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Dissociation between memory retention across a delay and pattern separation following medial prefrontal cortex lesions in the touchscreen TUNL task ☆

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ABSTRACT

The neural structures that support the retention of memories over time has been a subject of intense research in cognitive neuroscience. However, recently much attention has turned to pattern separation, the putative process by which memories are stored as unique representations that are resistant to confusion. It remains unclear, however, to what extent these two processes can be neurally dissociated. The trial-unique delayed nonmatching-to-location (TUNL) task was developed to assess spatial working memory and pattern separation function using trial-unique locations on a touch-sensitive screen (Talpos, McTighe, Dias, Saksida, & Bussey, 2010). Using this task, Talpos et al. (2010) showed that lesions of the hippocampus led to both impairments with a 6 s delay, and impairments in pattern separation. The present study shows that lesions of the medial prefrontal cortex lead to a different pattern of effects: impairment at the same, 6 s delay, but no hint of impairment in pattern separation. In addition, rats with medial prefrontal lesions were more susceptible to interference in this task. When compared with previously published results, these data show that whereas the prefrontal cortex and hippocampus likely interact in the service of working memory across a delay, only the hippocampus and not the medial prefrontal cortex is essential for pattern separation.

1. Introduction

The neural structures that support the retention of memories over time has been a subject of intense research in cognitive neuroscience. Recently, however, researchers have become increasingly interested in the putative process of *pattern separation*, through which memories are stored as unique representations that are resistant to confusion (Clelland et al., 2009; Gilbert, Kesner, & DeCoteau, 1998; Yassa & Stark, 2011). It remains unclear, however, to what extent these two processes can be neurally dissociated. To achieve this aim, both memory across a delay and pattern separation must be assessed using the same procedure. There is some very intriguing evidence using such an approach. Kesner and colleagues, for example, provided evidence that hippocampus lesions can impair both memory across a delay, and pattern separation (Gilbert et al., 1998; Kesner, Lee, & Gilbert, 2004; Lee & Kesner, 2002, 2003). However more selective dentate gyrus lesions could impair memory in a separation-dependent manner (Gilbert, Kesner, & Lee, 2001); CA3 lesions, in contrast, did not produce the same separation-dependent deficit, but rather impaired memory at all separations, and at the shortest delays (Gilbert & Kesner, 2006).

Subsequent studies using a number of different approaches have provided further evidence that spatial pattern separation involves cells within the dentate gyrus (Clelland et al., 2009; Goodrich-Hunsaker, Hunsaker, & Kesner, 2008; Kesner, 2007; McHugh et al., 2007). In contrast, the structure most often associated with the process of working memory – "holding information on-line" across a delay interval – is the prefrontal cortex (PFC) (Brown & Bowman, 2002; Courtney, Petit, Haxby, & Ungerleider, 1998). In the present study, we tested the hypothesis that whereas the hippocampus is important for both memory across a short delay and pattern separation (Kesner et al., 2004; Talpos et al., 2010), the PFC is likely to be important only for the former, with spatial pattern separation the selective domain of the dentate gyrus. To test this idea, we used the trial-unique delayed nonmatching-to-location (TUNL) task, developed to assess spatial working memory and pattern separation function using trial-unique locations on a touch-sensitive screen (Talpos et al., 2010). These authors examined task performance after excitotoxic lesions of the hippocampus on performance of TUNL under conditions in which either delay, or spatial separation, was varied parametrically. Hippocampal lesions had no effect at minimal delays and short separations, but significantly impaired performance when the delay period was increased, *or* the separation decreased. In the present study the effects of

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medial prefrontal cortex (mPFC) lesions were examined under these same conditions. We also tested the additional hypothesis that mPFC lesions would increase susceptibility to interference (Badre & Wagner, 2005; Jonides & Nee, 2006; Postle, Brush, & Nick, 2004).

2. General materials and methods

2.1. Subjects

Male 250–275 g Lister Hooded rats were obtained from Harlan, UK. Rats were group housed on a reverse light–dark schedule (lights on 7 pm–7 am) and tested during the dark phase. A restricted diet was employed to maintain rats at no less than 85% of free-feeding weight, with water available ad libitum. Rats were habituated to the facility and handling for one week prior to any behavioural training. This experiment was conducted in accordance with the United Kingdom Animals (Scientific Procedures) Act, 1986.

2.2. Apparatus

Med Associates (Vermont, USA) rat chambers were similar to those used in previous touchscreen studies (Talpos et al., 2010). The inner chamber is 30 cm wide, 25 cm deep, and 25 cm high consisting of a metal frame with clear Perspex walls. The floor consisted of stainless steel bars spaced 1 cm apart and 3 cm above a tray lined with filter paper. The touchscreen monitors register touch by infrared detectors (Craft Data Ltd., Bucks, UK; ELO Touchsystems, Wiltshire, UK; Displaze, Aylesbury, UK) interfaced by ELO touchscreen software (ELO Touchsystems Inc). The touchscreen monitor (4 cm × 29 cm viewable area, Craft Data Ltd., Chesham, UK) was covered by a black Perspex mask to create 14 active response windows 2 cm by 2 cm, separated by 0.9 cm and raised 16.5 cm from the floor. A spring-hinged 'shelf' was attached 16 cm above the grid floor. This shelf was at a 90° angle to the mask and had a depth of 6 cm with a width of 20.5 cm. Masks were attached to the screen leaving a gap of 5 mm between the mask and monitor to ensure that it would not trigger the touchscreen area. On the wall opposite from the monitor was a food magazine (ENV-200R2M) equipped with a 3 W light and infrared detector to register nose pokes (Med Associates Inc., Vermont, USA). The magazine was serviced by a pellet dispenser (Med Assoc. ENV-203-45) delivering 45 mg 5-TUL AIN-76A dustless pellets (TestDiet, Indiana, USA). Above the food magazine was a house light (3 W, Med Assoc. ENV-215M), and tone generator (Med Assoc. ENV-223HAM). Each operant box is housed within a sound-attenuating chamber equipped with a 28 V DC fan. The boxes and monitors were controlled using IBM Netvista and Dell Optiplex computers running custom programs written in Microsoft Visual Basic 6.0.

2.3. Behavioural methods

The TUNL task consists of two phases: sample and choice. At the sample phase one location within a grid of fourteen squares is illuminated. The rat must respond to the illuminated sample location, then return to the rear food magazine (sample is rewarded in 33% of trials) to initiate the choice phase. During the choice phase the sample square and a novel square are illuminated, and the rat must correctly non-match by selecting the novel square (Fig. 1). A delay can be placed between the sample and choice phases to tax working memory.

As previous discussions of the touchscreen have highlighted, an advantage of this method over two-lever tests such as in delayed non-matching to position (DNMTP) is that stimulus options are not limited to merely two locations (Talpos, Dias, Bussey, & Saksida, 2008). Although the TUNL task is similar to DNMTP in that two locations are used during a given trial, any of the thirteen alternative locations can serve as the correct stimulus on choice. Thus, unlike in DNMTP, the animal cannot know, during the delay, which location will be correct on choice – and therefore cannot orient toward it. Indeed, systematic video analysis of TUNL showed little evidence for performance-enhancing mediating behaviours (Talpos et al., 2010). The use of multiple locations confers an additional advantage; namely, pairs of locations can be chosen which are either close together, far apart, or somewhere in between. This allows assessment of pattern separation alongside the assessment of memory across a delay.

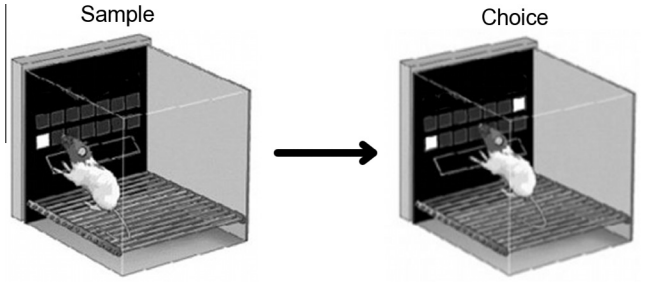

Fig. 1. The TUNL task. Images adapted from Talpos et al. (2010). A large separation condition is shown.

Pretraining followed a similar procedure to that previously reported (Talpos et al., 2010). Session length was 80 trials (sample + choice) or 1 h, with a 20 s intertrial interval (ITI) and no programmed delay between sample and choice phase. The trial structure of TUNL is described in Table 1.

Rats were trained to stable above-chance performance across separations and the 14 best performers were taken forward to the task proper. Rats were baselined pre-surgery on three conditions presented in separate sessions (two blocks of three sessions per condition): large separation, no (that is, minimum possible) delay (LND); large separation with 6-s delay (LWD); and small separation, no delay (SND). Large separation was defined as five locations as horizontal distance between active choice locations. Small separation was defined as two locations as horizontal distance between active choice locations. Each condition was given as a session of 40 trials in 1 h, cycling through the three conditions across days and punctuated with sessions of all separations and no programmed delay (as during acquisition) to minimise the adoption of possible mediating behaviours. Rats were assigned to sham and lesion groups based on baseline performance. Post surgery testing was conducted similarly to pre-surgery baselining. Initial short sessions of 10 and 20 sessions were used to ensure all animals were ready to complete sessions, before cycling though full sessions of all three conditions.

After exploration of LND, LWD, and SND, an interference condition was also tested to investigate whether early trials could interfere with later trials in a given session. In spatial working memory

Table 1
Trial structure of TUNL.

House light and magazine light on	
Nose-poke to magazine → Magazine light off, sample location illuminated	
Nose-poke to sample location →	33.3% of trials: tone, magazine light 1s, reward
	All trials: start delay timer
Delay timer end → Magazine light illuminated	
Nose-poke to magazine → Choice phase locations illuminated	
Incorrect response → House light off for 5 s followed by correction trial	
Correct response → Tone, magazine light on, reward delivered	
Reward collected → Magazine light off, ITI begins	