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Touchscreen tasks in mice to demonstrate differences between hippocampal and striatal functions

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ABSTRACT

In mammals, hippocampal and striatal regions are engaged in separable cognitive processes usually assessed through species-specific paradigms. To reconcile cognitive testing among species, translational advantages of the touchscreen-based automated method have been recently promoted. However, it remains undetermined whether similar neural substrates would be involved in such behavioral tasks both in humans and rodents. To address this question, the effects of hippocampal or dorso-striatal fiber-sparing lesions were first assessed in mice through a battery of tasks (experiment A) comprising the acquisition of two touchscreen paradigms, the Paired Associates Learning (dPAL) and Visuo-Motor Conditional Learning (VMCL) tasks, and a more classical T-maze alternation task. Additionally, we sought to determine whether post-acquisition hippocampal lesions would alter memory retrieval in the dPAL task (experiment B). Pre-training lesions of dorsal striatum caused major impairments in all paradigms. In contrast, pre-training hippocampal lesions disrupted the performance of animals trained in the T-maze assay, but spared the acquisition in touchscreen tasks. Nonetheless, post-training hippocampal lesions severely impacted the recall of the previously learned dPAL task. Altogether, our data show that, after having demonstrated their potential in genetically modified mice, touchscreens also reveal perfectly adapted to taxing functional implications of brain structures in mice by means of lesion approaches. Unlike its human counterpart requiring an intact hippocampus, the acquisition of the dPAL task requires the integrity of the dorsal striatum in mice. The hippocampus only later intervenes, when acquired information needs to be retrieved. Touchscreen assays may therefore be suited to study striatal- or hippocampal-dependent forms of learnings in mice.

1. Introduction

It is well established that memory is not a unitary process. Instead, different forms of memory exist and are supported by distinct brain regions (White & McDonald, 2002). Although dissociation studies have pointed to a contribution of other brain areas to specific memory processes (Squire, 2004), the relative functional roles of the hippocampus (HPC) and the dorsal striatum (DS) have been given particular interest over the past. Experimental studies have demonstrated a functional dissociation between these two regions, each lesion producing specific learning deficits depending on task demands (Knowlton, Mangels, & Squire, 1996; Packard, Hirsh, & White, 1989). Further work in rodents has widely promoted the role of the HPC in spatial learning and navigation (Paul, Magda, & Abel, 2009), in contextual memories (Maren, Aharonov, & Fanselow, 1997; Phillips & LeDoux, 1992), and in configural or relational forms of memory (Alvarado & Rudy, 1995; Alvarez, Wendelken, & Eichenbaum, 2002). In parallel, converging evidence has shed light on the nature of cognitive functions supported by the basal ganglia. Mainly based on conditioning paradigms, lesion studies have notably demonstrated the importance of three striatal subregions in learning processes: the nucleus accumbens is presented as a superintendent in Pavlovian conditioning learning (Parkinson, Olmstead, Burns, Robbins, & Everitt, 1999), whereas the dorsomedial striatum (DMS) orchestrates flexible "response–outcome" (R–O) associations resulting in goal-directed actions, and the dorsolateral striatum (DLS) supports habit learning through the establishment of rigid "stimulus–response" (S–R) associations (Balleine, Liljeholm, & Ostlund, 2009; Yin &

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Knowlton, 2006). The advent of neuroimaging techniques globally confirmed similar functional contributions for the HPC and DS in humans (Balleine & O'Doherty, 2010; Maguire et al., 2000).

While appetitive forms of instrumental learning are recognized to rather involve the DS than the HPC in classical operant tests, the HPC has been paradoxically shown to play a critical role in complex operant assays conducted in touchscreen chambers. HPC lesions impair pattern separation and spatial working memory processes in rodents (McTighe, Mar, Romberg, Bussey, & Saksida, 2009; Talpos, McTighe, Dias, Saksida, & Bussey, 2010). Furthermore, the touchscreen technology can be used to test the implication of the HPC in other aspects of cognition, such as associating a particular stimulus to a particular place (Barker & Warburton, 2011). Since it offers the possibility to dynamically manipulate the nature and spatial location of stimuli visualized on the screen across trials (Horner et al., 2013; Romberg, Horner, Bussey, & Saksida, 2013), this approach seems particularly adapted to assess the formation of associative memories resulting from the establishment of a relationship between visual stimuli and their paired spatial location.

Paired Associates Learning (PAL) paradigms appealing to such "object-in-place" associations are generally HPC-dependent (Gilbert & Kesner, 2002; Lee & Solivan, 2008; Yoon, Seo, Kim, & Lee, 2012). In line with these considerations, acquisition of the PAL touchscreen task depends on the HPC in humans, as demonstrated by e.g., the poor performance of Alzheimer's disease patients (Swainson et al., 2001; de Rover et al., 2011). However, the neurobiology of the corresponding touchscreen dPAL task recently developed in rats and mice (Bartko, Vendrell, Saksida, & Bussey, 2011; Talpos, Winters, Dias, Saksida, & Bussey, 2009) has never been examined.

In the present study, we assessed the effect of excitotoxic, fiber-sparing lesions circumscribed to the HPC or DS on the acquisition (experiment A) or retrieval (experiment B) of the dPAL task in mice. As previous findings had verified the possibility to combine this assay with others in a battery of cognitive tests (Delotterie, Mathis, Cassel, Dorner-Ciossek, & Marti, 2014), animals used in experiment A were also sequentially evaluated in more classical paradigms such as the touchscreen Visuo-Motor Conditional Learning (VMCL) and T-maze alternation tasks.

2. Materials and methods

2.1. Ethics statement

All procedures described in this article and related to the Care, Treatment and Use of animals were performed with the specific approval of the appropriate governmental agency (Regierungspräsidium Tübingen, Germany) in an AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International)-accredited facility. These procedures were also in compliance with European Union guidelines (European Community Council Directive 2010/63/UE). All efforts were made to minimize animal suffering and to respect the concept of the 3 Rs (reduce, refine, replace).

2.2. Animals

Three- to four-month old male C57BL/6JRj mice ($n = 54$ for experiment A, $n = 25$ for experiment B; Janvier, France) were used in this study. Upon their arrival, they were housed individually (temperature- and humidity-controlled room; 12 h light/dark cycle; lights on 06:00 h) in a cage ($26 \times 21 \times 14$ cm) with wood shaving bedding, and a red transparent plastic nest box and paper strips as environmental enrichment. Behavioral assessments were conducted during the light phase of the cycle. Food and water were available *ad libitum*, except during periods of evaluation in touchscreen devices. A mouse was first weighed 5 times over a one-week period to establish a baseline weight. Its free-feeding body weight was then slowly reduced to 90–85% of the initial value, which was maintained throughout the whole testing duration. In appetitive touchscreen tasks, animals were rewarded with half-diluted condensed milk (Milch Mädchen; Nestlé, Germany). After each daily session, they were immediately weighed and fed upon return to the home cage. Mice were trained 5–6 days/week in touchscreen devices.

2.3. Surgery

Mice were intraperitoneally anaesthetized with a cocktail of Xylazine at 10 mg/kg (Rompun® 2%; Bayer, Germany) and Ketamine at 100 mg/kg (Ketavet® 100 mg/ml; Pfizer, Germany) as described before (Van der Jeugd et al., 2009). After being placed in a stereotaxic frame (David Kopf Instruments, USA), N-methyl-D-aspartic acid (NMDA dissolved at 90 mM in a PBS solution; Sigma–Aldrich, Germany) was injected *in situ* through a 2-μL Hamilton syringe (Hamilton, Switzerland) adapted with a 33-gauge stainless steel needle (beveled Nanofil needle; World Precision Instruments, USA), either in the whole hippocampus (dorsal and ventral parts) or in the dorsal striatum. Appropriate coordinates had been defined according to Bregma and Lambda references on the basis of pilot studies. A total of 8 sites were used for HPC lesions and 4 sites for the striatal lesions (coordinates given in Table 1). A micro-pump (Ultra Micro Pump; World Precision Instruments, USA) was used to precisely deliver the excitotoxic agent (flow: 50–75 nL/min). In sham-operated mice, the cannula was successively inserted into the different sites of interest, but no vehicle injection was performed. When reflexes reappeared, animals received an intraperitoneal injection of Diazepam at 5 mg/kg (Diazepam 10 mg/2 mL dissolved in NaCl 0.9%; Ratiopharm, Germany) to avoid the genesis and spreading of potential seizures (Deacon, Bannerman, Kirby, Croucher, & Rawlins, 2002). Three hours later, mice were also subcutaneously administrated 1 mL of NaCl 0.9%. Mice were carefully weighed and observed over the course of the following week. In total the following numbers of operated mice were used for the behavioral studies: 11 HPC sham controls, 13 HPC lesioned mice, 12 DS sham controls, 14 DS lesioned mice in experiment A; 12 HPC sham controls and 13 HPC lesioned mice in experiment B.

2.4. Behavioral procedures

In experiment A, animals were lesioned, then successively trained in a battery of three cognitive tasks: the Paired-Associates Learning (dPAL) and the Visuo-Motor Conditional Learning (VMCL) tasks, both performed in touchscreen devices, and a continuous alternation task measured in a T-Maze (Fig. 1). In experiment B, a new batch of mice was first trained in the dPAL task, then lesioned, and later re-tested in the same paradigm. To allow a sufficient post-surgical recovery time and make sure the excitotoxic lesions

Table 1
Stereotaxic coordinates and injected volumes used to induce bilateral lesions of the hippocampus or dorsal striatum. All coordinates were calculated after determination of the Bregma point.

Site names	AP (mm)	ML (mm)	DV (mm)	Volume (nL)
HPC 1/5	−2.0	±1.2	−1.8	100
HPC 2/6	−2.5	±2.2	−1.9	100
HPC 3/7	−3.0	±3.2	−3.0	125
HPC 4/8	−3.0	±3.2	−4.0	125
DS 1/3	+0.3	±1.7	−3.1	300
DS 2/4	+0.3	±2.4	−3.1	300

AP: Antero-Posterior; ML: Medio-Lateral; DV: Dorso-Ventral axes; HPC: Hippocampus; DS: Dorsal Striatum.