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Processing of spatial and non-spatial information reveals functional homogeneity along the dorso-ventral axis of CA3, but not CA1

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ABSTRACT

The ventral hippocampus is thought to principally contribute to emotional memory, while its dorsal part would be more involved in spatial processes. However, few studies have investigated ventral hippocampal function in spatial or non-spatial memories devoid of strong emotional components, and conflicting results have emerged regarding the role of the dorsal hippocampus in non-spatial (object) recognition memory. Moreover, even fewer reports have dissociated the contribution of the hippocampal subfields CA1 and CA3 to those processes, despite growing evidence of a functional segregation between these subfields. In a recent study, we detected the immediate-early gene *Arc*, used as a marker of neuronal activity, during spontaneous spatial and non-spatial recognition memory tasks, and showed that dorsal CA3 was spatially tuned while dorsal CA1 processed spatial and non-spatial information to the same extent (Beer, Chwiesko, Kitsukawa, & Sauvage, 2013). Here, we analyze the pattern of *Arc* expression detected in ventral CA1 and CA3 to determine their role in spatial or non-spatial recognition memory, and investigate whether ventral CA1 and CA3 activation differs from that of their dorsal counterparts. We report that ventral CA1 and CA3 are recruited for both spatial and non-spatial memories, but more strongly for spatial memory (e.g. were spatially tuned), and that CA3 is functionally homogeneous along the dorso-ventral axis, but not CA1.

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1. Introduction

A popular concept in memory research is that the ventral hippocampus preferentially contributes to emotional processes, while its dorsal part plays a preponderant role in spatial domains. This concept was originally built upon tract-tracing studies which revealed strong projections between the ventral hippocampus and the limbic system, which plays an important role in emotional processes, while the dorsal hippocampus was shown to receive more projections from regions processing spatial information (Swanson & Cowan, 1977; see for a review Fanselow & Dong, 2010). These anatomical findings were further supported by numerous lesion, mutagenesis and electrophysiological studies that principally investigated ventral hippocampal function within the frame of emotionally loaded tasks, while dorsal hippocampal function was primarily studied in tasks relying on spatial information (see for reviews Bannerman et al., 2004; Fanselow & Dong, 2010; Kesner, 2007; Nakazawa, McHugh, Wilson, & Tonegawa, 2004). In comparison, much fewer studies have investigated the role of the ventral hippocampus in spatial memory, or the role of the dorsal hippocampus in non-spatial memory.

Interestingly, most of the studies that investigated spatial information processing in the ventral hippocampus in rodents and humans found evidence of its involvement in a variety of spatial memory tasks, including the Morris water-maze (Broadbent, Squire, & Clark, 2004; De Hoz, Knox, & Morris, 2003; Ferbinteanu, Ray, & McDonald, 2003; Gusev, Cui, Alkon, & Gubin, 2005; Loureiro et al., 2012; Nadel, Hoscheidt, & Ryan, 2013; Vann, Brown, Erichsen, & Aggleton, 2000). In addition, place cells were found in the ventral hippocampus of both humans and rodents, and recent anatomical studies showed that the medial entorhinal cortex ('home of the grid cells') strongly projects to the ventral hippocampus, suggesting that this region could be involved in the processing of spatial information (Agster & Burwell, 2013; Ekstrom et al., 2003; Hafting, Fyhn, Molden, Moser, & Moser, 2005; Jung, Wiener, & McNaughton, 1994; Kjelstrup et al., 2008). However, this issue has not been thoroughly investigated to date, and it is unclear whether the ventral hippocampus contributes to spatial processes to a similar extent as the dorsal hippocampus.

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In addition, the role of the ventral hippocampus in non-spatial processes has principally been studied within the frame of emotional tasks, such as fear conditioning paradigms. Meanwhile, its role in non-spatial memory tasks with limited emotional content, such as spontaneous object recognition memory, remains unclear (for a review see Bannerman et al., 2004). Indeed, most studies investigating this topic have focused on the dorsal part of the hippocampus, and report vastly different results that range from minimal to severe memory impairments following hippocampal damage; a discrepancy that is suggested to stem from methodological differences, such as task difficulty, delay period, extent of lesion damage, and other parameters (Broadbent, Gaskin, Squire, & Clark, 2009; Broadbent et al., 2004; Gaskin, Tremblay, & Mumby, 2003; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Nemanic, Alvarado, & Bachevalier, 2004; but also Barker & Warburton, 2011). Therefore, the role of the ventral and dorsal hippocampus in the processing of object information remains unclear, and whether their contribution to this process is comparable is also not known.

Finally, evidence for a functional segregation of the hippocampal subfields CA1 and CA3 has recently accumulated, as CA1 appears to play an important role in the processing of non-spatial information such as time, odors, or objects (Beer, Chwiesko, Kitsukawa, & Sauvage, 2013; Hampson, Simeral, & Deadwyler, 1999; Kesner, Hunsaker, & Gilbert, 2005; MacDonald, Lepage, Eden, & Eichenbaum, 2011; Wood, Dudchenko, & Eichenbaum, 1999), while CA3 would be involved to a limited extent in such processes (Farovik, Dupont, & Eichenbaum, 2009; but see Nakamura, Flasbeck, Maingret, Kitsukawa, & Sauvage, 2013). These studies have mainly focused on dorsal hippocampal function and rarely dissociated CA1 and CA3 functions within spatial and non-spatial tasks that have comparable experimental conditions. Therefore, it is not known whether the functional segregation observed at the dorsal level of the hippocampus holds for the ventral part, nor whether the contribution of ventral CA1 and CA3 is comparable to that of dorsal CA1 and CA3.

In a recent imaging study, we detected the expression of the immediate-early gene *Arc*, commonly used as a marker of cell activation, during spatial and non-spatial object recognition memory tasks in the dorsal hippocampus and the rhinal cortices (Beer et al., 2013; for a review see Sauvage, Nakamure, & Beer, 2013). In addition to the results on the rhinal cortices, we showed that dorsal CA1 was recruited to the same extent during spatial and non-spatial tasks, while dorsal CA3 was preferentially recruited during the spatial tasks. In the present manuscript, we analyzed the pattern of activation of the ventral part of CA1 and CA3 to investigate whether they are recruited during spatial and non-spatial recognition memory, and if so, to what extent. In addition, because *Arc* detection had been performed in ventral and dorsal CA1 and CA3 of the same brain sections, we compared ventral CA1 and CA3 results to those observed in dorsal CA1 and CA3 to evaluate whether CA1 and CA3 are functionally homogeneous along the dorso-ventral axis of the hippocampus.

We chose the *Arc* imaging technique because it is especially well-suited for the detection of brain activity in multiple distant brain sites simultaneously. This is still a challenge for lesion and in vivo electrophysiology studies because of limited spatial resolution or the limited number of simultaneous recording sites linked to these techniques, respectively. Importantly, *Arc* is particularly appropriate for the detection of brain activity during cognitive tasks, by not reflecting simple stress levels or motor activity, and by reflecting behavioral task demands better than other IEGs, such as c-fos and zif268. (Guzowski, McNaughton, Barnes, & Worley, 1999; Guzowski, Setlow, Wagner, & McGaugh, 2001; Nakamura et al., 2013; see for reviews Guzowski et al., 2005; Kubik, Miyashita, & Guzowski, 2007). In addition, *Arc* has been shown to be involved in multiple forms of plasticity processes, including long-term potentiation, which is thought to underlie memory function (for reviews see Guzowski et al., 2005; Sauvage et al., 2013; Shephard & Bear, 2011). In the present study, experimental conditions (handling, number of stimuli, locomotor and exploratory requirements, etc.) are identical across tasks, and only the parameters for memory retrieval vary: a spatial demand was applied or a previously explored object was replaced by a new one. Therefore, between-task comparisons of *Arc* expression are thought to reflect the only parameter differing between tasks: the detection of a novel location or the detection of a novel object.

2. Material and methods

2.1. Animals

12–14 weeks old male C57BL/6 mice ($n = 14$ total; $n = 4$–5 per task, $n = 5$ home-caged controls) bred at the Ruhr Universität Bochum were used. Animals were single caged and kept under reversed 12-h light/dark cycle (8:00 a.m. light off; 8:00 p.m. light on) and tested during their active phase. Animals had access to food and water *ad libitum*. All procedures were approved by the Ruhr Universität Bochum Institutional Animal Use Committee and the LANUV (8.87–51.04.20.09.323).

2.2. Behavioral paradigm

2.2.1. Apparatus and stimuli

The experimental apparatus was a $32 \times 32 \times 41$ cm square open field (made of Polyvinyl chloride, dark gray color) which was placed in a dimly lit room, with extra maze cues available. A video camera (Sony, HDR/CX500E) was used to record the animals' behavior under the 'night shot' setting. Behavioral performance was scored off-line. Two identical sets of two different objects (metallic bells) were used for the behavioral testing procedure, so that objects used during the recognition phase were duplicates of those used during the study phase. Previous pilot studies showed that animals could distinguish between the two visual stimuli, and had no aversion or preference for either of the stimuli used.

2.2.2. Habituation and testing schedule

Animals were habituated to the testing box and the experimental procedure over four days. Animals explored the empty open field for 20 min during days 1 and 2. Subsequently, on days 3 and 4, animals were habituated to the experimental conditions of the testing day (two 6 min-trials, 20 min inter-trial interval) and to the detection of novel locations and novel objects by placing different objects at different locations in the open field.

On the test day the paradigm posed a design in which spatial or non-spatial memory for visual stimuli were examined ($n = 4$–5 animals per condition). Animals were tested in groups of four, plus one home-caged control that was placed in the same room but did not perform the task. The test procedure included a study phase (6 min), a delay of 20 min, and a recognition phase (6 min) (see Fig. 1). During the study phase, animals were exposed to two identical stimuli (Fig. 1A). After the delay, if memory for space was studied, duplicates of the items from the study phase were placed in the open field, one at the same location, the other at a different location than experienced during the study phase (Fig. 1B). If non-spatial memory was studied, two stimuli were placed at exactly the same positions as the study phase, one stimulus was an identical copy, the other was a stimulus never encountered before (see Fig. 1C). During the 20 min delay, animals were returned to their home-cages. Stimuli and stimulus locations were counterbalanced

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