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Differential Arc expression in the hippocampus and striatum during the transition from attentive to automatic navigation on a plus maze

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ABSTRACT

The strategies utilized to effectively perform a given task change with practice and experience. During a spatial navigation task, with relatively little training, performance is typically attentive enabling an individual to locate the position of a goal by relying on spatial landmarks. These (place) strategies require an intact hippocampus. With task repetition, performance becomes automatic; the same goal is reached using a fixed response or sequence of actions. These (response) strategies require an intact striatum. The current work aims to understand the activation patterns across these neural structures during this experience-dependent strategy transition. This was accomplished by region-specific measurement of activity-dependent immediate early gene expression among rats trained to different degrees on a dual-solution task (i.e., a task that can be solved using either place or response navigation). As expected, rats increased their reliance on response navigation with extended task experience. In addition, dorsal hippocampal expression of the immediate early gene Arc was considerably reduced in rats that used a response strategy late in training (as compared with hippocampal expression in rats that used a place strategy early in training). In line with these data, vicarious trial and error, a behavior linked to hippocampal function, also decreased with task repetition. Although Arc mRNA expression in dorsal medial or lateral striatum alone did not correlate with training stage, the ratio of expression in the medial striatum to that in the lateral striatum was relatively high among rats that used a place strategy early in training as compared with the ratio among over-trained response rats. Altogether, these results identify specific changes in the activation of dissociated neural systems that may underlie the experience-dependent emergence of response-based automatic navigation.

1. Introduction

Upon engaging in a previously unfamiliar task, attentive performance is typically required to accomplish a desired outcome. After extensive practice, performance becomes fixed and automatic. This experience-dependent transition from the use of attentive to automatic performance strategies is commonly studied in the context of spatial navigation; attentive (place) strategies rely on memory of the position of spatial landmarks to flexibly locate a goal, whereas automatic (response) strategies rely on a series of fixed movements that compose an inflexible route. This strategy transition is readily observed in numerous species, including humans (Schmitzer-Torbert & Redish, 2002) and rodents (Hicks, 1964; Packard, 1999; Packard & McGaugh, 1996), supporting the value of model systems to investigate its underlying neural mechanics.

The plus (cross) maze (e.g., Tolman, Ritchie, & Kalish, 1946) is a simple apparatus consisting of four arms built off a central square that is frequently used to study the place-to-response transition in rodents. In particular, on a dual-solution task (one that can be solved using place or response navigation; Hicks, 1964; Ritchie, Aeschllman, & Peirce, 1950), animals are trained in a room with an enriched extra-maze environment to find a reward in a static location (e.g., the west arm) from a static start position (e.g., the south arm). To identify which strategy is dominant at any particular moment, a single trial (probe) is administered by starting the animal from the opposite position to that used during training. The new position puts at odds the route associated with each

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navigational strategy and thus permits simple identification of the primary mode of performance.

Using this dual-solution plus maze design coupled with reversible neural inactivation techniques, Packard and McGaugh (1996) demonstrated a double dissociation between the expression of place and response strategies and their neural correlates. The expression of place navigation required the dorsal hippocampus and not the dorsolateral striatum, and the expression of response navigation required the dorsolateral striatum and not the hippocampus (see also Packard, 1999; Packard, Hirsh, & White, 1989). Further studies showed that the dorsal striatum was functionally heterogeneous, implicating the medial region in flexible spatial navigation and the lateral region in fixed cue-based response navigation (Devan & White, 1999; Yin & Knowlton, 2004).

How the activation of these distinct neural systems relates to the experience-dependent transition from place-to-response navigation, however, remains relatively unexplored. Several studies suggest that either system can control behavior at early and late time points of training (Martel et al., 2007; Packard, 1999; Packard & McGaugh, 1996; Yin & Knowlton, 2004); note that Packard and McGaugh (1996) found inactivation of the hippocampus produced arm entries during probe trials at chance levels early in dual-solution task training suggesting that the ability to engage striatal-dependent response strategies may be delayed under some conditions. If the temporal dynamics of activation across brain regions map well onto those of strategy expression (obtained from either brain-intact animals or those with site-selective dysfunction) remains an open question. Is hippocampal activation high early in training when attentive strategies dominate? Does hippocampal activity change with practice and experience? Does activity within the dorsolateral striatum rise only after extensive training, coinciding with the emergence of automatic strategies? Does the strategy transition correlate with a particular pattern of activation across neural structures?

To begin to address these questions, the current work employed a dual-solution task to elicit the strategy transition from place to response navigation. Importantly, this behavioral design was paired with post-performance assessment of Arc/Arg 3.1 (Arc), an immediate early gene (IEG) and proposed marker of neural activity (e.g., Guzowski, McNaughton, Barnes, & Worley, 1999; Pinaud & Tremere, 2006; Vazdarjanova et al., 2006). For example, Arc transcription is enhanced in response to electrical stimulation, spatial exploration, and learning and memory (Daberkow, Riedy, Kesner, & Keefe, 2007; Guzowski, Setlow, Wagner, & McGaugh, 2001; Guzowski et al., 1999; Vazdarjanova et al., 2006; for review, see Bramham et al., 2010; Pinaud & Tremere, 2006). Moreover, the proportion of hippocampal neurons expressing Arc following exploration is comparable to the proportion of neurons encoding spatial information as measured by vivo electrophysiology (see Guzowski et al., 2006 for discussion; Wilson & McNaughton, 1993). Altogether, relating Arc expression measures in the hippocampus and striatum to navigation strategy should clarify how these dissociated neural systems are engaged and interact during the experience-dependent transition from attentive to automatic performance.

Complementary to this approach, we examined training-dependent changes in vicarious trial and error (VTE) behaviors. VTE refers to the tendency for rats to pause at a choice point and look back and forth toward potential destinations (Muenzinger, 1938; Muenzinger & Gentry, 1931; Tolman, 1948). As VTE is associated with deliberation (Papale, Stott, Powell, Regier, & Redish, 2012; van der Meer, Kurth-Nelson, & Redish, 2012) and place navigation (Gardner et al., 2013; Schmidt, Papale, Redish, & Markus, 2013), and correlated with hippocampal metabolism (Hu, Xu, & Gonzalez-Lima, 2006), this behavioral measure may further clarify the degree to which attentive systems are recruited during task repetition.

2. Methods

2.1. Animals

Sixty-four male Long-Evans rats (275–500 g; 2–4 months of age) were used for experimentation. These rats were bred in-house at George Mason University ($n = 47$) or ordered from Charles River Laboratories (Wilmington, MA; $n = 17$: ~175 g at the time of arrival). Locally and commercially derived animals were similarly distributed across experimental groups. Prior to experimentation, animals were housed two to three per cage. All methods were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the George Mason University Institutional Animal Care and Use Committee.

2.2. Apparatus

Rats were trained to find a food reward (Froot Loop cereal; Kellogg's) on a maze positioned in a room with a rich heterogeneous extra-maze environment (Fig. 1). We used a previously described multi-choice maze (the Opposing T's: OpT maze) set in a plus maze configuration (see Gardner et al., 2013; minor modifications are detailed). Briefly, four arm segments (north, east, south, and west) built off a central square (choice/decision point) were utilized. The south and north arms were potential starting positions, with identical opaque start boxes affixed to the ends of each arm. Reward cups were placed at the ends of the east and west arms. On any given run, three of the four arms were accessible, which restricted the maze to a "T" shape. The south, east, and west arms were open during training; the north, east, and west arms were open during probe trials. To limit falls during maze runs without restricting visual access to the extra-maze environment, clear Plexiglas railings were attached at the ends of each of the four arm segments.

2.3. Behavioral training

Food restriction and habituation were largely implemented as previously described (Gardner et al., 2013). Rats were individually-housed and maintained at 85% of their free-feeding weight throughout the experiment. While rats were brought down to their target weight, they were handled for five minutes each day. After being held a minimum of seven days and after meeting their target weight, rats were habituated to Froot Loop (FL) cereal (Fig. 1C: shaping) and given five minutes to explore the maze for each of two days (Fig. 1C: maze habituation).

The day after maze habituation, a one-time pre-training trial was administered after which training commenced. During these trials, an animal was placed in the south start box. After ~10 s, the front door to the box was remotely raised, using a pulley, providing the rat access to the maze. If a rat did not exit the start box after 180 s, the experimenter placed the animal on the maze directly in front of the box and closed its door to restrict re-entry. During all trials, the experimenter stood ~3 feet behind the south arm. The pre-training trial was unrewarded (no food was placed on the maze). On this trial, the arm first entered (with the full body excluding the tail) determined an animal's turn preference, and the opposite arm/turn was rewarded (with half of a piece of FL cereal) on all subsequent training trials for a given subject. This procedure ensured that all animals explored both arms at least once over the course of the experiment.

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