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Spatial decisions and neuronal activity in hippocampal projection zones in prefrontal cortex and striatum

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1. Introduction – theoretical bases

While place and grid responses in the hippocampal system are textbook examples of the cognitive basis of representations of abstract information on a single cell level, their functional significance can only be evaluated by how they impact other brain areas and behavior. This is underlined by the observation that hippocampal lesions induce only anterograde amnesia, while leaving previously consolidated memories intact, indicating a role for the hippocampus in the formation (and renewal) of memories that are successively stored elsewhere in the brain (Dudai, 2004; Frankland and Bontempi, 2005). Furthermore, since the hippocampal system has no direct projections to motor areas, its outputs must pass through other areas (whose cells do not have place responses) prior to reaching and influencing pre-motor, motor, autonomic motor and neuromodulatory control areas and hence making an impact on ongoing behavior. The principal areas receiving hippocampal system place-related signals can be crudely divided into four main functional groups: 1) hypothalamus, lateral septum, amygdala; 2) anteromedial thalamic nucleus/medial mammillary nucleus (see Hopkins, 2005), midline thalamic nuclei, supramammillary nucleus; 3) ventral striatum, medial prefrontal cortex, and 4) subiculum, pre- and para-subiculum, entorhinal, and parahippocampal cortices which have reciprocal connections with diverse cortical areas. These may be broadly summarized as respectively being associated with 1) autonomic, visceral and emotional functions, together implicated in higher cognitive functions leading to consciousness (Damasio, 1999), 2) theta rhythm modulation and coordination of brain circuit dynamics in general, 3) learning goal-directed behaviors, planning, sequencing, and action selection, 4) information re-processing, in particular memory consolidation.

The present chapter will focus primarily on the third system, but will also examine some aspects of the fourth, concerning relations with cortical areas. Our research has concentrated on these as most likely to be informative about the influence of hippocampal activity on goal-directed spatial orientation.

2. The Prefrontal cortex: main generator of planned behavior

Everyday life constantly requires choices among alternatives. From choosing the right time to switch lanes when driving a car, or selecting menu items for dinner, right up to making the most important choices in life, we engage some of the brain's most important features: the circuits involved in making *decisions*. Decision processes involve the evaluation and prioritization of one's needs and goals, and the analysis of information referring to the present, the immediate past, as well as our learned experience and knowledge relevant to the current context. The brain has to make predictions about possible upcoming events, and action outcomes. Those predictions need to be evaluated for risks and benefits in order to select the more advantageous option, and all this unfolds continuously, at multiple cognitive and computational levels, nested and intertwined with each other.

The prefrontal cortices are the central component of the “generator of planned behavior” (Dickinson, 1985). Behavioral planning and sequencing require diverse types of information concerning the current situation to be stored in a short-term memory buffer, or *working memory*, which has been shown to depend preponderantly on the prefrontal cortex (for reviews see Goldman-Rakic, 1987; Fuster, 2000). The decisions are then implemented via its direct lines of command to motor structures (which express behavior) as well as to autonomic and neuromodulatory structures that regulate the internal state of the brain and the body (Goldman-Rakic, 1987; Pandya and Yeterian, 1990; Barbas, 2000; Rolls, 2004).

From the functional point of view, the interaction between the prefrontal cortex and the hippocampus has been implicated in both working and episodic memory processing. *Working memory* maintains online the different pieces of information needed to assess and formulate decisions. The prefrontal neural basis of this sort of memory, in the form of self-sustained delay activity has been extensively studied from the experimental (Fuster, 2000; Goldman-Rakic, 1987) and theoretical point of view (for example in Amit and Brunel, 1997; Wang, 1999; Compte et al., 2000). Evidence for such memory-supporting activity has recently been observed in the rat prefrontal cortex as well (Baeg et al., 2003; Jones and Wilson, 2005). The prefrontal cortex's role in working memory for diverse modalities could be implemented through specific temporary functional linkages with other modality-specific cortical regions relevant to the current cognitive demands (see e.g. Postle, 2006). In rodents, for example, it has been shown that experimental interference with hippocampal function affects working memory (Aggleton et al., 1986; Knowlton et al., 1989; Wan et al., 1994). Moreover, the integrity of the hippocampal/prefrontal network seems necessary for normal working memory performance (Floresco et al., 1997). In this network, the two structures would play different, but complementary roles: Winocur (1992) showed that hippocampal lesions cause delay-dependent working memory deficits, whereas prefrontal lesions result into an delay-independent impairment. Taken together, these findings point to a role for the hippocampus more centered on the actual maintenance of information, with the prefrontal cortex more implicated in the monitoring and flexible use of such information (Moscovitch and Winocur, 2002). Thus, hippocampal and prefrontal activity would be coordinated for working memory in domains of hippocampal specialization, such as cue

configurations distributed in space and/or time.

The hippocampus and the prefrontal cortex are likely to collaborate in *episodic memory* processing as well, although this may engage other mechanisms. Complex, flexible goal-directed behavior, supported by prefrontal function, requires rich *contextual* information, that is, the ability to process a large amount of relational information, and reconstruct previous *episodes* which may be relevant for shaping the decision at hand. The hippocampal system can perform this task, by informing the combinatorial tangle of interrelationships between sensory inputs into a topological structure, reflecting the arrangements of cues in the external space. This is an important component of episodic memory, which indeed has been found to be largely dependent on hippocampal activity. The prefrontal cortex, besides monitoring and processing episodic memories, may also play an active role in the formation and maintenance of episodic memory (Ferbinteanu et al., 2006), for example with respect to encoding of the temporal aspects of an episode (Funahashi et al., 1993; Ninokura et al., 2003, 2004).

3. The hippocampal/prefrontal network.

Many anatomical and physiological lines of evidence also point to a close collaboration between the hippocampus and the prefrontal cortex: the prefrontal cortex is distinguished within the neocortex in that it receives direct hippocampal innervation (Swanson, 1981; Goldman-Rakic et al., 1984; Jay et al., 1989). In the rat, this projection originates in the ventral (temporal) portion of the CA1 hippocampal subfield and the subiculum and reaches prefrontal areas including infralimbic (Swanson, 1981), prelimbic (Ferino et al., 1987; Jay et al., 1989; Jay and Witter, 1991), medial orbital (Jay and Witter, 1991), and agranular insular (Verwer et al., 1997) areas. Notably, the dorsal hippocampus, whose neurons have the smallest firing fields and hence the most precise spatial representations sends no direct connections to the prefrontal cortex: rather the ventral hippocampus, with a lower incidence of spatially selective cells with larger fields (Jung et al., 1994; Poucet et al., 1994; Maurer et al., 2005) provides an input to the prefrontal areas. Furthermore, Tabuchi et al. (2003) observed a greater incidence of discharges during immobility at reward sites in ventral (temporal) than in dorsal (septal) hippocampal neurons. This is not consistent with interpretation as hippocampal place responses, which generally cease during immobility (when theta frequency rhythmic local field potentials are diminished). More recently Hok et al. (2007) have observed comparable, albeit with distinct properties, goal site related activity in dorsal hippocampus. Thus the hippocampal input to prefrontal cortex can concern diverse aspects of the current context.

The hippocampal to prefrontal connection has been extensively studied with electrophysiological methods: pulse stimulation of the ventral hippocampus elicits a short excitatory response in neurons in the prefrontal cortex, followed by a period of inhibition, and this shows both short-term and long-term plasticity (Laroche et al., 1990; Mulder et al., 1997). Monosynaptic hippocampal inputs were shown for prefrontal GABA-ergic interneurons as well (Tierney et al., 2004), so that the effect of the hippocampal projections on the prefrontal cortex can be described as a combination of excitation and feed-forward inhibition.

The inverse pathway, from the prefrontal cortex to the hippocampus, is mediated by

the parahippocampal cortices (Burwell and Witter, 2002). An interesting alternate relay between the two structures is represented by the nucleus reuniens of the thalamus (see Vertes, 2006 for a review).

The interaction between the prefrontal cortex and the hippocampus as major information relay for the ventral striatum and the midbrain dopaminergic structures will be discussed below.

4. Spatial representations and the prefrontal cortex

The strong hippocampal input, and the importance of spatial contextual information for decision making, hint at the possibility that the prefrontal cortex contains some sort of representation of space, as a part of a more generic encoding and processing of a behavioral situation. Such a representation would not likely be in the form of a stable, cognitive map representation of the spatial environment, such as that proposed to be the computational basis of navigation. Indeed, an intact prefrontal cortex is not needed for the acquisition and performance of navigational tasks such as the Morris water maze (Maaswinkel et al., 1996; de Bruin et al., 1997; Kesner, 2000). Rather, the prefrontal cortex may contain representations of higher order interactions (Banquet et al., 2005) between place and other factors relevant to behavior such as the presence or absence of a cue, a reward, the location of a goal, changing environmental contingencies, motor patterns, etc. The results of several experimental studies support this view. Jung et al. (1998) showed in rats performing behavioral tasks on mazes that the activity of prelimbic cortex cells was selective for particular task phases (approaching, leaving reward sites, etc.), particular behavioral patterns, such as body turns, or conjunctions of these same factors with place. In a delayed alternation task on a figure-8 maze, prelimbic cells were active on the central arm, depending on the previous choice arm, consistent with a role in maintaining a working memory-related trace (Baeg et al., 2003). Medial prefrontal cells show reward-related anticipatory activity (Pratt and Mizumori, 2001). In a place preference task (Hok et al., 2005), prelimbic and infralimbic cells showed place-related responses, with the goal area (which was dissociated from reward) disproportionately represented, so that the goal location was encoded by the overall ensemble activity.

Another perspective on the function of the prefrontal cortex, and in particular the prelimbic/infralimbic (PL/IL) areas, emerging from lesion experiments in rats (Ragozzino et al., 1999a,b; Birrell and Brown, 2000; Delatour and Gisquet-Verrier, 2000; Granon and Poucet, 2000) may be described as supporting the flexible attentional shift between contingency rules related to different sensory and behavioral dimensions. Hence, it may be argued that prefrontal place representations should be greatly influenced by the current task contingency rule, or by the information domains that are currently being attended to. For example, items such as the predicted goal/reward location, the position of a currently attended cue may be encoded in a prefrontal representation, and such encoding may be radically modified by a change in the contingency rule.

For our work the techniques of extracellular neurophysiological recordings of single unit activity and local field potentials in behaving animals have been selected in order to reveal the mechanisms underlying cognitive function in terms of the dynamic signal processing algorithms implemented by brain circuitry. The behavioral correlates of single

unit activity show the types of information discernible in the neural activity of hippocampal efferent structures, permitting comparison with the hippocampal system. Deductive reasoning then indicates what these structures may have received from the hippocampus as well as what other information must have arrived from other structures or via internal processing. Analyses of cross-correlations between discharges of neurons in hippocampus and downstream structures can indicate common sources of inputs and may even suggest transmission of signals from one structure to the next. Moreover such cross-correlations can be tested for behavioral modulation, hence providing evidence for selective gating of hippocampal output signals according to self-organizing principles of brain circuitry. Furthermore the comparison of local field potentials (LFPs) in the hippocampus and downstream structures can demonstrate the coherence or, alternatively, decoupling of the respective structures. Selective coherence of LFPs is hypothesized to be a mechanism of functional coupling of modular subsystems of the brain.

Battaglia, et al. (2005b, 2006) tested these hypotheses with multiple tetrodes recordings of the activity of prelimbic cell ensembles simultaneously with hippocampal LFP recording. This was done as the rats learned and performed a contingency shift task on a Y-maze, formed by three arms separated by 120 degrees, with a circular platform at the center. Rats started all trials from the same *departure* arm and, after the central barrier was lowered, they had to select among the two choice arms then go to the end to receive a chocolate milk reward. Concomitantly with the lowering of the barrier, one of the two arms, randomly selected for each trial, was illuminated. For each trial, the reward was available on only one arm. The baited arm was determined based on one of four possible contingency rules: 1) the right arm was always baited (*spatial orienting-right* rule), 2) the left arm was always baited (*spatial orienting-left* rule), 3) reward was available on the illuminated arm (*visual cue based-light* rule), 4) reward was available on the non-illuminated arm (*visual cue based-dark* rule; Figure 1A). Once the rat acquired the current rule (i.e., performance reached a criterion level), the rule was then switched (always in an extra-dimensional fashion, that is, from a spatial orienting rule to a visual cue-based rule or vice versa). The switch was not explicitly signaled to the rat in any way, so that it had to be inferred by the pattern of unexpectedly unrewarded trials. Rats typically took 3-6 experimental sessions, or 60-100 trials, to acquire the rule when the switch was towards a visual cue-based trial, much less time (typically one session) for a switch towards a spatial orienting rule.

The rat prelimbic cortex cells showed a variety of behavioral correlates (Battaglia et al., 2006), for example, certain neurons were active preferentially at the beginning of the trial, or during the run on the arm, or at the end of the trial, in either reward-dependent or independent fashions. At the beginning of the trial (therefore prior to the animal's selection of a maze arm), some cells encoded the position of the intended arm choice. In this way, these cells were encoding a response relevant to either a visual cue-based or a spatial orienting rule.

If we analyze the activity of these cells from the viewpoint of their spatial correlates, we are presented with a picture that reflects this high degree of flexible encoding. Similar to the results of Jung et al. (1998), these cells did show spatial correlates, but not (even transiently) resembling a static map of an environment as is found in the

hippocampal formation and entorhinal cortex: for the most part, space is represented as a function of its role in the task. Figures 1B-E shows some examples of firing rate maps for spatially selective prelimbic cells recorded in the Y maze task. For example, Figure 1B shows a neuron with selective firing immediately after choosing the left (Figure 1B₂), but not right (Figure 1B₁), arm during reward site approaches. The low firing rate is characteristic of prefrontal principal neurons. Figure 1C shows an example of a cell firing selectively at the reward sites at the end of the left arm, perhaps associating the behavioral choice and a possible negative or positive outcome. Figure 1D depicts a cell with a similar response on the right arm. For most cells, spatial information is encoded, in combination with task phases and other behavioral variables: Figure 1E shows a cell that fired preferentially after arrival at the left reward site.

Moreover, after a contingency shift was imposed, the prelimbic cortex responded with dramatic changes in the activity correlate many of its cells: certain cells acquired, or lost, responses in specific task phases, either abruptly, on in a way that closely followed the changes in the rat's strategy (Wiener, et al., 2006). These shifts in response properties bear similarities with the dramatic modulation of behavioral correlates described below in accumbens neurons in rats performing task shifts, or after maze rotation (Shibata et al., 2001). Here, shifts were also found for the spatial correlates of activity. Figure 2 depicts examples of firing rate maps for prefrontal cortex cells recorded in sessions when the rat reached the performance criterion mid-session and the contingency rule was then changed. These cells with position selective responses demonstrate dramatic changes following the rule shift. Figure 2A shows a cell with a prominent response on the left arm before the shift (while this was under a spatial orienting left rule there were five visits to the right arm, and activity is shown only prior to rewards, not after.). This activity moves to the start arm after the shift. Figure 2B shows a cell that showed an increase of firing rate on the start arm after the contingency change. In Figure 2C there is a decrease after the contingency shift.

To summarize, we have shown here prefrontal responses that carry information about place, even though place *per se* is not considered to be the most important correlate of prefrontal cell activity. These extended representations, compared to the hippocampal, or entorhinal ones, are of little utility for the animal to precisely *locate* itself in an environment. They seem more adapted for *guiding* the goal-directed behavior of the rat, and encoding potentially relevant variables in the task providing candidate templates for learning new reward contingencies. No fine grained place-field response was found in the prefrontal cortex, for example covering only a restricted portion of one arm, although activity was observed at points with specific behavioral significance such as the decision point or goal sites. This may reflect the hippocampal input (from the ventral portion of the hippocampus) that contains only a rather coarse place representation (Jung et al 1994). The prefrontal cortex could select such 'relevant' input information based upon temporal relations between activity in its afferent regions (including hippocampus) and reward onsets. In some way the hippocampus and prefrontal cortex would be coordinated to permit the brain to compare rewards on successive types of trials (left/right, light/dark) and elaborate a new rule –perhaps with the participation of the striatum and its learning mechanisms described below. The ventral hippocampal input would then provide spatial information in a form particularly suitable for selecting among a limited number of paths

at successive crucial choice points. A reduced representation of the environment is all that is necessary while precise topographic localization would render computations unnecessarily complex (Trullier et al., 1997). It would be interesting to probe the same cells in a task situation where place (that is, identification of a given arm) has no particular relevance for reward acquisition, and see whether that selectivity is lost.

Last, we would like to point at a possible parallel between these prefrontal activity shifts and the way the hippocampus can *remap* or switch to a partially or completely different representation of an environment (e.g. Barnes et al., 1997; Leutgeb et al., 2005), prompted by new or conflicting environmental inputs or the creation of a different context. Since the evidence presented above does not support the view that the prefrontal cortex encodes a 'topographic map' of the environment, the word "remapping" is inappropriate. Nonetheless, it is intriguing that these two phenomena take place in structures so closely related to each other. Note that Wiener, et al (1989) showed that the behavioral correlates of hippocampal neurons changed from coding olfactory cue configurations to spatial position when the rats shifted between an odor discrimination task and a water search task in the same arena (see also Markus et al., 1995). Remapping in the hippocampus, whether caused by changes in the spatial context or by changes in the behavioral task, can be characterized as a transition between two spatial representations (or, in any event, representation that keep into account the relationship between stimuli and locations). Thus hippocampal activity shifts correspond to changes in the behavioral context of the organism. On the other hand, the prefrontal code changes in correspondence with changing contingencies, which require altering the way the animal responds to stimuli and direct its behavior. This incorporates hippocampal information, but also incorporates reward contingencies and the relation between behavior patterns and its impact on the internal state. A second type of shift we observed in prefrontal neurons occurred when the animal shifted its behavioral pattern, adapting to the new contingency rules. It seems likely that these two codes and their dynamics are not completely uncoupled, rather, that they interact in rather sophisticated way, representing a fascinating subject of research for the future.

5. Ventral striatal and hippocampal activity

The substrate of these cognitive processes is not limited to the prefrontal cortex and hippocampus, rather it is distributed in a network including structures intimately connected to them, such as the amygdala, the striatum, particularly the nucleus accumbens, as well as midbrain dopaminergic structures. The striatum is the entry point to the basal ganglia, an ensemble of subcortical nuclei organized in parallel loops receiving inputs from different cortical areas including the hippocampal system and recurrently sending processed signals back to the prefrontal cortex through the mediodorsal thalamic nucleus (Alexander and Crutcher, 1990). It has been proposed that this architecture favors the selection of a motor or cognitive (decision) response on the basis of the present context (sensory, spatial and/or motivational) (Graybiel, 1998; Redgrave et al., 1999).

The input nucleus to the basal ganglia, the striatum, contains large segregated territories corresponding to these loops (Uylings et al., 2003). To broadly summarize, all

of the neuron groups in a given territory can be characterized by the prefrontal subregion and cortical regions they receive input from. It is informative to contrast the dorsal striatum (putamen and dorsolateral caudate) which primarily receives sensorimotor inputs and its counterpart the nucleus accumbens (in ventral striatum) which receives hippocampal and amygdalar inputs (e.g. Pennartz et al., 1994). Other intermediate subdivisions (between dorsal and ventral) correspond to different modalities, with unique convergences of diverse cortical inputs arriving in distinct foci.

Prescott et al. (1999) proposed that the basal ganglia carry out action selection which can be considered as a type of decision making. They cited the anatomical architecture as well as neurophysiological data implicating this system in motor decision-making (e.g., Guller et al., 2002). However, the respective roles of the prefrontal cortex and the striatum in decision making is not clear. Some authors suggest that they are in competition for the control of behavior, with the striatum controlling behavior requiring simpler decisions than the prefrontal cortex (Daw et al., 2005). Other authors propose that the striatum and the prefrontal cortex are cooperating together, the striatum taking into account candidates of possible responses 'biased' by the prefrontal cortex and making the final decision (Redgrave et al., 1999). However Pasupathy and Miller (2005) recently showed in electrophysiological experiments in monkey that while both the prefrontal cortex and the striatum adapt their neural responses with learning, the prefrontal cortex adapts more slowly than the striatum, and the former is more correlated to changes in the animal's behavior. This is consistent with the hypothesis of the basal ganglia gating the prefrontal cortex to bias the decision process taking place cortically (Frank et al., 2001).

Learning to adapt these selections could involve dopaminergic signals (Schultz et al., 1997). Recordings of dopaminergic neurons in monkey ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) fired at higher rates when an unexpected reward was encountered, but the response vanished as the reward became predictable, and was inhibited when an expected reward was omitted (Schultz, 1998; Schultz et al., 2000). This supports the idea that dopamine carry reward prediction error signals (Schultz et al., 1997). LTP and LTD have been observed at corticostriatal synapses after exposure to dopamine (Centonze et al., 2001; Reynolds et al., 2001) supporting the hypothesis that these signals are implicated in learning processes taking place in the striatum (Houk et al., 1995). The dorsal and ventral striatal territories mentioned above receive dopaminergic input from distinct zones, the ventral tegmental area and the pars compacta of the substantia nigra respectively (Haber et al., 2000; Joel and Wiener, 2000; Thierry et al., 2000; Ikemoto, 2002). These data suggest that dopamine release in the dorsolateral striatum would affect the learning of stimulus-response associations, permitting the establishment of a repertory of stereotyped, habitual and automatic actions (Houk et al., 1995; Graybiel, 1998 ; Miyachi et al., 2002). However, the role of the ventral striatum in learning is less clear. Hypotheses include driving stimulus-response learning in the dorsal striatum (Daw et al., 2006), learning to select trajectories or routes based on hippocampal afferences (Arleo & Gerstner, 2000), learning to select among navigation strategies (Girard et al., 2005), or learning to integrate amygdalar afferences to drive motivationally modulated goal-directed behavior (Dayan & Balleine, 2002). So much remains to understand about the precise involvement of the ventral striatum in behavior and

cognitive function.

While these ventral striatal regions have attracted our interest because of their rich interconnection with the hippocampal formation they are also well placed to play an important role in cognitive functions by virtue of their inputs from prefrontal cortex and amygdala, and their projections to premotor and neuromodulatory areas as well as to basal ganglia loops transiting through mediodorsal thalamic nucleus back to prefrontal cortex. In the rat, the caudal dorsomedial striatum receives bilateral inputs from lateral entorhinal cortical layers III and IV (McGeorge and Faull, 1989) – the former region also has head direction cell activity (Wiener, 1993). The nucleus accumbens receives inputs from medial and lateral entorhinal cortex layers II, III, IV and VI (therefore directly acquiring head direction and path integration information, the latter in the form of ‘grid cells’; Hafting et al. (2005); Sargolini et al. (2006). Furthermore, the nucleus accumbens shell receives a topographic projection from hippocampus via the subiculum, with the ventrolateral and rostral shell receiving dorsal (septal) hippocampal inputs and caudal and medial shell receiving ventral (temporal) hippocampal inputs (see Groenewegen et al., 1996). Since dorsal hippocampal neurons have a higher incidence of place correlated responses and smaller firing fields (Jung et al., 1994), it might be expected that this trend would be reflected in the response properties of neurons of the respective parts of the accumbens shell. This is however difficult to ascertain since the shell, named for its distribution as a thin (300-500 micron) layer surrounding the accumbens core, is rather difficult to access, particularly in the ventrolateral part.

6. Experimental data comparing ventral striatal and hippocampal responses

Our previous studies have examined the simultaneous activity of hippocampal and ventral striatal neurons in rats performing spatial orientation tasks. In one series of experiments, recordings were made in rats shuttling between one of two pairs of reward dispensers, each located on diametrically opposite edges of a circular platform (the sites were located at northeast, southeast, southwest and northwest positions). While hippocampal neurons demonstrated place (or, in a small subset of neurons, position-independent behavioral) correlates, ventral striatal neurons demonstrated selective responses for particular task related behaviors (Shibata, et al., 2001; also see Korshunov et al 1996; Wiener, 1996). Many of these responses occurred immediately prior to reward release. Interestingly these responses were often spatially modulated, that is, they were greater prior to arrivals at certain reward sites. While the identity of the preferred sites varied among neurons, there were always at least two. Thus this activity was distinct from place responses of hippocampal neurons which were selective for single sites only (Trullier, et al 1999). When the circular platform was rotated by 90°, or the animals were required to shift between cue approach and spatial mapping strategies, the place responses of the hippocampal neurons invariably remained stably fixed relative to the experimental room (see Figure 3). However the ventral striatal neurons underwent dramatic shifts in the amplitude of the responses following task contingency changes (see Figure 3). Thus we deduced that this task strategy selectivity was *not* a result of the hippocampal input. However the spatial modulation of the ventral striatal responses could well have derived from the hippocampal system inputs to this region.

In a subsequent study we found significant cross-correlations between simultaneously ipsilaterally recorded accumbens shell and hippocampal neurons in rats performing in a four arm (plus) maze (Tabuchi, et al., 2000). The cross-correlations were preferentially observed as the rats arrived at the reward arms, rather than after reward delivery or during arrivals at the maze center (see Figure 4). This points to a task-related modulation of the relation between hippocampal and accumbens shell activity. The most frequently observed latency for these cross-correlations was that of the hippocampal neuron discharging 10-20 msec prior to the accumbens shell neuron. This corresponds precisely to the latency of evoked potentials in the accumbens shell following electrical stimulation of the hippocampus (e.g., Albertin, et al., 2000). It is considered unlikely that single hippocampal neurons were monosynaptically evoking action potentials in single accumbens neurons for various reasons (such as the low peak firing rates of individual hippocampal neurons and the diffuseness of its axonal arborizations). However another explanation derives from observation of the timing of significant cross-correlations in our entire sample of recordings. As shown in Figure 5, the peak incidences of cross-correlations occurred at -360, etc (again accumbens neuron discharges are shown at time zero, and hippocampal CCR peak incidences are distributed along the x axis). The latencies between the successive peaks is 120 msec, corresponding to the theta rhythm. This suggests then that the correlated activity between these structures occurs preferentially during the theta rhythm. This correlates nicely with the relatively few CCRs following reward delivery when the rat was immobile and no theta would be expected. But this cannot account for the greater incidence of CCRs for runs toward the goals rather than toward the center. One possible explanation is that the hippocampal input to accumbens was gated off during this post-reward period, perhaps permitting the accumbens to more effectively attend to other inputs, or internal processing.

This plus maze task was designed to address the controversial issue of how goal sites are represented in the hippocampo-striatal system. Increasing evidence is becoming available about an effect of goal location on the hippocampal activity, for example in the form of a clustering of place field around the goal location (Hollup et al., 2001), a prospective encoding of the goal selected by the animal (Lee et al., 2006; Hok et al. 2007) or subtle, transient remapping effects (Jackson, 2006). The issue was raised in a neural network model of Burgess, et al (1994) employing hippocampal place activity for navigating toward goal sites. These authors hypothesized the existence of ‘goal cells’ which would discharge from the moment the goal was selected until the model avatar arrived at the goal site. Since the ventral striatum was proposed to be a limbic-motor interface (Mogenson et al., 1993) this area was recorded in our study. We found neurons that discharged along trajectories between task-relevant points in the plus maze. For example some neurons discharged action potentials from the instant the rat departed from the four reward sites until it arrived at the center of the maze. This was not simply a motor correlate since these neurons did not discharge during outward trajectories on the arms. In contrast other neurons discharged preferentially during the outward, but not inward trajectories. The latter group showed preferential firing for certain subsets of maze arms (see Figure 6). However, as found in Shibata et al. (2001), no striatal neurons

were selective for only a single arm in the manner of hippocampal neurons. Thus these neurons could well mediate goal directed spatial orienting behaviors based upon hippocampal input signals. This striatal activity could act to implement the prospective coding of hippocampal neurons since the latter do not continue to discharge until the animal arrives at the goal site. Note also that recently Hok et al. (2005) have shown comparable responses in the rat medial prefrontal cortex, which also projects to the striatum.

7. Hippocampal/cortical interaction and memory.

Sleep has been recognized as fundamental for the successful consolidation and storage of recently acquired memories. Brain activity during sleep (and behavioral inactive states) is highly structured, carries informationally relevant content and it is likely to be a crucial player in such consolidation processes. It has been shown in the rat hippocampus that several features of activity configuration taking place during a behavioral task are preserved during the subsequent sleep (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Lee and Wilson, 2002; Battaglia et al., 2005b) decaying during the first half hour of sleep after the task (Kudrimoti et al., 1999). In humans, the same hippocampal areas active during learning of a navigation task are also active during sleep, in a way that covaries with the improvement in navigation performance, as shown, for example, by the functional imaging studies of Peigneux et al., (2004). Outside the hippocampus, memory trace-carrying reactivation was also found in the rat and monkey neocortex (Hoffman and McNaughton, 2002; Ji and Wilson, 2007) and in the rat striatum (Pennartz et al., 2004).

The communication between the hippocampus and the neocortex is an important component of such mechanisms taking place during sleep: Marr (1970,1971) was the first to theorize that hippocampal memory reactivation during sleep has the role of orchestrating the neocortical activity so that a cortical memory trace can be formed, encompassing several different regions (for a review, see McNaughton et al., 2002). In fact, human neuropsychological data suggest a gradual transition of memories from an hippocampal dependent state to an hippocampal independent (presumably neocortically supported) state (Dudai, 2004). Activity-related gene expression techniques also confirmed that, as memories become more and more remote, the neocortical role in maintaining memories increases and the hippocampal role decreases (Bontempi et al., 1999; Ross and Eichenbaum, 2006).

These findings, taken together, strongly suggest that the hippocampus and the neocortex should exchange information during sleep. This communication may be mediated by the distinctive patterns of brain activity observed during sleep. During slow wave sleep, in particular, the neocortex alternates between states of generalized high activity (“up” states) and periods of global neural silence (“down”-states see e.g. Steriade and Buzsaki, 1990; Cowan and Wilson, 1994; Petersen et al., 2003). Up and down-states repeat themselves with a period of hundreds of milliseconds up to seconds (Steriade et al., 1993) in anesthetized and natural sleep states, and organize faster oscillatory phenomena such as sleep spindles (Amzica and Steriade, 1998). Up-states seem to be the result of the action of recurrent cortical excitation (Sanchez-Vives and McCormick, 2000) and inhibition (Timofeev et al., 2001).

The hippocampus shows a very different pattern of activity in slow-wave sleep: most of activity is concentrated in brief (50-100 ms), burst-like episodes of activity, breaking a state of almost complete silence with little regularity: the *sharp waves*. Sharp waves are probably generated by positive feedback in the recurrent collaterals of the CA3 hippocampal subfield. In CA1, they are accompanied by a 150-200 Hz oscillation in the local field potential (*ripple* oscillations; Buzsáki et al., 1992; Csicsvari et al., 2000). Sharp waves are a potent influence on the cortical activity in the entorhinal cortex (Chrobak and Buzsáki, 1994, 1996), and are correlated to spindle oscillations in the prefrontal cortex (Siapas and Wilson, 1998). Sirota et al. (2003) showed that cortical oscillations in somatosensory cortex and hippocampal activity are related on the short time scale: sharp waves are correlated with the hippocampal activity 50-100 ms earlier. They also showed that spindle and that spindle and delta oscillations in the cortex affect hippocampal activity, with hippocampal synaptic inputs phase-locked to the cortical oscillations, possibly influencing the generation of sharp waves, showing that the communication between the hippocampus and the neocortex can be bi-directional (see also Hahn et al., 2006).

Because hippocampal memory trace reactivation is strongest during sharp waves (Kudrimoti et al., 1999) it is attractive to think that sharp waves represent an input from the hippocampus to the rest of the brain, powerful and synchronized enough to orchestrate reactivation in the brain. In fact, the ventral striatal neurons that are modulated by hippocampal sharp waves show a higher degree of reactivation than their peers (Pennartz et al., 2004).

Using an extensive array of electrodes covering a large portion of the rat neocortex, Battaglia et al. (2004) demonstrated that up and down states are characterized by a large degree of coherence across the entire neocortex, with virtually all cortical neurons shutting down during a down state and global simultaneous activation during up states. Moreover, by looking at the sharp wave-triggered average of the global cortical activity, they were able to show that there was a probabilistic relationship between the occurrence of sharp waves and the transitions from down to up states. Figure 7A-D reproduces the sharp wave triggered averages. Both in periods of high delta/slow EEG activity (probably corresponding to deeper sleep) and in periods of low delta/slow EEG activity (probably corresponding to lighter sleep or quieter wakefulness) Cortical activity showed a peak for approximately the duration of the sharp wave, shown in the expanded scale in Figure 7 B,D. The sharp wave triggered averages also showed a slower trend, with the overall cortical activity before a sharp wave being on average smaller than after the sharp waves. Interestingly, in high delta periods, the cortical activity shows a relatively flat baseline up until the sharp wave, then a sudden increase, and a decline in the next ~10 s (Figure 7A). A different picture emerges from the low-delta EEG periods: here the activity declines in the 10s preceding the sharp waves, to return to baseline at the time of onset of the sharp wave, and remaining rather constant thereafter (Figure 7C). This picture is compatible with the idea that a fraction of the down to up transition correspond with the times of the sharp waves (on the time scale of seconds): in high delta periods, the up states are much shorter than the up states, (causing the decline visible after the sharp wave in Figure 7A), whereas the converse is true in low delta states (corresponding to a more excited brain state). In this functional regime, down states are rarer, shorter occurrence, whose transition into up states is probabilistically related to sharp waves,

yielding the trough in the sharp wave triggered average prior to the sharp wave in Figure 7C.

A 10s excerpt (Figure 7E) from our medial prefrontal recordings during sleep shows an example how this probabilistic relationship is expressed in the time course of prefrontal and hippocampal activity. Here, the clustering of hippocampal sharp wave events after prefrontal down-states, indicated by downward – positive – fluctuations in the prefrontal local field potentials (solid line) and corresponding drops in the global prefrontal unit activity (dashed line).

These lines of evidence point at an important correlation between the major collective phenomena in the dynamics of the neocortex and the hippocampus during slow-wave sleep, respectively, up/down states and sharp waves. The interaction is probably bi-directional: the results from stimulation experiments we reviewed in the section 3 indicate that the hippocampal activity can measurably affect the prefrontal cortex; on the other hand, the results by Sirota et al. (2003) and Hahn et al. (2006), for example, suggest an influence of cortical up states on the hippocampus. A theoretical possibility is that this reciprocal action is at the basis of a functional loop which subserve memory maintenance and consolidation: a hippocampal sharp wave may influence cortical activity in initiating an up state, and instating the reactivation of a memory item in the cortex. In turn, the up state may affect the activity in the subsequent hippocampal sharp wave, helping the hippocampus to maintain continuity of information processing in the silent period between sharp waves.

8. Conclusions

We presented here a brief overview of the neural representations in the rat prefrontal cortex and striatum in spatial tasks. While both structures seem to be strongly affected by position information (and possibly hippocampal input), the nature of their representation is deeply different from the map-like structure of hippocampal system activity. Both structure seem to be affected by combinations of factors such as task phase, current motor behavior, reward or lack thereof, and task relevant locations. The prefrontal cortex seems to be sensitive to the task-relevant cues, and exhibit a large deal of flexibility in changing its response characteristics when the reward contingency is changed, in accordance with its proposed role in attentional shifts. Spatial modulation of activity is often present in these two structure, but most likely in conjunction with some other influence, such as the factors mentioned above. When present, the wide scale of the spatial modulation is more reminiscent of the responses in the ventral hippocampus (where the hippocampal projections to the prefrontal cortex originate).

It seems to us that these data suggest the importance of the interactions among structures more implicated in self-location (such as the hippocampus), and structures associated with planning, behavioral selection and decision (the prefrontal cortex, the striatum). Such interactions seem to be relevant also during sleep, suggesting a role for coordinated hippocampal/cortical/striatal activity for memory consolidation. All these data, it seems to us, represent an invitation to pursue more and more in the future the study of multiple brain structures and their interaction, which may prove to be crucial for our understanding of the relationship between brain activity and behavior.

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Figure Legends

Figure 18-1. *A)* A schematic depiction of the contingency rules used for the Y-maze task and recording of prelimbic cortex neurons. The rat started each trial on the “departure” arm (at bottom) and had to select among the other two arms. In the *spatial orienting* rules, the rat had to always choose the right arm (spatial orienting right rule, left column) or the left arm (spatial orienting left rule, not shown), regardless of which arm was illuminated. With the *visual cue-based* light rules (middle column), the rat had to direct towards the illuminated arm. With the *visual cue-based* dark rule (right column), the rat had to choose the unlit arm. *B1, B2)* are occupancy-normalized firing rate maps for a PL neuron for trajectories from the start arm to the goal arm for right and left arm choices respectively. Activity was significantly different between left and right arms in the 2.5 s period following trial start (Kruskal-Wallis $p < 0.002$, cell 150712-1-7). *C)* A PL neuron with selective firing on the left arm for the 2.5 s period prior to and following reward site arrival (Kruskal-Wallis $p < 0.0001$; cell 201227-1-5). *D)* From the same tetrode as the neuron in C, this neuron fired selectively on the right arm (prior to and after reward site arrival Kruskal-Wallis $p < 0.006$; cell 201227-1-16). *E)* Another PL neuron with spatial selectivity (200111-2-6). There was a significant left-right difference in the post-arrival period (Kruskal-Wallis $p < 0.0001$). This difference does not correspond to a spatial asymmetry of rewarded and unrewarded trials (not shown). Scale is in impulses per second.

Figure 18-2. (A-E) Occupancy-normalized firing rate maps for prelimbic neurons recorded on the Y-maze task of Figure 18-1. The firing rate map obtained for the periods up until the contingency switch and thereafter are depicted, respectively, to the left and the right of each row. The contingency rule is indicated above each panel; the number corresponds to the order of presentation of this rule in the recording session. In A, there was activity on the left arm for the visual cue-based dark rule task. This disappeared when the contingency was changed to the spatial orienting left rule (A2). Note that this activity was not correlated with whether trials were rewarded (correct) or not. In B, the shift in contingency gave rise to an increase in activity in the start arm. In C, there was a change in spatial firing after the contingency shift. This is difficult to see in the firing rate maps because of the low firing rates of these neurons. This is more evident in C1' and C2', where the trajectories are shown in *gray* and locations where the neuron discharged are shown as *red points*. There is more activity at the end of the right arm in the spatial orienting right rule (C1) than the visual cue-based light rule.

Figure 18-3. Comparison of striatal and hippocampal recordings in rats alternating between performing beacon approach and place navigation tasks on the same platform

(overhead view shown *in inset in left histogram*). The rats had to shuttle between diametrically opposite reward sites. In the beacon approach task (B) the two active reward sites were cued by lights at the reward sites, while in the place navigation task (P) only northeast and southwest sites were rewarded – and these were unmarked. The platform was rotated after 5-8 trials as a challenge. Adjacent to the raster plots, B or P indicates the task and the number indicates a rotated position of the platform – different task configurations (*epochs*) are separated by horizontal bars. *Left*) Pre-reward response in a neuron of the ventral shell of the nucleus accumbens. The cell activity increased gradually as the animal arrived at the reward box, then stopped suddenly as the drop of water was delivered (at time zero). The cell did not fire at all during visits to the northeast or northwest corners, and had a maximum firing rate of only 4 impulses/s as the animal arrived at the southeast corner (not shown) - thus this prereward correlated firing was spatially modulated. This neuron showed significant changes in firing rate (arrows in right column) after changes in the task contingency and after a different reward box was rotated into this southwest corner. *Right*) Hippocampal place responses show no such sensitivity to task configuration changes. The inset shows a spatial plot of this activity. The green lines indicate the trajectories of the rat while the red squares show that the neuron fired when the rat left the reward box in the upper right corner. In the raster plot (synchronized with arrivals at the southwest reward site, this spatial response remained unchanged even after the animal was required to change its orientation strategy to place navigation. Adapted with permission from Shibata et al 2001 and Trullier et al, 1999.

Figure 18-4. In recordings from a rat performing a plus maze task, incidence of significant peaks in cross-correlations (CCR) histograms computed for three different task-related behaviors in a group of 18 cell pairs selected for having significant peaks (>3.0 SD of confidence limits) corresponding to the latency of the hippocampus to accumbens pathway (10-20 ms). For analyses 1 s observation periods were selected before or after three task events: arrival at reward sites, departure from reward sites and center arrivals. Note that there are fewer peaks in analyses for center arrivals than for reward box arrivals or departures, and a greater number of peaks are found for latencies corresponding to connections from hippocampus to accumbens. Reproduced with permission from Tabuchi et al, 2000.

Figure 18-5. Incidences (*counts*) of significant peaks in CCRs of 154 hippocampus-nucleus accumbens cell pairs for analyses of 1-s observation periods prior to the instant that the rats arrived at any of the boxes. The histogram shows the number of cell pairs with significant peaks of hippocampal activity in a time window ranging 300 ms prior to and after the occurrence of each nucleus accumbens action potential (bin width, 10 ms). Most frequently occurring peaks were at -20 ms (hippocampus firing prior to accumbens) and at intervals of 100–110 ms, corresponding to the hippocampal theta rhythm. Reproduced with permission from Tabuchi et al, 2000.

Figure 18-6. Goal coding in ventral striatal neurons. *Top row*) This ventromedial caudate neuron discharged as the rat walked from the maze center to the reward sites at the ends of the arms. In these overhead views of the plus maze, cell firing is indicated by *red*

crosses and position samples with no firing as *blue dots*. This activity is spatially modulated: ANOVA post-hoc tests ($p < .05$) confirmed that the firing rate during the period from 1.0 to 0.5 seconds prior to arrival at boxes 1 and 2 is significantly greater than that for box 4 and also that the rate during approaches to box 2 was greater than for box 3. (Box 1 is to the lower right and numbering continues counter-clockwise.) *Bottom row*) Another ventromedial caudate neuron continuously active during displacements to the goal boxes but not the maze center. This activity was also spatially modulated, but with a different profile than the neuron above. Adapted with permission from Mulder et al 2004.

Figure 18-7. A) Peri-event time histogram (PETH) of cortical population activity during periods of identified global oscillations in the delta/slow range, centered on hippocampal sharp wave events (error bars = SEM; bin size, 100 ms). B) Same PETH, with an expanded scale (bin size, 20 ms). C) Sharp-wave-triggered PETH (bin size, 100 ms) of cortical firing during periods in which oscillations in the delta/slow range were absent. D) Same PETH shown on an enlarged scale (bin size, 20 ms). E) Recording of prelimbic cortex local field potentials (solid black line, depicted negative-up) and global instantaneous unit activity (gray dashed line), and hippocampal sharp wave/ripple events (inverted triangles). Cortical down-states were evident in the LFP trace (indicated by arrows), with successive transition to up-states. A-D adapted with permission from Battaglia et al, 2004; E from Battaglia FP, Khamassi M, Peyrache A, Douchamps, V, Tierney P & Wiener SI (unpublished results).

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Figure 18-1

A

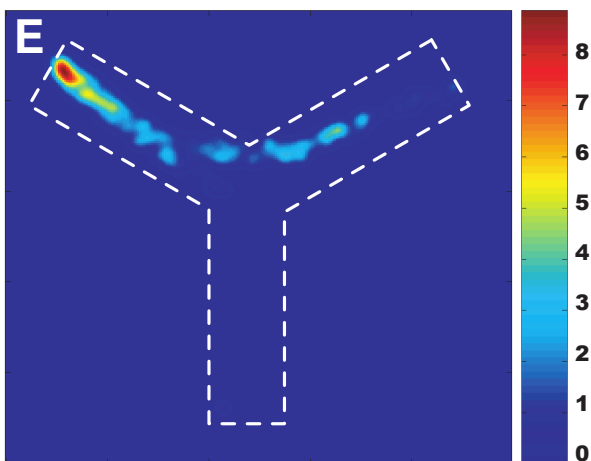
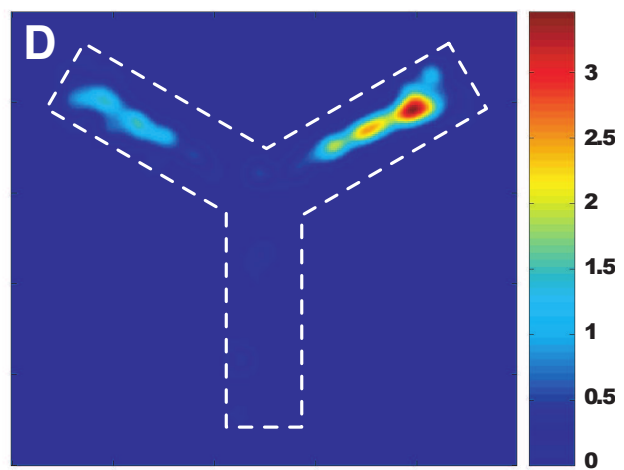
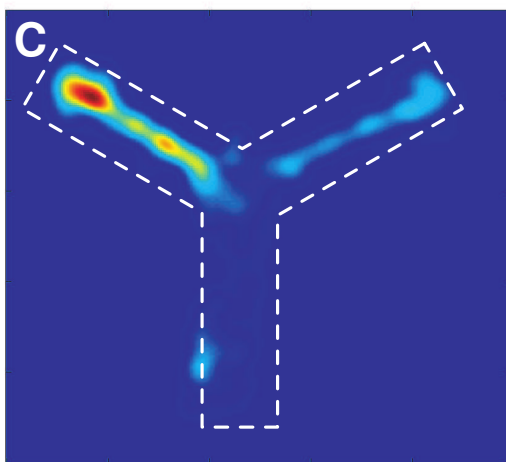
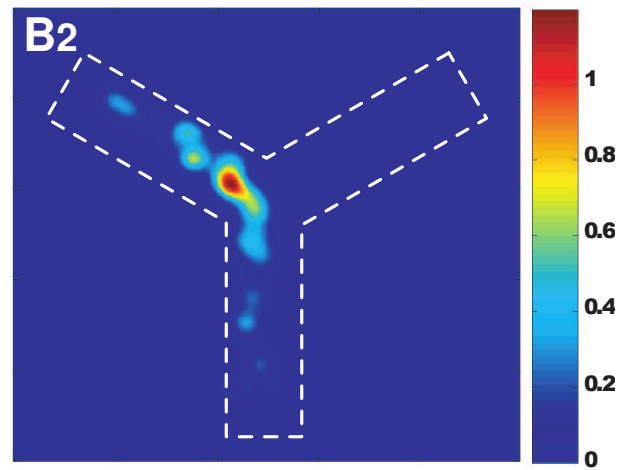
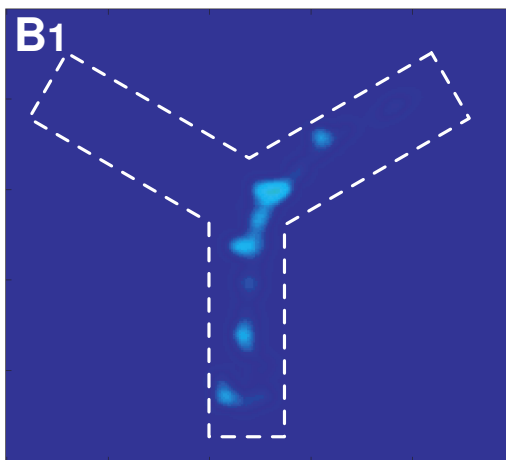
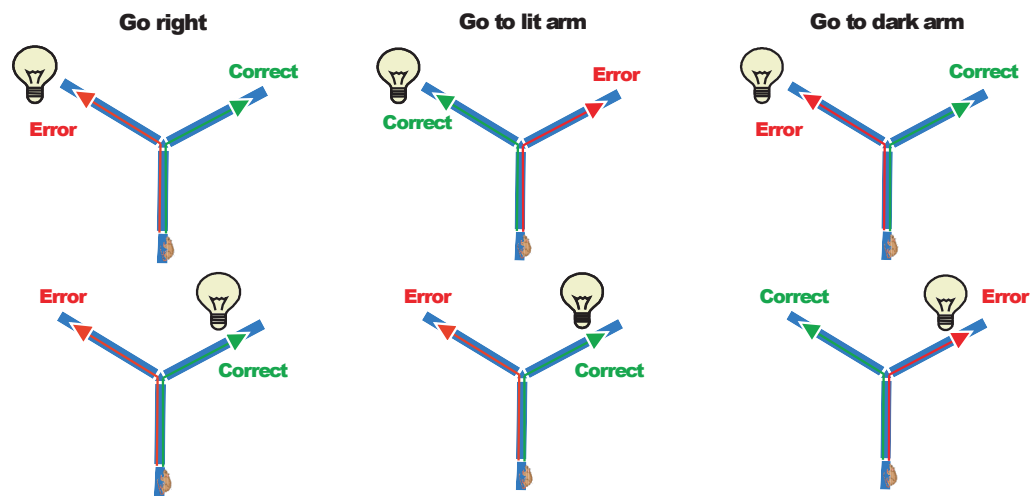


Figure 18-2

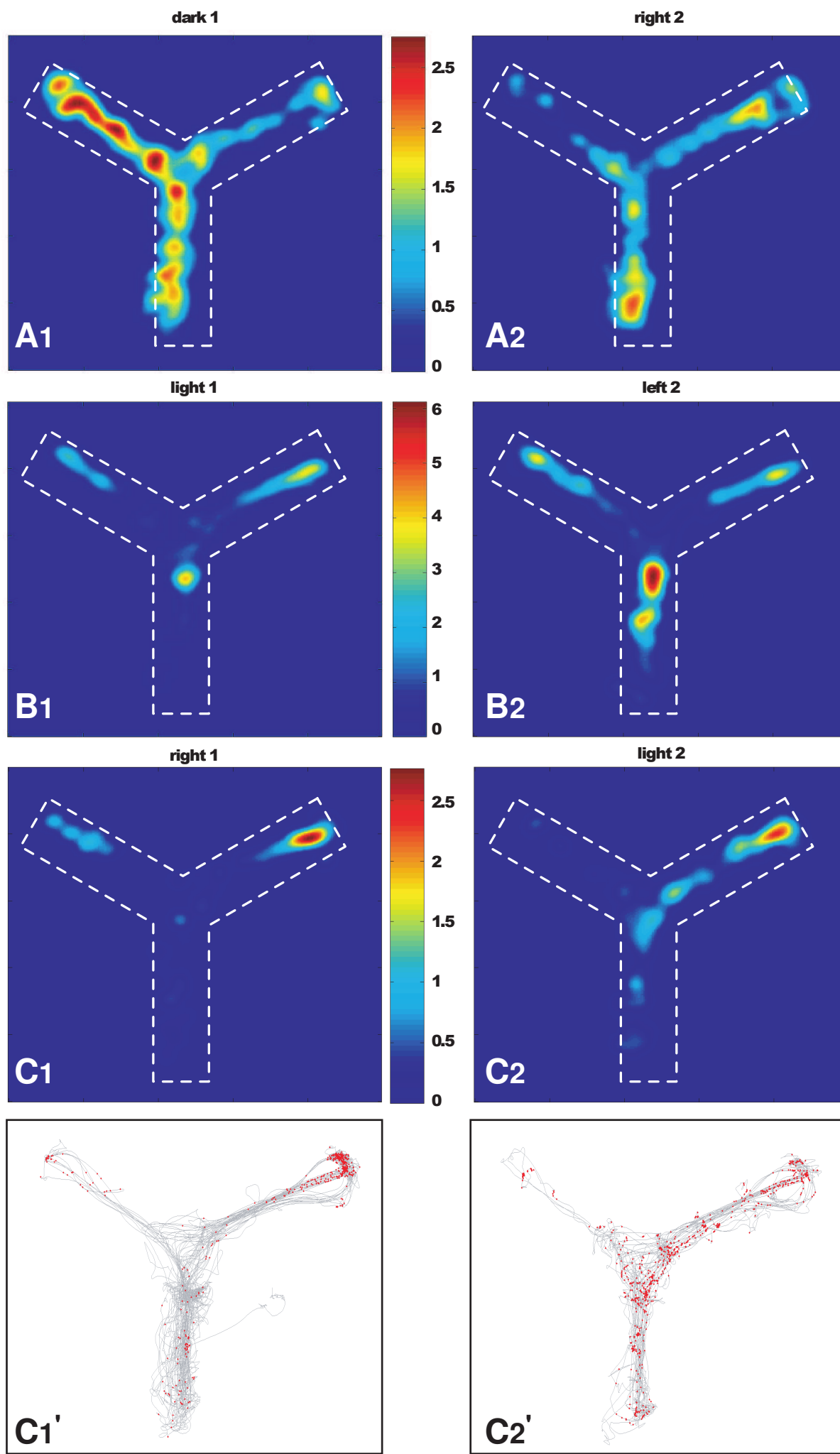


Figure 18-3

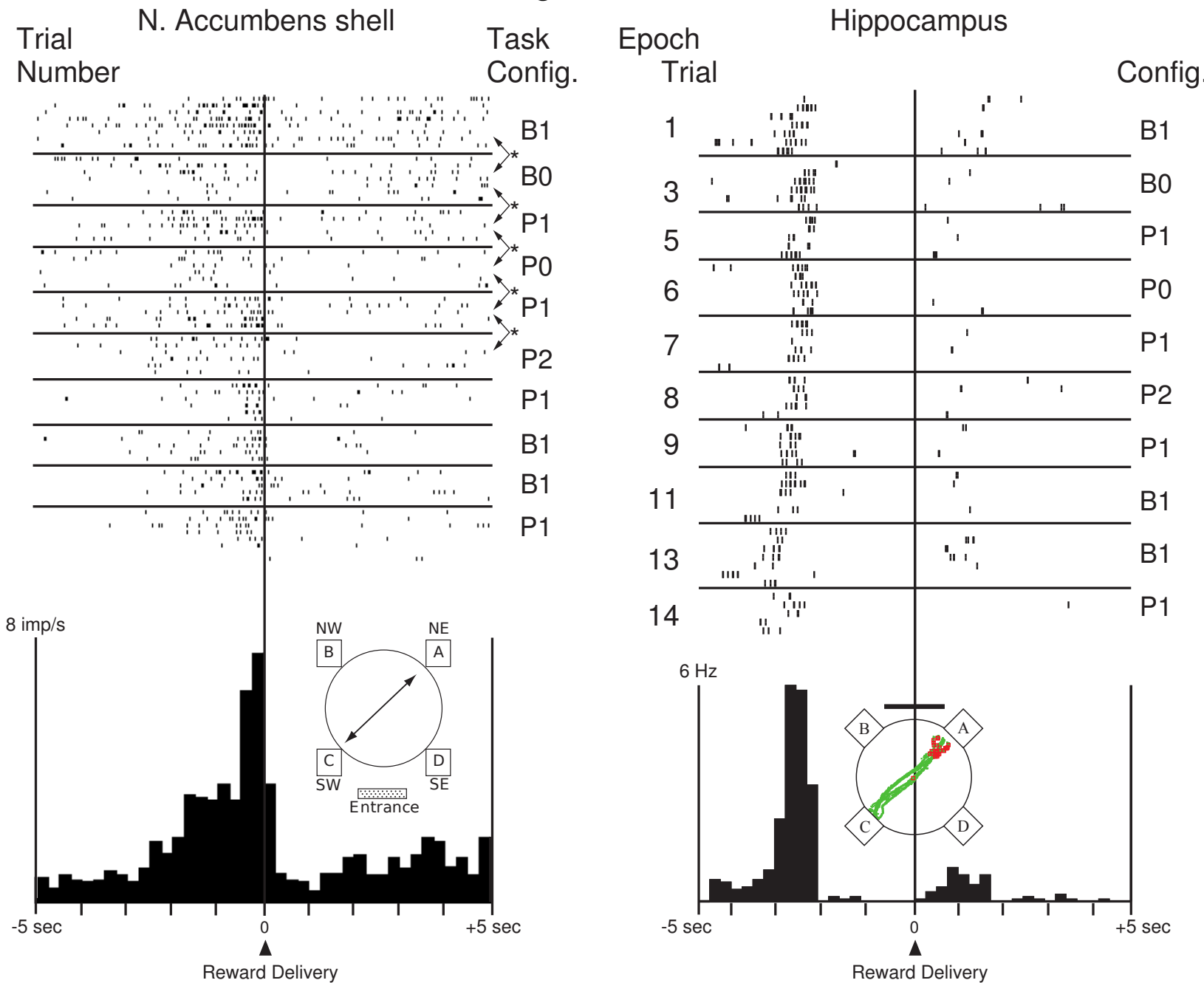


Figure 18-4

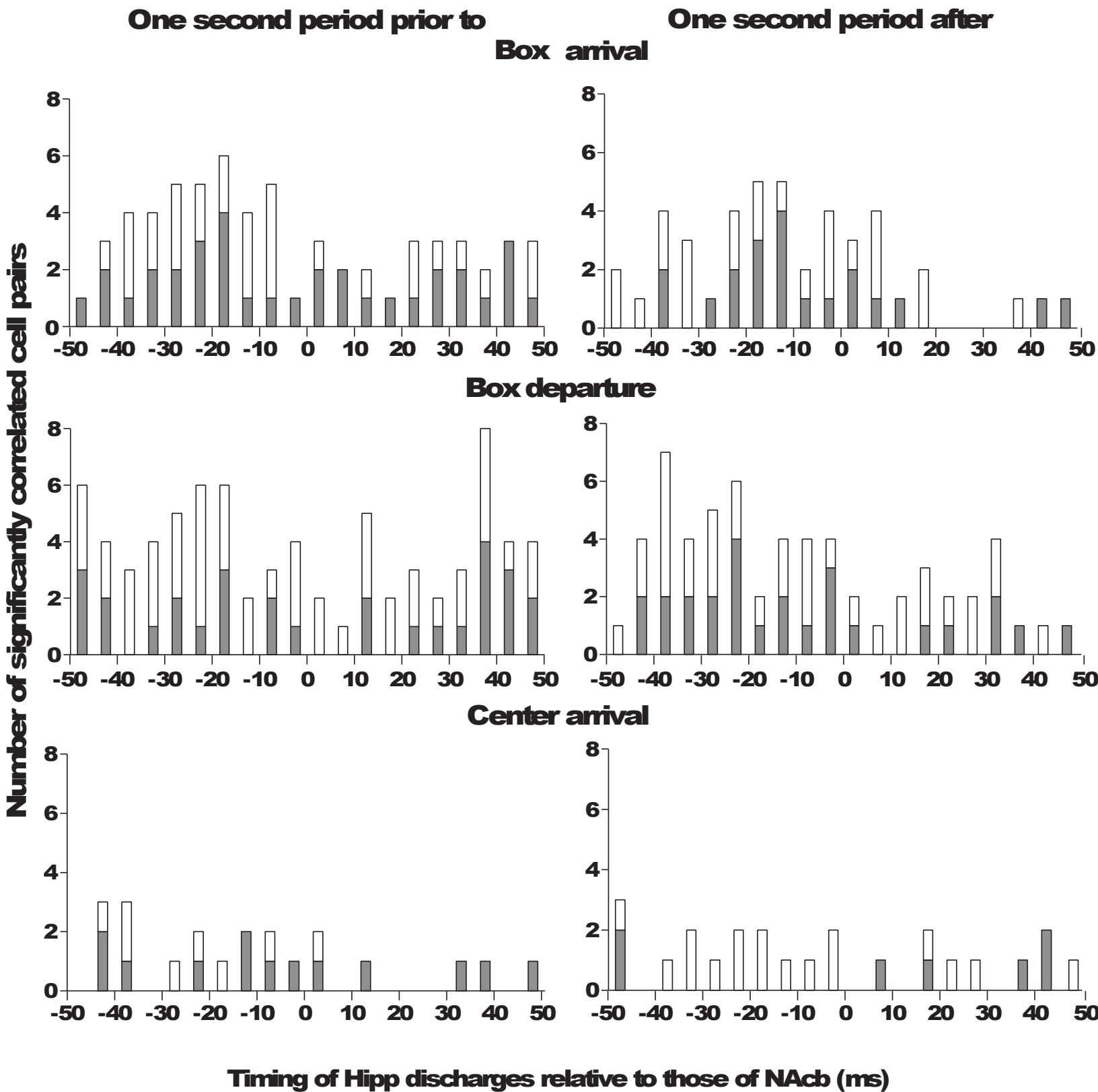


Figure 18-5

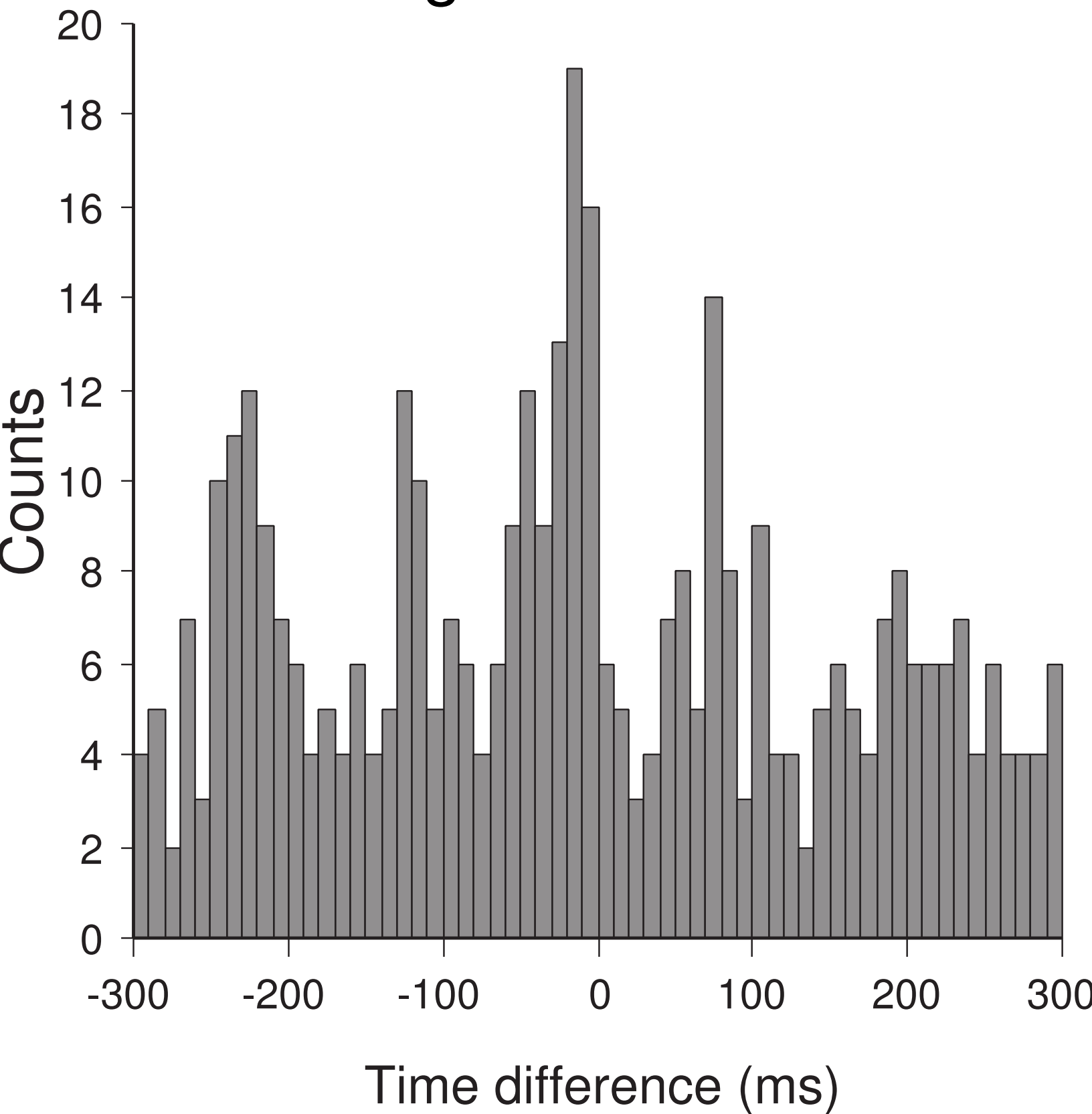


Figure 18-6

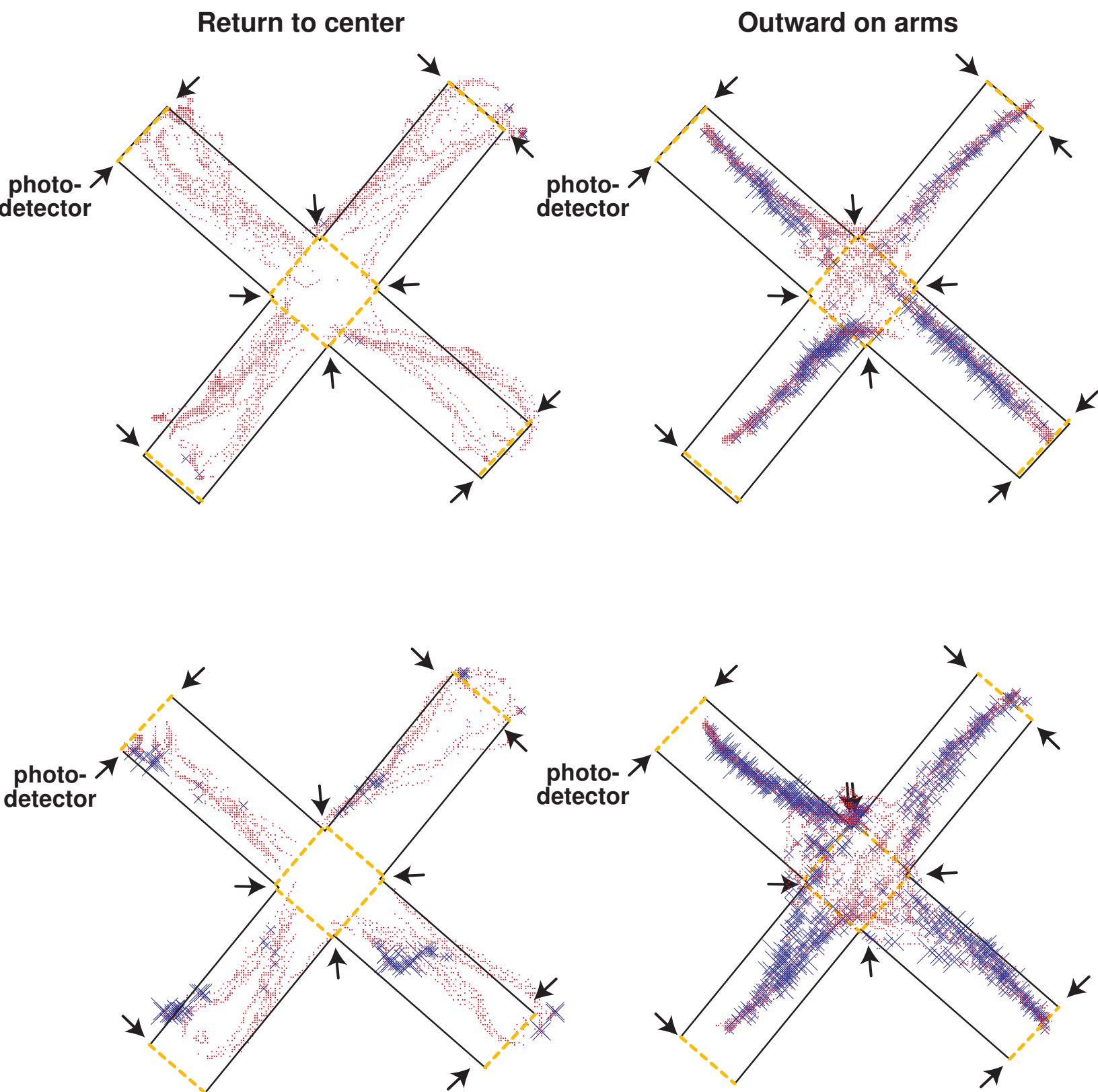


Figure 18-7

