GOAL-DIRECTED DECISION MAKING

COMPUTATIONS AND NEURAL CIRCUITS

EDITED BY
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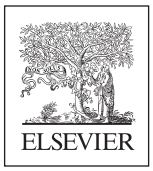

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CHAPTER 6

Goal-Directed Sequences in the Hippocampus

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Humans make goal-directed decisions every day. New data suggest that other mammals also make goal-directed decisions. Current theories hypothesize that goal-directed decisions arise from search processes through imagined forward models by which we work out the consequences of specific actions then choose from among those actions based on the utility of the outcomes (Niv, Joel, & Dayan, 2006). In this chapter, we will review the processes that underlie goal-directed decision-making in mammalian brains and make the case that the hippocampus is a key component of the imagination process. First, however, we will need to address the question of imagination because if you need imagination for goal-directed decision-making and nonhuman animals make goal-directed decisions, then we need to determine what imagination is, neurally, so that we can measure it in nonhuman animals.

In humans, the term *episodic future thinking* refers to the capacity to imagine an autobiographical experience that happens in the future (Buckner & Carroll, 2007). Episodic future thinking engages the same neural mechanisms as remembering past experiences (Addis, Wong, & Schacter, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007; Schacter et al., 2012). The fact that recall of past events is fragile (Talarico & Rubin, 2003) and varies depending on the presently available cues (Loftus & Palmer, 1974) suggests that remembering past experiences, like imagining future outcomes, entails flexibly retrieving previously stored information and recombining that information into an imagined situation. Studies involving aging populations (Schacter, Gaesser, & Addis, 2013), amnesiacs (Cole, Morrison, Barak, Pauly-Takacs, & Conway, 2016; Hassabis, Kumaran, & Maguire, 2007; Kurzcek et al., 2015; Race, Keane, & Verfaellie, 2011; Tulving, 1985; Zeman, Butler, Muhlert, & Milton, 2013), patients with Alzheimer's disease (Haj, Antoine, & Kapogiannis, 2015; Irish & Piolino, 2016) and prefrontal lesions (Ramussen & Bersten, 2016) all show a reduction in both remembering the past and imagining the future. Imaging studies have shown that a similar neural network is activated during episodic future thinking and remembering past experiences, including the medial temporal lobe, retrosplenial cortex, medial prefrontal cortex (mPFC), and lateral temporal and parietal regions (Addis et al., 2007; Hassabis, Kumaran, Vann, et al., 2007;

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Schacter, Addis, & Buckner, 2007). Additionally, the ventromedial prefrontal cortex may facilitate access to the conceptual knowledge of a scenario necessary to simulate an episodic event, as well as the valuation of these events (Bonnici et al., 2012; Kumaran, Summerfield, Hassabis, & Maguire, 2009; Lin, Horner, Bisby, & Burgess, 2015; Peters & Buchel, 2010).

Theoretically, planning requires the ability to predict consequences of actions and outcomes, and thus requires a model of the world, including both a categorization of the states of the world and the transitions between those states. In reinforcement learning models, determining action policies through planning is termed "model-based decision-making" because of its dependence on a model of the world (Niv et al., 2006; Sutton & Barto, 1998).

Although they cannot demonstrate it linguistically, behavioral observations and neural recordings suggest that rodents are capable of developing these models of the world. Tolman (1948) termed this a "cognitive map." Tolman was led to this conclusion through the observation of latent learning: In an early study by Tolman and Honzik (1930), rats were trained in a complex maze full of turns and dead ends. The end of the maze contained food reward that one group of rats received after reaching the end of the maze; the second group of rats had a barrier between them and the reward and were taken out of the maze once they reached the end. The rats that had access to the food reward learned the maze quickly; however, the rats that did not have access to the food reward failed to run the maze reliably. Interestingly, after 10 trials, these rats then had access to the food reward and their performance on the maze immediately improved, even outperforming the original group of rats. The data show that the rats had learned the maze, even if they lacked the motivation to run it.

Tolman's "cognitive map" concept was that the rat had an internal representation of the structure of the environment. From this internal representation of the structure of the environment, it is theoretically possible to simulate the possible actions and to imagine the consequences of your actions. Computationally, this allows the discovery of shortcuts (O'Keefe & Nadel, 1978; Redish, 1999; Samsonovich & Ascoli, 2005) and the evaluation of the consequences of one's actions in the light of one's current needs (Niv et al., 2006). Importantly, planning using the cognitive map could be contrasted with situation—action decisions, in which one learns to take an action in response to the current situation, with no explicit representation of the consequences of the action (Daw, Niv, & Dayan, 2005; Hull, 1943; Niv et al., 2006; van der Meer, Kurth-Nelson, & Redish, 2012). Tolman hypothesized that rats (and people) were learning the structure of the world so that they could later plan action paths through it, while Hull hypothesized that rats (and presumably people) were learning what actions to take in given situations.

This dichotomy between Tolman's cognitive map and Hull's stimulus-response can be most easily seen in the T-choice plus maze (Barnes, Nadel, & Honig, 1980; Packard & McGaugh, 1996; Tolman, 1948; Fig. 6.1). In this task, rats are first allowed to explore a plus-shaped maze, presumably allowing them to derive the structure of that maze. They

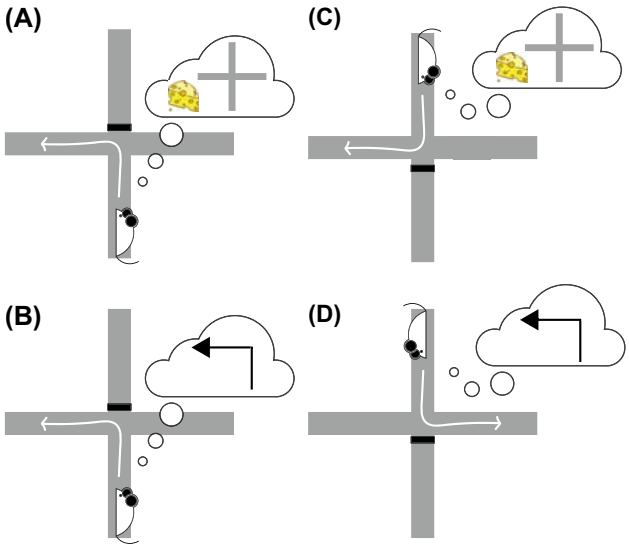

Figure 6.1 The plus maze task can dissociate which navigational strategy the rat is using (Packard & McGaugh, 1996). (A) In this plus maze task, rats are trained to turn left from the South arm to the West arm. The rat can either use a planning-based (Tolmanian) algorithm, in which it knows where it is (on the South arm) and knows where it wants to go (to the West arm), (B) or the rat can use a situation–action association (Hullian) algorithm (bottom mazes), in which it knows to turn left when placed on the maze. (C and D) When a rat is placed on the North arm, it is possible to determine which navigation strategy the rat is using. A Tolmanian rat uses spatial cues to make this decision and goes to the place (where the food reward is located). In contrast, a Hullian rat will continue to turn left, this time ending up on the East arm. Rats with limited training show Tolmanian choices, turning left to the West arm, but rats with extended training show Hullian responses, turning right to the East arm.

are then trained to turn left from the South arm to the West arm. The rat can learn this task either through a planning-based (Tolmanian) algorithm, in which it knows where it is (on the South arm) and knows where it wants to go (to the West arm), or through a situation–action association (Hullian) algorithm, in which it knows to turn left when placed on the maze. Although these two algorithms are not dissociable from the South arm, when a rat is placed on the North arm, these algorithms produce different behaviors. A Tolmanian rat will turn right to the West arm, taking a different action to achieve the same result, while a Hullian rat will turn left to the East arm, taking the same action but achieving a different result. Of course, it is not that one of these options is correct and the other wrong, but they are different generalizations of the changed situation. Rats with limited training show Tolmanian choices, turning right to the West arm, but rats with extended training show Hullian responses, turning left to the East arm (Packard & McGaugh, 1996).

This task has been extensively studied. Manipulations that make the cognitive map easier to learn (more cues, rats with better vision) shift rats toward Tolmanian mapping

processes (Chang & Gold, 2004), as do manipulations that make learning the situation–action associations less useful (Gardner et al., 2013; Schmidt, Papale, Redish, & Markus, 2013). Importantly, anterior dorsolateral striatum is a key structure in the development of the Hullian situation–action process (Chang & Gold, 2003; Kesner, Bolland, & Dakis, 1993; Packard, 1999; Packard & McGaugh, 1992, 1996; Yin, Knowlton, & Balleine, 2004), while the hippocampus, mPFC, and the posterior dorsomedial striatum are critical to behavioral flexibility and the use of the cognitive map in Tolmanian decisions (Bissonette & Roesch, 2017; Chang & Gold, 2003; Packard, 1999; Packard & McGaugh, 1992, 1996; Ragozzino, Detrick, & Kesner, 1999; Rich & Shapiro, 2007, 2009; Yin et al., 2004). As can be seen in the plus maze example, the cognitive map is easiest to study in the light of navigation, where the map can be directly observed and map-based navigation can be contrasted with learning specific routes (i.e., action sequences). In this navigation framework, a map places external information onto a coordinate system, allowing one to infer novel relationships between them (Gallistel, 1990; O'Keefe & Nadel, 1978; Redish, 1999). Importantly, a map is more than a coordinate system. While a map requires a coordinate system as input, the map is the relationship between the external information and the coordinate system and is unlikely to include the coordinate system internally (Redish & Touretzky, 1997). Extensive evidence suggests that the hippocampus maintains these relationships of objects in the environment in regard to each other and to the animal by relating them to this extrahippocampal coordinate system. This cognitive map would then allow an animal to have awareness of its environment irrespective of any particular sensory input and to mentally combine different parts of the environment even if they have never been experienced at that same time (O'Keefe & Nadel, 1978; Redish, 1999; Worden, 1992).

When rats reach a choice point, they often pause, orienting and reorienting toward their potential routes—a behavior termed vicarious trial and error (VTE; Gardner et al., 2013; Hu & Amsel, 1995; Muenzinger, 1938; Muenzinger & Gentry, 1931; Redish, 2016; Tolman, 1938). VTE is seen during early learning and decreases with task proficiency (Tolman, 1939). VTE increases with changes in task demands (Blumenthal, Steiner, Seeland, & Redish, 2011; Steiner & Redish, 2012) or by increasing the number of choices/options (Bett et al., 2012). We have found that VTE increases in rats when learning and/or using a hippocampal place strategy, during strategy conflicts, and immediately after error trials, again suggesting that rats are engaged in deliberation during VTE (Schmidt et al., 2013). VTE is most likely a behavioral reflection of indecision in deliberative decision-making (Amemiya & Redish, 2016; Gardner et al., 2013; Papale, Stott, Powell, Regier, & Redish, 2012; van der Meer et al., 2012; see Redish, 2016 for a review).

In humans and rodents, the hippocampus and prefrontal cortex are both engaged during spatial navigation and planning (O'Keefe & Nadel, 1978; Redish, 1999; Spiers & Maguire, 2007). For example, in a recent fMRI study by Kaplan et al. (2017), participants

were trained on novel spatial navigation paradigm where they needed to plan paths of varying difficulty on novel mazes. The authors found that the prefrontal cortex and the hippocampus were both engaged during navigation planning. Interestingly, the functional connectivity between these two structures was higher when planning required more deliberation and preceding correct choices. Similarly, the rodent hippocampus and mPFC are functionally engaged during deliberative decision-making, showing increased coherence in the theta frequency specifically at choice points and phase locking of mPFC neurons to hippocampal theta oscillations (Benchenane et al., 2010; Hyman, Zilli, Paley, & Hasselmo, 2005; Jones & Wilson, 2005; Siapas & Wilson, 1998). Lesions to the hippocampus impair VTE behavior (Bett et al., 2012; Hu & Amsel, 1995); however, disrupting normal hippocampal functions can actually lead to an increase in VTE behavior (Papale, 2015; Robbe et al., 2007). This leads us to hypothesize that the hippocampus is not the driving force for VTE behavior but that VTE is engaged by another neural system. Wang et al. (2015) proposed that during decision-making, the lateral prefrontal cortex generates numerous potential action plans (i.e., take this choice, skip this choice) and that this information is sent to the hippocampus, which retrieves the stored representations related to these specific actions. The hippocampus then iteratively engages the mPFC as it sorts through different hippocampal-generated behavioral simulations, in order to determine the best choice of action. Lesion studies have found that the mPFC facilitates behavioral flexibility during new learning (Ragozzino et al., 1999), the same time period when VTE behavior is prevalent. In further support of this hypothesis, our lab has recently found that disrupting the mPFC with Designer Receptors Exclusively Activated by Designer Drugs reduces VTE behavior (Schmidt & Redish, 2016, *Society for Neuroscience Abstract*). Recent studies have found that mPFC is engaged during strategy changes, particularly during times when VTE is increased (Benchenane et al., 2010; Bissonette & Roesch, 2017; Powell & Redish, 2016).

HOW CAN WE EXAMINE EPISODIC FUTURE THINKING/MENTAL TIME TRAVEL?

Exactly how can we measure episodic future thinking or mental time travel in rodents? Try as we might, we have so far been unable to get our rats to fill out any of our post-behavioral training questionnaires. Instead, one must infer cognition through behavioral observation, which historically engendered much debate about the reliability of such inferences (Hull, 1943; MacCorquodale & Meehl, 1948; Skinner, 1948; Watson, 1913). However, the recognition that imagination entails activation of the same neural systems as during active perception and action suggests that it may be possible to observe episodic future thinking (mental time travel), even in nonlinguistic animals such as rodents (Johnson, Fenton, Kentros, & Redish, 2009). Imagination of sensory objects activates

the same sensory areas as when those objects are perceived (Haxby, Connolly, & Guntupalli, 2014; Kosslyn, 1994; O'Craven & Kanwisher, 2000; Pearson, Naselaris, Holmes, & Kosslyn, 2015). Similarly, imagination of motor actions activates the motor areas (Jeannerod, 1994; Rizzolatti & Craigero, 2004). It has even been possible to use these imagination processes to directly observe planning in humans (Abram, 2017; Doll, Duncan, Simon, Shohamy, & Daw, 2015).

Doll et al. (2015) trained subjects on the two-step decision task (Daw, Gershman, Seymour, Dayan, & Dolan, 2011; Fig. 6.2). In this task, subjects are given two choices (C1 = A or B). This choice leads to a second layer of two possible choices (C2 = C or D, or C3 = E or F). Choosing A in C1 leads to C2 (C vs. D) 80% of the time and C3 (E vs. F) 20% of the time, while choosing B in C1 leads to C2 20% of the time and C3 80% of the time. Choosing C, D, E, or F leads to a probabilistically delivered reward. The key to this task is that the probability of reward delivery changes slowly over time, so the goal of the task is to return to a winning outcome. Because planning systems take the structure of the world into account, after a rare transition (A → C3 or B → C2), a planning-based (Tolmanian) algorithm would choose the other choice (A → C3 → E/F → reward → B; B → C2 C/D → reward → A), while a habit/procedural/do-it-again situation–action association (Hullian) algorithm would repeat the original choice (A →…reward → A; B →…reward → B). Thus, this task is able

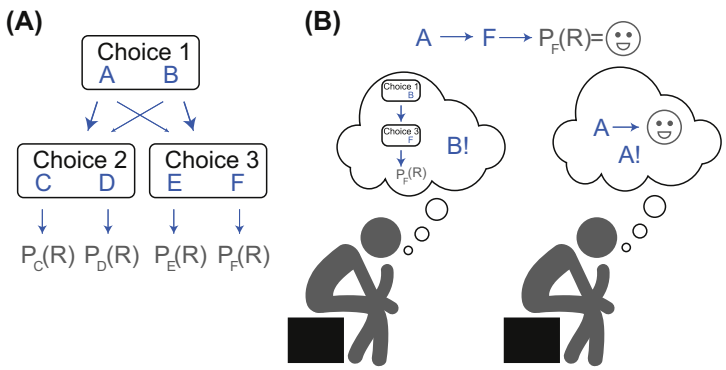

Figure 6.2 Two-step decision task (Daw et al., 2011). (A) In this task, subjects are initially given a choice (Choice 1 = A or B). This leads to a second layer of two possible choices (Choice 2 = C or D or Choice 3 = E or F). Choosing A in Choice 1 leads to Choice 2 (C or D) 80% of the time and Choice 3 (E or F) 20% of the time, while choosing B in Choice 1 leads to Choice 2 20% of the time and Choice 3 80% of the time. Choosing C, D, E, or F leads to a probabilistically delivered reward. The probability of reward delivery changes slowly over time, and the goal is to return to a winning outcome. (B) Because planning systems take the structure of the world into account, after a rare transition (A → Choice 3 or B → Choice 2), a planning-based (Tolmanian) algorithm would choose the other choice (A → Choice 3 → E/F → reward → B; B → Choice 2C/D → reward → A), while a habit/procedural/do-it-again situation–action association (Hullian) algorithm would repeat the original choice (A → …reward → A; B → …reward → B). Thus, this task is able to differentiate Tolmanian planning processes from Hullian situation–action processes.

to differentiate Tolmanian planning processes from Hullian situation—action processes, much like the plus maze described earlier. Doll et al. (2015) designed this task using cues that could be differentiated in fMRI (faces, tools, body parts, landscapes) and found that when subjects showed planning behaviors, the fMRI signals indicated imagination of the upcoming cues.

A similar process can be used in neurophysiological recordings from awake, behaving nonhuman animals (such as rats) (Johnson et al., 2009). Pyramidal cells in the hippocampus, aka "place cells," show spatially specific firing properties (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978; Redish, 1999), typically showing a peak firing in a small location in the environment and remaining mostly quiet in the rest of the environment. The area of maximal firing is referred to as the "place field." The place fields of different cells are distributed throughout the environment (Muller, 1996), creating a maplike representation of the environment (O'Keefe & Nadel, 1978; Redish, 1999). In addition to firing at the rat's current location, place cells also show rare extrafield firing, i.e., firing occasionally in locations separate from their place field. This nonlocal firing is typically seen at feeder/reward sites (see Redish, 1999 for review) and decision points (Johnson & Redish, 2007). With large enough neural ensembles, it is possible to decode the information represented within the ensemble (Wilson & McNaughton, 1993; Zhang, Ginzburg, McNaughton, & Sejnowski, 1998). During these extrafield firing events, decoding reveals nonlocal representations of space (Jensen & Lisman, 2000; Johnson & Redish, 2007; Pfeiffer & Foster, 2013).

More recent studies have determined that during this nonlocal firing, the place cells are activated in behaviorally relevant sequences that can represent trajectories the rat previously traversed or could traverse (Davidson, Kloosterman, & Wilson, 2009; Foster & Wilson, 2006; Gupta, van der Meer, Touretzky, & Redish, 2010, 2012; Pfeiffer & Foster, 2013; Skaggs & McNaughton, 1996). What was once believed to be noise is now hypothesized to reflect the rodent "thinking" about another location. The answer to how the hippocampus engages in episodic future thinking thus lies in the firing sequences of hippocampal place cells and their relation to local field potentials.

Place cell ensemble firing sequences are typically seen during two oscillatory events (Fig. 6.3): sharp-wave ripple complexes (SWR; 150 ms 150—220 Hz burst events), which occur during sleep and awake quiescence (Buzsaki, Leung, & Vanderwolf, 1983; O'Keefe & Nadel, 1978), and theta oscillations (more continuous 6—10 Hz processes), which occur during movement and attentive states (Buzsaki, 2002; O'Keefe & Nadel, 1978; Vanderwolf, 1969). During sleep (Kudrimoti, Barnes, & McNaughton, 1999; Lee & Wilson, 2002; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994) and quiet wakefulness (Csicsvari, O'Neill, Allen, & Senior, 2007; Diba & Buzsaki, 2007; Foster & Wilson, 2006; Gupta, van der Meer, Touretzky, & Redish, 2012; Jackson, Johnson, & Redish, 2006; Jadhav, Kemere, German, & Frank, 2012; O'Neill, Senior, & Csicsvari, 2006; Pfeiffer & Foster, 2013; Singer, Carr, Karlsson, & Frank,

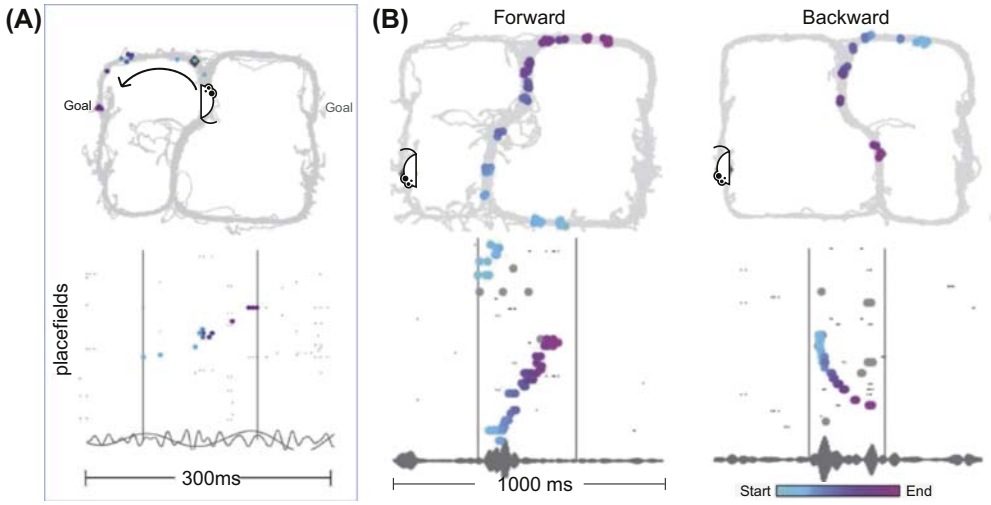

Figure 6.3 Examples of sequences. (A) Top: example of theta sequence while the rat is located at the choice point. Each place field center is represented by a *colored dot* (place in sequences corresponds to color bar in bottom right panel, blue is early, pink is later). Bottom: place cells sorted relative to the rat's location over a single theta cycle. Local Field Potential filtered for theta (6–10 Hz) and gamma (40–100 Hz). (B) Example of sharp-wave ripple sequences for forward (top left) and backward (top right) sequences. Bottom: place cells sorted relative to the rat's location over a sharp-wave ripple. *(Adapted with permission from Gupta et al. (2010, 2012).)*

2013), brief episodes of high-amplitude, fast-frequency SWR dominate the local field potential in CA1 and CA3 as a result of synchronous CA3 and CA1 activity (Buzsaki, 2015; Buzsaki et al., 1983; Csicsvari, Hirase, Mamiya, & Buzsaki, 2000). During SWR, place cell assemblies "replay" spatial trajectories previously traversed in a temporally condensed manner. These reactivation and replay sequences were first observed during sleep after behaviors (Buzsaki, 2015; Pavlides & Winson, 1989; Wilson & McNaughton, 1994). Note that reactivation and replay during sleep are examples of imagination and mental time travel—representations of other places and other times, such as reactivation of recently experienced behaviors on a track, while the rat rests on a separate platform.

From their first discovery, SWR sequences were hypothesized to facilitate memory consolidation, by continually recapitulating previous experiences during sleep (Alvarez & Squire, 1994; Buzsaki et al., 1983; Gais & Born, 2004; Marr, 1971; Sutherland & McNaughton, 2000). During sleep, pyramidal cell firing sequences are generally replayed in the original order of firing (forward replays) supporting their theorized role in memory consolidation. However, when SWR sequences were discovered during awake quiescence, not only did they fire in the original order of the trajectory traversed but also in the reverse order (backward replay; Csicsvari et al., 2007; Foster & Wilson, 2006;

Gupta et al., 2010). They also traversed novel trajectories never before experienced by the rat (Gupta et al., 2010), which suggests that they likely play a role in exploring the cognitive map (Derdikman & Moser, 2010; Samsonovich & Ascoli, 2005), much like mind-wandering in humans (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016).

Other studies, however, have found that firing during wake SWRs can predict the subsequent path of the animal. Pfeiffer and Foster (2013) trained rats on a goal-directed navigation task to forage for food reward between randomly distributed locations and a stationary "home" location. During events with large multiunit cellular activity, though not specifically during SWR, but usually coinciding with, sequences represented trajectories to behaviorally relevant locations; for example, when the rat was away from the home location, sequences predicted trajectories going home; however, this was not seen during random foraging (Fig. 6.4). Interestingly, these trajectory events were not simply paths in front of the rat; sequences represented future paths regardless of the head direction of the rat. Similar to Gupta et al. (2010), sequences even represented novel trajectories back to the home location.

The specific roles played by reactivations during SWR events remain unclear. There is some evidence that sequences during awake quiescence are more variable than sequences during sleep (Wikenheiser & Redish, 2013), including both forward and backward sequences, and seem to be related to attended areas of the maze, such as recent and future paths (Davidson et al., 2009; Foster & Wilson, 2006; Pfeiffer & Foster, 2013; Silva, Feng, & Foster, 2015), as well as novel and important, but not recently experienced, paths (Gupta et al., 2010). One possibility is that the sequences seen during quiet waking states are akin to imagination in the human default mode network (Raichle et al., 2001), allowing the novel connection of new concepts (Samsonovich & Ascoli, 2005). Another possibility is that it is a potential substrate for memory retrieval to be used in planning processes (Carr, Jadhav, & Frank, 2011; Pfeiffer & Foster, 2013; Schmidt & Redish, 2013). Disrupting SWRs in waking states impairs working memory and learning (Jadhav et al., 2012) and increases VTE behavior (Papale, Zielinski, Frank, Jadhav, & Redish, 2016).

Jadhav et al. (2012) selectively disrupted awake SWR events in rats trained on a hippocampal-dependent spatial alternation task. In the W maze, the rats were rewarded for alternating between the three arms of the maze. When the rats were on the outside arm, they were rewarded for entering the center arm of the maze. When the rats were on the center arm, however, they were only rewarded for visiting the outermost arm that was not previously visited (i.e., left—center—right—center—left). This allowed the comparison between two arm trajectories, one with a memory component and the other without. Awake SWR ripples were disrupted through a stimulation electrode targeting the ventral hippocampal commissure. Electrical stimulation within 25 ms of SWR detection disrupted SWR events and multiunit activity. Interestingly, SWR disruption impaired spatial working memory on the W maze by selectively impairing outbound

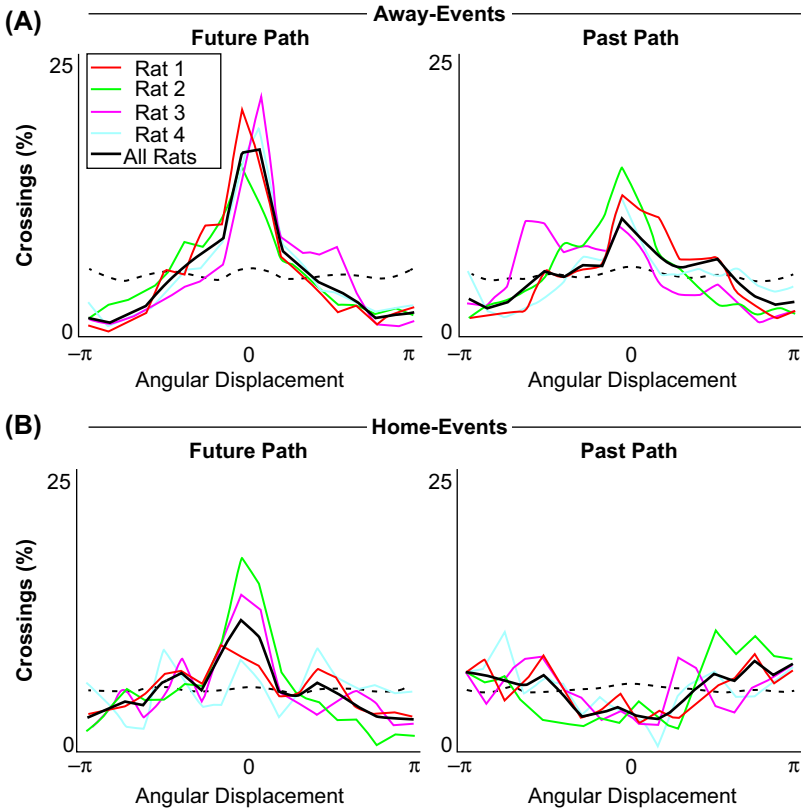

Figure 6.4 Sequences depict future trajectories to home location. (A) In order to determine whether sequences predicted future paths, the angular displacement between the future projected path and the actual future and previous paths taken were measured. The angular displacement was measured between the projected and actual trajectories at progressively increasing radii from the rat's location. Angular displacements at zero represent trajectories taken that matched with the predicted trajectory. (A) Differences between future paths and projected paths to goal locations were concentrated around zero angular displacement and more uniformly distributed when compared to the past path. (B) Differences between future paths and projected paths to home locations showed weaker relationships. *(Adapted with permission from Pfeiffer and Foster (2013).)*

trials while sparing inbound trials. These deficits were found despite no overall change to place cell firing characteristics or fields as well as intact sleep SWR sequences. These data suggest that disrupting awake SWR impaired spatial memory performance by disrupting the link between recent and remote experiences that SWR are believed to provide.

In contrast, sequences during sleep seem to be more veridical (i.e., forward) (Skaggs & McNaughton, 1996; Wikenheiser & Redish, 2013) and include both the hippocampal sequence and the consequence of those sequences (seen as activation of reward-related information in downstream nucleus accumbens, Lansink, Goltstein, Lankelma,

McNaughton, & Pennartz, 2009; Pennartz et al., 2004). Reactivation during sleep is generally hypothesized to facilitate the consolidation of contextual information by strengthening synaptic connections and transferring information from the hippocampus to the cortex (Sutherland & McNaughton, 2000). Supporting a role for replay as goal-directed exploration, Lansink et al. (2008) found that ventral striatal reward-related information appeared time-locked to hippocampal replays—cells representing the appropriate reward site fired at the end of SWR sequences replaying approaching that reward site. Disruption of SWRs during postbehavior sleep disrupts learning and consolidation effects (Ego-Stengel & Wilson, 2010; Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009), and activation of dopaminergic signals during sleep-based reactivation leads to learning of that reactivated site as a goal (de Lavilleon, Lacroix, Rondi-Reig, & Benchenane, 2015). Recently, de Lavilleon et al. (2015) stimulated dopamine neurons every time a specific place cell was active during sleep SWRs and found that rats preferred to approach that goal the next day.

Sequences seen during theta oscillations, in contrast, represent time-compressed spatial trajectories that could facilitate spatial navigation and planning (Foster & Wilson, 2007; Wikenheiser & Redish, 2015). Johnson and Redish (2007) found that theta sequences serially traverse potential routes. Subsequent studies suggest theta sequences run to the potential goal locations (Gupta et al., 2012; Wikenheiser & Redish, 2015). Therefore, the activation of these sequences may support different behavioral processes whether they are active during SWR or theta oscillations.

In 1993, O'Keefe and Recce reported that the relationship between hippocampal cell firing and the theta rhythm changed as an animal passed through the place field—with spiking beginning at the end of each theta cycle on entry and precessing earlier and earlier as the animal passed through the field. This phenomenon, termed *phase precession*, because the phase of firing precesses as the animal runs through the field, has been robustly replicated by numerous labs (Dragoi & Buzsaki, 2006; Foster & Wilson, 2007; Gupta et al., 2012). Several labs quickly noted that this phenomenon meant that there was a sequence within each theta cycle, progressing along the path of the animal (Jensen & Lisman, 1996; Skaggs & McNaughton, 1996; Tsodyks, Skaggs, Sejnowski, & McNaughton, 1996). Two important questions remained: (1) Were the sequences a consequence of phase precession or vice versa? (2) Were the sequences running from behind the animal to the location of the animal, from the animal forward, or from behind to in front?

Studies attempting to answer the first question found that in well-learned environments, sequences better described the data than phase precession. Dragoi and Buzsaki (2006) found that the timing between pairs of cells better explained the data than the phase of firing of each of those cells. Other labs looking at learned environments have found that the sequences can occur without phase precession—Johnson and Redish (2007) found that during VTE, sequences alternated between options, even though no phase precession was occurring. Comparing place field firing on the running wheel

with and without a goal, phase precession occurred when there was a goal (Pastalkova, Itskov, Amarasingham, & Buzsaki, 2008), but when there was no goal, the phase of firing remained constant (Hirase, Czurko, Csicsvari, & Buzsaki, 1999), suggesting that without a goal, the rat was running the same sequence over and over again (Lisman & Redish, 2009).

Although it would seem that phase precession and theta sequences are two ways of looking at the same phenomenon, Feng, Silva, and Foster (2015) recently found that one could get phase precession without sequences. On the first pass through a place field, cells phase precessed but did not line up into sequences until the second pass, because while individual cells phase precessed on the first lap, the starting phase shifted from cell to cell, so they did not start line up to create sequences. Recently, Wang, Roth, and Pastalkova (2016) examined whether theta sequences are dependent upon internally generated neural activity or if sensory input is sufficient. Silencing the medial septum, which provides theta input to the hippocampus, disrupted theta sequences while preserving firing fields. These data suggest that while phase precession could arise from sensory input, theta sequences are integrally generated by hippocampal network dynamics and not sensory input. So far, theta sequences have always been observed to follow the rat's direction of motion, even when animals move backward. Cei, Girardeau, Drieu, Kanbi, and Zugaro (2014) geared a car so that when the rat ran forward, the car ran backward. Similarly, Maurer, Lester, Burke, Ferng, and Barnes (2014) trained a rat to actually walk backward. In both of these cases, both phase precession and theta sequences ran along the trajectory of the rat (i.e., not the direction the rat was facing), implying that these sequences are encoding the path of the rat.

An important question about theta sequences is whether they are about the future path of the rat or about the past path already run. As Skaggs and McNaughton (1996) noted, this could be determined by where these phase precessions crossed in different approaches to a place field: If sequences were about the past, place cell firing on two paths that crossed would cooccur at the start of the place field, while if sequences were about the future, the two paths that converged would converge at the end of the place field. Later data definitively proved that multidirectional place fields in open environments and bidirectional fields in linear tracks converged at the end of the field, implying that these sequences were running from the animal forward, predicting future paths of the animal (Battaglia, Sutherland, & McNaughton, 2004; Huxter et al., 2008; see Lisman & Redish, 2009 for review). Further studies have consistently shown that place fields align from lap to lap at the end of their place fields, even if the starting point can change (Wikenheiser & Redish, 2015; Zheng et al., 2016). Newly formed place fields emerge from back to front, with firing first locked to the end of the place field and later expanding backward to earlier positions with subsequent experience (Bittner et al., 2015; Mehta, Barnes, & McNaughton, 1997; Monaco, Rao, Roth, & Knierim, 2014).

However, in more complex mazes, these results were more complicated, with sequences appearing behind the animal (running from behind to where the animal was) when the animal approached a goal and sequences appearing in front of the animal as it left the goal (running from the location of the animal forward to future positions) (Gupta et al., 2012). Direct examination of these sequences suggested that the sequences ran to the actual goal of the animal, bypassing earlier potential goals that the rat planned to skip (Wikenheiser & Redish, 2015).

As mentioned, VTE is believed to behaviorally reflect the neurophysiological generation and evaluation of future actions. During VTE, place cells transiently "sweep" forward, in a serial manner, spatially representing specific routes to goal locations (Amemiya & Redish, 2016; Johnson & Redish, 2007; Papale et al., 2016). These sequences are consistent with the results of Gupta et al. (2012) who found that theta sequences appear to segment the maze in a task-related manner, representing areas ahead of the animal as it left maze locations. In contrast to the nonlocal representations seen during SWR, the sequences seen during VTE occur during strong theta oscillations (Johnson & Redish, 2007; Papale et al., 2016).

Theta sequences are believed to only represent in a forward direction, unlike SWR sequences that show representations in both the forward and backward directions. This suggests that theta sequences may support planning, but their exact role in goal-directed decision-making is not yet clear. In order to elucidate the role of theta sequences in planning, Wikenheiser and Redish (2015) trained rats in a foraging task on a circular maze for food reward. Rats ran in a circle with three evenly dispersed reward sites, each site with a different fixed-length delay required in order to receive the food reward. The rats encountered a series of stay/go decisions where the rat could wait out the delay for the food reward or skip the current reward site and travel to the next reward site. The rat's choices could be qualified into three behaviors: one-segment, in which the rat ran to the next reward site and waited out the delay; two-segment, in which the rat skipped the next reward site but stopped at the second, subsequent reward site to wait out the delay; and three-segment, in which the rat skipped the next two reward sites, returning to the original reward site (i.e., running a full lap around the circle) before waiting out the delay (see Fig. 6.6). This task permitted the authors to examine how theta sequences are connected to goal-directed decision-making by examining how far theta sequences "looked ahead" during these one-, two-, and three-segment trials. Theta sequences were compared on the first segment of all the three trajectory types, which held the behavior constant and only varied in the goal destination. The distance traveled for the theta sequences were commensurate with the trajectory length, shortest for one-segment, longer for two-segment, and longest for three-segment trajectories. In contrast, when approaching their goal locations, theta sequences were comparable for all three trial types. Taken together these data suggest that hippocampal theta sequences do facilitate planning mechanisms for goal-directed decision-making.

Theta sequences are also necessary for correct performance on hippocampal-dependent behavioral paradigms. A study by Robbe et al. (2007) measured the effects of cannabinoids on theta and SWR oscillations, as well as theta sequences. Cannabinoids impair memory in hippocampal-dependent tasks in humans and rodents alike (Litchtman, Diemen, & Martin, 1995; Litchman & Martin, 1996; Robbe et al., 2007). In the Robbe et al. (2007) study, place cells were recorded from CA1 in rats under the influence of a cannabinoid receptor (CB1) agonist on a hippocampal-dependent spatial alternation task (Ainge, van der Meer, Langston, & Wood, 2007). In addition to the decreasing power in the theta and SWR frequencies, CB1 agonists severely impaired the temporal synchrony of hippocampal pyramidal cells without affecting the overall population firing rates. In a subsequent study, Robbe and Buzsaki (2009) replicated the behavioral deficits on the hippocampal-dependent spatial memory task and temporal organization of cell firing. Interestingly, the rodents showed more VTE and likely increased indecision. Despite the preserved place field firing characteristics, coordinated place cell firing and likely theta sequences were disrupted. This study demonstrated that disrupting the organization of theta sequences increased VTE and impairs behavioral performance on hippocampal-dependent tasks.

On the flip side, clonidine is an α-adrenergic autoreceptor agonist that decreases tonic levels of noradrenaline pharmacologically; behaviorally it decreases indecision in humans (Coull, Middleton, Robbins, & Sahakian, 1995; Jakala et al., 1999), potentially by limiting mental exploration. Similarly, clonidine in rodents also suppresses VTE behavior and, therefore, increases decisiveness (Amemiya, Noji, Kubota, Nishijima, & Kita, 2014). In a subsequent study, Amemiya and Redish (2016) examined whether the reduced VTE behavior seen in rats given clonidine also resulted in reduced mental exploration. Consistent with other results (Johnson & Redish, 2007; Papale et al., 2016), theta sequences represented both the chosen and unchosen paths during VTE under saline but more often represented the chosen path during non-VTE behavior. Interestingly, clonidine suppressed theta sequences that represented the unchosen path during VTE, suggesting that clonidine induced decisiveness resulted from a reduction in mental exploration of options.

Anatomical and physiological studies support the hypothesis of an inverse relationship between SWR and theta oscillations. Subcortical inputs to the hippocampus have suppressing effects on CA3 recurrent excitation, thereby suppressing SWR events (Buzsaki, 2015; Buzsaki et al., 1983; Vandecastelle et al., 2014). Numerous studies have shown that during theta oscillations, SWR are suppressed via presynaptic cholinergic muscarinic receptors (Hasselmo, 1995, 1999, 2006), cannabinoid CB1 receptors (Robbe et al., 2007), as well as cholinergic inputs from the medial septum (Vandecastelle et al., 2014). Lesions that reduce theta oscillations, including lesions to the medial septum, fimbria fornix, and entorhinal cortex, all increase SWR events (Buzsaki, 2015; Buzsaki et al., 1983).

OPEN QUESTIONS

There are still many unknowns regarding sequences. Despite the decades of research, we are still unclear about how sequences are generated. What is the mechanistic relationship between sequences and phase precession? Are they controlled by the same mechanism? Do we need sequences for planning? When engaging in episodic future thinking, humans may mentally travel serially along all the required steps to reach a goal but in other cases may only mentally travel to the final outcome (Schacter, Benoit, & Szpunar, 2017; Suddendorft, 2013). How much do sequences help the rodent plan their future paths? Are there differences between dorsal and ventral hippocampal sequences given that place field size can vary along the septotemporal axis (Jung, Wiener, & McNaughton, 1994; Kjelstrup et al., 2008; Royer, Sirota, Patel, & Buzsaki, 2010), potentially reflecting a gradient of contextual representation along the dorsal–ventral axis (Schmidt, Satvat, Argraves, Markus, & Marrone, 2012).

How are sequences generated?

Early models suggested that sequences were a passive product of theta phase precession or at least a product of the same mechanism that generates phase precession (Lisman & Redish, 2009; Maurer & McNaughton, 2007; O'Keefe & Recce, 1993; Skaggs, McNaughton, Wilson, & Barnes, 1996). However, sequences can still be seen within each theta cycle, even when the rat is paused. For example, Johnson and Redish (2007) found theta sequences occurring while the rat was paused during VTE; although there were sequences proceeding ahead of the rat within each theta cycle, the cells themselves did not phase precess. As mentioned above, Feng et al. (2015) found that theta sequences and phase precession can be dissociated, at least upon first exposure to an environment. Without experience of the maze, place cells did show phase precession, but the ensemble failed to show sequences; however, one traversal of the track was sufficient to organize the place cell assembly, so that sequences appeared on the second traversal.

Recently, it has been suggested that theta sequences/phase precession could be generated by the entorhinal cortex. The entorhinal cortex sends spatial and sensory information to the hippocampus. The medial entorhinal cortex has a plethora of spatially firing cells, including grid cells, border cells, and head direction cells (Hafting, Fyhn, Molden, Moser, & Moser, 2005; Sargolini et al., 2006; Solstad et al., 2008; Quirk, Muller, Kubie, & Ranck, 1992). Unlike place cells, which fire in a specific location in the environment, grid cells in the entorhinal cortex fire in a triangular grid that spans the length of the environment (Hafting et al., 2005; Sargolini et al., 2006). A computational model by Jaramillo, Schmidt, and Kempter (2014) suggests that phase precession is generated by grid cells and then driven onto downstream structures like the hippocampus. This model is supported by data showing that interfering with grid cells in the entorhinal cortex impairs phase precession and theta sequences in the hippocampus (Schlesiger et al., 2015).

Sanders, Renno-Costa, Idiart, and Lisman (2015) suggest that the phase precession, generated in the entorhinal cortex, is imposed upon downstream place cells to produce sequences that can travel linearly ahead of the animal. In this model, sequences only go forward, yet sweeps have been found to go around corners (Gupta et al., 2012; Johnson & Redish, 2007) even in enclosed mazes (Amemiya & Redish, 2016). One possibility is that sequences going around corners may depend on the cognitive map and the hippocampus itself.

How much do sequences improve/increase/predict planning?

Because theta sequences usually represent trajectories in front of the rat, they are believed to be necessary for planning future paths, instead of replaying the past. Redish et al. have found that theta sequences occurring during behavioral tasks where the rat is engaged in more deliberative/planning behaviors subsequently decrease when the behavior automates (Amemiya & Redish, 2016; Johnson & Redish, 2007; Papale et al., 2016; Regier, Amemiya, & Redish, 2015). On the multiple T-maze, for example, Johnson and Redish (2007) found that theta sequences initially go down both arms of the maze, but then, as the rat proceeds to know its target, the sequences go down only one direction. Furthermore, as the rat starts to automate its behavior, the length of the sequences decreases with experience. Redish et al. have suggested that this entails three stages: deliberation, planning, and automation (Redish, 2016; van der Meer, Johnson, Schmitzer-Torbert, & Redish, 2010).

Though the cumulative data suggest that SWR and theta sequences facilitate planning and spatial navigation, exactly how much do they improve or predict behavior? Pfeiffer and Foster (2013) suggest that there is an increase in SWR sequences toward the goal of the rat just before movement; however, while highly significant, this is a very small increase of only 3%. Nevertheless, studies do suggest that increased coordination between cells during SWR predicts improved performance.

Singer et al. (2013) have found increased place cell firing coordination during SWR on correct trials on a hippocampal-dependent spatial navigation task. As previously described, the hippocampal-dependent W maze (Kim & Frank, 2009) requires the rat to alternate between outbound trials (i.e., left arm—center arm—right arm—center arm). The proportion of cells that had coordinated activity during SWR was measured across learning. During early learning, when the behavioral performance was close to chance, coordinated activity during SWR failed to predict whether the next trial would be correct or incorrect (Fig. 6.5). However, when performance was greater than 65% place cell coordinated firing during SWR was greater preceding correct trials. Further analyses revealed that coordinated firing could predict correct or incorrect performance on a trial-by-trial basis, during early learning. Because this was a binary choice, the SWR activity increased the ability to predict the path of the animal by 10% (60% compared to

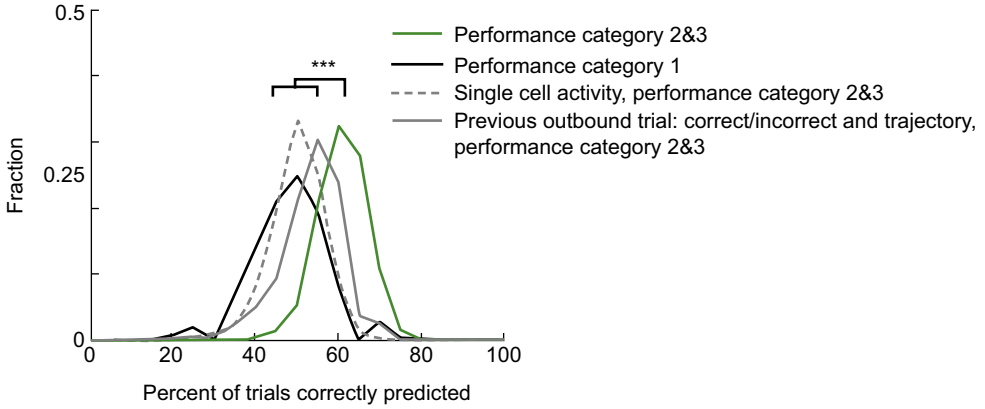

Figure 6.5 Pairwise spiking activity during SWRs accurately predict subsequent trial outcome. The proportion of coactive cell pairs was predictive of trial-by-trial performance for performance categories 2 and 3 (65%–85% and >85%; *green line*). In contrast, coactive cell pairs for performance category 1 (<65%; *black solid line*) were closer to chance. Predications based on single-cell activity were slightly better than chance (*gray dashed line*), as was the model based on prior outbound trial trajectory. *SWR*, sharp-wave ripple. *(Adapted with permission from Singer et al. (2013).)*

chance of 50%). Once at asymptotic performance firing coordination failed to predict correct or incorrect trials, thereby suggesting that coordinated firing during SWRs were no longer necessary once the task was well learned (i.e., the task was potentially automated).

In a similar unpublished analysis, Wikenheiser and Redish (2015) used linear discriminant analysis on decoded SWR representations to predict which feeder the rat would run to next on their three-step goal task described earlier. They decoded 200 ms windows centered on SWR events using a standard one-step Bayesian decoding operation with a uniform prior (Zhang et al., 1998) and then averaged the representation across space (thereby ignoring any temporal information in the representation). Thus, each SWR event produced an averaged decoded probability distribution over 100 spatial bins. For prediction analyses, only SWRs that occurred when the animal's speed was <5 cm/s were included. Each decoded distribution was categorized using linear discriminant analysis. A unique training set was constructed for each event by randomly drawing a subset of probability distributions, with equal numbers of one-, two-, and three-step cases. The distribution to be categorized was never included in the training set. Analysis was performed within each session, with statistics across sessions. To generate shuffled distributions, they followed the same classification procedure, as described above, except the identity of the training set that was randomized. They found an increase in prediction of the outbound target (where the rat was going to go on the next trial) of approximately 12% (45% relative to chance of 33%); shuffled data came out as chance (Fig. 6.6). Interestingly, it was also possible to predict the previous goal

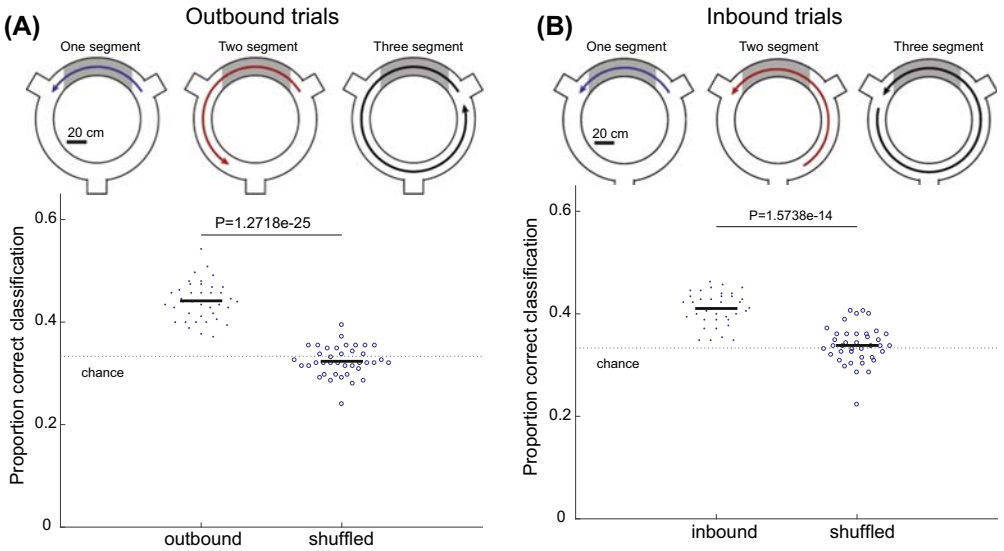

Figure 6.6 SWR sequences predict future paths. (A) We used linear discriminant analysis on decoded SWR representations to predict which feeder the rat would run to next (outbound prediction) and (B) which feeder the rat had arrived from (inbound prediction). We decoded 200 ms windows centered on ripple events (one-step, uniform prior) and then averaged the representation across space (thereby ignoring any temporal information in the representation). Thus, each ripple event produced an averaged decoded probability distribution over 100 spatial bins. For prediction analyses, only ripples that occurred when the animal's speed was <5 cm/s were included. Each decoded distribution was categorized using linear discriminant analysis. A unique training set was constructed for each event by randomly drawing a subset of probability distributions, with equal numbers of one-, two-, and three-step cases. The distribution to be categorized was never included in the training set. This analysis was performed within each session, so each dot on the plots represents one behavioral session. To generate shuffled distributions, we followed the same classification procedure, as described earlier, except the identity of the training set was randomized. All *P* values indicated on the plots come from paired t tests comparing the fraction of correctly predicted trials in each session to the fraction correctly achieved by the shuffles. *SWR*, sharp-wave ripple.

(where the rat had just come from) with similar proportions (41% relative to chance of 33%, for an increase of 8%).

Can theta sequences go backward?

Though SWR sequences have been observed to proceed in both forward (along the experienced path of the rat) and backward (against that experienced path) directions (Davidson et al., 2009; Foster & Wilson, 2007; Gupta et al., 2010), theta sequences seem to only go forward, consistent with a role in planning. Are theta sequences capable of going backward? As noted above, both Cei et al. (2014) and Maurer et al. (2014) found that theta sequences proceeded along the trajectory of the rat, even when that trajectory

was opposite to the head direction of the rat. That is, both of these studies found that when the rat ran backward, the theta sequences proceeded along the experienced trajectory of the rat. Taken together these studies imply that theta sequences reflect the future path of the rat, not the direction the rat is facing.

CONCLUDING THOUGHTS

Deliberative decision-making encompasses understanding and exploring the environment, imagining and predicting possible outcomes, evaluating the outcomes, and then taking action. During the imagining and planning stage, humans engage in episodic future thinking, where they project themselves into the future situations (Buckner & Carroll, 2007). Sequences seen in rodents could facilitate a rodent analogue of episodic future thinking. Though research suggests that SWR sequences support planning (Pfeiffer & Foster, 2013), that disrupting them impairs future planning (Jadhav et al., 2012), and that SWR sequences provide information about the future goal such that it is possible to improve one's prediction of that goal from coactivation within SWRs (Singer et al., 2013; Wikenheiser & Redish, unpublished data in Fig. 6.6), what role SWRs play in goal-directed decision-making remains unclear. Similarly, although research suggests that theta sequences run along the trajectory of the rat (Cei et al., 2014; Foster & Wilson, 2007; Maurer et al., 2014) to the goal (Amemiya & Redish, 2016; Gupta et al., 2012; Papale et al., 2016; Wikenheiser & Redish, 2015), when the goal is clear, the specific role of theta sequences is unclear. During VTE (which is essentially an indecision between goals, Redish, 2013, 2016), theta sequences run to alternate goals, but so far it has not been possible to predict which goal an animal will take during those indecisive trials (Amemiya & Redish, 2016; Johnson & Redish, 2007; Papale et al., 2016; Redish, 2016).

Moreover, the distinction between episodic future thinking in humans and sequences in rodents should not go unnoticed. Though sequences appear to traverse a traditional series of events (Gupta et al., 2012), episodic future thinking in humans rarely progresses through the entire series of events to reach the end goal. Humans typically project directly to the end goal and after evaluating their respective outcomes, then consider the series of steps required to accomplish that outcome (Newell, Shaw, & Simon, 1959; Kurth-Nelson et al., 2012; Suddendorft, 2013).

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