Neurobiology of Learning and Memory 106 (2013) 71–86

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Non-spatial pre-training in the water maze as a clinically relevant model for evaluating learning and memory in experimental TBI

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ARTICLE INFO

Article history:
Received 1 March 2013
Revised 11 June 2013
Accepted 9 July 2013
Available online 18 July 2013

Keywords:
Traumatic brain injury
Controlled cortical impact
Implicit memory
Water maze
Spatial memory
Thigmotaxis

ABSTRACT

Explicit and implicit learning and memory networks exist where each network can facilitate or inhibit cognition. Clinical evidence suggests that implicit networks are relatively preserved after traumatic brain injury (TBI). Non-spatial pre-training (NSPT) in the Morris Water Maze (MWM) provides the necessary behavioral components to complete the task, while limiting the formation of spatial maps. Our study utilized NSPT in the MWM to assess implicit and explicit learning and memory system deficits in the controlled cortical impact (CCI) model of TBI. 76 adult male Sprague–Dawley rats were divided: CCI vs. sham surgery, NSPT vs. No-NSPT, and cued vs. non-cued groups. NSPT occurred for 4d prior to surgery (dynamic hidden platform location, extra-maze cues covered, static pool entry point). Acquisition (d14–18), Probe/Visible Platform (d19), and Reversal (d20–21) trials were conducted with or without extra-maze cues. Novel time allocation and search strategy selection metrics were utilized. Results indicated implicit and explicit learning/memory networks are distinguishable in the MWM. In the cued condition, NSPT reduced thigmotaxis, improved place learning, and largely eliminated the apparent injury-induced deficits typically observed between untrained CCI and sham rats. However, among NSPT groups, incorporation of cues into search strategy selection for CCI rats was relatively impaired compared to shams. Non-cued condition performance showed sham/NSPT and CCI/NSPT rats perform similarly, suggesting implicit memory networks are largely intact 2 weeks after CCI. Place learning differences between CCI/NSPT and sham/NSPT rats more accurately reflect spatial deficits in our CCI model compared to untrained controls. These data suggest NSPT as a clinically relevant construct for evaluating potential neurorestorative and neuroprotective therapies. These findings also support development of non-spatial cognitive training paradigms for evaluating rehabilitation relevant combination therapies.

1. Introduction

The Morris Water Maze (MWM) is a commonly used task for assessing spatial navigation and place learning (D'Hooge & De Deyn, 2001; Vorhees & Williams, 2006). Behavioral factors such as suppression of thigmotaxis and recognition of the hidden platform as an escape are essential to MWM performance, and can be impaired after injury (Cain, Boon, & Corcoran, 2006). These deficits can affect searching behavior, which limits the acquisition of navigation and other skills required to effectively solve the task. The spatial mapping component of the MWM is largely hippocampus-dependent (Morris, 1989; Wolff, Gibb, Cassel, & Dalrymple-Alford, 2008) and reliant on explicit awareness and incorporation of extra-maze cues in locating the platform, while other implicitly learned, non-specific task components are hippocampus-independent (Cain et al., 2006).

Non-spatial pre-training (NSPT) provides exposure to implicitly learned task components, important for navigation and non-spatial search strategy development. NSPT can suppress thigmotaxis and facilitate acquisition of behaviors associated with successful task completion (Hoh & Cain, 1997). Furthermore, Packard and McGaugh (1996) showed that place- and response-learning can occur concurrently or independently of one another in rats. We hypothesized that NSPT may eliminate or reduce the requirement of learning non-spatial strategies for successful post-injury navigational behavior in the MWM, consistent with previous studies demonstrating that pre-training can alleviate deficits resulting

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http://dx.doi.org/10.1016/j.nlm.2013.07.006

from sex differences (Beiko, Lander, Hampson, Boon, & Cain, 2004; Perrot-Sinal, Kostenuik, Ossenkopp, & Kavaliers, 1996), age (Carrasco, Vicens, & Redolat, 2006), lesions (Cain et al., 2006; Lukoyanov, Lukoyanova, Andrade, & Paula-Barbosa, 2005), or drug administration (Dyer & Cain, 2007; Morris, 1989; Saucier, Hargreaves, Boon, Vanderwolf, & Cain, 1996).

The MWM is used in multiple models of experimental traumatic brain injury (TBI) to demonstrate cognitive deficits (e.g. Darrah et al., 2011; Hamm, Temple, O'Dell, Pike, & Lyeth, 1996); and increased platform latencies are typically considered the result of hippocampus-mediated learning and memory deficits. After TBI, rats have difficulty mastering the spatial components of the task and can have a reduced capability to learn the general strategies needed to locate the platform (Saucier et al., 1996). Notably, persistent thigmotaxis is indicative of prominent, long-lasting cognitive impairments post-TBI (Bramlett, Green, & Dietrich, 1997; Hamm et al., 1992). Unlike lesion studies, the controlled cortical impact (CCI) injury model of TBI results in damage to structures important for both implicit and explicit components of effective spatial navigation in the MWM, including the hippocampus, thalamus, striatum, and amygdala (Mair, Burk, & Porter, 2003; Packard, 2009; Packard & Knowlton, 2002; Wolff et al., 2008). Implicit and explicit learning and memory networks have not been studied in experimental TBI. However, some clinical literature suggests implicit networks are less affected than explicit learning and memory networks by TBI (Schmitter-Edgecombe, 2006; Vakil, 2005). Implicit learning strategies are used during cognitive rehabilitation to acquire skills and information relevant to everyday functioning for populations, including those with dementia, amnesia, and TBI (Rothi et al., 2009; Schmitter-Edgecombe, 2006; Steenbergen, van der Kamp, Verneau, Jongbloed-Pereboom, & Masters, 2010; Vakil, 2005). Further, explicit feedback regarding strategies for task completion can be disruptive during activities utilizing implicit learning and/or memory strategies (Jacoby, 1991; Schmitter-Edgecombe, 2006).

Given the lack of knowledge regarding how learning and memory networks are affected by experimental TBI, we used MWM performance to examine these networks in the CCI model. We hypothesized that implicit memory would be relatively preserved, and NSPT would facilitate cognitive performance in the MWM where both explicit and implicit memory and learning are required. Also, we hypothesized that the presentation of explicit feedback (i.e. extra-maze cues) to the CCI group receiving NSPT would worsen navigational behavior during specific task conditions where cognitive flexibility and pliancy are needed to adapt to new task rules (e.g., VP, and reversal trials). We postulated that the VP represents an egocentric cue by which the rat can formulate spatial search strategies to more effectively solve the task. Finally, we hypothesized that elevated platform latencies and reductions in spatial strategy selection for CCI/NSPT rats, compared to Sham/NSPT rats, are more representative of spatial navigation deficits in our CCI model compared to traditional testing, which has implications for interpreting MWM results involving pre-clinical assessment of new treatments and interventions. The work may serve as a starting point to develop experimental cognitive training paradigms that parallel clinical practice and can be evaluated in combination with other rehabilitation relevant treatments to lay the ground work for effective rehabilitation focused clinical trials in TBI.

2. Materials and methods

2.1. Subjects and experimental groups

2.1.1. Animals

Animal procedures were carried out with the approval of the University of Pittsburgh Institutional Animal Care and Use Committee. Seventy-six young adult male Sprague–dawley rats with an average weight (343.44 ± -3.20 g) at injury were used. Rats were housed in pairs in suspended wire mesh cages with ad libitum access to food and water, constant ambient temperature (21 ± 1 °C), and 12 h light cycle (7:00 a.m.–7:00 p.m.) Behavioral tests were performed by experimenters blinded to treatment groups.

2.1.2. Experimental groups

Rats were divided into 8 groups according to injury status (CCI vs. sham), exposure to NSPT (NSPT vs. No-NSPT) in the MWM, and use of extra-maze spatial cues (Cued vs. Non-Cued) during acquisition testing (d14–d18 post injury) with a stationary hidden platform. Probe (d19), followed by Visible Platform (d19), and reversal trials (d20–21) also conducted. All MWM testing conditions were performed with each group. Sham groups had 8 rats/group, and injured groups had 11 rats/group.

2.1.3. Controlled cortical impact

The CCI injury device is described in detail by Dixon, Clifton, Lighthall, Yaghmai, and Hayes (1991) and was utilized previously by our group (Darrah et al., 2011; Wagner et al., 2007b; Wagner et al., 2004, 2007a). Rats underwent unilateral parasagittal CCI or sham surgery. A craniectomy (~6 mm) was made between bregma and lambda in the right hemisphere between the central suture and the coronal ridge. The cortical injury was delivered at ~18° angle, such that the impactor was perpendicular with the dural plane. The impact was delivered to a depth of 2.8 mm at 4.0 m/s. Shams underwent all procedures except the impact. Post-operative flexion and righting reflexes were monitored as previously described (Dixon et al., 1991; Wagner et al., 2002, 2007a,b).

2.2. Motor testing

Beam balance and beam walking tasks were completed to assess gross and fine motor function, respectively, as previously described (Dixon et al., 1991; Wagner et al., 2002, 2007a,b). Rats were pre-trained on both beam tasks on the day prior to surgery, and performance was pre-assessed on the day of surgery to determine a baseline score. Rats completed 3 trials daily for both the beam balance and beam walk on d1–6 post surgery. For the beam balance task, the duration of time spent balancing on a narrow beam (1.5 cm width) elevated (90 cm) from the ground was assessed (up to 60 s per trial). For beam walk trials, latency to traverse a narrow beam (2.5 × 100-cm) and reach the goal box was recorded. Beam walk trial time began when an adverse stimulus (white noise and bright light) was presented, and stopped upon entry into the goal box. If the rat fell from the beam prior to reaching the goal box, it was assigned a latency of 60 s. The average time across trials for each rat was calculated.

2.3. The Morris Water Maze

2.3.1. Apparatus and trial procedures

The water maze consisted of a blue pool measuring 180 cm in diameter and 60 cm, and an opaque escape platform measuring 10 cm in diameter and 26 cm high. The pool was filled with water (26 ± 1°C) to a height of 28 cm such that the hidden platform was submerged 2 cm below the surface of the water. The pool was located in a room (2.5 × 2.5 m) typically with large visual cues (black geometric shapes) fixed to the white walls. For each trial, rats were introduced into the pool hindquarters first, placing the forelimbs on the wall. A 4 min inter-trial interval was observed, during which the rats were placed in a heated incubator box. All trials, with the exception of the probe trial, had a maximum duration of 120 s, and a 30 s platform habituation. If the rat did not find the platform