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Serial position functions following selective hippocampal lesions in monkeys: Effects of delays and interference☆

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ABSTRACT

We examined the role of the hippocampus in list-memory processing. Three rhesus monkeys that had extensive experience in this task and had demonstrated full abstract-concept learning and excellent list memory performance (Katz et al., 2002; Wright et al., 2003) received bilateral neurotoxic hippocampal lesions and were re-tested in the serial list memory task. Effects of delays on memory performance were measured in all monkeys, whereas the effects of proactive interference were assessed in only one. Despite a slight change in performance of one of the three animals during re-learning of the same/different task, selective hippocampal damage had little or no effects on list memory accuracy. In addition, the hippocampal damage did not impact serial list position functions (SPFs) but slightly altered the dynamic of the SPF curves. Finally, even more remarkable was that accurate memory performance of one animal remained intact despite the use of small set size of 8 items that created high proactive interference across lists thereby eliminating any use of familiarity judgments to support performance. Together the findings indicate that, with short list items and extensive training in the task (i.e., reference memory), monkeys with selective hippocampal lesions may be able to use alternative memory processes (i.e., working memory) that are mediated by structures other than the hippocampus.

1. Introduction

Over the past decade, the contributions of the hippocampus and medial temporal lobe cortex to recognition have generated a host of studies in many species, but at the current time the specific role of each of these brain structures remains heavily debated. An example is provided by the recent issue of the journal "Hippocampus" (2010, vol. 20) exposing the different views fueling this debate. One of the reasons this controversy has lasted so long is the disagreement over how to measure hippocampal and cortical contributions to recognition memory. Recognition memory in humans is commonly assessed with list learning tasks in which participants study a set of stimuli (pictures of objects, visual patterns, faces, or words), and after a delay, judge whether the stimuli are familiar (included in the list) or new. Studies on human amnesic patients with damage to the hippocampus or adjacent cortical areas (Aggleton and Shaw, 1996; Bowles et al., 2007; Holdstock et al., 2002; Mayes et al., 2003; Mishkin et al., 1998; Reed et al., 1997; Stark et al., 2002; Vargha-Khadem et al., 1997) and functional imaging studies (Yonelinas and Parks, 2007; for reviews, see Eichenbaum et al., 2007; Skinner and Fernandes, 2007; Wais, 2008) have suggested that the hippocampus is involved in recognition memory only when participants fully recollect the items (i.e., the items and all other information associated with the items, such as whether the words were shown in red or green or the pictures were emotionally positive or negative), but not when they simply used familiarity judgments (was the item in the list or not?), which are supported by the medial temporal cortical areas. Another view, however, proposed that the strength of the memory traces is the critical attribute such that memory traces with strong or weak memory load may require the hippocampus and medial temporal cortex, respectively (Squire et al., 2007; Wixted et al., 2010).

Animal studies have attempted to resolve this disagreement but without convincing success so far. For example in monkeys, recognition memory has generally been investigated using delayed matching-to-sample (DMTS) or delayed nonmatching-to-sample (DNMTS) tasks in which the animal has to indicate which of two stimuli has been seen earlier by choosing either the familiar (match) or the novel (nonmatch) stimuli presented together

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during a choice test. Generally, these tasks employed a large pool of stimuli (500 to thousands). Memory is then further assessed by increasing the delays between the sample presentation and the choice or by increasing the list of items to be remembered. Using these tasks, lesion studies have provided conflicting results. Thus, whereas some studies have reported recognition deficits at the long delays or long lists following selective hippocampal lesions (Beason-Held et al., 1999; Zola et al., 2000), others found no impairment (Baxter and Murray, 2001; Murray and Mishkin, 1998; Nemanic et al., 2004). One potential limitation with the nonhuman primate studies is that the DMTS and DNMTS paradigms may rely on memory processes different from those that support the list memory tasks in humans (see Nemanic et al., 2004). The memory processes supporting DNMTS performance could include familiarity judgment, working memory, or retrospective processing, which could recruit brain areas other than the hippocampus, such as the medial temporal and prefrontal cortices known to be critical for normal performance on DNMTS tasks (Bachevalier and Mishkin, 1986; Brown and Aggleton, 2001; Ennaceur et al., 1996; Fahy et al., 1993; Gaffan and Murray, 1992; Kolb et al., 1994; Meunier et al., 1993; Miller et al., 1996; Murray and Bussey, 1999; Nemanic et al., 2004; Pihlajamaki et al., 2004; Simons and Spiers, 2003; Suzuki et al., 1993; Xiang and Brown, 2004).

In an attempt to investigate further the reasons for this disagreement and enable better comparisons with results from the human literature, the present study employed a serial list memory task similar to that used in humans (Wright et al., 1985) to re-assess the effects of selective hippocampal lesions on recognition memory in monkeys. In this task, animals are presented with a short list of items on a computer monitor followed by a probe test. The probe test presents either an item seen in the list or a new item together with a white rectangle. To receive a reward, the animal has to touch the item on the screen if it was an item of the list or touch the white rectangle if the item was new. The serial list memory task offers several advantages relative to the previous matching tasks. First, as compared to the DNMTS task in which both the familiar and new items are present together on the screen during the animal's selection (familiar versus novel), the serial list memory task presents only one item necessitating a "yes/no" or "same/different" response. Thus, the forced-choice response in the DNMTS task may favor the use of familiarity/novelty judgment that are more dependent upon the medial temporal cortex to the detriment of same/different relational representations and retrieval strategies, which depend more heavily upon the hippocampus (Damasio et al., 1985; Eichenbaum et al., 1989, 2007; O'Keefe and Nadel, 1978; Rudy and Sutherland, 1989, 1992; Shapiro and Olton, 1994; Sutherland and Rudy, 1989).

Another important advantage of the serial list memory task over the DNMTS in the investigation of the participation of the hippocampus in recognition memory is that the list memory task can better dissociate different memory processes. In a previous study comparing serial list memory abilities in pigeons, monkeys and humans, Wright et al. (1985) demonstrated that the typical serial U-shaped position function with good (long-term) memory of the first list items (primacy effect) and a good (short-term) memory of the last list items (recency effect) normally found in human studies was also present for pigeons and monkeys. Furthermore, the authors demonstrated that in those three species, the shape of the serial-position function changed with varying the retention intervals between the end of the list and the probe test. That is, at short retention delays, recognition memory increased monotonically with better memory for the last items of the list; for intermediate delays, the serial list curve had U-shape functions with better memory for the first and last items than for the middle ones; lastly, for long retention delays, recognition memory decreased monotonically with better memory for the first items of the list. The authors suggested that these dynamic changes in serial-position functions reflect the participation of two or more memory processes. This conclusion is strengthened by the numerous demonstrations showing that the primacy and recency effects can be independently altered. Variables that selectively affect the recency effect include: moderate to long retention delays (e.g., Gardiner, 1974; Glanzer and Cunitz, 1966; Postman and Phillips, 1965; Roediger and Crowder, 1976; Wright et al., 1985); auditory vs. visual modality of stimulus presentation (e.g., Crowder, 1986; Crowder and Morton, 1969; Murdock, 1966; Wright, 2007); and knowledge about the end of the list (Watkins and Watkins, 1974). Variables that selectively affect the primacy effect include: fast presentation rates (Glanzer and Cunitz, 1966), long list lengths (Murdock, 1962), very short retention delays in single-item recognition tasks (Wright et al., 1985), alcohol intoxication (Jones, 1973), and mental retardation (Belmont and Butterfield, 1971).

Interestingly, there exists also neuropsychological evidence to support this functional dissociation of memory processes in serial list learning task. Thus, different brain areas seem to independently support the primacy and recency effects. The prefrontal cortex known to be critical for working memory processes and perirhinal cortex known to mediate short term memory have been associated with the recency effect (Barker and Warburton, 2011; Goldman-Rakic, 1987; Kesner, 1985; Saffran and Marin, 1975; Warrington et al., 1971; Warrington and Shallice, 1984; Weiskrantz, 1987), whereas the hippocampus has been associated with long-term (primacy) memory (e.g., Baddeley and Warrington, 1970; Hermann et al., 1996; Hopkins and Kesner, 1995; Hopkins et al., 1995; Kesner, 1998; Kesner and Novak, 1982).

The advantages provided by the serial list learning task over the DMTS and DNMTS offers an improved method with which to assess the role of hippocampus in recognition memory. More importantly, task manipulations, such as length of the delays and magnitude of the proactive interference across list items, may inform recent theories concerning the precise role of the hippocampus in recognition memory (see reviews of the current neural models in the review Hippocampus, 2010, vol. 20). Therefore, in this study, three rhesus monkeys with extensive experience in a serial list memory task were used (Katz et al., 2002; Wright et al., 2003). All monkeys had demonstrated full abstract-concept learning and excellent list memory performance before receiving bilateral neurotoxic lesions of the hippocampal formation. After recovery from surgical procedures the monkeys were then re-tested in the serial list learning task.

2. General methods

All procedures were approved by the Animal Care and Use Committee of the University of Texas Health Science Center at Houston in Houston, TX and carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize the number of animals used, as well as any pain and suffering.

2.1. Subjects

Subjects were three, 6–12 year-old, rhesus monkeys (*Macaca mulatta*) of both sexes, weighing 5–12 kg (Cuba, Gracie, and Slim). They were housed individually and maintained on a 12:12 h light–dark cycle. Multi-vitamins were given daily and fresh fruit weekly. All three monkeys received presurgical training on a two-item same/different task and then list memory (Katz et al., 2002; Wright et al., 2003). Experimental training sessions were conducted 5–7 days a week. On testing days, access to food (Purina Monkey Chow) and water in their home cages was restricted about 15 h