Brain Research Bulletin 116 (2015) 34–44

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Prefrontal cortex and hippocampus in behavioural flexibility and posttraumatic functional recovery: Reversal learning and set-shifting in rats

Hana Malá, Lykke Grønbech Andersen, Rie Friis Christensen, Anita Felbinger, Julie Hagstrøm, David Meder, Hadley Pearce, Jesper Mogensen*

The Unit for Cognitive Neuroscience, Department of Psychology, University of Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 5 February 2015
Received in revised form 17 May 2015
Accepted 18 May 2015
Available online 29 May 2015

Keywords:
Prefrontal cortex
Hippocampus
Reversal learning
Set-shifting
Behavioral strategy
Functional recovery

ABSTRACT

Within one experiment and one T-maze, we examined the consequences of (i) bilateral lesions of the anteromedial prefrontal cortex (PFC), (ii) bilateral transections of the fimbria-fornix (FF), or (iii) combined lesions of both PFC and FF (COMB) on rats' ability to perform reversal or set-shifting. Postoperatively, the animals were trained to perform a spatial discrimination go-right task. This was followed by (1) a spatial reversal go-left task (reversal learning), or (2) a visual pattern discrimination task (set-shift). Neither single (PFC or FF) lesion nor combined (COMB) lesions affected the animals' ability to acquire the original spatial discrimination task. Regarding the reversal learning, the performance of the PFC and the FF groups was not significantly different from that of the sham operated control animals (Sham). In contrast, animals with combined lesion of both structures were impaired on both error rate and acquisition speed relative to all other groups. Regarding the set-shifting, all lesioned groups were impaired relative to the Sham group both regarding the error rate and the acquisition speed. There was, however, no difference in the degree of impairment between the lesioned groups. We conclude that both the PFC and the hippocampus contributed to the mediation of the reversal learning and set-shifting. During functional recovery of reversal learning, these two structures exhibited a mutual dependency, whilst the functional recovery of set-shifting was mediated by a substrate outside these two structures.

1. Introduction

The ability to react flexibly in an ever-changing environment represents a prerequisite for successful survival of any species. Flexible behaviour is characterized by prompt and accurate responses whereby the individual meets the demands of a given situation. Behavioural shifts of responses within one cognitive dimension as well as across cognitive dimensions represent one such form of behavioural flexibility. Behavioural shifts within one dimension (e.g. shift according to shape or according to spatial position), also denoted as intra-modal shifts (Ragozzino et al., 1999a), shifts between responses (Mogensen et al., 2003a), and reversal learning (Birrell and Brown, 2000) represent a simpler form of flexible switching and are acquired more easily. Behavioural shifts across cognitive dimensions (e.g. shift from shape to odour or from spatial position to visual cue), also denoted as cross-modal shifts (Ragozzino et al., 1999a), strategy set-shifting (Birrell and Brown, 2000; Floresco et al., 2008a), and shifts between strategy (Mogensen et al., 2003a) require more time to acquire and effort to perform. The current study focuses on the role of the prefrontal cortex (PFC) and the hippocampus in reversal learning and set-shifting, and not the least on their interaction (and possible cooperation) during posttraumatic functional recovery of such processes.

1.1. The prefrontal cortex in flexible behavioural switching

Besides other forms of executive function, the lateral PFC is associated with strategy selection and strategy shift (e.g. Alexander and Stuss, 2000; Bechara et al., 1994; Block et al., 2007; Duncan, 2010; Fuster, 2001; Hoshi and Tanji, 2004; Shallice et al., 2007, 2008; Stuss et al., 2000). In rodents, the anteromedial part of the PFC represents a functional homologue structure to the dorsolateral surface of the PFC in humans and primates (Birrell and Brown, 2000; Kolb, 1984; Uylings and van Eden, 1990; Uylings et al., 2003).

* Corresponding author at: The Unit for Cognitive Neuroscience, Department of Psychology, University of Copenhagen, Oester Farimagsgade 2A, DK-1353 Copenhagen K, Denmark. Tel.: +45 35324873; fax: +45 35324802.
E-mail address: jesper.mogensen@psy.ku.dk (J. Mogensen).

http://dx.doi.org/10.1016/j.brainresbull.2015.05.006
0361-9230/

The involvement of this structure in flexible behaviours in rodents is supported by solid experimental evidence (e.g. de Bruin et al., 1994; Floresco and Magyar, 2006; Granon and Poucet, 1995; Lee and Solivan, 2008; Mogensen and Holm, 1994; Mogensen et al., 2003b; Rich and Shapiro, 2007). Behavioural switching in particular has been investigated on several occasions utilizing both traditional (e.g. a rodent analogue of the Wisconsin Card Sorting Task) and novel (e.g. operant chamber based) testing paradigms (Birrell and Brown, 2000; Floresco et al., 2006b, 2008a; Joel et al., 1997; Mogensen et al., 2003a; Ragozzino et al., 1999a).

1.2. The hippocampus in flexible behavioural switching

The hippocampus also appears to play a role in flexible behavioural switching, although the nature of this role is disputed. Davidson and Jarrard (Davidson and Jarrard, 2004) – inspired by an earlier model of Gray and McNaughton (Gray and McNaughton, 1983) – suggested that complex learning and memory problems are based on disruption of more fundamental associative processes, such as the simple inhibitory learning about a previously established excitatory association. Reversal tasks have provided a useful testing paradigm and several studies report clear hippocampal involvement, i.e. impairment of reversal conditioning and contextual reversal learning after hippocampal lesions (Berger and Orr, 1983; Jarrard et al., 2012; Kosaki and Watanabe, 2012; Silveira and Kimble, 1968; Winocur and Olds, 1978). Relatively little is known about the hippocampal involvement in set-shifting. There are individual studies reporting set-shifting impairment (shift to a new rule) after neonatal hippocampal lesions (Brady, 2009; Marquis et al., 2008) and one study reporting impaired cross-modal switching after a selective lesion of septal cholinergic neurons (Fitz et al., 2008).

1.3. Interaction between the prefrontal cortex and the hippocampus during behavioural switching

The mediation of flexible behaviour ultimately requires an ongoing interaction between multiple memory and executive systems. There is a rapid information exchange between the PFC and hippocampus during the consolidation of information as the PFC gradually modulates the expression of memories that originally depended on the hippocampus (Takehara-Nishiuchi and McNaughton, 2008). These two brain regions also contribute to the mediation of a number of the same tasks (Floresco et al., 1997; Lee and Solivan, 2008; Mogensen et al., 2007) and it is therefore highly relevant to scrutinize their cross-talk both during the task acquisition process and during the process of posttraumatic functional recovery. Numerous studies have investigated the contribution of either the PFC or the hippocampus to task acquisition [e.g. Birrell and Brown, 2000; Davidson and Jarrard, 2004; Floresco et al., 2008b; Jarrard and Davidson, 1991; Jung et al., 1998; Kosaki and Watanabe, 2012; Mogensen et al., 2003a,b; Ragozzino et al., 1999b). However, studies examining the role of these two structures within a single behavioural paradigm are less frequent (Floresco et al., 1997; Kosaki and Watanabe, 2012; Lee and Solivan, 2008; Mogensen et al., 2004a, 2005, 2007). Posttraumatic functional recovery studies from our laboratory indicate that the hippocampus contributes to the neural substrate for the functional recovery after prefrontal lesions and vice versa in a number of different tasks (Mogensen et al., 2004a, 2005, 2007). These and other studies (e.g. Floresco et al., 1997; Kosaki and Watanabe, 2012; Lee and Solivan, 2008) have also emphasized that both the neural and cognitive mechanisms of posttraumatic functional recovery after a given type of brain injury differ across behavioural tasks and test conditions. Such results are at odds with models of posttraumatic recovery suggesting recovery to be mediated by preserved parts of the lesioned structure, as well as models suggesting that the information processing of the lesioned structure is relocalized to another part of the brain which then performs an information processing identical to the one lost to trauma.

In order to enhance our knowledge of these mechanisms we examined the consequences of (i) bilateral ablation of the anteromedial prefrontal cortex, (ii) transection of the fimbria-fornix of the hippocampus, or (iii) bilateral ablation of the anteromedial prefrontal cortex *and* transection of the fimbria-fornix of the hippocampus on reversal learning and set-shifting (reversal within a spatial domain and a set-shift from a spatial to a visual domain). The testing was carried out *within one experiment* and *one apparatus* (see Section 2.1 for details). Such a design enabled us to make direct comparisons across the lesion groups.

2. Material and methods

2.1. Subjects and experimental groups

2.1.1. Subjects

Ninety-one experimentally naive, male Wistar albino rats weighing 280–300 g (age 8–9 wks) at the beginning of the experiment served as subjects. The animals were housed two per cage under controlled conditions of temperature ($22 \pm 2\,^{\circ}C$) and humidity ($50 \pm 5\%$). The animal quarters were kept on a 12 h light cycle (commencing at 7.00 am). All experimental procedures were performed during the light phase. Throughout the experiment the animals had free access to water. They were fed commercial rat chow once daily after behavioural training and testing. With the exception of the period of surgery and postoperative care, they were maintained at 85% of their ad libitum body weight. A natural growth of approximately one gram per day was taken into account. The animals were randomly divided into four lesion groups: (1) sham surgery, (2) bilateral ablation of the anteromedial prefrontal cortex, (3) bilateral transection of the fimbria-fornix, (4) bilateral ablation of anteromedial prefrontal cortex combined with a bilateral transection of fimbria-fornix. Within each lesion group, half of the animals were trained to perform a reversal (within a spatial strategy), and the other half was trained to perform a set-shift (from spatial strategy to a visually guided strategy). Thus, the experimental groups were the following:

1. Sham surgery and performing reversal (Sham/RS) ($n = 12$).
2. Sham surgery and performing set-shift (Sham/SS) ($n = 12$).
3. Bilateral ablation of the anteromedial prefrontal cortex and performing reversal (PFC/RS) ($n = 11$).
4. Bilateral ablation of the anteromedial prefrontal cortex and performing set-shift (PFC/SS) ($n = 12$).
5. Bilateral transection of the fimbria-fornix and performing reversal (FF/RS) ($n = 12$).
6. Bilateral transection of the fimbria-fornix and performing set-shift (FF/SS) ($n = 12$).
7. Bilateral ablation of the anteromedial prefrontal cortex combined with bilateral transection of fimbria-fornix and performing reversal (COMB/RS) ($n = 10$).
8. Bilateral ablation of the anteromedial prefrontal cortex combined with bilateral transection of fimbria-fornix and performing set-shift (COMB/SS) ($n = 10$).

All experimental procedures were approved by the Danish National Review Committee for the use of Animal Subjects ("Dyreforsøgstilsynet"). All procedures were in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).