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Environmental enrichment enhances systems-level consolidation of a spatial memory after lesions of the ventral midline thalamus

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ABSTRACT

Lesions of the reuniens and rhomboid (ReRh) thalamic nuclei in rats do not alter spatial learning but shorten the period of memory persistence (Loureiro et al. 2012). Such persistence requires a hippocampo-cortical (prefrontal) dialog leading to memory consolidation at the systems level. Evidence for reciprocal connections with the hippocampus and the medial prefrontal cortex (mPFC) makes the ReRh a potential hub for regulating hippocampo-cortical interactions. As environmental enrichment (EE) fosters recovery of declarative-like memory functions after diencephalic lesions (e.g., anterior thalamus), we studied the possibility of triggering recovery of systems-level consolidation in ReRh lesioned rats using a 40-day postsurgical EE. Remote memory was tested 25 days post-acquisition in a Morris water maze. The functional activity associated with retrieval was quantified using c-Fos imaging in the dorsal hippocampus, mPFC, intralaminar thalamic nuclei, and amygdala. EE enhanced remote memory in ReRh rats. Conversely, ReRh rats housed in standard conditions were impaired. C-Fos immunohistochemistry showed a higher recruitment of the mPFC in enriched vs. standard rats with ReRh lesions during retrieval. ReRh rats raised in standard conditions showed weaker c-Fos expression than their sham-operated counterparts. The reinstatement of memory capacity implicated an EE-triggered modification of functional connectivity: EE reduced a marked lesion-induced increase in baseline c-Fos expression in the amygdala. Thus, enriched housing conditions counteracted the negative impact of ReRh lesions on spatial memory persistence. These effects could be the EE-triggered consequence of an enhanced neuronal activation in the mPFC, along with an attenuation of a lesion-induced hyperactivity in the amygdala.

1. Introduction

Encoding, consolidating, and retrieving memories require interactions among distributed neuronal assemblies. To endure, declarative-like memories undergo systems-level consolidation, a gradual process that anchors them in brain regions other than where they have been initially formed (rev Frankland & Bontempi, 2005: Winocur, Moscovitch, & Bontempi, 2010). Indeed, when recent, such memories are supported by the hippocampus. After a while, however, part or all of them depend on subregions of the medial prefrontal cortex (mPFC; e.g., Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Lopez et al., 2012; Maviel, Durkin, Menzaghi, & Bontempi, 2004; Restivo, Vetere, Bontempi, & Ammassari-Teule, 2009). Such neuroanatomical redistribution of engrams over time likely involves an information flow from the hippocampus to the mPFC and back. One or more relay structures contribute to this bidirectional information flow. The reuniens and rhomboid (ReRh) nuclei show a connectivity pattern making them a potential hub between the hippocampus and the mPFC, from which both receive and send projections (e.g., Cassel et al., 2013; Hoover & Vertes, 2012). In rats, damage to the ReRh obliterates neither learning nor retrieval of a recent spatial memory in a water maze. What it precludes, however, is the transformation of a recent memory into a remote one at the systems level. Indeed, rats with ReRh lesions learn the location of a hidden platform in a water maze normally, they still remember this location after 5 post-acquisition days, but are impaired at a 25-day delay (Loureiro et al., 2012). These findings point out the ReRh nuclei as contributors to memory consolidation at the systems

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level (rev Cassel et al., 2013; Griffin, 2015; Pereira de Vasconcelos & Cassel, 2015). Interestingly, recent evidence suggests that the same might be true in humans (e.g., Thielen, Takashima, Rutters, Tendolkar, & Fernández, 2015) and accelerated forgetting has been described in patients with thalamic dysfunctions (stroke, epilepsy), although without any evidence for alterations in the ventral midline thalamus (e.g., Fitzgerald, Valentin, Selway, & Richardson, 2013; Mair et al., 2015; Tu, Miller, Piguet, & Hornberger, 2014).

Physical and social environmental enrichment (EE) produces marked effects at various structural and functional levels of the adult rodent brain. For instance, at a molecular level, genes involved in neurotransmission, production of neurotrophic factors, synaptic excitability, and more generally plasticity undergo increased expression under the influence of EE (e.g., Fischer, 2016; Nithianantharajah & Hannan, 2006; Novkovic, Mittmann, & Manahan-Vaughan, 2015; Rampon, Jiang, et al., 2000; Will, Galani, Kelche, & Rosenzweig, 2004). Structurally, macroscopic and microscopic effects of EE have been described for decades in various brain regions: cortical thickening (e.g., Bennett, Rosenzweig, & Diamond, 1969; Diamond, Ingham, Johnson, Bennett, & Rosenzweig, 1976; Rosenzweig & Bennett, 1967), increased dendritic branching and length, proliferation of dendritic spines, enlargement of synapses (e.g., Greenough, Hwang, & Gorman, 1985; Rampon, Tang, et al., 2000; Van Praag, Kempermann, & Gage, 2000), and local volume changes (e.g., Scholz, Allemang-Grand, Dazai, & Lerch, 2015) are a few examples of EE-induced effects on the brain. EE also improves cognition, especially memory functions (e.g. Brenes et al., 2016; Novkovic et al., 2015; Rampon, Tang, et al., 2000) and it produces beneficial effects in a variety of models of brain lesions and neurodegenerative diseases (e.g., Fischer, 2016; Hannan, 2014; Will et al., 2004). Yet, the underlying mechanisms remain poorly understood. Recently, EE-triggered positive cognitive effects were found after lesions of the anterior thalamic nuclei (e.g., Harland, Collings, McNaughton, Abraham, & Dalrymple-Alford, 2014; Loukavenko, Wolff, Poirier, & Dalrymple-Alford, 2016), which, like the hippocampus, are associated with declarative-like memory processes (Aggleton & Brown, 2006). Furthermore, EE was shown to affect thalamocortical neurotransmission by acting on synaptic strength and plasticity (Mainardi et al., 2010). Therefore, in the present study, we investigated remote memory performance in rats with ReRh lesions that were enriched for 40 days and subsequently trained in a water maze task (Loureiro et al., 2012). Following a probe trial given 25 days post-acquisition, c-Fos expression was evaluated in the hippocampus, the mPFC, the intralaminar thalamic, and the amygdalar nuclei. Our results show that EE enhanced the ability of rats with ReRh lesions to consolidate a memory at systems-level or allowed ReRh rats to regain normal memory functions. Immediate early gene imaging data indicate that the reinstatement of this capacity is associated with recovery of memory-triggered mPFC neuronal activation along with a reduction of the lesion-induced increase of baseline activity in the amygdala.

2. Materials and methods

2.1. Animals, surgery and housing conditions

The study adhered to the regulations specified by the European Committee Council Directive adopted on September 22, 2010 (2010/63/UE) and the French Department of Agriculture (decree 2013-118, February 1st, 2013). Fifty-five male Long-Evans rats (Janvier Labs, Le Genest-Saint-Isle, Saint-Berthevin, France) were used. They were aged 2.5 months at their arrival in the laboratory (250–275 g) and 3 months at the time of surgery (300–325 g). All animals were housed in quiet facilities under a 12 h light/dark cycle (lights on at 7:00 a.m.) with food and water *ad libitum*. Temperature and hygrometry were controlled (22 ± 2 °C and 50 ± 10%, respectively). Before surgery, rats were handled individually for 2 min each day over 5 consecutive days. All rats were housed in groups of five in transparent plastic cages (56 × 35 × 19 cm) until surgery.

2.2. Surgery

Rats were anaesthetized with sodium pentobarbital (68.4 mg/kg/i.p.). They were placed in a stereotaxic apparatus with incisor bar set at −3 mm below the interaural line. Neurotoxic fiber-sparing lesions (n = 31 rats) targeting the Reuniens and Rhomboid nuclei (ReRh) were made using slow microinfusions of 0.1 M N-methyl-D-Aspartate over 5 min (0.1 μl/site; Sigma-Aldrich, ST Quentin Fallavier, France), dissolved in phosphate-buffered saline (PBS; pH = 7.0) via an infusion needle (Ø 0.28 mm) using a motorized infusion pump and a 2 μl Hamilton syringe. The infusion needle was left *in situ* for 6 additional min to ensure diffusion of NMDA into each site before slow retraction. The sham-operated rats (n = 24) were infused with PBS instead of NMDA. As in Cholvin et al. (2013), the coordinates of the 3 infusion sites were (in mm): AP: −1.5, −2.1, and −2.7 (from bregma), DV: −7.0, −7.1, and −7.2 (from skull), ML: ±1.8, ±1.8, and ±1.9 (from midline of the sagittal sinus); a ML angle of ±15° was used to avoid the sinus (Paxinos & Watson, 2007). At the end of surgery, all rats were placed under a warm lamp for 20–30 min to recover and returned for a two-week recovery period to a standard cage (40 × 24.5 × 18.5 cm).

2.3. Enriched vs. standard housing conditions

When rats had recovered from surgery, a 40-day period of enrichment was started: half the rats (n_{ReRh} = 15, n_{Sham} = 12) were randomly assigned to an enriched environment condition (EE, 9 rats in a big cage; ReRh- and sham-operated rats were mixed), and the other half (n_{ReRh} = 16; n_{Sham} = 12) maintained in standard housing conditions (SE, 1 rat/cage with no objects). Enriched housing cages were of metal wire mesh (112 cm long × 40 cm wide × 40 cm high) and contained numerous objects (Perspex tunnels, PVC tubing, plastic balls, metal chains, ladders, boxes, glass cups and plates, and plastic toys) that were changed on a daily basis. Food and water location within the cage was also changed daily. Three enriched housing cages were placed in a colony room and the rats were moved from one cage to another every day (see Loukavenko, Ottley, Moran, Wolff, & Dalrymple-Alford, 2007). The objects and their organization were changed in all cages every three days. The standard housing condition consisted of rats housed one per cage (made of transparent plexiglas with a lid made of wire mesh). These cages enabled auditory, visual, and olfactory experience, as was also the case in the enriched rats, but prevented tactile contact with other rats. All rats (enriched- and standard- housing condition) were housed in the same room. Finally, standard rats were handled daily (7 days/week) as we had to handle (move them from one cage to another) their congeners from the enriched cages during the 40-day period of differential housing. With the exception of handling, this standard condition was identical to the condition used previously to investigate the role of ReRh in spatial memory persistence (Loureiro et al., 2012). Although very different from isolation, individual housing might be considered a mild chronic stress inducing body weight alteration, among others (e.g., rev Pritchard, Van Kempen, & Zimmerberg, 2013); average body weight in standard rats was no different from that recorded in their EE counterparts (see Suppl Fig. 1). In addition, blood samples were collected 39 days after the