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# Functional interactions between dentate gyrus, striatum and anterior thalamic nuclei on spatial memory retrieval

M. Méndez-Couz, N.M. Conejo*, H. González-Pardo, J.L. Arias

*Laboratory of Neuroscience, Department of Psychology. Instituto de Neurociencias del Principado de Asturias (INEUROPA), University of Oviedo, Plaza Feijóo s/n, 33003 Oviedo, Spain*

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ABSTRACT

The standard model of memory system consolidation supports the temporal reorganization of brain circuits underlying long-term memory storage, including interactions between the dorsal hippocampus and extra-hippocampal structures. In addition, several brain regions have been suggested to be involved in the retrieval of spatial memory. In particular, several authors reported a possible role of the ventral portion of the hippocampus together with the thalamus or the striatum in the persistence of this type of memory. Accordingly, the present study aimed to evaluate the contribution of different cortical and subcortical brain regions, and neural networks involved in spatial memory retrieval. For this purpose, we used cytochrome c oxidase quantitative histochemistry as a reliable method to measure brain oxidative metabolism. Animals were trained in a hidden platform task and tested for memory retention immediately after the last training session; one week after completing the task, they were also tested in a memory retrieval probe. Results showed that retrieval of the previously learned task was associated with increased levels of oxidative metabolism in the prefrontal cortex, the dorsal and ventral striatum, the

Abbreviations: AcC, nucleus accumbens core; AcSh, nucleus accumbens shell; Ba, amygdala, basal nucleus; Ce, amygdala, central nucleus; Me, amygdala, medial nucleus; AD, anterodorsal thalamic nucleus; AV, anteroventral thalamic nucleus; DS, dorsal striatum; Cg, cingulate cortex; CA1d, Cornus Ammonis 1 of the dorsal hippocampus; CA1v, Cornus Ammonis 1 of the ventral hippocampus; CA3d, Cornus Ammonis 3 of the dorsal hippocampus; CA3v, Cornus Ammonis 3 of the ventral hippocampus; CO, cytochrome c oxidase; DGd, dentate gyrus of the dorsal hippocampus; DGv, dentate gyrus of the ventral hippocampus; dH, dorsal hippocampus; Ent, entorhinal cortex; IL, iinfralimbic cortex; LM, lateral nucleus of the mammillary bodies; LS, lateral septum; MM, medial nucleus of the mammillary bodies; mPFC, medial prefrontal cortex; MS, Medial septum; MD, mediodorsal thalamic nucleus; MWM, Morris water maze; N, Naïve group; PAR, parietal cortex; PRh, perirhinal cortex; PFC, prefrontal cortex; PrL, prelimbic cortex; PM, premammillary nucleus; M1, primary motor cortex; R, Retrieval group; RSA, retrosplenial agranular cortex; RSG, retrosplenial granular cortex; SMR, spatial reference memory; SuM, supramammillary nucleus of the mammillary bodies

*Corresponding author. Fax: +34 985 10 41 44.
E-mail addresses: mendezlopmarta@uniovi.es (M. Méndez-Couz), conejonelida@uniovi.es (N.M. Conejo), hgpardo@uniovi.es (H. González-Pardo), jarias@uniovi.es (J.L. Arias).

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anterodorsal thalamic nucleus and the dentate gyrus of the dorsal and ventral hippocampus. The analysis of functional interactions between brain regions suggest that the dorsal and ventral dentate gyrus could be involved in spatial memory retrieval. In addition, the results highlight the key role of the extended hippocampal system, thalamus and striatum in this process. Our study agrees with previous ones reporting interactions between the dorsal hippocampus and the prefrontal cortex during spatial memory retrieval. Furthermore, novel activation patterns of brain networks involving the aforementioned regions were found. These functional brain networks could underlie spatial memory retrieval evaluated in the Morris water maze task.



## 1. Introduction

The standard model of memory system consolidation supports the temporal reorganization of brain circuits underlying long-term memory storage (Bontempi et al., 1999; Frankland and Bontempi, 2005) by including interactions between the dorsal hippocampus and the medial prefrontal cortex (mPFC). According to this hypothesis, the initially hippocampus-dependent memories are later stored within hippocampal–cortical networks, and finally in the neocortex (McClelland et al., 1995, Squire and Alvarez, 1995; Frankland and Bontempi, 2005; Smith and Squire, 2009; Leon et al., 2010). This idea is consistent with the active role of the medial prefrontal cortex (mPFC) during memory retrieval, probably acting as a match and mismatch comparator that prevents the hippocampus from re-encoding existing memories (Frankland and Bontempi, 2005). Evidence from numerous studies indicates that different brain networks are activated during early or late stages of spatial learning involving memory acquisition (Conejo et al., 2004, Fidalgo et al., 2014) or consolidation (Deiana et al., 2011). However, brain networks involved in long-term memory retrieval as compared with those involved during memory acquisition or consolidation are not well known.

In addition to the dorsal hippocampus and the cortex, other brain regions have been suggested to be involved in spatial memory retrieval. In particular, it has been reported a possible role of particular thalamic nuclei (Loureiro et al., 2012a), the striatum (Iaria et al., 2003) or the ventral portion of the hippocampus (Loureiro et al., 2012b) in the persistence of a spatial memory. In this regard, Aggleton and Brown (1999) postulated an "extended hippocampal system" in which the thalamus together with the dorsal hippocampus would be required for successful performance of several memory tasks. Moreover, particular subdivisions of the striatum have been proposed as key regions in procedural, implicit or habit memory systems (Packard et al., 1989; Fidalgo et al., 2012a) and they have also been associated with behavioral flexibility (Palencia and Ragozzino, 2005; Ragozzino, 2007). On the other hand, the ventral portion of the hippocampus is usually considered to be associated with the modulation of stress, emotions, and affects (Moser and Moser, 1998; Bannerman et al., 2004) whereas spatial memory processes are almost exclusively associated with the dorsal hippocampus. However, recent studies have proposed a functional continuity along the hippocampus required for behavioral performance based on rapid place learning (Bast et al., 2009) that is also reported during retrieval of a recent spatial memory task, since studies in rodents showed activation in both the dorsal and ventral hippocampus during this task (Bontempi et al., 1999; Maviel et al., 2004).

In a previous paper (Conejo et al., 2010) we reported the functional brain networks related with the acquisition of spatial reference memory in the Morris water maze. In addition, we demonstrated the temporal dynamics of brain networks activated during the acquisition of spatial memory. In a recent paper (Conejo et al., 2013) we showed that inactivation of the dorsal hippocampus impaired long-term spatial memory retrieval. Moreover, functional brain networks between the mPFC and the dorsal hippocampus were differentially activated after unilateral or bilateral hippocampal inactivation. However, the role played by different cortical and subcortical brain regions in spatial memory retrieval and their potential functional interactions during this process have still not been addressed.

For this purpose, we used quantitative cytochrome c oxidase (CO) histochemistry as a reliable marker of brain metabolic capacity because CO activity represents an index of mitochondrial metabolic competence (Bertoni-Freddari et al., 2001) associated with energy demands of neurons after prolonged stimulation (Wong-Riley, 1989; Gonzalez-Lima and Jones, 1994). CO histochemistry has been successfully used in previous studies to map changes in brain metabolism involved in a variety of behavioral tasks in different animal species (Agin et al., 2001; Puga et al., 2007). Moreover, studies in rats reported changes in CO activity related to learning and memory tasks performed in the water maze (De la Torre et al., 1997; Villarreal et al., 2002; Riha et al., 2011; Fidalgo et al., 2012b; Conejo et al., 2013). CO histochemistry will be used to map changes in regional brain CO activity correlated with the retrieval of a previously learned spatial task. This method can be applied both to detect differences in the metabolic capacity of specific brain regions and to investigate their functional connectivity (Sakata et al., 2000). In this regard, brain regions that are functionally coupled and their coordinated changes can be expressed as changes in the strength of pairwise correlations of CO activity between brain regions, as previously reported (Sakata et al., 2000; Puga et al., 2007). Considering all of the above mentioned, the present study aimed to evaluate the contribution of different cortical and subcortical brain regions, and the neural networks involved in long-term spatial memory retrieval tested in the Morris water maze.