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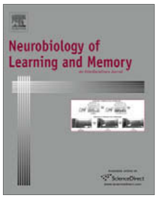

Effects of rodent prefrontal lesions on object-based, visual scene memory

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ABSTRACT

It has been suggested that certain prefrontal areas contribute to a neural circuit that mediates visual object memory. Using a successive go/no-go visual scene discrimination task, object-based long-term memory was assessed in two rodent prefrontal regions. Rewarded trials consisted of a standard scene of four toy objects placed over baited food wells. The objects and their locations composing the standard scene remained constant for the duration of the study. Trials in which one of the standard scene objects was replaced with a novel object were not rewarded. Following the establishment of a significant difference between latency to approach the rewarded standard scene compared to latency to approach non-rewarded scenes, quinolinic acid or control vehicle was infused into either the prelimbic and infralimbic cortices or the anterior cingulate cortex. Following a 1 week recovery period, subjects were retested. Animals with prelimbic/infralimbic cortex lesions displayed a profound and sustained deficit, whereas, animals with anterior cingulate cortex lesions showed a slight initial impairment but eventually recovered. Both lesion groups acquired a simple single object discrimination task as quickly as controls indicating that the deficits on the original scene discrimination task were not due to motivational, response inhibition, or perceptual problems.

1. Introduction

The rodent prefrontal cortex is believed to be involved in a number of high-level processes such as attention, working memory, planning, decision making, response inhibition and the regulation of emotion needed to carry out complex cognitive and social behaviors. Several lines of evidence including cytoarchitectural (Krettek & Price, 1977; Van Eden & Uylings, 1985), efferent/afferent connectivity (Berendse, Galis-de Graaf, & Groenewegen, 1992; Leonard, 1969; Maurice, Deniau, Glowinski, & Thierry, 1998; Sesack, Deutch, Roth, & Bunney, 1989; Wright & Groenewegen, 1995), neurochemical (Ragozzino, 2000; Sesack, Hawrylak, Matus, Guido, & Levey, 1998; Steketee, 2003; Zahrt, Taylor, Mathew, & Arnsten, 1997), and early gene expression (Graybiel, Moratalla, & Robertson, 1990; Morrow, Elsworth, Inglis, & Roth, 1999) indicate that the rodent prefrontal cortex can be parsed into distinct sub-regions. Furthermore, it has been proposed that functional properties of these individual sub-regions may be uniquely specialized (Dalley, Cardinal, & Robbins, 2004; Heidbreder & Groenewegen, 2003; Kesner, 2000) in a way that corresponds to the specific functional sub-regions of primate prefrontal cortex (Granon & Poucet, 2000; Kesner, 2000; Kolb, 1984; Preuss, 1995). The anterior cingulate cortex (AC) and the prelimbic–infralimbic cortices (PL–IL) are two territories within the rodent medial prefrontal cortex that have been shown to be functionally dissociable in terms of behavioral sensitization to psychostimulants (Tzschentke & Schmidt, 2000), temporal sequencing versus attention (Delatour & Gisquet-Verrier, 2001; Gisquet-Verrier, Winocur, & Delatour, 2000) and cost/benefit decision making versus rule learning (Walton, Bannerman, Alterescu, & Rushworth, 2003). The present study aims to contribute further to the mounting body of evidence pointing to distinct functional specificities of the rodent AC and PL–IL.

A great deal of evidence exists implicating the rodent AC in complex cognition. Lesions to this area disrupt performance on a wide array of cognitively demanding tasks such as ones that emphasize visual object conditional associations (Passingham, Myers, Rawlins, Lightfoot, & Fearn, 1988; Winocur & Eskes, 1998) memory for temporal order (Chiba, Kesner, & Gibson, 1997; Kesner, 1998) or frequency information (Kesner, 1990), the use of prospective codes (Kesner, Farnsworth, & DiMattia, 1989), behavioral sequencing (Delatour & Gisquet-Verrier, 2001), attentional selectivity (Passetti, Chudasama, & Robbins, 2002), and spatial win-shift rules (Seamans, Floresco, & Phillips, 1995). However, there is also evidence that mnemonic functions of the AC may be driven in a domain specific manner. For example, although lesions of this area create short-term memory impairments for information related to egocentric responses (Kesner, Hunt, Williams, & Long, 1996;

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Kesner et al., 1989; Ragozzino & Kesner, 2001), comparable lesions do not disrupt performance on an analogous working memory test for affect (DeCoteau, Kesner, & Williams, 1997).

The PL–IL receives afferents from sensory, motor, and limbic structures (Krettek & Price, 1977). Specifically, the CA1 region of the hippocampus projects selectively to the PL–IL (Jay & Witter, 1991; Swanson, 1981) and likely supports this prefrontal subregion's central role in emotion, memory, and high-order cognition. Damage to the PL–IL promotes anxiety-related behaviors (Heidbreder, Thompson, & Shippenberg, 1996) disrupts extinction of conditioned fear (Morgan, Romanski, & LeDoux, 1993), increases impulsivity (Chudasama et al., 2003), impairs passive-avoidance (Jinks & McGregor, 1997), and disrupts the ability to shift between place- and response-based learning strategies (Ragozzino, Detrick, & Kesner, 1999). As with the AC, the PL–IL seems to be critical for some categories of working memory but not others. For example, lesions to this area impair spatial working memory (Brito & Brito, 1990; Delatour & Gisquet-Verrier, 1996; Fritts, Asbury, Horton, & Isaac, 1998; Ragozzino, Adams, & Kesner, 1998) but not working memory for affect (DeCoteau et al., 1997).

The rodent PL–IL may also contribute to the processing of detailed information in the visual domain. Damage to PL–IL impairs visual object working memory (Kesner et al., 1996; Ragozzino, Detrick, & Kesner, 2002) and flexible switching between visual-cued and spatial learning (Ragozzino et al., 1999). However, no deficits are found for comparable lesions in simpler visual conditional discrimination tasks (Bussey, Muir, Everitt, & Robbins, 1997; Delatour & Gisquet-Verrier, 1999). One interpretation of this set of findings is that the PL–IL is specifically recruited when task performance requires highly effortful processing. This idea is consistent with literature suggesting that attentional demands and task difficulty are an important consideration for understanding rodent PL–IL involvement (Granon & Poucet, 2000). Similar conclusions have been reached by those studying the dorsolateral prefrontal cortex of human and non-human primates (Owen, Evans, & Petrides, 1996; Petrides, 1996).

Based on a synthesis of literature across mammalian species, a rule-based model of prefrontal fractionation has been proposed that incorporates both domain specificity and information complexity (Kesner, 2000; Wise, Murray, & Gerfen, 1996). A scene discrimination task developed by DeCoteau and Kesner (1998) may be a useful paradigm to test this idea. The task involves presenting rats with different scenes of toy objects. In the visual object version of the task, the spatial arrangement of the scene remains consistent from trial to trial, but a single toy object making up the scene may change. Animals are required to discriminate scenes containing a novel object from scenes containing a standard set of objects. An advantage to this paradigm is that the complexity of the task can be systematically manipulated. For example, a difficult version of the task may require animals to discriminate scenes composed of multiple objects, whereas the simplest form may require animals to discriminate scenes composed of a single object. The present study utilizes the rodent visual scene paradigm to assess the contribution of the PL–IL and AC regions to object-based memory. The role of processing complexity will be assessed by having animals complete a challenging four-object scene discrimination task followed by a less effortful, single object version of the task.

2. Method

2.1. Subjects

Fifteen adult male Long-Evans rats were randomly assigned to the object scene discrimination task. All rats were maintained at approximately 85–90% of their free feeding weight with free access to water. They were housed individually in metal hanging cages on a 12 h:12 h light/dark cycle. All surgical and experimental protocols conformed to St. Lawrence University IACUC, University of Utah IACUC, and AAALAC protocols and regulations.

2.2. Apparatus

The testing apparatus was a shuttle box consisting of an 84 cm × 27 cm painted wood floor, and four 30.5 cm high, nontransparent, red[1] Plexiglas walls. Two removable guillotine doors, likewise constructed of nontransparent, red Plexiglas, placed 25 cm from either end of the box effectively divided the box into three separate compartments (two start/end areas and a central runway). A 5 × 4 matrix of 2 cm in diameter and 1.5 cm deep food wells, separated by 2.5 cm, was drilled in the floor at both ends of the apparatus. A top-down view of the floor of the box is shown in Fig. 1A. All testing was conducted during the light phase of the light:dark cycle.

2.3. Design and stimulus material

The object-based scene discrimination task required the animal to distinguish a standard scene from scenes where one of the objects had been replaced with a new object. Discriminations were assessed using a successive go/no-go paradigm whereby successful performance entailed approaching scenes that resulted in reinforcement (positive) and not approaching scenes that did not result in reinforcement (negative). Prior to each trial, subjects were placed behind a start door in one of the apparatuses end compartments; the guillotine door associated with the opposite end compartment was removed and a scene of toy objects was arranged over that compartment's matrix of food wells. The standard scene consisted of four toy objects placed over food wells baited with 1/2 pieces of Froot Loop cereal. All objects were affixed to 5 cm in diameter rubber-coated base to prevent the release of odors from within the food wells. The arrangement and type of objects in the standard scene remained unchanged for the duration of the experiment. Fig. 1B depicts the arrangement of the objects for standard scene. The replacement of any one of the standard scene's four objects with an object selected from a 120 novel object set was the sole demarcation of an object-based transformed scene. The covered food wells in the transformed scene were not baited. Fig. 1C illustrates the four possible spatial locations for an object-based transformation.

Fourteen trials consisting of six standard scenes and eight transformed scenes were randomly presented each day, 5 days a week. The eight daily non-reinforced trials were generated by replacing each of the four standard scene objects twice. The dependent measure was the latency (s) from the opening of the start door to the movement of the first object by the animal (the maximum latency for each trial was 10 s). Rats were trained until they reached the criterion based on 140 trials of a 3 s or greater mean latency difference between the standard scene and the transformed scenes.

2.4. Surgery

Once rats reached criterion, they were given either anterior cingulate cortex ($n = 5$), pre- and infralimbic cortex ($n = 5$), or vehicle control lesions ($n = 5$) under Nembutal anesthesia (55 mg/kg, i.p.). All lesions were made by slowly infusing with a Hamilton syringe 0.6 μl of quinolinic acid (21 mg/ml) at each stereotaxic coordinate. Coordinates for pre- and infralimbic lesions were as follows: AP (Anterior, Posterior) = +3.5, ML (Medial, Lateral) = ±0.6, DV (Dorsal,

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[1] For interpretation of color in Fig. 1, the reader is referred to the web version of this article.