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Dissociable roles of the dorsal striatum and dorsal hippocampus in conditional discrimination and spatial alternation T-maze tasks

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ABSTRACT

The roles of the dorsal hippocampus (DH) and dorsal striatum (DS) in the learning and retention of conditional discrimination (CD) rules is a subject of debate. Although previous studies have examined the relationship between the DH and DS and the performance of CD tasks in operant chambers, the relative contributions of these two brain regions to the retention of CD rules requiring an association between a cue and a spatial location have not been characterized. We designed an experiment to assess the roles of the DH and DS in the retention of a visuospatial CD task by transiently inactivating either structure with muscimol in separate groups of rats and measuring performance on a previously learned CD task. The performance of two other groups of rats on a previously learned delayed spatial alternation (DA) task was also measured following inactivation of either DS or DH, which allowed us to control for any possibly confounding effects of spatial cues present in the testing room, length of the intertrial interval period on the performance of the CD task, and muscimol on sensorimotor or motivational processing. Muscimol inactivation of dorsal striatum, but not dorsal hippocampus, impaired CD performance, while inactivation of dorsal hippocampus, but not dorsal striatum impaired DA performance. These results demonstrate a double dissociation between the roles of the DH and DS in these two tasks, and provide a systematic characterization of the relationship between these two brain areas and CD performance.

1. Introduction

Substantial evidence suggests that the hippocampus and striatum are involved in dissociable forms of learning and memory (Mishkin, Malamut, & Bachevalier, 1984; Packard & Knowlton, 2002). The hippocampus supports allocentric spatial memory (Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe and Nadel, 1978), conscious declarative memory (Squire 1986, 1992; Tulving & Markowitsch, 1998), and the formation of conjunctive representations (Rudy & Sutherland 1989, 1995). In contrast, the striatum maintains unconscious procedural memories, which are responses that are strengthened during trial-and-error learning (Mishkin & Petrie, 1984; Phillips & Carr, 1987; Squire, Knowlton, & Musen, 1993).

Despite an extensive knowledge of the behaviors that the hippocampus and striatum respectively mediate, there are tasks for which the roles of these two brain structures remain unsettled. Two-choice conditional discrimination (CD), in which a reinforced response is conditional upon the presentation of a specific cue (i.e., if A, do X, if B, do Y) is an example of a task in which the contribution of the hippocampus is debated. Rats with hippocampal damage learn a serial-feature positive CD task (in which a response is reinforced following the serial presentation of two cues; either cue presented alone does not predict reward) at a significantly slower rate than intact rats; post-learning performance of this task is also disrupted following hippocampal lesions (Ross, Orr, Holland, & Berger, 1984). These results support the theory that the hippocampus is necessary for configural conditional discriminations in which the discriminanda consist of two or more elements of the environment that must be bound together into a unitary representation (Rudy & Sutherland, 1989). Other studies have demonstrated that the retention of an elemental CD rule (in which a single element serves as a discriminandum), but not a configural rule, is impaired following hippocampal lesions (Whishaw & Tomie, 1991). Further experiments have found that hippocampal disruption does not impair CD learning (Marston, Everitt, & Robbins, 1993), and that deficits in CD learning are different between animals that have aspiration lesions of the hippocampus and animals that have ibotenate lesions of the hippocampus (Jarrard & Davidson, 1991). These results suggest that different experimental factors, such as the manner in which neural function is disturbed and the time-point of neural inactivation (prior to learning vs. post-learning) can influence the degree to which cognitive and behavioral impairments are observed in CD tasks following hippocampal damage. One other factor that may influence the extent to which the hippocampus is involved in CD tasks is

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whether or not the task can be solved using a stimulus-response association. In these cases, damage to the striatum, but not the hippocampus, should selectively disrupt task learning and performance. In support of this view, damage to the dorsal striatum impairs both the acquisition (Featherstone & McDonald, 2005; Winocur & Eskes, 1998) and post-learning retention (Adams, Kesner, & Ragozzino, 2001) of elemental CD tasks that can be solved using a stimulus-response strategy.

Conditional discrimination tasks that require a spatial response, such as tasks in which a conditional cue is associated with the location of a reward on a maze, are a particular variant of CD problem that is less well characterized with regard to the involvement of the dorsal hippocampus (DH) and dorsal striatum (DS). Spatial alternation, in which the location of a reward in an upcoming trial is contingent upon the response made in a previous trial (i.e., if the animal made a left turn on the previous trial, it must make a right turn on the upcoming trial), is a CD problem in which both the discriminanda and the response are based on the spatial location of the animal. Delayed spatial alternation, in which alternate visits to opposite goal arms are separated by an intertrial delay period, is dependent on DH (Ainge, van der Meer, Langston, & Wood, 2007; Czerniawski, Yoon, & Otto, 2009; Dudchenko, Wood, & Eichenbaum, 2000). This result indicates that the hippocampus is necessary for CD problems that involve a spatial cue (previous response of the animal) and a spatial response (making a right or left turn on a T-maze). The acquisition of CD tasks that require the animal to form a conditional association between a non-spatial cue and a reward location is also reliably disrupted by hippocampal damage (Modo, Sowinski, & Hodges, 2000; Murray & Ridley, 1999; Ridley, Timothy, MacLean, & Baker, 1995). Hippocampal lesions and ischaemic brain damage limited to hippocampal subfield CA1 both produce impairments in the acquisition of a Y-maze task in which an animal must associate the appearance of a floor insert with the location of a reward (Modo et al., 2000; Murray & Ridley, 1999). These data suggest that CD learning that requires an animal to form an association between a conditional cue and the spatial location of a reward may be a special case of conditional discrimination for which the hippocampus is necessary. However, interpretations of these results are hindered by the lack of a controlled study that eliminates possibly confounding experimental variables. For example, the pre-training lesions employed in these studies (Modo et al., 2000; Murray & Ridley, 1999) prevent the distinction between the effects of hippocampal damage on acquisition and retention of CD rules to be made. Jarrard and Davidson (1991) have also shown that rats with aspiration lesions of the hippocampus (which damage axonal fibers of passage to upstream structures) are impaired in their ability to learn a CD task in an operant chamber, but that rats with ibotenate lesions of the hippocampus (which destroyed more hippocampal tissue than the aspiration lesions, but spared fibers of passage) acquired the CD task at the same rate as intact animals. These data suggest that the lesioning technique employed can affect the degree to which the performance of animals with hippocampal damage is impaired in CD tasks, highlighting the need for a consistent method of neural disruption across studies. One such method of disruption is the utilization of muscimol, a $GABA_A$ receptor agonist that temporarily inactivates neuronal activity at the site of its infusion. Muscimol offers two distinct advantages over conventional lesioning techniques; its effects are temporary, allowing for the creation of within-subjects experimental designs, and unlike lesions, muscimol does not create any permanent damage to either cell bodies or fibers of passage (Beaumont, Chilton, Yamamura, & Enna, 1978; Majchrzak & Di Scala, 2000).

Although previous studies have attempted to characterize the role of the DH in the acquisition of maze-based conditional discrimination tasks, whether or not the DH is necessary for the retention of such tasks remains an open question. In addition, the role of the DS in CD performance that requires a spatial response has not been examined. Brain inactivation technique, behavioral apparatus, behavioral testing room, and the motor pattern used by the animal to complete the task are all external variables that can affect behavior and limit the interpretation of results. Therefore, it is necessary to employ an experimental design that limits the influence of these possibly confounding variables by making behavioral comparisons across distinct tasks that take place in the same experimental setting.

In order to systematically examine the relative contributions of the DH and DS to conditional discrimination performance in a maze, we trained different groups of rats on two different tasks that took place on the same T-maze, in the same behavioral testing room, had an equal number of trials per session, had the same intertrial interval period (30 s), and required the rat to use the same motor pattern. This type of approach has been used in the past to differentiate the roles of the striatum and hippocampus in spatial and response tasks respectively (Packard, Hirsh, & White, 1989; Packard, Winocur, & White, 1992), but to our knowledge is the first time it has been used to characterize the roles of these two brain regions in CD performance. One of the tasks was a delayed alternation (DA) task, in which rats were required to alternate between the left and right goal arms following a 30-s delay period on successive trials. Both hippocampal lesions and temporary inactivation of the hippocampus with muscimol have been shown to produce performance deficits in this task (Ainge et al., 2007; Czerniawski et al., 2009; Dudchenko et al., 2000). The other task was a visuospatial conditional discrimination (CD) task, in which the texture and visual appearance (either wood or black mesh) of a floor insert presented at the start of each trial acted as a cue that predicted the baited goal arm. Between trials, rats waited on an intertrial interval (ITI) pedestal for 30 s. This task has previously been shown to be sensitive to hippocampal damage in a Y-maze (Modo et al., 2000; Murray & Ridley, 1999). After rats learned to perform either the DA or CD task efficiently at a predetermined criterion level, either DH or DS was inactivated with muscimol, and performance was assessed.

2. Materials and methods

2.1. Subjects

Thirty seven male, adult, Long-Evans Hooded rats (Harlan, Indianapolis) were housed individually in a temperature and humidity-controlled colony room on a 12 h light-dark cycle. Rats were given a 1 week acclimation period with ad libitum access to food and water, and were thereafter food-deprived to 90% of their free-feeding weight during handling, pretraining, and behavioral testing.

2.2. Behavioral apparatus and pretraining

Both tasks were performed on a modified wooden T-maze, consisting of a central stem (116×10 cm), two goal arms (56.5×10 cm each), and two return arms (112×10 cm each) (see Fig. 1). Each section of the maze was surrounded by 6 cm high wooden barriers. Between trials, animals waited on an intertrial interval (ITI) pedestal located at the base of the maze. The pedestal was blocked off from the maze by a large, removable wooden barrier. The training room was dimly lit with a compact fluorescent bulb, contained a noise generator that played low volume white noise during pretraining and testing sessions, and had black curtains that completely encircled the testing area with various visual cues attached. Before rats began behavioral testing, they were han-