igor Perkon and Marco Gigante
provided outstanding technical help and thus made the work much easier.

This work was supported by Human Frontier Science Program grant RG0043/2004-C, European Community grant BIOTACT - 21590, Italian University and Research Ministry grant 2006050482_003, and grants from the Friuli Venezia Giulia region and the Italian Institute of Technology.

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Abstract

Understanding the mechanisms by which sensory experiences are stored is a longstanding challenge for neuroscience. Previous work has described how the activity of neurons in the sensory cortex allows rats to discriminate the physical features of an object contacted with their whiskers. But to date there is no evidence about how neurons represent the behavioral significance of tactile stimuli, or how tactile events are encoded in memory. To investigate these issues, we recorded single-unit firing and local field potentials from the CA1 region of hippocampus while rats performed a tactile task. On each trial, the rat touched a plate with its whiskers and, after identifying the texture of the plate, turned to the left or right to obtain its reward. Two textures were associated with each reward location. Over one-third of the sampled neurons encoded the identity of the texture: their firing differed for the two stimuli associated with the same reward location. Over 80 percent of the sampled neurons encoded the behavioral significance of the contacted texture: their firing differed according to the reward location with which it was associated. Texture and reward location signals were present continuously, from the moment of stimulus contact through the entire period of reward collection. The local field potential power spectrum varied across the different phases of behavior, showing that signals of single-units were present within a sequence of different hippocampal states. The influence of location was examined by training rats to perform the same task in different positions within the room. The responses of neurons to a given stimulus in different locations were independent. This was not the case for reward location signals: neurons that carried a signal in one location were more likely to carry a signal in the other location.

In summary, during a touch-guided behavior, neurons of the CA1 region represent both non spatial (texture identity) and spatial (reward location) events. Additional experiments were carried out, on another set of rats, to generalize some of the above findings from the tactile to the auditory modality. On each trial, the rat leaned into the gap and heard one of four sounds which were distributed along a vowel continuum from "A" to "I". After identifying the sound, the rat turned to the left or right to obtain its reward. Two sounds were associated with each reward location, and the experiment was repeated on 2 platforms. As in the tactile task, more than 80 percent of neurons

represented reward location and more than 25 percent of neurons represented the identity of the sound (the vowel). The role of context on the stimulus and reward location signals was the same as in the tactile experiments. Representations of sounds were independent across 2 platforms but the representations of reward location were not: neurons that carried a signal in one location were more likely to carry a signal in the other location. These responses were absent during passive listening to the sounds.

List of abbreviations:

PoM - posteromedial complex of the thalamus

VPM - posteromedial nucleus of the thalamus
S1 - primary somatosensory cortex
S2 - secondary somatosensory cortex
S3 - tertiary somatosensory cortex
PV - parietal ventral area (also, S3)
PM - medial Parietal cortex
PL - lateral parietal cortex
PTLp - posterior parietal cortex
LEA - lateral entorhinal area
MEA - medial entorhinal area
POR - postrhinal area
CA(1-3) - cornu ammonis subfields of hippocampus 1 to 3 respectively
mPFC - medial prefrontal cortex
ACd - anterior cingulate cortex
Fr-2 - frontal area 2
DG - dentate gyrus (fascia dentata of hippocampus)
LFP - local field potential

Introduction

Whisker-mediated tactile perception in rats is remarkably efficient: in the dark, rats can extract shape, position, texture and other features from just a few touches – with as little as 100 ms between first contact and decision (Heimendahl et al. 2007). In recent years there has been substantial progress in understanding the neuronal coding of surface roughness in the whisker sensory pathway (Arabzadeh et al. 2005; Arabzadeh et al. 2006; Jadhav et al. 2009; Wolfe et al. 2008) but nothing is known about how neurons represent the meaning of tactile stimuli in the context of behavior, or how tactile events are encoded in memory. Through the process of learning, the mapping between sensory inputs and actions can be shaped. Similar stimuli can be associated with different actions; thus they become, by experience, members of different behavioral categories. At the same time, dissimilar stimuli can be associated with the identical action; they become members of the same category. To learn categories, an association must be formed between a sensory cue, an action, and the successful acquisition of the reward.

Since the description of patient HM (Scoville & Milner 1957) the neuroscience community has recognized the medial temporal lobe and, in particular, the hippocampus as a structure crucial for the acquisition of declarative and episodic memory (Tulving & Donaldson 1972; Cohen & Eichenbaum 1993). We have designed a texture categorization task in which animals have to associate two different stimuli with the same location of reward. Previously most of the research of the categorization behavior was done either in humans or nonhuman primates (Freedman & Miller 2001; Hampson et al. 2004). We introduce behavioral paradigm, in which rats can perform a complex categorization behavior. Using rats instead of nonhuman primates has many advantages. The main advantage is the relative simplicity of the surgical procedures and higher stability of chronic recordings, lower cost and potential availability of transgenic models. We are using categorization task as a tool to study "object identity" related firing of neurons e.g. to neuronal responses to the stimuli belonging to the same behavioral category. Categorization and place related neuronal activity cannot be fully segregated by the current experimental design and thus neuronal basis of the formation of categories is not discussed. Experimental findings are discussed in the context of strategies implemented by the brain to store new episodes. Next, an experiment to generalize some of the findings from the tactile to the auditory modality is described.

Neuroanatomy of high level tactile processing and memory.

Very little is known about the functional organization of tactile information processing beyond the primary somatosensory cortex. In this brief review we were trying to bring together all known neuroanatomical data about the projections arising from primary somatosensory area till the final stage of processing – hippocampus, focusing on the hypothetical tactile "What" pathway. Current work is a follow up on the work which have described the processing of "texture" information in the primary somatosensory cortex (Heimendahl et al. 2007) but it is only the first step in a larger research program that aims at understanding of the transformation of somatosensory information in the brain. We have decided to focus on the hippocampal representation of the tactile guided task as a theoretical end point of the sensory processing. We shall treat our result in the hippocampus as the final product of the transformation implemented by the brain, but in order to study the transformation we need to know which brain structures are involved. Precise knowledge of neuroanatomy can also lead to scientific breakthroughs in the understanding of the information processing by suggesting locations for electrophysiological recordings (Hafting et al. 2005). By the comparison of various sensory pathways scientists may unravel general principles of information processing algorithms implemented by the evolution within the brain.

Anatomy of whisker afferents

The primary afferent terminations converting mechanical energy into neuronal discharges are located in the whisker shaft (Rice et al. 1986). The follicle of a large whisker contains nerve terminals from about 200-300 neurons whose cell bodies are located in the trigeminal ganglion. Whisker deflections or vibrations lead to stretching of the membrane of the afferent fibers, and induce a train of action potentials which travel upstream via the trigeminal nuclei in the brainstem where the first synapse of the pathway is located. The second synapse, which is located in the thalamus, is reached after the fibers cross the midline.

Organization of the thalamic input to the barrel cortex

There are two distinct territories within the primary somatosensory cortical area (S1): septa and barrels (Kim & Ebner 1999; Alloway 2008). The interbarrel area (or septa) receives inputs exclusively from the posteromedial complex (POm), whereas the barrel area receives inputs from both the POm and ventral posterior medial nucleus (VPM) (Lu & Lin 1993). Inputs from VPM and POm target different laminae within the barrels. VPM input mediates the lemniscal pathway from the nucleus principalis of the brainstem and terminates mainly on the neurons in layer 4 and layers

5b and 6A of the barrel cortex, while POm conveys paralemniscal input from the nucleus interpolaris of the brainstem and terminates mostly in layer 5A and layer 2 (Bureau et al. 2006). Barrels form projections to secondary somatosensory cortex while septal circuits project to the contralateral S1, primary motor cortex and send feedback projections to POm of the thalamus. It has been proposed that such differential connectivity provides the anatomical basis for two functional streams: the septal stream, which is probably related to the control and sensing of whisking, and a barrels stream which is specialized in processing and analyzing the content of touch signals and thus providing information about the identity of palpated object (Alloway 2008).

Somatotopically organized areas

Anatomical and electrophysiological studies have identified at least three somatotopically organized regions: primary somatosensory area (S1) (Woolsey & Loos 1970; Welker 1971; Chapin & Lin 1984), secondary somatosensory area (S2) (Fabri & Burton 1991; Gonzalez & Sharp 1985; Carvell & Simons 1986;. Carvell & Simons 1995; Koralek et al. 1990), parietal ventral area (Area PV or S3) (Remple et al. 2003). The maps in S2 and PV regions differ in the extent of projections destined for the same body region. The head region (vibrissae, upper and lower lips) is larger in S2 than in PV, whereas the opposite is true for the proximal body regions (arm, leg and trunk) (Fabri & Burton 1991). Other regions that show terminations following the injection of anterograde tracer into S1 are Medial Parietal area (PM), Lateral Parietal area (PL) and Parietal Rhinal. The latter is not discussed below since the definition of the region is unclear and the projections were not present in all the cases reported in the literature (Fabri & Burton 1991). Labeled cells and fibers were observed in area PM - a region posterior to S1-S2. The cytoarchitecture of PM shows characteristics of isocortex, i.e., all cortical layers can be recognized. This region show signs of a rough topographic organization: the head appears lateral, joining the head of S1, and the rest of the body is medial. There is no clear separation between proximal and distal regions for the limbs (Fabri & Burton 1991). The fibers terminate in all cortical layers except layer 1. PM fills a gap between SI and visual areas in the rodent cortex and has been suggested to be analogous to primate areas 5 and 7 (Chapin & Woodward 1982). Another region posterior to S2-PV and lateral to PM has been identified as parietal lateral (PL). No topography was seen in PL. Although there are reports of projections of paws and soma regions into posterior parietal cortex (PTLp), but whisker representation has been shown to avoid this region (Kolb & Walkey 1987).

Connection with Amygdala

Unlike in cats and monkeys, no direct projections from either S1 or S2 to amygdala have been found in the rat (Shi & Cassell 1998). Parietal insular cortex is a likely candidate to mediate the flow of somatosensory information to amygdala as it receives projection from POm of the thalamus as well as abundant S2 input, which is believed to carry nociceptive information (Shi & Cassell 1998)..

Somatosensory Input to the Hippocampal Formation

Perirhinal cortex in rats consists of the upper bank of the rhinal sulcus (homolog of Brodmann area 36 in primates) and the lower bank of the rhinal sulcus (homolog of area 35). The upper bank receives an average of 7 percent of its input from parietal areas. The parietal projections to the area originate from caudal levels of the parietal cortex. The origin of the input is distributed across S2, S1, and PTLp, but the largest proportion arises in PTLp. PTLp and S2 project more heavily to the rostral part of the upper bank of the perirhinal cortex than to its caudal part. Only the rostral extreme of the upper bank receives any input from the primary somatosensory area. In contrast, all rostrocaudal levels of the lower bank of perirhinal cortex receive about 5 percent of their input from parietal cortices; the largest portion arises in S2. Rostral parietal cortex projects rostrally in the lower bank and caudal levels project caudally. In all cases, the projections arise in layers 2, superficial 5, and deep 6 (Burwell & Amaral 1998). Unlike the primary visual area, whose input to the perirhinal cortex is limited to the caudal portion of the area, the input from barrel cortex spans the whole length of the perirhinal cortex; this means that the rostral part of the perirhinal cortex receives only somatosensory input (Naber et al. 2000b).

The parietal input to the postrhinal cortex (POR) arises primarily from posterior parietal cortex and accounts for 7 percent of the region's total input. Layer 5 provides the predominant input with somewhat less arising in layers 2 and 6. All portions of the posterior parietal cortex project to the postrhinal cortex. A small input appears to arise from S1, but the input comes entirely from the portion of S1 that lies adjacent to the rostral border of the dorsal part of PTLp. This region may be a transitional area between S1 and PTLp. Posterior parietal input is more than 70 times stronger than that of the somatosensory cortex, indicating a very small contribution of the somatosensory input to the Postrhinal cortex (Burwell et al. 1995; Burwell & Amaral 1998).

Entorhinal cortex is the gateway to the hippocampus proper. It consists of 2 areas: Lateral Entorhinal Area (LEA) and Medial Entorhinal Area (MEA). LEA receives a stronger input from Perirhinal cortex while MEA is mostly supplied via the Postrhinal (Burwell et al. 1995; Burwell &

Amaral 1998; Witter et al. 2000). LEA receives only a small portion of its input (less than 3 percent) from parietal areas. The input arises in layers 2, superficial 5, and 6 of the caudal portions of S2 and PTLp. A weak input arises in layer 6 of caudal S1. More rostral portions of LEA appear to receive a slightly heavier input from S2, whereas more caudal portions receive slightly heavier input from PTLp. The MEA receives substantially more input from parietal areas, about 9 percent. As is true for the LEA, the parietal input arises in layers 2, superficial 5, and 6. The more caudal portions of S2 and PTLp provide the stronger input. Most of the parietal input to the MEA terminates in the regions bordering the parasubiculum. This portion of the MEA receives 15 percent of its input from parietal areas, whereas the remaining areas receive less than 3 percent. A fairly substantial input to this portion of the MEA arises from caudal S1. Those projections arise only in layer 6.

Prefrontal Connections

Although there are direct projections from somatosensory areas to the medial temporal lobe (see above) somatosensory information might also reach hippocampus via the prefrontal cortex. In this chapter we describe how the projections from somatosensory areas are organized in the prefrontal areas. Somatosensory information can reach prefrontal areas via several channels (Eden et al. 1992; Conde et al. 1990; Hoover & Vertes 2007). 1. Direct projections of somatotopically organized regions: Projections from S1 to prefrontal areas are sparse and negligible, and most of them are mediated either via the dysgranular somatosensory cortex or via S2. These areas project mostly to the dorsal part of the mPFC. The dorsal part of the mPFC, comprising the anterior cingulate cortex (ACd) and Frontal area 2 (Fr-2), receive most of the input from the somatotopic areas. The rostral one-third of cytoarchitectonic areas Fr-2 and ACd can be considered as mPFC subfields, where afferents from the primary motor area, the hind- and forelimb areas, dysgranular part of the primary somatosensory area, the secondary somatosensory area and the posterior agranular area terminate. Its connections with the somatosensory and motor cortices suggest that it is somatotopically organized, with head and forelimb represented more laterally and somewhat more rostrally than trunk and hind limbs. The latter projections overlap the mediodorsal projection area (prefrontal cortex) more than projections from areas representing the forelimbs. Based on anatomical and lesion studies it is possible that this prefrontal region resembles premotor or supplementary motor cortex of primates.

Connections relaying somatosensory information, probably in a highly processed form, come from the perirhinal cortex and reach prelimbic and infralimbic areas. This part differs from the caudal portion of the mPFC. It receives abundant input from the mediodorsal nucleus of

thalamus, limbic structures, olfactory brain, from the motivational centers in the hypothalamus and from the visceral receptors. This part of medial prefrontal cortex is believed to be an analogue of the dorsolateral prefrontal cortex of primates (Vertes 2004; Hoover & Vertes 2007).

Structure of the hippocampus

The hippocampal formation consists of hippocampus proper (Cornu Ammonis and Fascia Dentata), entorhinal cortex and subicular complex (Witter et al. 2000). Hippocampus proper (we refer to it later as simply hippocampus) receives sensory input from entorhinal cortex via the trisynaptic and monosynaptic pathways.

The trisynaptic pathway starts in layer 2 neurons of entorhinal cortex and terminates in the outer and middle molecular layer of the dentate gyrus and on CA3 neurons. Dentate gyrus sends mossy fibers to CA3. CA3 sends Shaffer collaterals recurrently to itself and to CA1. CA1 projects to subiculum and subiculum returns the signal to the deep layers of entorhinal cortex. The monosynaptic pathway is a shortcut projection from layer 3 neurons of the entorhinal cortex to CA1 and subiculum (Steward & Scoville 1976; Witter & Amaral 1991). Apart from above mentioned connections, it has been shown perirhinal cortex has direct projections to subiculum and a part of CA1 (Naber et al. 2000a; Naber & Witter 1998). As a result the structure of connections between entorhinal cortex and hippocampus can be described as a combination of sequential and parallel loops (via trisynaptic pathway with multiple shortcuts directly connecting entorhinal cortex with each of the hippocampal subfields and subiculum). Entorhinal cortex has connections which link deep and superficial layers (Witter & Moser 2006).

Medial temporal lobe structures in object discrimination

Structures of the medial temporal lobe are involved in recognition memory (Squire et al. 2007). A crucial role in object discrimination is believed to be played by perirhinal cortex (reviewed in (Winters et al. 2008)), as to the function of hippocampus, its role in the memory for objects is controversial. Findings range from severe learning deficit (for example (Brasted et al. 2003; Wilson et al. 2007), to no deficit (Ennaceur et al. 1996), and even some anecdotal cases of improved performance under certain conditions (Moore & McCleary 1976). Altogether, there is a consensus that the learning of object/place associations requires intact hippocampus (for example (Murray & Ridley 1999; Eacott & Norman 2004). In addition to the abovementioned differences found between hippocampus and perirhinal cortex, dual-process theories of recognition memory have suggested that the perirhinal cortex mediates familiarity-based memory, whereas the hippocampus plays a critical role in recollection (Aggleton & Brown 1999; Fortin et al. 2004), but some authors

have proposed that the difference between hippocampal and perirhinal cortex come not from the different roles they play in familiarity and recollection but from their relative contribution in the representation of strong and weak memories (Squire et al. 2007). We have chosen the task for the animals based on the assumption that the learning this task might depend on the intact hippocampus. We suggest this based on several facts: 1. The task require the animals to learn the "meaning" of objects. 2. The "meaning" of objects that the animals are supposed to learn is spatial. The task can be interpreted as variant of an object – place association which has been shown to depend on the intact hippocampus (Eacott & Norman 2004). Although we do not have any direct causal evidence of the hippocampal in the performance or acquisition of the task (we haven`t done any hippocampal lesions), but we think that potential neuronal representation can serve as an indirect prove of hippocampal involvement in the acquisition of the stimulus place association. Even if the hippocampus is not required for the performance of the task it is highly possible that we shall see the "history" of the learning process in the firing of the hippocampal neurons, because the life of these animals is relatively impoverished and there is no pressure for them to learn new things.

Firing properties of hippocampal neurons

Since the discovery of "place cells (O'Keefe & Dostrovsky 1971) the firing properties of hippocampal neurons have been studied under many different conditions in many different species. We review the key findings in rodents as they are directly related to the current work. It has been shown that place cells respond to different manipulations of the environment such as the displacement of distal and nearby cues. Place fields of hippocampal neurons follow the rotation and displacement of proximal and distal landmarks if the latter are moved (Muller & Kubie 1987). Discrepancy between the rotation of proximal and distal landmarks produces remapping of the place fields (the formation of a new representation of the environment) (Bures et al. 1997). Place fields do not appear immediately; it usually takes 15-20 min of exploration (Wilson & McNaughton 1993) for them to appear. Thereafter, they can remain stable for days and weeks. Spatial representations can undergo plastic changes driven by the long term exposure to the environments of different shape, and such changes can persist for months (Lever et al. 2002). With experience place fields can expand backwards (Mehta et al. 1997) (to the area that the animal passes through while approaching the prior place field) and sometimes shift towards reward location (Lee et al. 2006). Under some conditions, place fields are concentrated on behaviorally relevant spaces, such as reward location (Hollup et al. 2001). Place cells become directional (Markus et al. 1995).

Place cells demonstrate theta phase precession (O'Keefe & Recce 1993). Theta phase precession is a progressive advance in the phase of firing of action potentials as the animal runs

from the periphery to the center of the cells place field, it is not limited to spatial domain, but is a network property which depends on the strength on dendritic depolarization (strength of the input of any modality) (Harris et al. 2002). Because place fields partially overlap and spikes corresponding to adjacent place fields can appear within one theta cycle, theta phase precession can serve as a mechanism for the compression of sequences of events (Skaggs et al. 1996; Itskov et al. 2008).

The activity of hippocampal neurons is organized into cell assemblies (Harris et al. 2003). Cell assemblies are populations of neurons discharging together, each of which will dominate the activity for about 25 ms. The activity of such ensembles in the inter trial intervals can predict the animal's mistakes and actions in the hippocampus-dependent behavioral task, suggesting that such cell assemblies might represent the internal processing and planning of the animal (Pastalkova et al. 2008) and not mere consequence of the external stimuli (Harris 2005).

Hippocampal place cells not only represent the actual position of the animal but can also represent future locations (Frank et al. 2000; Wood et al. 2000; Ferbinteanu & Shapiro 2003), past locations (Ferbinteanu & Shapiro 2003), intended locations (Johnson & Redish 2007), and trajectories (Ji & Wilson 2008).

When the environment is inhomogeneous in terms of behavioral relevance of different places, the more relevant places are over represented (Kobayashi et al. 1997; Hollup et al. 2001) or elicit extra (outside place field) spikes (Hok et al. 2007) at the goal location.

The hippocampal representation of space has been shown to follow attractor dynamics (Wills et al. 2005); the attractor states are formed during the exposure to different environments and the history of exposure can affect the representation making the transitions between states smooth (Leutgeb et al. 2005).

One of the most intriguing properties of hippocampal cells is their ability to recapitulate acquired experience during slow wave sleep (Pavlides & Winson 1989; Wilson & McNaughton 1994; Lee & Wilson 2002), REM sleep (Louie & Wilson 2001) and even when the animal is awake (Foster & Wilson 2006; Diba & Buzsáki 2007; Karlsson & Frank 2009). Such reactivation occurs not only in hippocampus but also in the neocortex (Hoffman & McNaughton 2002; Peyrache et al. 2009; Ji & Wilson 2007).

Apart from spatially related firing, many non spatial factors have been shown to affect firing of hippocampal neurons. Among such factors were different odors (Wood et al. 1999; Wiebe & Stäubli 1999; Wiebe & Staubli 2001; Komorowski et al. 2009), conjunctions between odors and places (Wood et al. 1999; Komorowski et al. 2009), sounds (Sakurai 1994, Moita et al. 2003), task contingencies (Hampson et al. 1999; Wood et al. 1999), nests (Lin et al. 2007) and stimuli eliciting startle responses (Lin et al. 2005) .

Recently in has been proposed that spatial and non spatial information is represented by the

same neurons: spatial factors determine the place field of the neurons while the rate is defined by non spatial variables (Leutgeb et al. 2005) such as color or shape of the box in which the rat is running or the trajectory which the rat follows.

Although a lot is known about the firing of hippocampal neurons many questions still remain unanswered: One of the key questions of the current work is to understand how spatial and nonspatial information interact with each other. Whether the representation of object will be an abstract location independent of the location of the animal or will be always confined to the place field of the neuron? The aim of the current work was to study how hippocampal neurons represent meaningful objects, places and their interactions.

Whisker mediated texture discrimination behavior and the coding of roughness in whisker sensory pathway

Texture discrimination in rats has been investigated using, as stimuli, different grades of sandpaper (Guic-Robles et al. 1989; Guic-Robles et al. 1992; Heimendahl et al. 2007; Ritt et al. 2008) and cylinders with grooves of different spacing (Carvell & Simons 1990; Prigg et al. 2002). This behavior has been shown to be whisker (Guic-Robles et al. 1989) and barrel cortex (Guic-Robles et al. 1992) dependent.

Texture coding in the whisker pathway was studied in anesthetized (Arabzadeh et al. 2005; Arabzadeh et al. 2006) and awake behaving animals performing discrimination task (Heimendahl et al. 2007; Ritt et al. 2008) and touching different objects without any discrimination involved (Wolfe et al. 2008; Jadhav et al. 2009). The majority of studies agree that the roughness of texture is represented in the kinetic profile of whisker vibrations. Rougher textures produce more high frequency events because of higher number of “stick and slip” events. These events cause neurons to fire at a higher rate for rougher textures (Arabzadeh et al. 2005; Heimendahl et al. 2007; Wolfe et al. 2008; Jadhav et al. 2009).

We have designed an experiment in order to study how hippocampal neurons represent meaningful stimuli in different locations. These results demonstrate that hippocampal neurons encode both spatial (reward location) and non spatial variables (stimulus identity). The representation of non spatial stimuli is context-specific and, although we have found neurons representing stimuli in multiple locations, the number of such neurons did not exceed one expected from the independent representation of each context. This suggests that hippocampus stores events on the fly without any structure (Marr 1971), and the structure to the memory is probably added later when the memory trace is consolidated and reorganized in the neocortical neuronal ensembles (Marr 1970; Marr 1971; McClelland et al. 1995; Hoffman &. McNaughton 2002; Buzsaki 2005).

Materials and Methods

All experiments were conducted in accordance with National Institutes of Health, international, and institutional standards for the care and use of animals in research and were supervised by a consulting veterinarian.

Subjects

For the experiments based upon tactile discriminations, Six Wistar rats (Harlan Italy, S. Pietro al Natisone, Italy) weighing about 350 g were housed individually and maintained on a 14--10-h light-dark cycle. Food was restricted to 15 g of rat chow (Harlan) per day; throughout the experiment, rats continued to gain weight. Water was given during training as a reward and was also available ad lib for 1 h after training.

Apparatus

The arena was situated in a Faraday room and was illuminated by light-emitting diodes (LEDs) discharging at infrared wavelength (880 nm) in which albino rats have negligible visual function. The apparatus was custom-made in aluminum and consisted of a rectangular platform (36 x 11 cm, elevated 30 cm above the table) whose shorter edge faced an octagonal platform (side length, 10 cm) across a gap of adjustable width (Figure 1, Results section). An overhead camera (Panasonic) recorded the session at 25 frames per second.

There were four discriminanda, each 3 X 10 cm. Texture 1 was a smooth acrylic Plexiglas plate. Texture 2 was made by pressing P100 sandpaper (mean grain size, 162 micron) onto a heated acrylic Plexiglas plate. This procedure left the plate with a rough surface – a negative mold of P100. Textures 3 and 4 were an undulating acrylic glass surface cut from a shower screens with different patterns (Figure 1M). These discriminanda were mounted with the surface turned upward by 45 degree with respect to the vertical. All textures had the same size, perimeter shape, and odor. Potential olfactory cues were removed from textures by washing them at least once every session. In addition, we switched between several different exemplars of the same texture to make sure that rats were not using cues attached to one particular object.

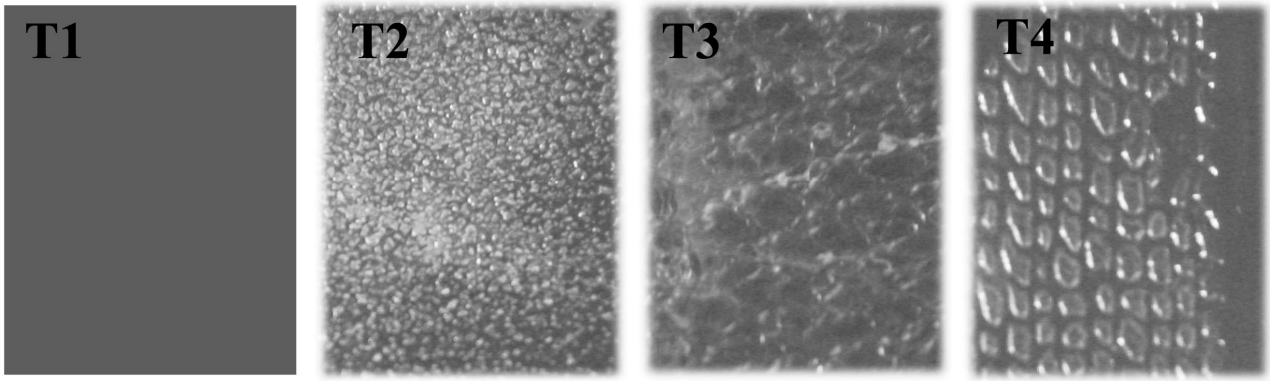

Figure 1M. Tactile stimuli. *T1 was a smooth acrylic Plexiglas plate. T2 was a mold replica of P100 sandpaper. T3 and T4 were an undulating acrylic glass surface cut from Plexiglas shower screens with different patterns.*

Texture discrimination within a single context

For one week, each rat was handled and habituated to the training arena under dim visible light. Then, the visible light was switched off and only invisible infrared illumination remained. For the rest of the experiment, training sessions were held once a day for about 1 h, usually during the dark phase of the light-dark cycle. During training, the rat learned to go to one of the two possible reward locations according to the contacted texture. Two textures were associated with one reward location and the third was associated with the opposite location. Rats were trained with a fixed association across all sessions. Animals were trained gradually: first they were trained to discriminate between 2 different textures (selected randomly) until they reached stable performance. Then, one of the textures was substituted with a new discriminandum and training continued until the performance became stable again. Finally animals were presented with all 3 textures in the same session. All rats reached stable (>75 percent) performance. After animals performed 3 sessions at above chance level they were implanted with an array of 6 independently movable tetrodes (details see below).

On each trial, the rat perched on the front edge of the rectangular platform and extended itself forward to contact the discriminandum with its whiskers. After palpating the texture, the rat withdrew and turned either to the left or to the right to lick the water spout (Figures 1 and 2). Only if it approached the correct drinking spout was it given a water reward (0.2 ml); for an incorrect choice, it received no water. The next trial started after a delay of 3 seconds with respect to the crossing of the light barrier located adjacent to the drinking spout.

Between trials, the discriminanda mount was turned about its vertical axis by a computer-controlled stepping motor. This allowed for quick, randomized, and automated switching between

discriminanda. The session lasted until the rat failed to return to the discriminandum, meaning it was satiated, usually after 100-200 trials.

Categorization task in two contexts

Additional experiments were performed two investigate two factors: (1) categorization, such that multiple stimuli were always associated with the same action, (2) performance of the same task in two different contexts. Two rats were trained in this task. The basic training was identical to 3-texture categorization task (one platform task) except for the modifications described below. In the beginning rats were trained on one of the platforms (counterbalanced between the rats) until the animals learned to discriminate all 4 textures following the procedure described above; this took approximately 1.5-2 months.

Next, the animals were exposed to a new platform where they were required to perform the same discrimination and give the same behavioral response (turn left or right, in self-centered coordinates, according to texture identity). Platforms differed not only in the location within the room but also by their floor texture, so that even by tactile cues animal would know that it was in a different context. Surprisingly, none of the animals showed immediate transfer of knowledge or generalization from the first to the second platform and so it took about 1 extra week of training before their performance reached a stable level of > 75 percent correct. After animals performed 3 consecutive sessions at this criterion they were implanted with an array of 12 independently movable tetrodes (details see below).

The recordings were made in the following order: (1) The rat was put by the experimenter on one of the platforms where it typically did ~60 trials, (2) it was then moved to the opposite platform where it performed another 60 trials, (3) the procedure was repeated one more time, so that the rat worked on each platform at least 2 times. The lights were turned on between the blocks so the animal could be visually oriented.

Surgery

After reaching a performance level of more than 75 percent on three consecutive sessions, rats were anaesthetized with a mixture of Zoletil (30 mg per kg) and Xylazine (5 mg per kg) delivered intraperitoneally. Small screws were fixed in the skull as a support for dental cement. One of the screws served as a ground electrode. A craniotomy was then made above left dorsal

hippocampus, centered 3.0 mm posterior to bregma and 2.5 mm lateral to the midline. Dura mater was removed. Craniotomy location was covered with biocompatible silicon (KwikSil; World Precision Instruments). An 8-tetrode (Neuralynx) drive (3 texture categorization task) or 12-tetrode microdrive (4 texture categorization task) was positioned above the craniotomy and attached by phosphate dental cement. Rats were given the antibiotic enrofloxacin (Baytril; 5 mg per kg delivered through the water bottle) and the analgesic caprofen (Rimadyl; 2.5 mg per kg, subcutaneous injection) for a week after surgery. For 10 d after surgery, they had unlimited access to water and food. Recording sessions in the apparatus began thereafter.

Electrophysiological recordings

Tetrodes were made of 25 micron Platinum-Iridium wire (California Fine Wire); they were advanced individually by rotation of a screw in the drive. After passing through a unity-gain head stage (Neuralynx), signals were transmitted through a cable to the amplifiers (Cheetah Data Acquisition system; Neuralynx). Neuronal data were successfully collected from 4 animals trained in a 1 platform task (77, 57, 49 and 33 neurons in 3 texture task) and 2 animals from 2 platform task (385 and 365 from each rats respectively). The spike signals were amplified by a factor of 1,000–5,000, band pass filtered between 600 Hz and 6 kHz, and digitized at 32 kHz; events that reached a user-set threshold were recorded for 1 ms. Spikes were sorted offline on the basis of the amplitude and principal components by means of semiautomatic clustering algorithms (KlustaKwik, written by K. D. Harris, Rutgers University, Newark, New Jersey). The resulting classification (for an example of spike sorting see Figure M2) was corrected and refined manually with MClust software (A. D. Redish, University of Minnesota, Minneapolis, Minnesota). Most often 4-8 tetrodes yielded single units with a pronounced refractory period. The maximum number of simultaneously recorded neurons was 60 (minimum 4). Only well separated units with refractory period, and stable waveform and firing rate over the course of a session were considered in the analysis.

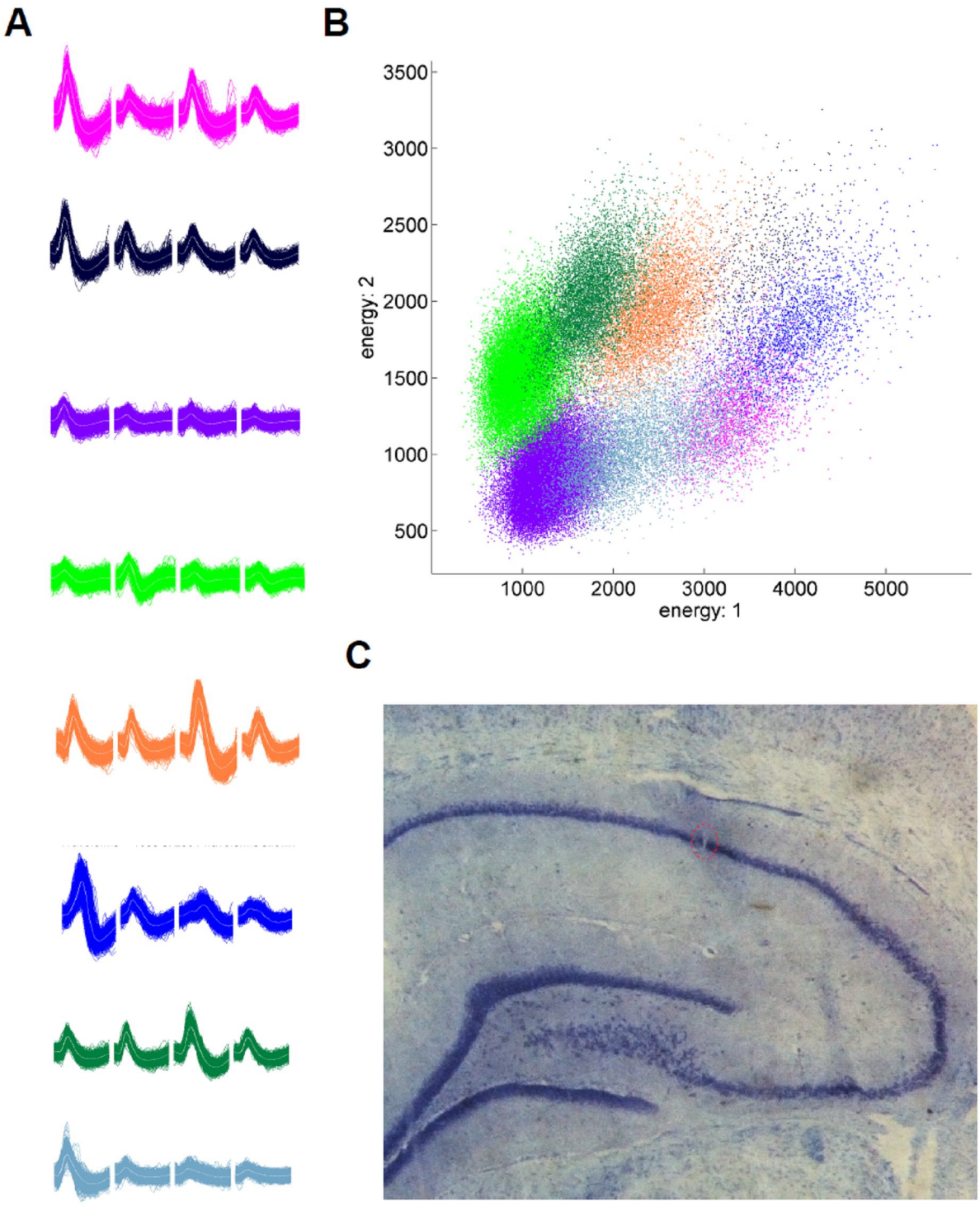

Figure M2. Example of spike sorting procedure. A. *Waveforms of eight single units isolated from one of the tetrodes.* ***B****. Scatter plot of waveform energy from first 2 channels of the tetrode demonstrating separation of units.* ***C****. Histological section from one of the animals. Red circle demonstrate electrode track within CA1 subfield of hippocampus.*

Data analysis

Information Measures

Our main hypothesis was that hippocampal neurons participate in the on-line storage and recall of the texture categorization experience. Therefore, we needed to estimate the quantity and statistical significance of the signal carried by the firing rate modulations of individual neurons on single-trials. For this purpose, Shannon's Mutual Information (Shannon 1948; Cover & Thomas 1991), hereafter referred to simply as information (Rieke et al. 1997). The results reported here depend on the use of information in different ways. First we give a general introduction to the information formula, and then explain the applications to reward location and texture signals.
In general, the information that any signal X conveys about a second variable Y can be described by Equation 1:

$$I(X,Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log \left(\frac{p(x,y)}{p_1(x)\, p_2(y)} \right) \qquad \textbf{(1)}$$

Where:
X – Stimulus condition (texture or reward location)
Y – Neuronal response (spike count)

Information measured by Eq. 1 quantifies the reduction of uncertainty about the stimulus condition (X) gained by a single-trial observation of the spike count (Y). (Rieke et al. 1997).Since we used base two logarithms, the information is measured in bits, one bit of information correspond to the uncertainty reduction by a factor of two. The probabilities in the above formulas are not known a priori and must be estimated empirically from a limited number, N, of experimental trials for each stimulus. For some recordings in our dataset, N could be as low as 30. Limited sampling of response probabilities can lead to an upward bias in the estimate of mutual information (Optican et al. 1991; Panzeri & Treves 1996; Golomb et al. 1997; Victor 2000; Paninski 2003). The bias magnitude depends on the number of trials per stimulus or behavior: as N increases, the estimated probabilities become more accurate, and the bias decreases. We have used a bias subtraction procedure described here (Panzeri & Treves 1996) the value of bias was subtracted from the raw information of Equation 1, provided that N is at least two to four times greater than the number of different possible response classes (Panzeri & Treves 1996; Pola et al. 2003), X, which was the case

in our data.

Reward location and texture information carried by the temporal profile of response

The first problem was to quantify the information carried by the time-varying firing rate of individual CA1 neurons in single-trials. If the firing rate of a neuron differed according to the trial condition (e.g. stimulus Reward location) uniformly over the entire duration of the trial, a simple measure of whole-trial spike count would be sufficient. But neurons might encode events by changes in firing rate in very small windows (e.g. during whisker contact with the texture), or by divergent temporal profiles of firing which give the same overall count. In both cases, whole-trial spike count would not detect the signal; a measure of temporal coding was necessary. To avoid this problem, we measured the information over the whole duration of the trial (from 2 seconds before the animal received water reward to 2 seconds after it). To measure the mutual information at each point in time, instantaneous firing rate was measured counting spikes in a 400 ms window sliding with a step of 25 ms. The analysis provided a temporal profile of the signal of interest. 400 ms integration window was selected as the one providing the highest average information values for both reward location and texture information.

Statistical tests of significance for the selection of "Texture neurons" and "Reward location neurons"

Due to the large number of tests, an apparent peak value of information along the profile might incorrectly lead us to classify a neuron as informative. To exclude this possibility, we took a conservative measure of information.

We have chosen average information value across 4 seconds of trial as our measure. To determine whether the average value of information (averaged across time) was significantly greater than could be expected by chance, we scrambled the labels of texture or reward location and regenerated the temporal profile of information 200 times. We again took the average quantity of information across time as our measure. Then from the distribution of values of average information from the data with scrambled labels, we calculated the mean and its standard deviation. The threshold of significance for the real value of average information was set as 5 standard deviations from the mean of the information with scrambled labels (this corresponds approximately to $p=0.000005$ (uncorrected for multiple tests for normally distributed data as was the case in our dataset) which approximately corresponds to $p<0.01$ if corrected for multiple comparisons with the most stringent Bonferroni correction. The null hypothesis H0 was that stimulus condition (reward location or texture) had no influence on the statistic. The result of this analysis gave us a set of

neurons designated texture coding and/or reward coding neurons. Only the signals from identified "Texture neurons" and "Reward location neurons" were considered for the average profiles.

Local field potentials

To measure local field potentials (see example of reward aligned raw and filtered voltage trace in figure M3), a copy of the signal from an electrode that was used for the recording of spikes, and located in the CA1 pyramidal layer was amplified by a factor of 1,000, band pass filtered between 0.1 Hz and 400 Hz, and digitized at 8 kHz. The reference electrode for these recordings was the bundle of steel guide tubes resting on the brain surface, above the recording site. Time-frequency representations of artifact-free trials (>95 percent in each session), aligned by reward trigger, were obtained by convolution of initial LFP waveforms with Morlet wavelets (EEGLAB toolbox). For plotting, each single time-frequency point was compared by means of paired t-test against power in the baseline at the same frequency. As a baseline we took the time period from 2.5 to 1.5 seconds before touch, i.e. approximately from 3.5 to 2.5 seconds before reward, which corresponds to the interval during which the rat was idle. Thus, the spectrogram presents the mean of the power of all sessions, expressed in dB (a logarithm of ratio of power to the power in the baseline).

Ripple events are high frequency oscillations recorded in CA1 region of the hippocampus that come from the simultaneous discharge of the majority of the pyramidal neurons in the field CA3, which project directly to CA1. Ripple events has been shown to appear during immobility and reward consumption. Because in our task animals did not run and were consuming reward for a large amount of time during which the neuronal activity has been analyzed it is important to verify that the activity reported does not come from the unspecific firing of the majority of neurons associated with ripples. To detect ripple events LFP voltage traces were band pass filtered between 120 – 240 Hz. Ripple events were identified as events that surpassed the threshold of 5 standard deviations and during which at least 50 percent of simultaneously recorded pyramidal cells fired action potentials. The second measure was introduced in order to avoid licking artifacts being identified as ripple events. The methods yielded reliable automatic detection of ripple events. Interneurons and pyramidal cells in hippocampus were separated based on their firing rate, spike width and first moment in the autocorrelation function (Csicsvari et al. 1999). The separation between neuron types was used only in ripple detection procedure.

Filtering was done in Matlab. 200 order FIR Kayser window filters were constructed and

analysed in Matlab, Filter Design and Analysis toolbox. All the filters had linear phase delay at all the frequencies, the filtering was performed in Matlab using a zeros phase delay algorithm (filtfilt function). Anyway the filtering procedure could not affect the conclusions since no conclusions depend on the phase of the oscillations, but all depend on the power.

Tests of independence

We have observed that texture signals could be present in more than 1 location. We were interested in whether the probability that a neuron will carry information in the second location was influenced by the presence or absence of information in the first location. To do this we first calculated the probability that a neuron can carry texture signal (*pTex*) in any of the four locations (turn right platform A, turn left platform A, turn right platform B turn left platform B).

$$pTex = \frac{(nT_1 \times 1 + nT_2 \times 2 + nT_3 \times 3 + nT_4 \times 4)}{4 \times nNeurons} \quad \textbf{(2)}$$

Where:

* $nT_{1\text{-}4}$, is the number of neurons carrying 1 2 3 or 4 signals respectively.

* nNeurons is the total number of neurons.

Then we calculated the expected probability that a neuron will carry 1 2 3 or 4 signals:
PtexI, where I =1 2 3 or 4.

Equation 3:

$$PtexI = \frac{4!}{I!(4-I)!} \times pTex^{I} \times (1-pTex)^{4-I} \quad \textbf{(3)}$$

To measure the statistical difference between the number of neurons carrying 1- 4 signals and the number of such neurons which can appear by chance (from random independent coding of 4

signals) we performed a permutation test.

Histology

After the recordings were finished the animals were transcardially perfused with 10 percent formalin. The brains were sliced in to coronal sections which were stained with cresyl violet. Electrode tracks were localized on the serial sections (Figure M2 C).

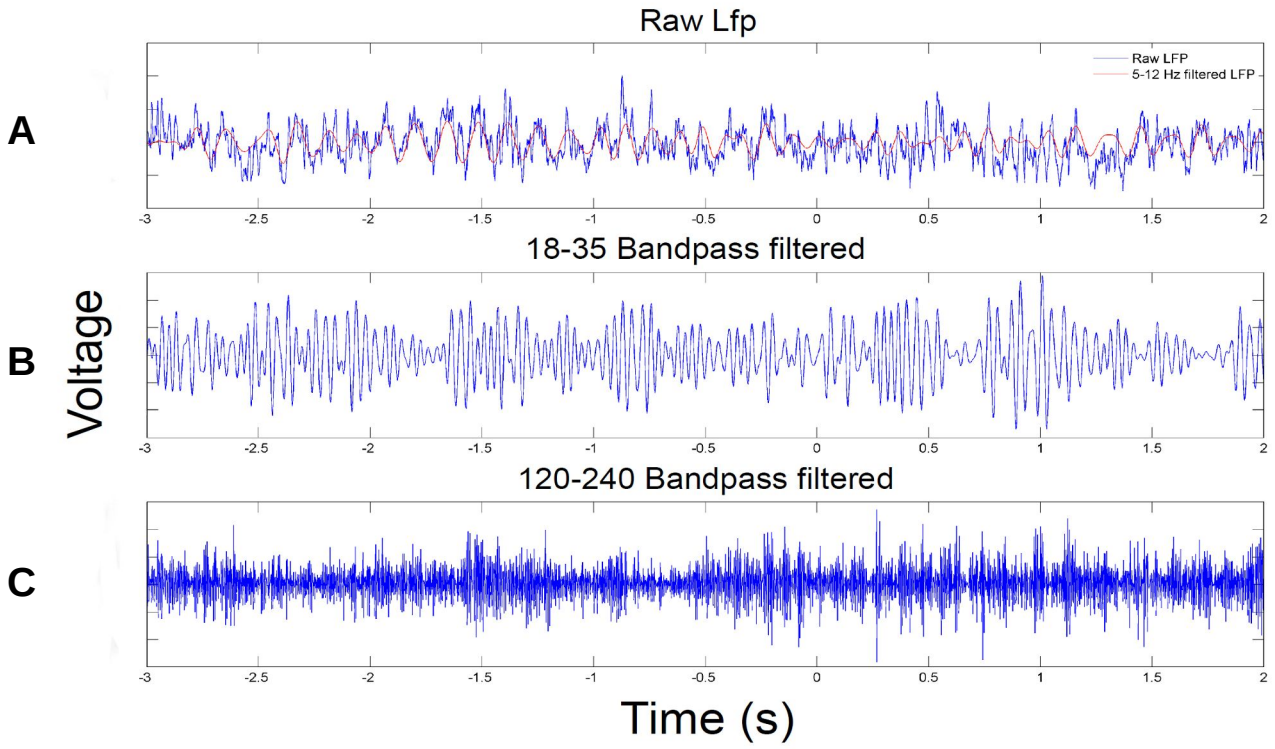

Figure M3. Reward aligned local field potentials. A. *Raw local field potential voltage trace (blue) and 5-12 Hz (theta) filtered voltage trace (red) aligned on the moment of reward delivery.* ***B****. 18-35 Hz (beta and low gamma) band pass filtered voltage trace.* ***C****. 120-240 Hz band pass filtered local field potential signal.*

Sound Categorization experiment

The task can be run in the same behavioral apparatus by positioning audio speakers in the space between the platforms A and B so that the sound source is in front of and lateral to the rat. On each trial the rat had to lean into the gap until its presence was detected by an infrared beam. Then, one of the 4 sound stimuli was played through the 2 loudspeakers. After identifying the sound, the animal had to turn to either its left or right to receive a water reward. Sound identity determined the reward location. Training methods were similar to those used in the tactile categorization task. The only difference was that, in order to draw the animal's attention towards the reward location early in the training process, each stimulus was followed by a 30 ms burst of white noise played from direction where the rat was supposed to turn. The loudness of this directional cue was gradually faded out over 1 week until no direct reward location cue remained. We used artificial vowels as stimuli (Bizley et al. 2009). More specifically, we created 4 artificial single formant vowels with 150 Hz pitch which differ in the frequency of the first formant and could be described as roughly similar to human vowels "A" , "O" , "E" , "I" as the frequency of the first formant increases (1220, 2280, 3350, 5200 Hz respectively). In order to permit future lines of research involving "morphing" between sounds, the vowels were created as elements along a continuum. Intermediate sounds can be readily generated for future work. Stimuli (Figure M4) consisted of 3 repetitions of 200 ms stimuli were tempered with 100 ms cosine square ramps ("A" "A" "A" etc). The rest of the methodology was the same as we have previously described for the tactile categorization task.

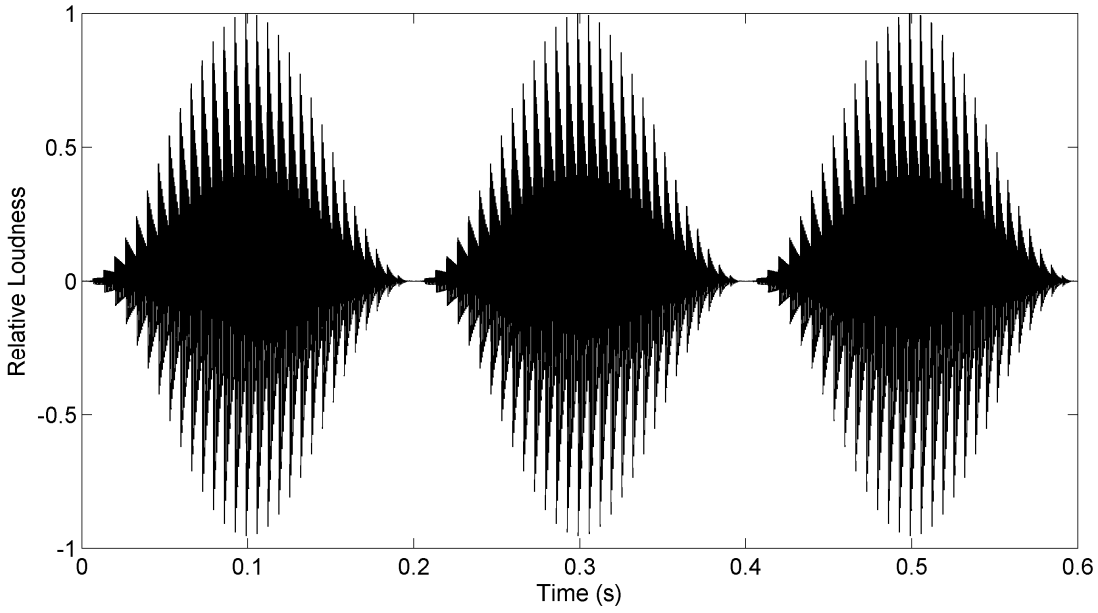

Figure M4. Waveform of the sound stimulus. *As sound stimuli we used triplets of artificial vowels (see text) tempered with 100 ms cosine square ramps. This is a waveform of the "A" vowel*

triplet.

Results

Behavioral task

The aim of this study was to identify the neuronal signals in the rat hippocampus representing tactile stimuli and the behavioral action associated with those stimuli. Animals were trained to use their whiskers to touch and discriminate between textured surfaces. In one set of experiments, the number of textures was three, textures T1-T3; in a second set of experiments, the number of textures was four , textures T1-T4). For two of the textures of different roughness, rats had to turn its head to one side in order to receive water reward. Experiments were performed in an arena illuminated only by infrared light; thereby eliminating potential visual cues (see Materials and Methods for more details). We performed two different experiments: we shall refer to them as the one platform task and the two platform task.

One platform task.

Four rats were trained in this task. The animals were always located on platform A and had to lean into the gap and touch the texture with their whiskers (Figure 2 A-B). Depending on the identity of texture rats had to turn to the right or to the left to get water reward. Texture-reward location associations were fixed for each animal but were varied across 4 rats. Rats were able to learn all possible combinations of textures.

Two platform task.

Two rats were trained in the two-platform task. Rats were initially trained on one of the platforms (counter balanced between rats) until they learned the task. The difference from the previous task was one additional texture that animals had to learn, T4 (see Methods). As a result, rats learned to associate two different textures with each of the two reward locations. After this part of training was accomplished the animals were exposed to a new platform. They had to apply the same association rule in the egocentric frame of reference. It took at least 3 - 5 days for the animals to learn the task in the new location. They showed consistently lower performance in the location that was introduced later in the training (Wilcoxon sign rank test $p<0.00001$, median Performance in the first location - 90.2 percent correct, median Performance second location - 80.1 percent

correct). We consider this as behavioral evidence that the animals formed two unique representations of the task for two locations in which there were trained.

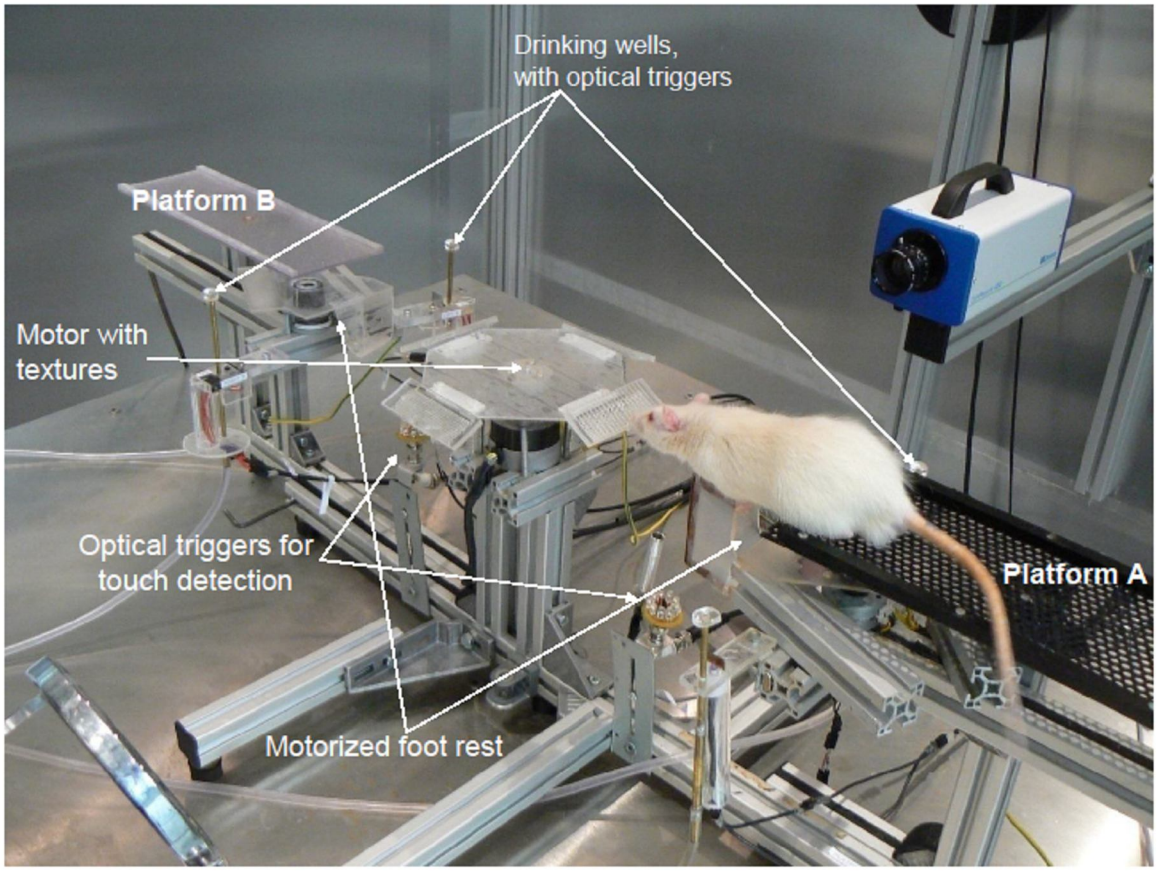

Figure 1. Behavioral apparatus. *Photograph of the experimental setup taken under visible light. For the one platform experiment, rats were located always on platform A. For the two platform experiment, animal context was alternated between platforms A and B. Approach of the animal towards the texture was allowed only after the motorized foot rest was extended so the animal could reach the texture. In front of the texture on each of the platforms were optical triggers for touch detection and for the detection of beginning of turn (i.e. the moment when the animal retracted from the texture). Animal's response was detected by another set of optical triggers which were located immediately adjacent to the drinking wells.*

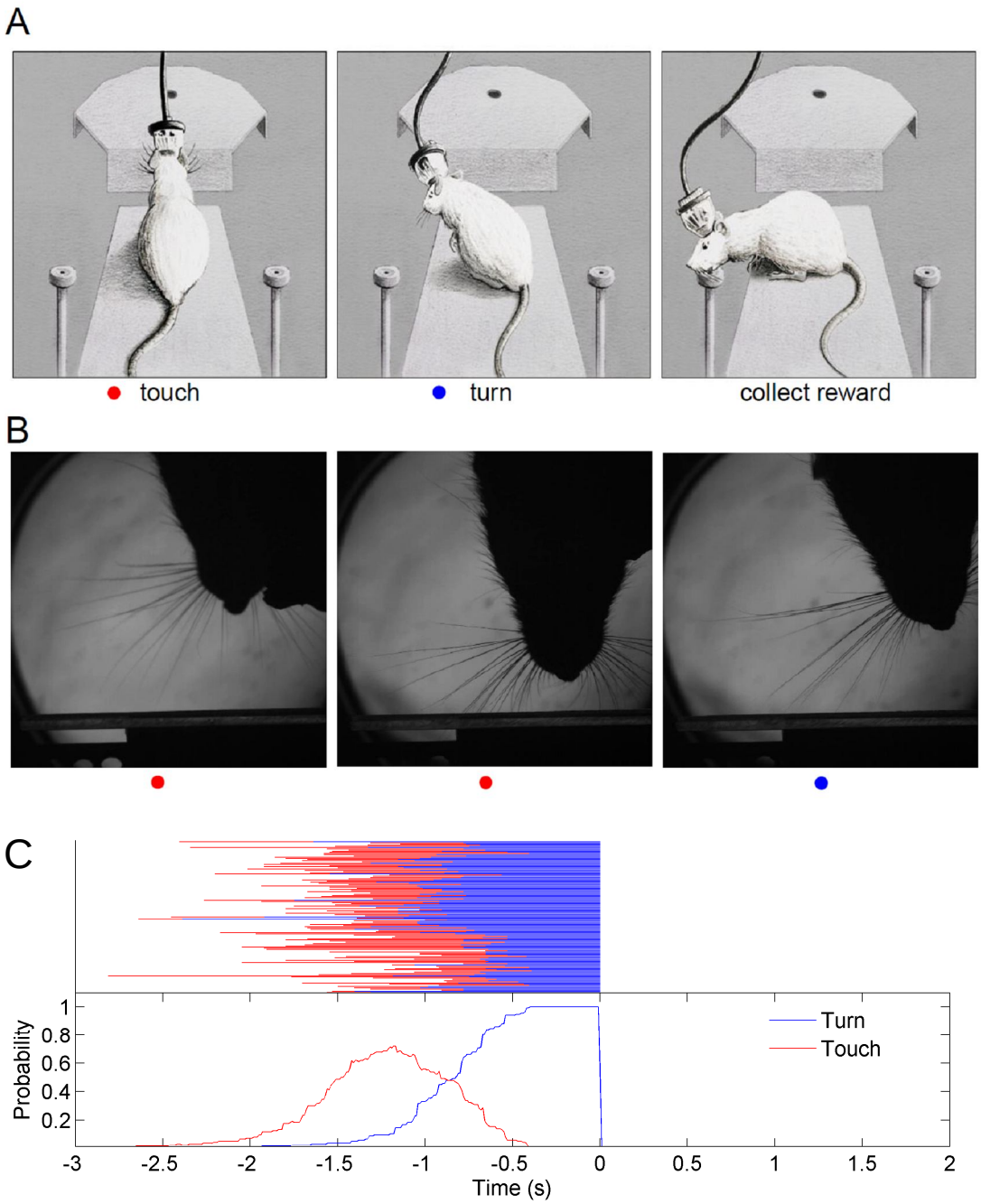

Figure 2. Behavioral task and the time course of animal behavior. ***A****. Illustration of the behavior. On each trial rat approached towards the texture and touched it with its whiskers. When the animal took the decision which texture was presented it turned to the right or to the left drinking spout where there water reward was delivered.* ***B****. Captures from high speed video recording of touch behavior demonstrating how rats use their whiskers for texture discrimination.* ***C****. Probability distributions of "touch" and "turn" events (data from the optical triggers) when behavior is aligned on reward delivery.*

Rats were trained until highly stable performance was reached (>75% correct). Their behavior was stereotypical (fig 2C). It usually took around 500 ms for rats to touch the texture (median=530 ms, interquartile range 375 ms – 766 ms) and around 800 ms to turn towards the water spout (median 812 ms, interquartile range 656 ms – 1032 ms). To analyze the neuronal activity all the spike trains were aligned to the instance when the water reward was released.

We recorded both pyramidal cells and interneurons in CA1 region of hippocampus resulting in 967 neurons recorded from six rats. Separation between interneurons and pyramidal cells was used only for the ripple detection procedure (see Materials and Methods). All the results correspond to correct trials only. First we are going to present data form one platform task.

Texture Representation – one platform task

The behavioral task was designed in a way to allow us to study responses related to the identity of objects. The analysis of texture representation was limited to the responses elicited by two different textures that were associated with the same reward location.

We designed a statistical test in order to identify neurons that carry significant quantity of "texture" information in their firing rate (See Materials and Methods). The representation was limited to a small group of neurons: 21 out 217 neurons. Although the number of such neurons was small their representation was significant (Figure 3) (median = 0.16 bits, inter quartile range: 0.12 – 0.19 bits). These neurons represented the identity of the palpated texture and this activity cannot be explained by spatial factors such as the location of the animal or behavioral variable such as the action the rat was performing or planning to perform. “Texture” information in these neurons appeared when the animal was touching the texture and in some neurons persisted or reappeared until the moment when the water reward was released.

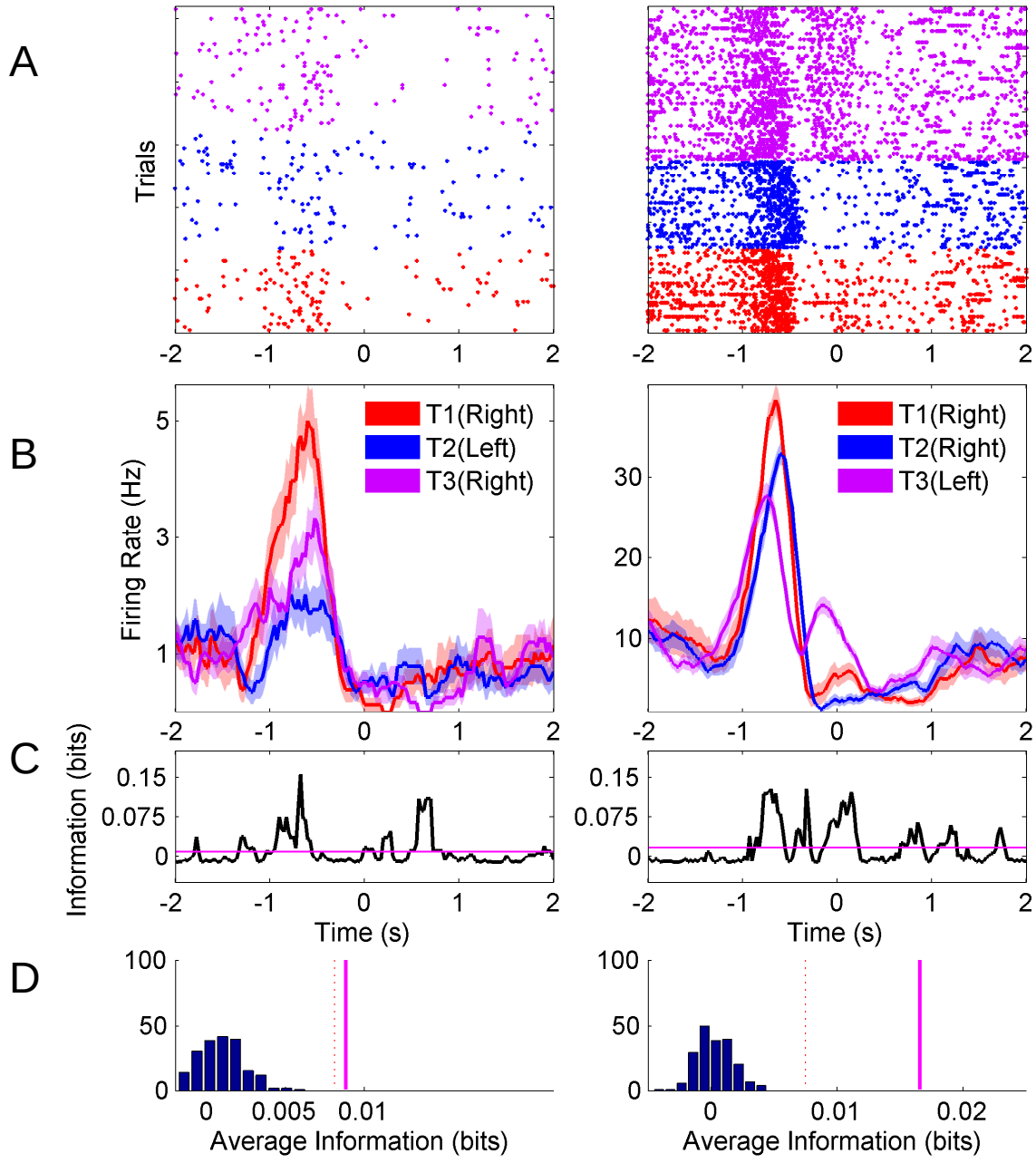

Figure 3. Texture representation in the one-platform task. *Examples of two "texture neurons" from two different animals (2 columns of figures). Zero on the x - axis is the moment when water reward was delivered.* ***A****. Raster plots. The trials are grouped by the identity of texture, each dot represents an action potential.* ***B****. Peristimulus time histograms (PSTH).* ***C****. Mutual Information between the identity of texture and firing rate over time. Information was calculated only between two textures associated with the same reward location (A: T1 and T3; B: T1 and T2). Magenta line – average amount of texture information in this neuron.* ***D****. Illustration of the method that was used to find neurons that carry significant amount of " texture" information. Distribution of average information values of 200 permutations of texture labels (blue bars). Red dotted line – 5 standard deviation of the mean from the average amount of "texture" information in 200 permutations,*

magenta line – average amount of texture information in this neuron. D

Representation of reward location – one platform task

The majority of neurons fired selectively according to the reward location on each trial (Figure 4). Reward location cells fired during the turn or planning of the turn toward the reward location. It is possible that these neurons do not only encode place but might encode the action the animal is planning or performing or even the sensory category to which the texture belongs to in an abstract way. The “reward location” cells were detected using the permutation method described above for the "texture neurons". 169 of 217 neurons (78%) modulated their firing rate depending on the reward location toward which the animal was turning (median information value = 0.22 bits, inter quartile range: 0.12 - 0.42 bits).

Texture Representation – two platform task

The activity of hippocampal neurons is strongly modulated by the position of the animal (O'Keefe 1976; Wood et al. 1999). For this reason, we tested whether the representation of identical sensory features would vary according to the location of the animal. Neurons were considered to be "texture neurons" if they carried a significant quantity of information (measured as described before) in any of the two texture pairs on either of the two platforms. Out of 750 neurons 252 (~34 %) carried texture signals (median info = 0.17 bit, inter quartile range: 0.13-0.23 bits). Unlike the case for barrel cortex, the roughness of texture did not determine the firing rate. The majority (218 of 252) of the "texture" neurons distinguished between the textures associated with only one reward location on only one platform(fig. 5) and a small number of neurons(Figure 6) carried texture signal associated with more than one location.

The representation of texture appears to be stronger in the two platform task (35 percent of neurons involved vs 10 percent in one platform task). This difference can come from two factors: 1. probably the main factor is the number of locations in which neurons can represent texture (4 in the two platform task and only one in the one platform task), 2. the difficulty of the task (three texture vs four texture discrimination). Future experiments separately addressing these issues are needed find out the reason for the strength of the texture representation.

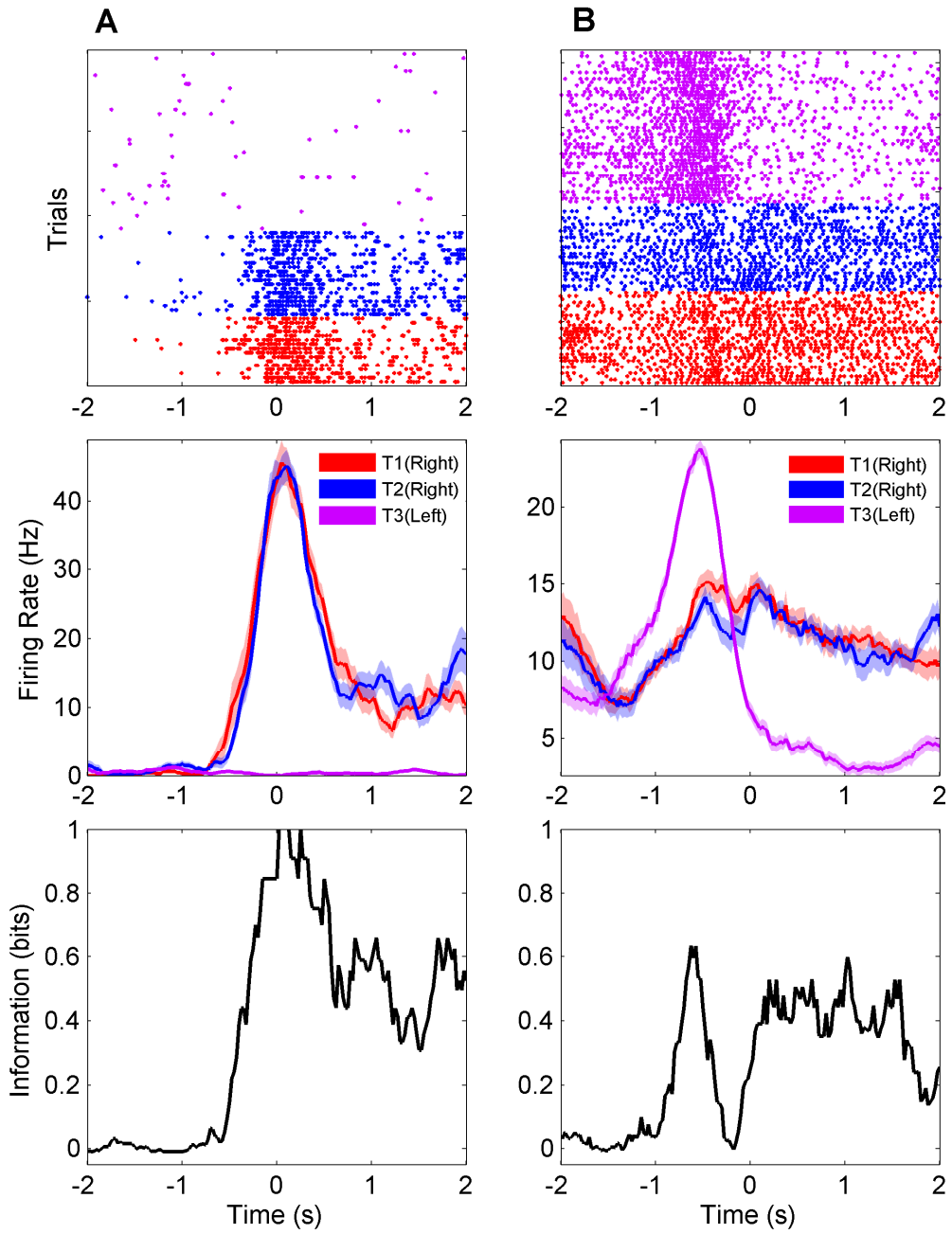

Figure 4. Reward location representation in the one-platform task*. Zero on the x - axis is the moment when water reward was delivered. Upper plots – raster plots. The trials are grouped by the identity of texture, each dot represent an action potential. Middle – peristimulus time histograms (PSTH). Lower – Mutual Information between the reward location (right vs left) and firing rate over time.*

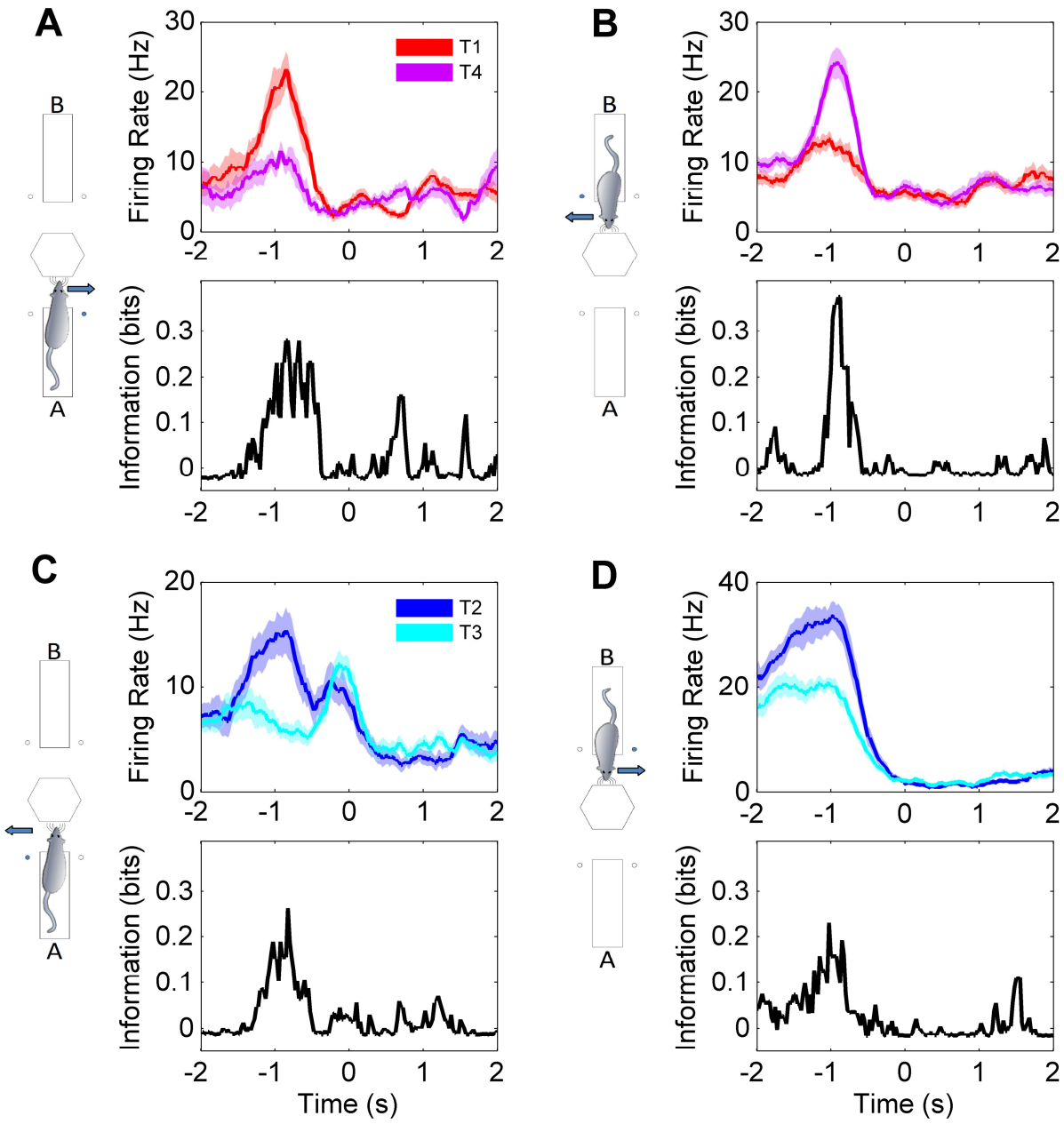

Figure 5. Texture representation in the two platform task - 1. *Firing properties of four example "texture" neurons. Response to only one (significant) pair of stimuli is shown for each neuron. The association and platform are depicted by icons. All neurons of the figure represented texture for only one pair of stimuli in one location.*

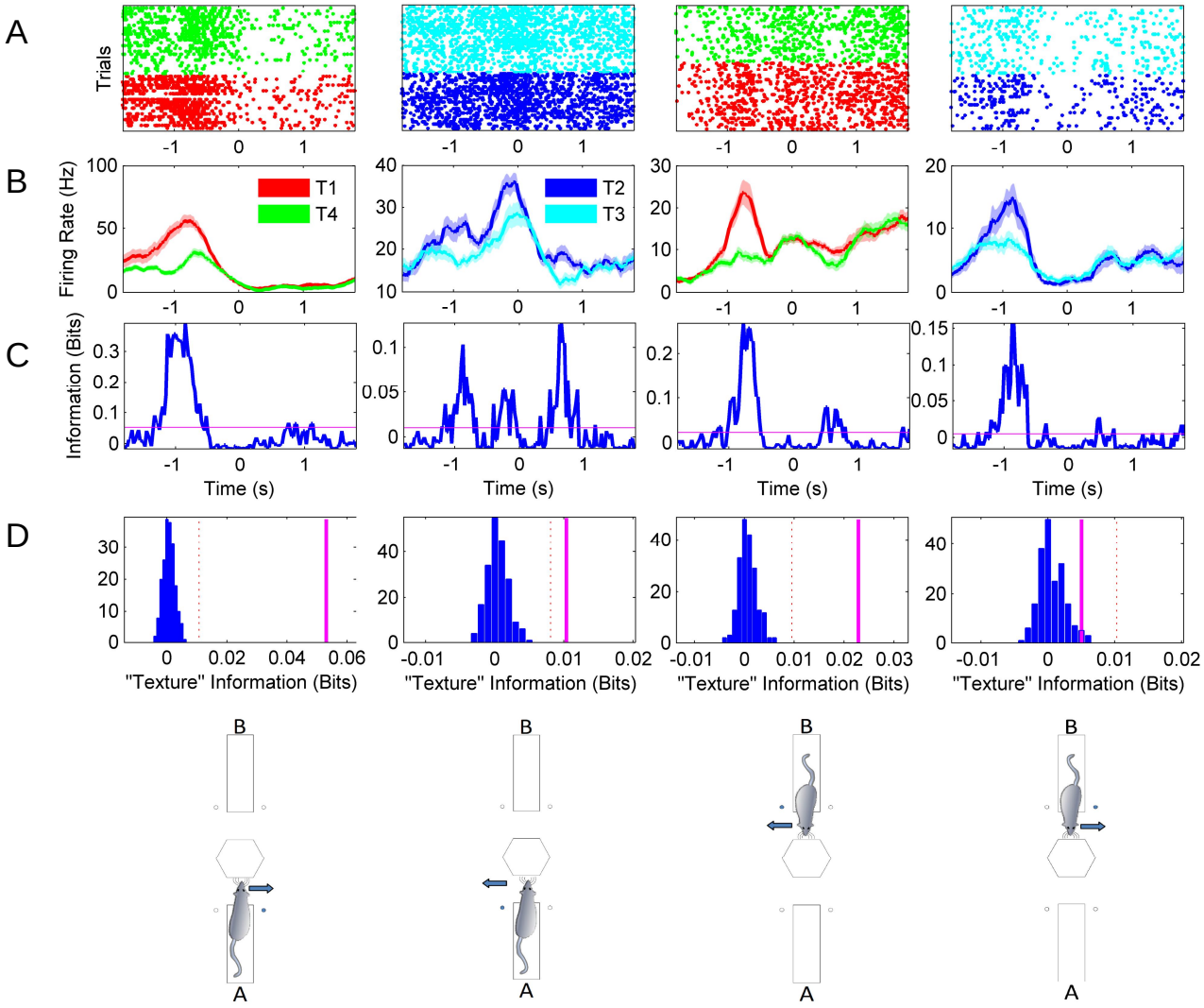

Figure 6. Texture representation in the two platform task-2. *Complete demonstration of texture related firing for one example neuron that represents texture in three locations**.** Zero on the x - axis is the moment when water reward was delivered.* ***A****. Raster plots. The trials are grouped by the identity of texture, each dot represents an action potential.* ***B****. Peristimulus time histograms (PSTH).* ***C****. Mutual Information between the identity of texture and firing rate over time. Information was calculated only between two textures associated with the same reward location. Magenta line – average amount of texture information.* ***D****. Distribution of average information values of 200 permutations of texture labels. Red dotted line – 5 standard deviation of the mean, magenta line – average amount of texture information. Icons in the bottom of the picture illustrate the location of the animal (which side the animal turned).*

Independence of texture signals between different locations.

If a neuron's probability of carrying texture in each location is independent, then the likelihood of a neuron carrying texture information in 0, 1, 2, 3, or 4 locations will be directly predictable from its likelihood of carrying texture information in general. This is what we found (figure 7). Two alternative models may be excluded. First is the absence of any place-modulation: "a texture neuron is a texture neuron, everywhere". In that case, signals would be concentrated in a smaller number of texture neurons, each neuron carrying information at 3 or 4 locations. The second excluded model is an absolute modulation of texture by place: "you may be a texture neuron in this place and only in this place." In that case, signals would be concentrated in a larger number of texture neurons, each carrying information at 1 location only. But we found texture neurons for 2 and 3 locations (figure 6 for an example) and the number of neurons which represent texture in multiple locations is well predicted by the simplest possible model (and is not significantly different from it $p>0.1$, permutation test) – independence of representations .

Representation of reward location – two platform task.

We have examined the properties of "reward location neurons" on 2 platforms. Of 750 neurons, 632 fired selectively for the reward location at least on one of the platforms (Information median value = 0.18 bits, inter quartile range: 0.12 - 0.31 bits). Of these 632 neurons, 273 represented reward location only on one platform (Figure 8 A) and 359 encoded reward location on both platforms (Figure 8 B-C). We found that the number of neurons that represent reward location on both platforms is significantly greater than would be predicted based upon the a priori probability of encoding reward location in any context (permutation test, $p<0.0001$). Thus, unlike the coding of texture, the coding of reward location was *not* accomplished independently. In shorthand, neurons tended to encode reward location on neither platform, or on both platforms. One half of the neurons that represented reward location on both platforms fired more action potentials for the same reward location (Figure 8 B) while the other half inverted their preference (Figure 8 C). The inversion of preference can have an alternative explanation: Perhaps some neurons encoded the task in an allocentric frame of reference – they could fire every time when animal turns towards the right or the left side of the room.

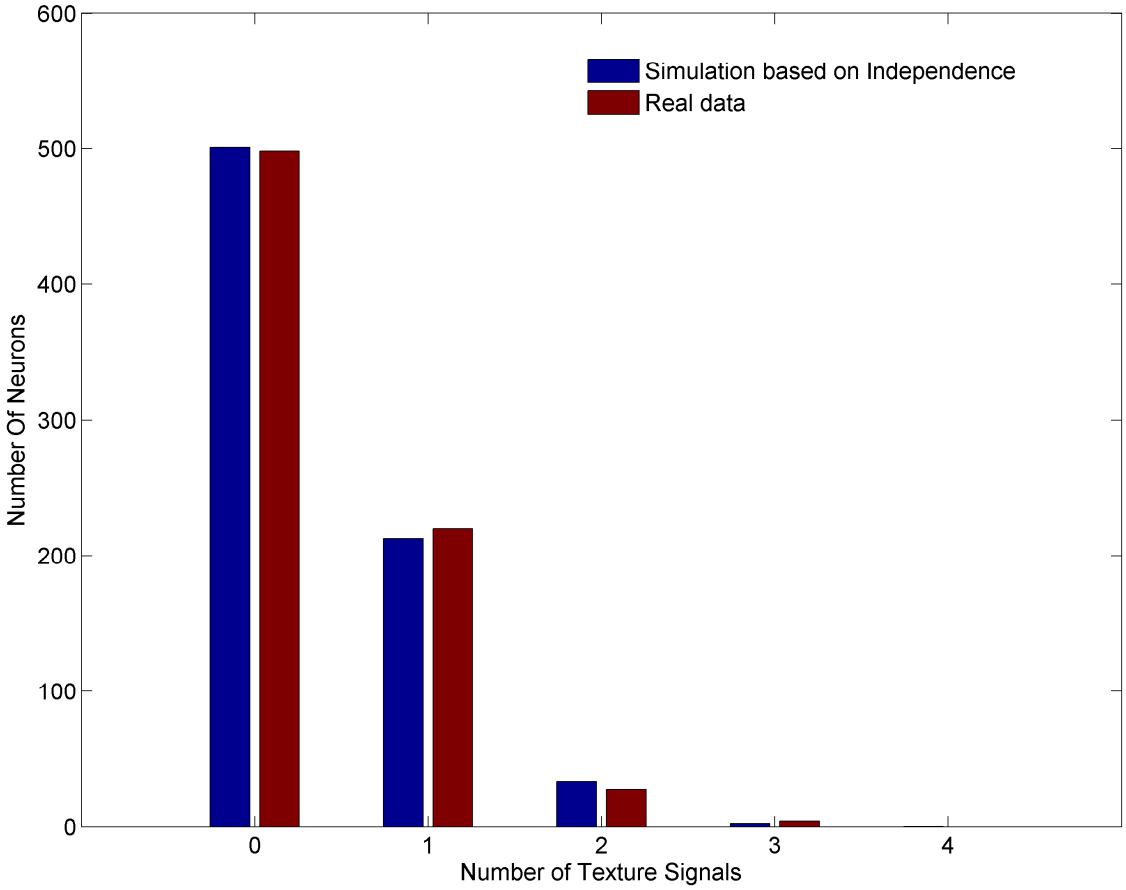

Figure 7. Independence of texture representations across different locations. *We consider that neuron has a possibility to represent texture in four locations (right -platform A, right – platform B, left - platform A, left - platform B), this way each neuron can carry from zero (not representing texture) up to four (representing texture in all four locations) texture signals. Blue bars demonstrate how many neurons will carry different number of texture signals if all the four representations are independent. Figure demonstrates a very close match between observed and simulated condition.*

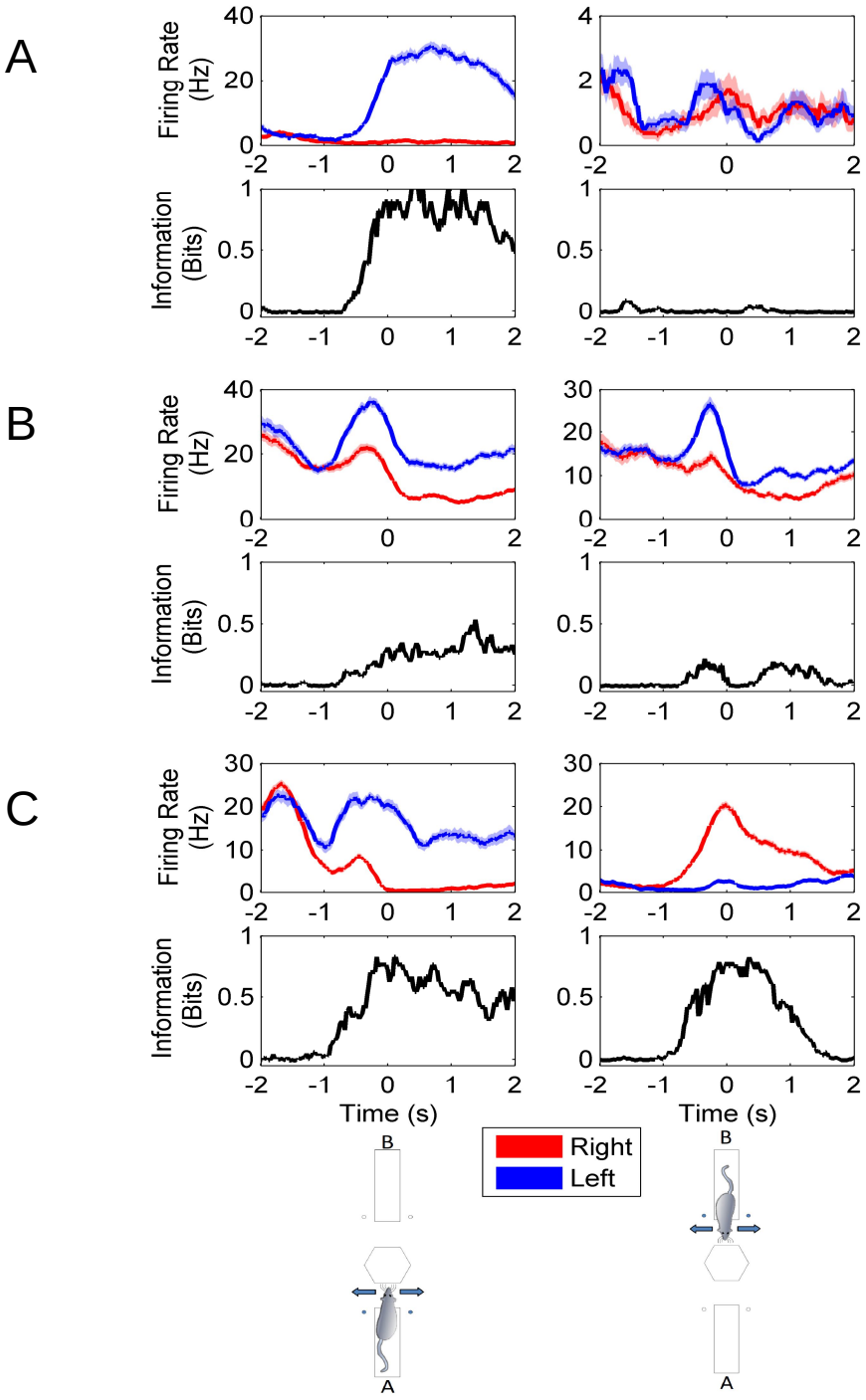

Figure 8. Reward location representation in the 2 platform task. *Firing properties of 3 example "reward location" neurons.* ***A****. Neuron representing reward location only on one of the platforms.* ***B****. Neuron representing the same reward location on both platforms but with different strength and firing at different rate.* ***C****. Neuron representing reward location on both platforms but firing for different reward location on each platform.*

Time course of texture and reward location signals and their relation to behavior and the brain states

We analyzed the time course of texture and reward location signals (Figure 9A). For each neuron, only the signals that contained a significant quantity of information were considered (i.e. a neuron that carried a significant amount of information about the texture only when the animal was associated with the right drinking spout on platform A). “Texture information” appeared after the rats touched the texture, several hundred milliseconds before the information about the reward location started to appear.

A crucial finding is that “Texture information” did not drop to zero even after the contact with the texture was concluded. It was still present as the animal turned toward the reward location and when water reward was delivered. Such persistence of information might help the animal to link the stimulus with the reward when they are separated in time as they are in our experiment. In any case, the presence of a signal about an episode which occurred but is now terminated must be, by definition, an explicit memory trace.

The dynamics of information was accompanied by transitions in the brain states. During the approach to and contact with the texture (Figure 9B), there was a significant increase in LFP power (Figure 9C) in the theta and beta range (7-12 Hz; 15-20 Hz; Figure 6B, $p=0.0002$, permutation test, Bonferroni-corrected). During reward collection, there was a sharp drop in theta power ($p<0.0001$), and an increase in power in the beta and lower gamma range (20-35 Hz, $p=0.0016$). Theta power remained very low throughout the period of reward collection.

It has previously been shown that so called ripple events occur when the animal is consuming a reward (Buzsáki 1986). These events are reflected in the firing of the majority of pyramidal cells in CA1 and CA3 (Csicsvari et al. 1999; Dragoi et al. 1999) and are associated with memory replay (Lee & Wilson 2002; Foster & Wilson 2006).

However, the suppression of theta power was not associated with ripple events: less than 5 percent of the trials had ripple events within 2 seconds of the nearest reward (Figure 10). Most of them occurred when the rat was idle and not performing the task (10-200 seconds from the nearest reward, with the typical inter trial interval around 6-8 seconds).

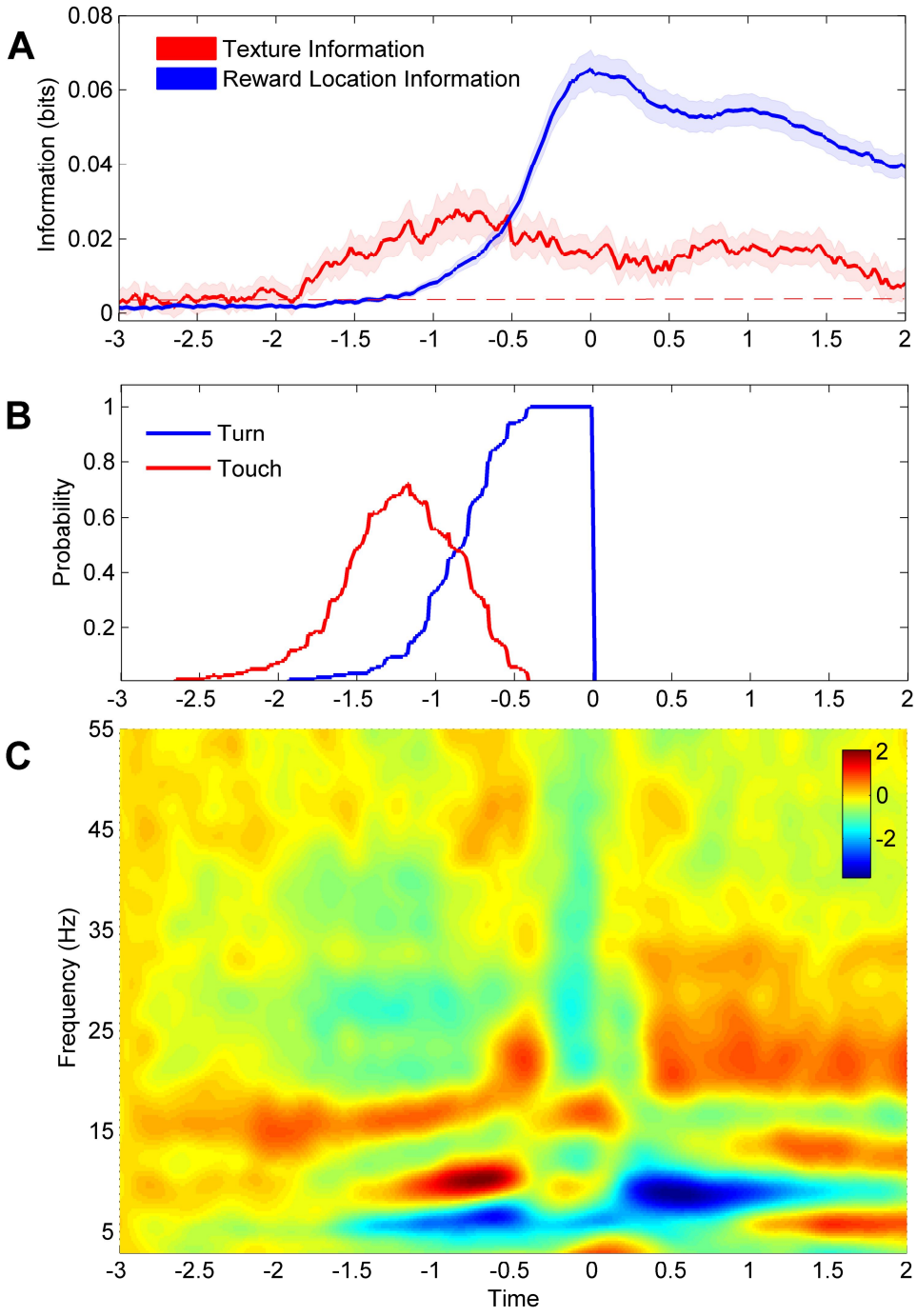

Figure 9. Temporal profile of texture and reward location information, relation to local field potential oscillations. ***A****. Average temporal profile of "texture" and "reward location" information of all "Texture" and "Reward location" neurons.* ***B****. Probability distribution of touch and turn epochs in behavior when aligned to reward delivery.* ***C****. Event related spectral perturbation of local field potential. Colorbar represent change in power relative to baseline (1 second before rat approached the texture) in dB.*

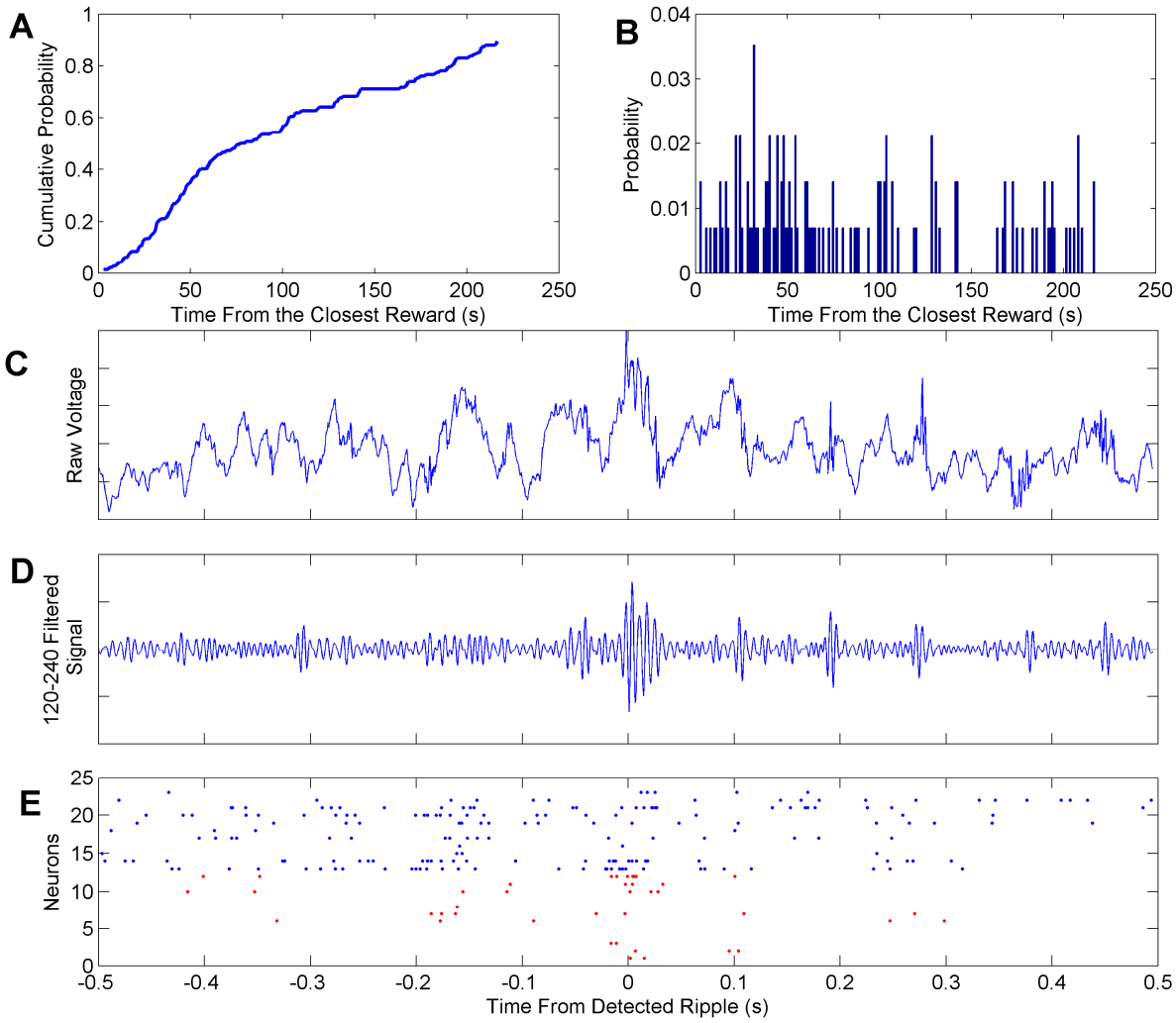

Figure 10. Ripple events. A*. Cumulative probability of observing a ripple event as a function of distance from the closest in time to reward delivery event.* ***B****. Probability to observe a ripple event from the closest in time reward delivery event.* ***C****. Raw (unfiltered) hippocampal local field potential voltage trace aligned on the maximum of the ripple event.* ***D****. 120-240 Hz band pass filtered local field potential of the same voltage trace.* ***E****. Raster plot of 23 simultaneously recorded neurons aligned on the ripple event. Red – pyramidal cells, blue- interneurons.*

Sound Categorization experiment (a pilot study)

The tactile categorization experiment provided insights into the sensory processing functions of the hippocampal system, but at the same time there are several limiting factors in investigations based upon active tactile sensation. The main limit is the difficulty of establishing control over the precise physical properties of the stimulus and the precise time at which it is delivered. Both these problems occur because, in texture categorization, it is the rat that creates the stimulus by movement of its own sensors. The rat determines when and how to touch the texture; the best we can do as experimenters is monitor the behavior closely and form our own best estimates of the stimulus parameters. To overcome these obstacles, in collaboration with Prof. Jan Schnupp, we have developed an auditory categorization task (for more details see Materials and Methods).

In a pilot experiment, we were able to train 2 rats to classify 4 vowels into 2 classes ("A" and "E" - turn right, "O" and "I" - turn left). After performance reached a consistent level of 80% correct, we implanted electrodes in hippocampus of one rat, from which we recorded 225 single-units; unfortunately the second rat died (unrelated to the experimental manipulations, probably due to an infectious disease) before surgery could be accomplished. Firing properties of hippocampal CA1 neurons in the sound categorization experiment were similar to those described in the previous chapter of this thesis in the texture categorization experiment. Methods of analysis (e.g. Mutual Information) were identical to those described earlier.

Vowel specific firing

As was true for the tactile experiments, a neuron was judged as coding stimulus identity if its activity differed significantly for the two stimuli associated with the same reward location. Measured in this way, 57 of 225 recorded neurons carried significant amount of information about the identity of the sound. Like "texture neurons," these "sound neurons" modulated their firing rate in a stimulus-specific manner after the presentation of sound.

Precise control of the stimulus allowed us to see new kind of responses previously not described. The neuron illustrated in Fig. 11 increased its firing rate in the presence of the sound 'e' but only when the rat was on platform B. Like some "sound neurons", this one responded to each individual vowel in triplet (Figure 11D).

In an analysis similar to the one carried out on the texture data, we asked whether the coding of sound identity by a given neuron in one of the four locations (turn right platform A, turn left platform A, turn right platform B, turn left platform B) would predict the coding of sound identity by the same neuron different locations. As before, three models of hippocampal function can be

distinguished by this analysis. A given neuron might have a strong disposition to carry sound signals independently of the animal's location; at the same time, other neurons would never carry sound signals in any location. The neuronal population would be comprised of sound coders and non-sound coders. The second model is that every neuron would encode strictly the conjunction of location and sound. In this manner, a neuron that carries a sound signal in one location could absolutely not carry a sound signal in any other location. The third model is that in each location, the set of neurons carrying sound signals is "selected" independently of the set of neurons in the other location. The test is carried out simply by comparing the number of neurons carrying sound information in 0, 1, 2, 3 or 4 locations to the values predicted by independence based on the a priori probability of a signal (Figure 12).

The result is that the observed number of neurons carrying sound information in 0, 1, 2, 3 or 4 locations could not be distinguished (permutation test $p>0.05$) from the number of neurons predicted if sound representation in different locations were independent.

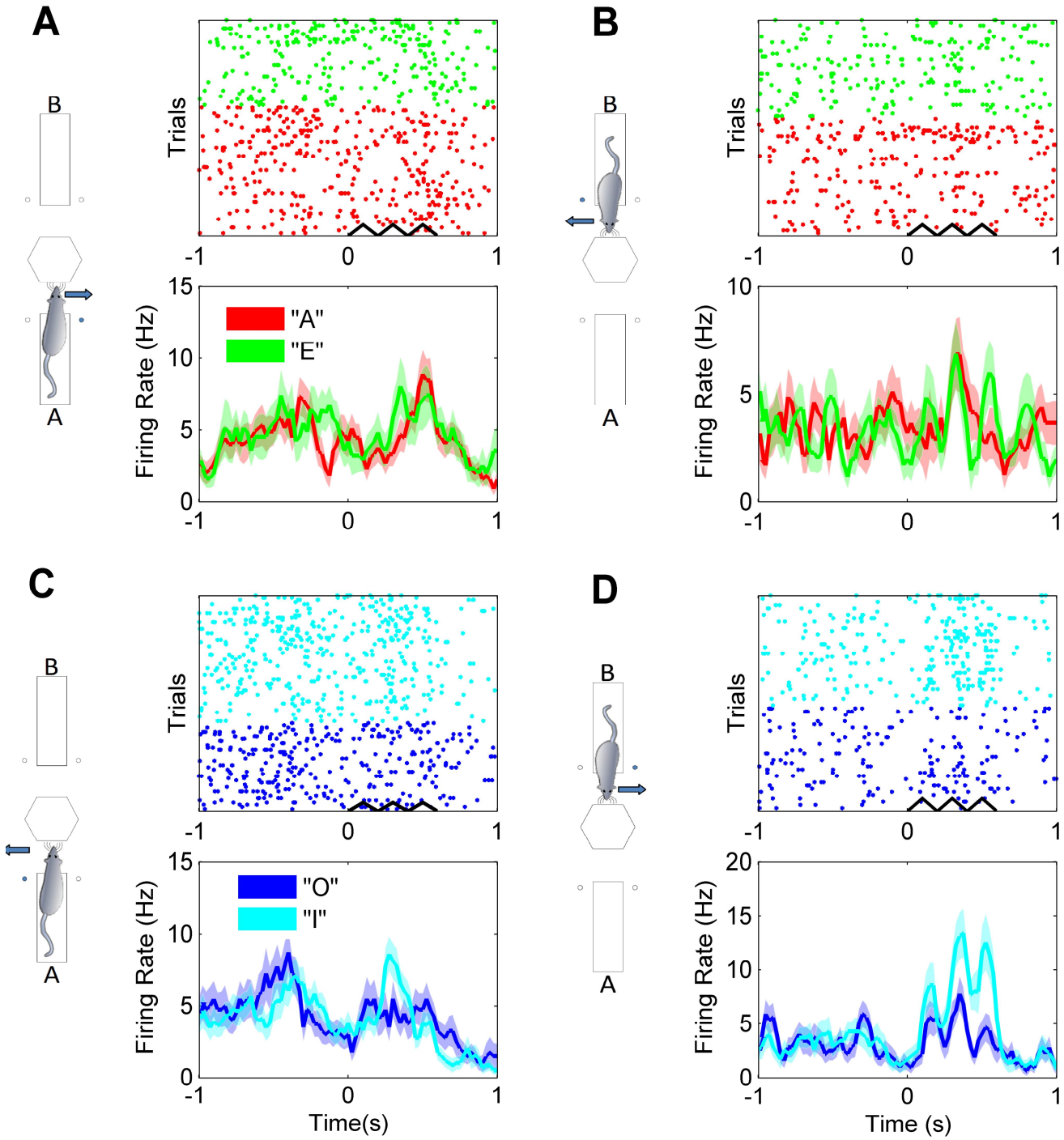

Figure 11. Sound (vowel) - specific responses in hippocampal neurons. *All plots are aligned to the moment of sound presentation. For this neuron, response to sounds was prominent at only one of the four locations (**D**). The neuron not only responded in a sound-specific manner but fired for each individual vowel in a triplet. Sound onsets and the fluctuation of their loudness are schematically depicted as saw like figure on the raster plots.*

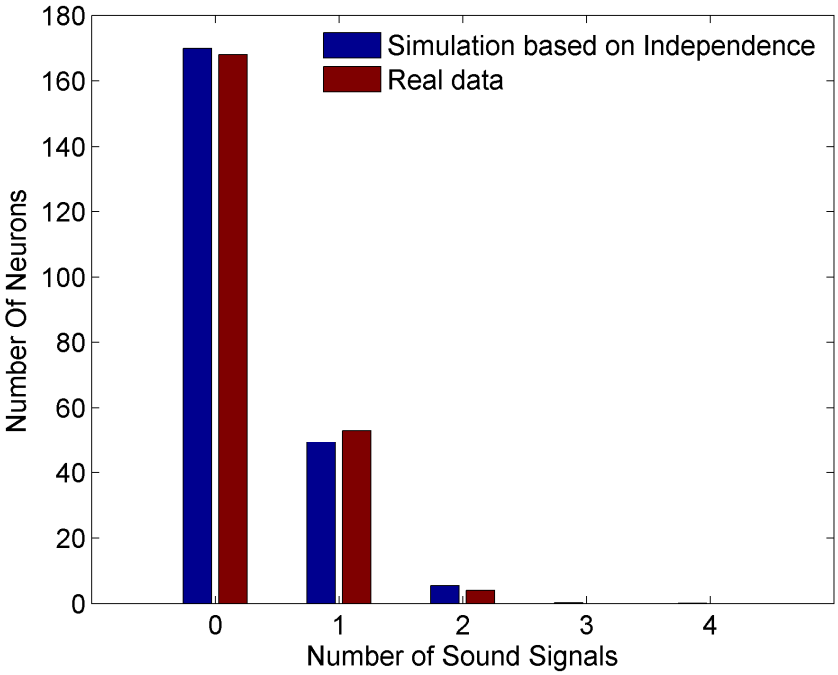

Figure 12. Independence of sound representations in different locations. *We consider that neuron has a possibility to represent sound in four locations (right -platform A, right – platform B, left - platform A, left - platform B), this way each neuron can carry from zero (not representing texture) up to four (representing sound in all four locations) texture signals. Blue bars demonstrate how many neurons will carry different number of sound signals if all the four representations are independent. Figure demonstrates a very close match between observed and simulated condition.*

Reward location related responses

The majority of neurons (193 of 225) represented reward location in their firing (Figure 13). Most of the neurons carried reward location signals on both platforms (137 neurons) and only 56 neurons carried a reward location signal on just a single platform. This distribution was unlikely to occur by chance ($p<0.000001$, permutation test) and confirms the finding from the tactile experiment that representations of reward location are not independent between two platforms. In other words, a neuron that carries a reward-location signal when the rat is on one platform is likely to carry a reward location signal also when the rat is on the other platform. Neurons without a signal on one platform are likely to not have a signal on the second platform. In this fundamental way, reward location signals differ from sound and texture signals. We have found no significant correlation between the amount of sound and reward location information (Spearman Rho=0.07;

p=0.3). Moreover, the joint probability of sound and reward location information was equal to the product of the two (permutation test) (Figure 14).

Responses to sounds during passive listening.

After the behavioral sessions, we recorded neuronal activity while the rats were exposed to the same sounds that were played during the task. The rat was in its cage, placed on a platform, so the acoustic signal was equivalent but no actions could be taken. Animals showed no explicit behavioral response to the sounds (e.g. lateral orientation, rearing on hind legs, attempts to reach the reward spout). We found no neurons that responded to sounds during passive listening - all observed responses were present only when animals were engaged in active discrimination behavior.

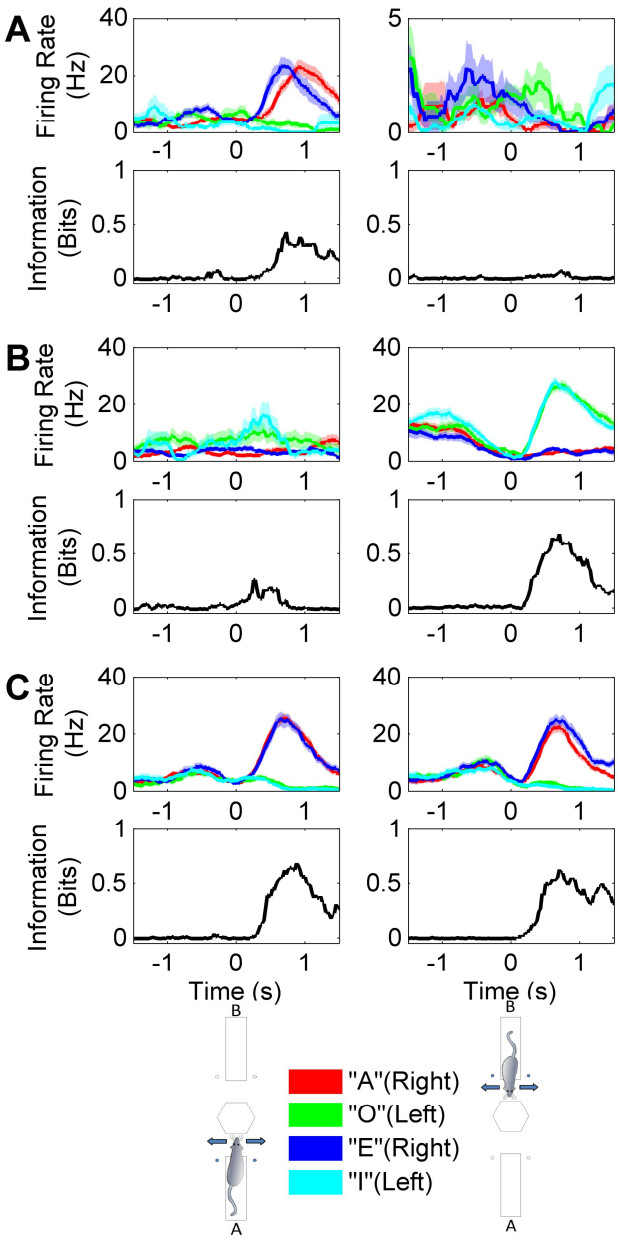

Figure 13. Reward location specific firing of 3 example neurons. *All plots are aligned of the moment of sound presentation. (**A**)Neuron representing reward location only on one of the platforms; (**B**) on both platforms but with different strength; (**C**) on both platforms with the same strength.*

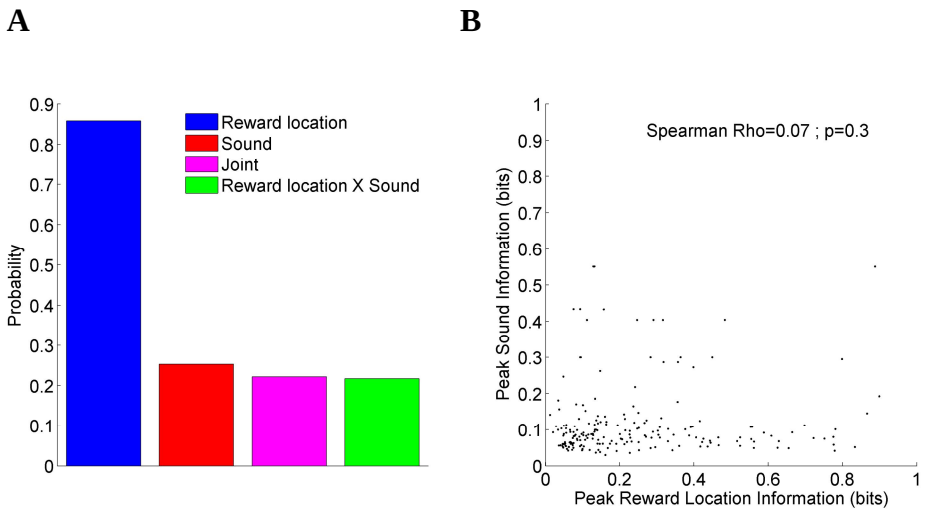

Figure 14. *A. Independence of the representations of sound and reward location. Height of the bars show the fraction (probability) of hippocampal neurons that represent reward location (blue), sound (red), both sound and reward location (magenta). Green bar represent which fraction of neurons would represent both reward location and sound if their representation were independent (the product of probabilities). B. Scatter plot showing absence of correlation between the amount of "sound" and "reward location" information.*

Discussion

We have found that hippocampal neurons in the CA1 field of the rat hippocampus represent both spatial and non spatial (texture or and sound) information. The representation of non spatial stimuli does not reflect the physical properties of the stimulus (roughness of texture): differently from barrel cortex, there was no tendency for coarser textures to evoke a greater firing rate. The texture representation was strongly modulated by animal's location. Sensory stimuli were always represented in conjunction with the context in which they appeared. Some neurons could discriminate more than one pair of stimuli in more that one location, but the likelihood of a given neuron encoding more than one stimulus was determined only by the prior probability of encoding single stimulus pairs. Thus, texture signals were distributed across the population independently for each reward location and for each context (platform).

In contrast the representations of reward location were not independent between two contexts: more neurons encoded reward location on both platforms that was expected by the prior probability per platform. Analogous results were obtained in the sound categorization experiment. In addition neurons never responded to sounds when rats were not engaged in the task. Based on our results we propose a model of hippocampal memory function: we suggest that neurons are selected to encode sensory stimuli randomly and the only factor contributing to the selection is their current biophysical state. Neurons are not committed to encode any given stimulus. In our view, no property of a neuron predisposes it to be a texture, sound, or reward location neuron. A neuron may encode any event or combination of events.

Object related firing of hippocampal neurons

We have found that around 30 percent of neurons in hippocampus represent the identity of palpated object or the perceived sound in the firing. This representation was location specific – the majority of neurons encoded the stimulus when the animal was located only in one place. We found no difference in the response to auditory or tactile stimuli. Considering the total number of sensory modalities processed by the rat brain, the finding that 30% of neurons in each task encoded the

sensory stimulus implies that processing could not be limited to one modality per neuron. We suggest that hippocampal neurons are multimodal in their nature and the differences in coding, if such can occur, will appear only due to different behavioral demands.

The first person to describe object-related firing of hippocampal neurons was O'Keefe (J. O'Keefe 1976; J. O'Keefe 1999). He found neurons that modulated their firing rate in the place field when the animal experienced a particular object inside it or was engaged in particular behavior there. He called them misplace cells. For example some cells increased their firing rate when the rat was sniffing or when unexpectedly found its food bowl empty, but only when the animal was located within the place field of these neurons.

Later studies elaborated, quantified and extended these findings to different modalities conditions, and tasks but the essence remained that hippocampal neurons in rats (we must stress that some properties, particularly the importance of space, may be special for the rat) fire always in restricted sections on the environment (place fields) and that firing rate within the place field can be influenced by many different factors.

Two main lines of research followed the discovery of place and misplace cells: one was the attempt to understand the mechanisms of place field formation and the second was the attempt to find how hippocampal neurons represent memory episodes. This second line of research coincided with the goal of putting hippocampal activity in a more general memory perspective, not limited to space. The first school used either navigation tasks and random foraging task combined with manipulations of environment in which the animal was running (O'Keefe & Burgess 1996; Lever et al. 2002; Wills et al. 2005; Leutgeb et al. 2004) (and many others); the second school concentrated on discrimination tasks (mostly olfactory) (Wood et al. 1999; Komorowski et al. 2009), working memory, and memory encoding and retrieval (Wiebe & Staubli 2001; Wiebe & Stäubli 1999; Manns et al. 2007). Our experiment combined both spatial and nonspatial information in a context of a categorization behavior. Due to the constrains of the experimental design we were not able to provide a detailed characterization of the spatial tuning of the neurons. The only measure in our results which can be compared to “place cells” was reward location related firing. There are at least two ways to explain the firing of the reward location cells. Although we identify one set of neurons as “reward location cells,” their firing might be associated with any of several other variables i.e. the action the animal performed to reach reward, or even the category(Freedman et al. 2001; Hampson et al. 2004) arising from the grouping of 2 textures associated with the same action. This second possibility is particularly intriguing because the presence of “category cells” in rat hippocampus would indicate a general principle in common with human hippocampal neurons (Quiroga et al. 2005). In humans, many hippocampal neurons fire selectively for a set of stimuli that are grouped by meaning or identity (star wars characters, Jennifer Aniston) even when the sensory

properties of the stimuli are different and no action is associated with them. Future experiments where the action can be dissociated from the perceptual category are currently being prepared in this laboratory to disambiguate these alternative possibilities.

Olfactory information in hippocampus

Hippocampal neurons in rats were shown to respond to stimuli of different modalities. Very similar firing properties of hippocampal neurons have been observed by several different groups using different versions of olfactory discrimination task. Because some of the findings are very similar to the we have described for somatosensation and audition we believe that some of the experiments not yet performed in these modalities will yield results similar to the ones obtained using olfactory discrimination. It is also important to stress the similarities between the neuronal responses to olfactory stimuli reported in the literature and somatosensory and auditory in the current experiment because olfaction has a privileged position among the senses in hippocampus. All sensory modalities apart from olfaction project to hippocampus through obligatory relay in the entorhinal cortex (Burwell et al. 1995; Witter et al. 2000). On the other hand, there are direct olfactory projections from olfactory bulb and piriform cortex to ventral hippocampus (Vanderwolf 2001). Reports from several groups in different experimental conditions have shown olfactory responses in hippocampal neurons (Wood et al. 1999; Wiebe & Stäubli 1999; Deshmukh & Bhalla 2003; Komorowski et al. 2009). In a landmark study Wood demonstrated that neurons in hippocampus encode both spatial and odor information, but the majority of neurons fire for the conjunction of space and odor (Wood et al. 1999). And recently Komorowski described the development of such odor in place neurons and showed that their development is correlated with the acquisition of the odor place association task (Komorowski et al. 2009), while the firing of place cells does not change with the acquired performance.

Auditory and somatosensory information in hippocampus

Auditory responses have been observed by several groups (Christian & Deadwyler 1986; Sakurai 1994; Moita et al. 2003). Moita has shown the acquisition of response to a tone during single trial fear conditioning in rats. Responses to the conditional tone not only developed with learning but were also restricted to the place fields of neurons (like misplace cells of O'Keefe).

There exists only one publication describing the firing of hippocampal neurons in relation to whisker guided behavior (Pereira et al. 2007). The authors recorded hippocampal activity in

response to trigeminal nerve electrical stimulation and whisker deflections in anesthetized, awake head fixed as well as awake behaving rats performing aperture width discrimination. They found firing rate modulation in response to whisker deflections and trigeminal nerve shock in both anesthetized and passively stimulated rats. But the activity present in behaving rats could not be attributed to tactile signals because the two touch inputs in question (wide vs narrow aperture) were also associated with separate actions toward two different reward locations. The responses during the performance of the task could be attributed to the reward location. The “tactile” neurons in that study thus resembled the reward location neurons in the present experiment (for example figure 4 and figure 8). But the “texture” neurons in the present fired differently for two different textures associated with the same reward location. Taking this fact in consideration, we claim to have described the first somatosensory induced modulation of firing of hippocampal neurons during touch guided task (for example figures 3, 5 and 6). Firing properties of our “texture” neurons fit well in the description of the misplace cells. Texture modulation of firing was mostly limited to one location, although we haven't monitored place fields of the neurons directly, it is reasonable to assume the ”coding” of texture was present only within the place field of a neuron i.e. only on one of 4 turn locations (Figure 5).

Persistence of texture signals. Bridging the temporal gap.

We found that neuronal information about the palpated texture does not disappear with the disappearance of sensory input. Rather, it persists and even shows a slight increase in strength simultaneous with reward consumption, as does the signal related to reward location (see Figure 9). This reward-associated increase of texture information overlaps in time with the suppression of activity at the theta frequency (8-12 Hz) in local field potential. We suggest that the recurrence and persistence of texture information can bring stimulus and reward adjacent in time to allow the rules of synaptic plasticity to work (Levy & Steward 1983).

The average time courses in Fig. 9 were generated from single-neuron profiles of many different shapes. These included single peaks (early, late, or in-between) and multiple peaks (for example, Figures 3, 5 and 6). There were very few neurons that maintained information continuously throughout the whole trial. The transient nature of the episode information in single neurons, in contrast to the lower but persistent signal seen in the population average, brings to mind an intriguing model of short term information storage – the signals may be “handed over” continuously from neuron to neuron from the time of first stimulus contact until the start of the next trial. The physiological necessity of such signal bursts might come from the adapting nature of single neurons. The bombardment of the network by inhibitory inputs from local interneurons tends

to bring neurons quickly down to baseline firing rate, but only after the signal has been relayed to other neurons.

The main generator of theta rhythm is the medial septum, which provides cholinergic and GABAergic input to hippocampus. We suggest that during texture sampling the increase in theta power reflects a strong cholinergic and GABAergic influence that suppresses excitatory intrinsic and recurrent transmission, leaving the afferent input from entorhinal cortex intact (Ault & Nadler 1982; Hasselmo et al. 1992; Hasselmo et al. 1996). This state would favor the encoding of new events into the memory (Hasselmo & Bower 1993) and is reflected in our data by the first peak of texture information. When the animal receives the water reward, we speculate, the septal influence becomes weaker and, probably, the monoaminergic influence starts to dominate. These factors may shift the network into a recall and consolidation mode, reflected by the sustained texture information in the absence of sensory input.

Possible role of remapping in bridging the temporal gap

Since the discovery of the place-coding properties of hippocampal cells in 1971(O'Keefe & Dostrovsky 1971) many additional properties of hippocampal neurons have been uncovered. One of the most intriguing is remapping. Remapping of place fields was first observed by Muller and Kubie in 1987 (Muller & Kubie 1987). The authors described hippocampal place cells that change their place fields in response to the changes in environment (either changes in the size or shape, of the box). They interpreted this phenomenon as a change in the spatial representation of the environment triggered by external stimuli. Later, remapping has been shown for many kinds of alteration of the environment: when the lights were switched off (Quirk et al. 1990) or the color of the cue card (Bostock et al. 1991) or the box itself (Anderson & Jeffery 2003) changed from white to black or the odor of the box changed (Anderson & Jeffery 2003) etc.

Remapping has been also observed when animals had to perform different tasks in the same environment. It was first shown by Wiener and colleagues (Wiener et al. 1989), who trained rats to perform an odor discrimination task followed by running in the same environment. They found that the place activity in the running task did not predict the firing in olfactory discrimination task .Markus (Markus et al. 1995) trained rats either to run randomly or to gather food in specific locations in the same arena, and showed that about one third of place cells remapped depending on whether the rat was running randomly or was gathering food in the predetermined locations. Place cells became directional if the rat was running linearly (following the food pellets which were placed in lines) but not when the food was scattered randomly. Moita (Moita et al. 2004) showed

that after the acquisition of a conditioned fear response place cells can remap as well.
Several studies have reported that hippocampal activity can change depending on the trajectory of the rat (Frank et al. 2000; Wood et al. 2000; Ji & Wilson 2008), or its past experience and future expectations (Ferbinteanu & Shapiro 2003).

Turning to our own data, it is possible that texture contact can change the spatial representation during touch and until the next stimulus is presented. In other words, texture signal may cause rate remapping (Anderson & Jeffery 2003; Leutgeb et al. 2005) of the representation of reward location where the rat is turning. This way the bridging of "sensory" information between the stimulus and reward might arise from the nature of spatial representation: it has been shown that on a linear track adjacent place fields partially overlap and it was proposed (Skaggs et al. 1996) and later demonstrated (Itskov et al. 2008) that within 1 theta cycle some of the neurons represent both past and future places. This way the activation of only one of the place cells from such sequence can allow auto-associative recall of the whole sequence of locations that led to successful acquisition of reward. We suggest that such texture triggered remapping of the place cells can be spread forward from the place where texture was palpated to the location of reward (Wallenstein et al. 1998) and, maybe, together with the recurrence triggered by the suppression of theta activity can support associative learning between events that are separated in time. This might provide a physiological basis for one of the key functions of hippocampus – learning of discontinuous events (Rawlins 1985; Wallenstein et al. 1998).

Firing properties of hippocampal neurons in human hippocampus and comparison with rats

Animal research has provided us with a vast phenomenology but its ultimate goal is the understanding of the human brain. It seems that single neuron recordings in human subject reveal different properties from the ones reported in rats and monkeys. We shall briefly review the main discrepancies and will attempt to unify the data in a single framework.

Recordings form human subjects are made in order to localize the epileptic focus in the case of pharmacologically intractable epilepsy. Place related activity has been demonstrated during a virtual navigation task (Ekstrom et al. 2003). The authors demonstrated that some neurons in the medial temporal lobe fired selectively when subjects "passed" a particular location in a virtual environment, they also found neurons that fired selectively for particular landmarks. Quiroga demonstrated that some neurons in hippocampus fire selectively representing the identity of famous people and landmarks (Quiroga et al. 2005; Quiroga et al. 2009). The firing of these neurons is invariant to any physical properties of the images and represents the semantic content of the image;

firing can be evoked by the presentation of a written word and even upon hearing of the word or sounds related to the person or concept (Quiroga et al. 2009). Hippocampal activity has recently been studied during a free recall (Gelbard-Sagiv et al. 2008). Neurons not only responded to in an invariant and category specific manner to video fragments but some of them kept firing after the stimulus was gone, sometimes as long as 30 second. After finding neurons selectively firing for some of the stimuli, the subjects were asked to recall what they have seen, their subjective experience was recorded. The same neurons that fired during the watching of a particular movie clip fired also when subjects recalled this clip during a free recall paradigm.

Such striking level of invariance of hippocampal neurons in humans doesn't seem to be compatible with high level of context dependence of hippocampal representations in the rat. We think that the difference does not come from any difference in hippocampal function but rather is related to the different in the organization of cortical input to hippocampus. Invariance for objects in humans has been found not only in hippocampus but has been reported for the majority of structures within the medial temporal lobe (starting from the parahippocampal cortex) (Quiroga et al. 2009) and is also present in the inferior temporal cortex of nonhuman primates (Hung et al. 2005; Kreiman et al. 2006). In rats, on the contrary, a portion of medial entorhinal cortex contains explicit representation of the animal location (Hafting et al. 2005). It is plausible that different cognitive demands and ecological niche between humans and rats led to the dichotomy in the functional organization of the hippocampal input, but it is also possible that the mechanisms of the hippocampal function remained unaltered. None of the studies of hippocampal firing in rats to date forced the animals to form abstract representations, although it has been recently shown that rats are capable of doing so (Zoccolan et al. 2009). Future experiments targeted to study object shape and position invariance in the rat may resolve the discrepancy between the human and rat hippocampal research

Different modalities share the same rules

In a pilot sound categorization experiment we have found that the firing of neurons is not restricted to tactile modality. There was almost no difference in the firing properties of neurons in response to tactile or auditory stimuli. The auditory experiment allowed us to test neuronal response properties outside the context of the task during passive listening, where we demonstrated that neurons did not respond to sounds unless the latter are meaningful. Probably the absence of neuronal response to sounds during passive listening reflect the fact that this experimental condition formed a new context for the animal and because learning this context was not necessary for the animal (no motivation) no representation has been formed or the absence of motivation led to a very

small representation of these episodes which our sparse recording method could not detect. These findings and the anatomical data suggest that hippocampus acts as a general system for episodic or episodic like memory: episodes are represented as a whole (what, where and when) and that hippocampal rules (especially the independence of the encoding of episodes) are general across modalities. It is not clear from the current experiment whether the same neurons can represent both tactile and auditory events. New experiments in which the animals are trained in both tasks can answer this question.

Relationships between the encoding of texture and reward location

We didn't find any systematic relationship between the representation of reward location and texture. In one of the rats trained in the two platform texture categorization task these representations were independent and uncorrelated, while the second rat showed a small (Spearman Rho = 0.3) but significant correlation between the 2 kinds of signals. The third animal that we trained in the sound categorization experiment showed no systematic relationship between the sound and reward location signals (Figure 14). It is possible that such differences between the animals stem from different strategies the rats used in order to solve the task. We are currently designing a method to disentangle this and other possible confounds in our analysis of the neuronal representations of texture (sound) and reward location.

Independence of the encoding of episodes

We have shown that neurons could represent texture in more than 1 location, using simple numerical simulation we have demonstrated that the proportion of neurons that have 2 and more "texture" signals depend only on the prior probability of occurrence of the "texture" signal (figure 7). The same was true for the encoding of sounds (figure 12).

We propose a model of how neurons get recruited into the representation of memory traces of current events (Figure 15). The probability that a neuron will encode texture in location A among active neurons is approximately 0.2 in our dataset, so this will lead that 3 out of 15 neurons will be recruited. When the animal decides that texture can be used to solve the task another subset of neurons is recruited for texture representation. But because the probability that some neurons are already recruited in location A and because stimulus representations across 2 locations are

independent some neurons will represent texture in both locations. The number of these neurons can be calculated if one knows the probability that the neuron can be recruited by the stimulus. This suggests that the probability that neuron will get involved in the representation of a sensory event depends only on the state of the neuron at the moment of occurrence of the sensory event (random fluctuations of the membrane potential, levels of calcium or density of ion channels etc). Such scheme for memory storage has been proposed by David Marr (Marr 1971) for his simple memory system which he associated with arhicortex (especially hippocampus), but no quantitative proof has been found up to date. We think that that our experimental results point to such a process.

The main prediction of this model is that the selective stimulation of random subset of hippocampal neurons when the animal is learning new stimulus will result in recruitment of these neurons to represent the stimulus. Such memory writing experiments might lead to a breakthrough on to a different level of brain machine interface which might allow direct recording of signals in to the memory of individual.

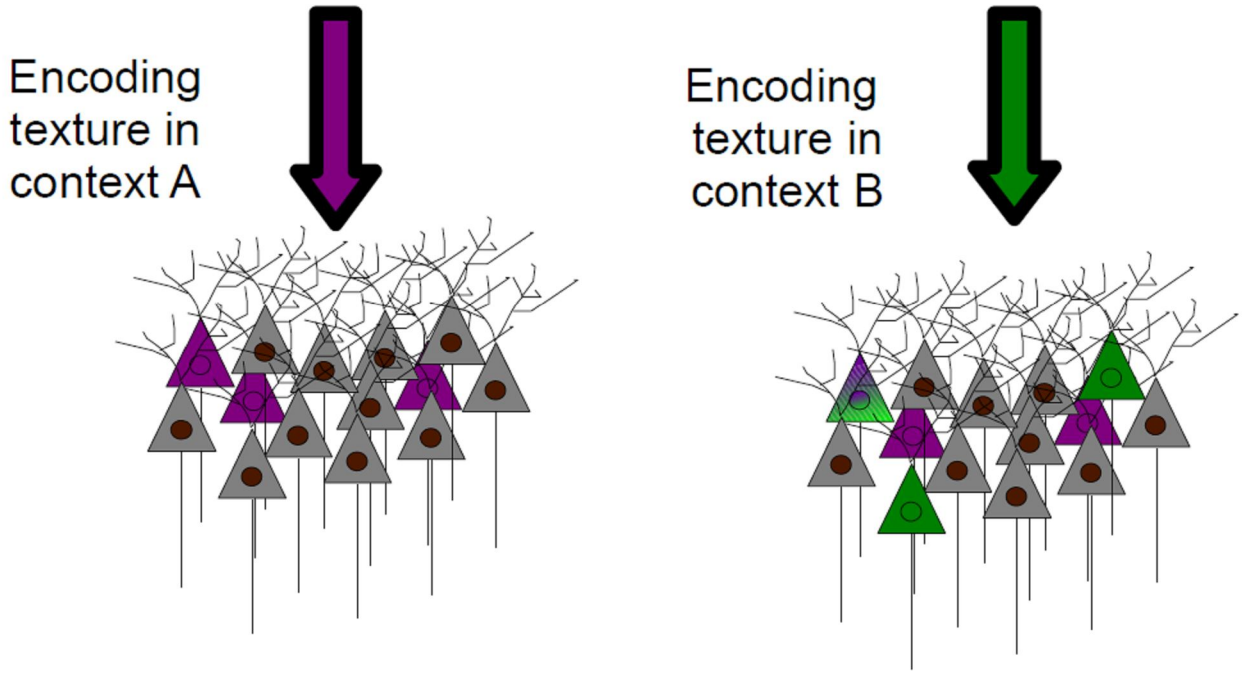

Figure 15. Independence of encoding of events in memory*. When the animal is learning a stimulus in the context A (magenta arrow) some neurons are recruited into the representation of this stimulus (neurons in magenta). The representation of stimulus is linked to its context (e.g. location). Upon the need to learn stimulus in a different context B (green arrow) another set of neurons (in green) is recruited. Because the representations across different contexts are independent some of the neurons (neuron with mixed color) will be recruited into both representations and will appear to encode stimulus in both contexts.*

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