

A Role for Dorsal and Ventral Hippocampus in Inter-Temporal Choice Cost-Benefit Decision Making

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Previous studies suggest a preferential role for dorsal hippocampus (dHPC) in spatial memory tasks, whereas ventral hippocampus (vHPC) has been implicated in aspects of fear and/or anxiety. In this study, we tested the hypothesis that vHPC may be a critical subregion for performance on a delay-based, cost-benefit decision making task. Rats chose between the two goal arms of a T maze, one containing an immediately available small reward, the other containing a larger reward that was only accessible after a delay. dHPC, vHPC, and complete hippocampal (cHPC) lesions all reduced choice of the delayed high reward (HR) in favor of the immediately available low reward (LR). The deficits were not due to a complete inability to remember which reward size was associated with which arm of the maze. When an equivalent 10-s delay was introduced in both goal arms, all rats chose the HR arm on nearly all trials. The deficit was, however, reinstated when the inequality was reintroduced. Our results suggest an important role for both dHPC and vHPC in the extended neural circuitry that underlies intertemporal choice.

Keywords: hippocampus, dorsal, ventral, response selection, intertemporal choice

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Orbitofrontal cortical (OFC) lesions affect how long rats are willing to wait for rewards (Mobini et al., 2002). Compared to controls, rats with OFC lesions display an increased preference for the goal arm of a T maze containing an immediately available low reward (LR) over the goal arm containing a higher reward (HR) that is only available after a delay (Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006). Rats with hippocampal (HPC) lesions also exhibit impulsive choice and prefer immediately available rewards over delayed rewards (Cheung & Cardinal, 2005; Rawlins, Feldon, & Butt, 1985). For example, Rawlins and colleagues trained rats with HPC aspiration lesions and controls on a task in which one arm of a Y maze was continually reinforced (CRF) and the other reinforced on only 25% of trials (partially reinforced arm – PRF). During the training phase, when no delays were present on either arm, all rats showed a clear preference for the CRF arm. During the test phase, the reward in the PRF arm (when present) was still available immediately, but access to the reward on the CRF arm was delayed by 10 seconds. After the introduction of the delay, controls continued to choose the CRF arm, but HPC lesioned rats switched their preference to the immediate PRF arm.

As the hippocampal lesions employed by Rawlins et al. (1985) were aspiration lesions, it is not clear whether the impulsivity

observed on this delay-based, cost-benefit decision making T maze task was due to hippocampal cell loss or due to damage to fibers of passage or cerebrovasculature caused by this kind of surgical manipulation. A recent study by Cheung and Cardinal (2005) has shown that cytotoxic hippocampal lesions do produce impulsivity in an operant version of this task. Therefore, the first aim of the present study was to see if the preference of HPC lesioned rats for an immediately available low reward over a delayed high reward on the T maze task was also present following cytotoxic, fiber-sparing lesions of the HPC.

The second aim of the present study was to assess the effects of hippocampal lesions on a T maze paradigm similar to that employed by Rudebeck et al. (2006), and thus allow direct comparison with the effects of orbitofrontal lesions. There are a number of procedural differences between the Rawlins et al., (1985) and Rudebeck et al. (2006) studies (e.g., continuous/partial reinforcement vs. high/low rewards; preoperative vs. postoperative training on the task). We now tested the effects of hippocampal lesions using the same paradigm that has previously demonstrated impulsive choice in OFC lesioned rats.

Furthermore, in the study by Rawlins et al. (1985), HPC lesioned rats showed a clear preference for the CRF arm when there was no delay on either arm. The third aim of the present study was to extend this investigation to see whether or not HPC lesioned rats would be impaired when using a double-delay procedure in which a 10s delay was introduced into both goal arms, and thus interposed between the choice point and receiving either the LR or HR (e.g., Rudebeck et al., 2006).

The fourth aim of the present study was to assess the effects of hippocampal lesions on a similar version of the T maze decision making task, but in which the cost associated with the HR was in terms of physical effort rather than delay to reinforcement. Ante-

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rior cingulate cortex (ACC), but not OFC, lesions affect how much effort rats decide to invest for rewards, as measured by a reduced willingness to climb over a barrier to obtain a high reward when the alternative is a lower reward requiring less effort (Rudebeck et al., 2006). In the present study, we now assessed whether any role of the hippocampus in cost-benefit decision making was specific to tasks in which the cost was in terms of delay to reinforcement, or whether it also extended to other kinds of costs such as physical effort.

The final aim of this study was to investigate the relative contributions of the dorsal and ventral HPC subregions to cost benefit decision making. The HPC has long been associated with learning and memory, particularly within the spatial domain (O'Keefe & Nadel, 1978), but more recent studies suggest that these spatial functions are largely subserved by the septal portion of the HPC (dorsal in rodents, posterior in primates), whereas a lesser role is played by the temporal region (ventral in rodents, anterior in primates). Septotemporal differences in spatial processing are consistently found following selective cytotoxic lesions in rats, with dorsal but not ventral lesions resulting in robust and reliable deficits in spatial reference (Moser, Moser, Forrest, Andersen, & Morris, 1995) and working memory tasks (Bannerman et al., 1999).

This functional differentiation is consistent with the anatomical connectivity along the septotemporal axis. The dorsal HPC receives highly processed sensory information via the entorhinal cortex (Dolorfo & Amaral, 1998), consistent with a role in spatial information processing. In contrast, the ventral HPC shares greater connectivity with structures such as the amygdala, hypothalamus, and orbitofrontal cortex (OFC), which are more commonly associated with emotional processing. Indeed, ventral but not dorsal HPC lesions produce anxiolytic effects on unconditioned tests of anxiety (Deacon, Bannerman, & Rawlins, 2002; Kjelstrup et al., 2002; McHugh, Deacon, Rawlins, & Bannerman, 2004). These findings are consistent with a more general role for the hippocampus in the integration of multimodal sensory and emotionally salient contextual information to guide response selection (Gray & McNaughton, 2000). Given the involvement of the OFC in the delay-based, cost-benefit decision making task (Rudebeck et al., 2006), it is interesting to note that the direct projections from the CA1 field of the hippocampus to the OFC are only present in the more ventral/caudal regions of the hippocampus in the rat (Jay & Witter, 1991). This suggests that the ventral HPC may play a key role in the delay-based, cost benefit decision making T maze task, in contrast to other mnemonic versions of the T maze task where it is not required (Bannerman, Yee, Good, Heupel, Iverson, & Rawlins., 1999; Hock & Bunsey, 1998). Therefore, the final aim of this study was to test the hypothesis that the vHPC may be the critical subregion for performance on the delay-based, cost-benefit decision making task.

We therefore compared the effects of complete, dorsal and ventral, cytotoxic HPC lesions on a T maze task in which rats chose between an immediately available LR and a delayed HR (Rudebeck et al., 2006). In addition, performance was also compared under conditions in which an equivalent delay was present in both the HR and LR arms. For comparison, a second experiment examined response choices when the HR was associated with additional effort (climbing over a barrier), with less effort (no

barrier) required to obtain the LR (Rudebeck et al., 2006; Walton, Bannerman, & Rushworth, 2002).

Materials and Method

Animals. This study used 40 male Lister hooded rats (Harlan Olac, Bicester, U.K.) that were ~2 months old and experimentally naïve at the start of training. Rats were housed in groups of two or three on a 12hr light/dark cycle (lights on at 7:00 a.m., with testing during the light phase). During the experiment rats were maintained on a restricted diet at ~85% of their free-feeding weight but had access to water ad libitum in their home cages. The experiments described were conducted in accordance with the United Kingdom Animals Scientific Procedures Act (1986) under project license number PPL 30/1989.

Apparatus

The rats were tested on an enclosed, high-sided wooden T maze placed 42 cm above floor level (Rudebeck et al., 2006). The start arm joined two goal arms. Each arm was 60 cm long, 10 cm wide, and had 40 cm walls. A raised metal food well (2.5 cm diameter, 2 cm high) was situated at the far end of each goal arm, 2.5 cm from the back wall. Runners were installed in each of the goal arms permitting one "guillotine" door (50 cm high \times 9 cm wide \times 0.6 cm thick) to be inserted 5 cm along the goal arm (from the junction in the T maze) and a second identical guillotine door 5 cm before the food well (Rudebeck et al., 2006). Doors delayed access to the HR food well after the animal had made a choice (Experiment 1) and also prevented access to the other goal arm during forced trials (Experiments 1 and 2). The maze and doors were painted a uniform gray color throughout.

In Experiment 2, animals had to exert additional effort to obtain the HR by climbing over a barrier (Rudebeck et al., 2006; Walton, Bannerman, Alterescu, & Rushworth, 2003; Walton et al., 2002). Six different barriers were used (15 cm, 20 cm, 25 cm, 30 cm, 35 cm, or 40 cm in height), each constructed from wire mesh in the shape of a 3-dimensional right-angled triangle. The rat had to scale the vertical face of the barrier and descend the slope to get to the food well.

Preoperative Training for the Delayed Reward Task

During food deprivation, the rats were weighed and handled by the experimenters on a daily basis and then thoroughly habituated to the T maze. Over the first 10 days of preoperative training, rats learned to associate one arm of the T maze with the LR and the other arm with the HR in the absence of any delays. In all trials in Experiment 1, the food well in the HR arm contained 10 food pellets (45 mg Formula A/I; Noyes, Lancaster, NH), whereas the food well in the LR arm contained 2 pellets. Allocation of the HR and LR to the left and right arms of the T maze was fully counterbalanced (50% HR = right, LR = left; 50% HR = left, LR = right).

At the start of every training session each rat received two forced trials (one to the HR arm and one to the LR arm) during which a door prevented access to the other arm of the T maze. On each choice trial, the rat was placed in the start arm and allowed to enter either the LR or HR arm. Upon entering either goal-arm, the

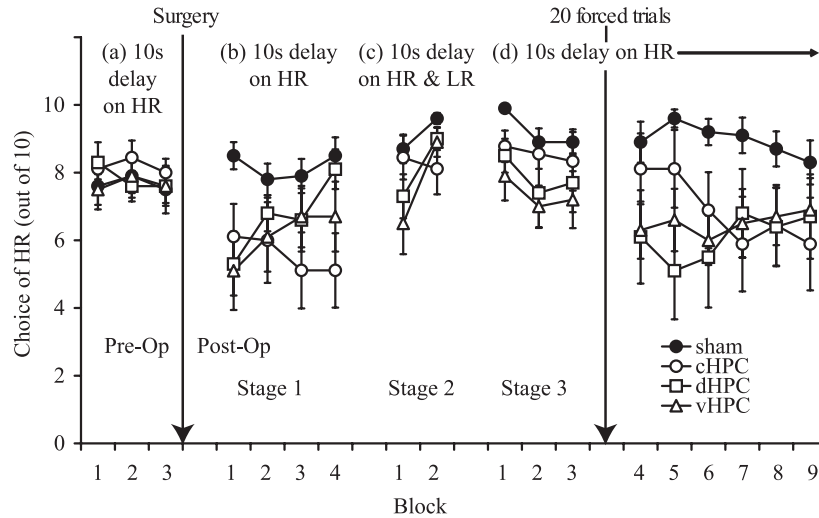


Figure 1. Mean high reward (HR; 10 pellets) choices out of 10 (\pm SEM) in the intertemporal choice task for rats with complete hippocampal (cHPC), dorsal hippocampal (dHPC), ventral hippocampal (vHPC) or sham lesions. Rats received 2 pellets for choosing the low reward.

door behind the rat was closed and the door preventing access to the food was immediately lifted. In other words, there was no delay cost associated with the HR arm during this initial stage of training. For the first 6 days of training, rats received two choice trials per day and for an additional 4 days the rats received five choice trials per day.

Once all the animals reliably chose the HR on more than 80% of trials, a 5s delay was introduced to the HR arm. On trials where rats entered the HR arm (on choice or forced trials) the door would close behind them and they would be detained in the arm for 5s. At the end of this detainment period the door preventing access to the food well was opened and the rat could eat the 10 pellets. No delay was associated with the choice of the LR arm.

Preoperative Testing for the Delayed Reward Experiment

After three days (15 choice trials) of testing with a 5s delay in the HR arm, the delay was increased to 10 seconds and 6 days of testing began. These 30 choice trials (3 blocks of 10 trials) provided a preoperative baseline (Figure 1a). As with all other training days, each session began with two forced trials (one to each arm, with HR first or LR first, counterbalanced with respect to day). Rats were run in squads of five or six giving an approximate intertrial interval of 10 minutes.

Surgery

The assignment of rats to surgical groups was counterbalanced with respect to preoperative performance at the 10s delay and with respect to the right-left allocation of the HR and LR. Rats received either excitotoxic bilateral lesions encompassing the dorsal hippocampus (dHPC; $n = 10$), ventral hippocampus (vHPC; $n = 10$), or complete hippocampus (cHPC; $n = 10$); or sham surgery (sham; $n = 10$). At the time of surgery, the rats weighed between 327 g and 438 g. All rats were anesthetized with Avertin (0.29 g/kg, i.p.) and placed in a stereotaxic frame with the head level between

bregma and lambda. An incision was made along the midline, and a drill was used to remove the portion of bone overlying the injection sites. Lesions were made by injecting N-methyl-D-aspartate (NMDA; Sigma Chemical, Poole, U.K.), dissolved in phosphate buffered saline (pH 7.4), at a concentration of 10 mg/ml, at the coordinates specified in Bannerman et al. (2002; see also Supplemental Information, Table S1). Injections of between 0.025 and 0.1 μ l were made over 15-60s (0.1 μ l/min) with a 5- μ l microsyringe (Scientific Glass Engineering, Milton Keynes, U.K.) mounted on a stereotaxic frame using a modified 34-gauge needle. The syringe was left in place for 60s after each injection to allow diffusion of the neurotoxin away from the injection site. Sham surgery involved anesthesia followed by a midline incision, craniotomy, and then suturing. One rat died shortly after surgery leaving a final experimental cohort of 39 rats (cHPC, $n = 9$; other 3 groups, $n = 10$).

Procedure

Experiment 1: Intertemporal choice on the T maze (postoperative testing). After 14 days postoperative recovery, rats were returned to a restricted feeding schedule (\sim 85% of free feeding weight) and testing resumed. Postoperative testing was divided into three main stages. The first stage followed an identical protocol to the preoperative baseline testing except that four blocks (40 trials) were run (Figure 1b). In brief, following two forced trials at the start of each session, rats received five choice trials per day in which access to the food in the HR arm (10 pellets) was delayed by 10 seconds whereas access to the food in the LR arm (2 pellets) was granted immediately. In stage 2, the delay in both the HR and LR arms was set to 10 seconds (20 trials; Figure 1c). In stage 3 (Figure 1d), the original parameters (HR = 10s; LR = 0s) were reinstated. During the 1st three blocks of testing in stage 3 (30 trials), the majority of rats continued to select the HR arm and therefore received very little exposure to the new contingence-

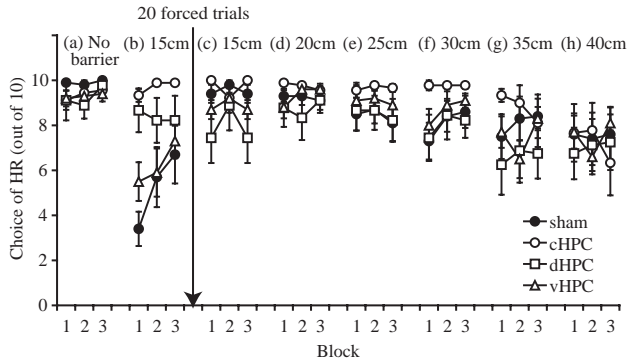


Figure 2. Mean high reward (HR, 4 pellets) choices out of 10 (\pm SEM) in the effort-related choice task for rats with complete hippocampal (cHPC), dorsal hippocampal (dHPC), ventral hippocampal (vHPC) or sham lesions. Rats received 2 pellets for choosing the low reward.

cies in the LR arm (i.e., that reward was no longer delayed in this arm). The rats were therefore given only forced trials for two days (20 forced trials in total, 10 to HR arm, 10 to LR arm) to expose them fully to the contingencies in both arms before testing continued for a further six blocks (60 trials).

Experiment 2: Effort-related reward on the T maze. The purpose of Experiment 2 was to examine the effect of associating extra effort with the HR arm by inserting a barrier. Training followed directly from Experiment 1 and the same HR/LR arm allocations were kept, for example, if the HR was in the left arm in Experiment 1, then it remained in the left arm for Experiment 2. However, the size of the HR was reduced to 4 pellets with the LR staying at 2 pellets (based on Walton et al., 2002). As with Experiment 1, all sessions began with 2 forced trials (1 into each arm) but 10 choice trials were run per day. Rats were given a minimum of 30 trials to regain the HR/LR associations without any cost being associated with the HR arm. Those who did not choose the HR arm on 80% of trials on three consecutive days were given additional training. Once all animals met all criteria, a further 3 days of testing (30 trials) provided a period of baseline testing with no barrier in place (Figure 2a). The smallest barrier (15 cm) was then introduced and 3 blocks (30 trials) were run (Figure 2b). Following these 3 blocks, all rats received forced trials only over two days (10 forced trials per day, 20 in total) with the 15 cm barrier in place to ensure adequate exposure the reward/effort contingencies. Thereafter, the rats received 30 trials at each barrier height (15 cm (after forced trials), 20 cm, 25 cm, 30 cm, 35 cm, 40 cm; Figure 2, c-h), giving a total of 240 choice trials over 24 blocks.

Data Analysis

Data were subjected to analysis of variance (ANOVA) using a general linear model in SPSS (Version 11, Chicago). All tests of significance were performed at $\alpha = .05$ and full factorial models (SPSS's Type III sum-of-squares method) were used. All graphs show group means plus/minus 1 standard error of the mean (SEM).

Histology

At the end of behavioral testing, rats were injected with Euthatal (200 mg/ml sodium pentobarbitone; 200 mg/kg) and perfused

transcardially with physiological saline (0.9% NaCl) followed by 10% formol saline (10% formalin in 0.9% NaCl). Their brains were then removed and placed in formol saline solution and subsequently transferred to a 30% sucrose-formalin solution for 24 hr, frozen, and sectioned (50 μ m) horizontally. All sections were then stained with cresyl violet.

Results

Histology

Complete (cHPC), dorsal (dHPC), and ventral (vHPC) hippocampal lesions were highly reproducible and highly selective and consistent with previous studies in this laboratory (Bannerman, Grubb, Deacon, Yee, Feldon, & Rawlins, 2003; Bannerman, et al. 1999; Deacon et al., 2002; McHugh et al., 2004). In all cases, cell loss was restricted almost exclusively to the hippocampal subfields, with little if any damage to adjacent structures such as the subiculum or entorhinal cortex, and no damage beyond these structures. In the cHPC and dHPC lesioned rats, there was complete loss of pyramidal and granule cells in the dorsal part of Ammon's horn and the dentate gyrus, respectively. In the dHPC group there was little if any evidence of damage beyond Plate 108 (Paxinos & Watson, 1998). In the vHPC lesioned rats there was little or no damage evident before Plate 109. In the cHPC and vHPC lesioned rats there was some very restricted sparing at midhippocampal levels, involving the most posterior portion of the CA1 subfield and the dentate gyrus, at the apex of the hippocampus as it starts to curve downward. In the cHPC and vHPC groups, the lesion then became complete once more as it extended into the ventral hippocampus, until the most ventral tip of the hippocampus at which point some sparing once again became apparent, and mainly involved the most posterior portion of the dentate gyrus. No rats were excluded on histological grounds. Reconstructions and photomicrographs of the lesions are available in the supplemental information (Figures S1-S4).

Experiment 1: Delayed reward. Data for each block of Experiment 1 is presented in Figure 1, which also serves as a timeline for each stage of delayed-reward testing. Three blocks of testing were run prior to surgery. As group allocation was determined by performance at this stage, there were no differences between the groups as confirmed by a repeated-measures ANOVA [model: $\text{Group}_4 \times (\text{Block}_3 \times \text{S}_{39})$], which found no effect of group or block and no interaction (all F s < 1 ; all p $> .7$).

Postoperative testing was divided into three stages, as shown in Figure 1. During the four blocks of testing in stage 1, the sham group showed a strong preference for the HR arm. In contrast, the cHPC lesion group showed an increased preference for the LR arm. The partial lesion groups (dHPC and vHPC) also showed an increased preference for the LR arm but to a lesser extent than the cHPC group. Interestingly, the overall chance levels of responding in the cHPC group were largely due to a bimodal pattern of responding: some rats consistently chose the HR arm whereas others consistently chose the LR arm (see also Rawlins et al., 1985). These data were analyzed with a repeated-measures ANOVA [model: $\text{Group}_4 \times (\text{Block}_4 \times \text{S}_{39})$], which found a significant main effect of lesion group, $F(3, 35) = 2.90$; $p < .05$, but no effect of block, $F(3, 105) = 1.09$; $p = .36$, or group \times block interaction, $F(9, 105) = 1.36$; $p = .22$. Post hoc comparisons

(Fisher's LSD test) revealed that the cHPC and vHPC groups chose the HR arm significantly less than the sham group ($p < .05$). The dHPC group also chose the HR arm less than the shams but this difference was not significant. A separate ANOVA was carried out, directly comparing performance of the dorsal HPC group to the ventral HPC group based on the a priori assumption that different patterns of connectivity to and from these regions implicate the ventral but not dorsal HPC in delayed-based intertemporal choice. However, the ANOVA revealed no difference between the groups, $F(1, 18) = 0.35$; $p = .56$ and no group \times block interaction, $F(3, 54) = 0.41$; $p = .22$.

In the second stage of postoperative testing (Figure 1c), access to food in both the HR and LR arms was subject to a 10s delay. With equal delay in both arms, all groups showed a high and equivalent preference for the HR arm such that by the second block all groups chose the HR on more than 80% of trials. The two blocks of data in the second stage were compared to blocks 3 and 4 from the previous stage [model: $\text{Group}_4 \times (\text{Stage}_2 \times \text{Block}_2 \times \text{S}_{39})$]. The analysis revealed a main effect of testing stage, $F(1, 35) = 21.78$; $p < .001$, and block, $F(1, 35) = 11.80$; $p < .005$, but no main effect of group, $F(3, 35) = 2.30$; $p = .1$. In addition, there was a stage \times group interaction, $F(3, 35) = 3.01$; $p < .05$. Analysis of simple main effects revealed that there was only an effect of lesion group in the first stage of testing (blocks 3 & 4), $F(3, 35) = 2.87$; $p < .05$, but not the second stage, $F(3, 35) = 1.54$; $p = .22$. Analysis of simple main effects also revealed an effect of stage within the cHPC lesion group $F(1, 35) = 23.1$; $p < .001$, who made significantly more HR choices in stage 2.

In stage 3 of testing (Figure 1d), the original parameters were reinstated (HR = 10s delay; LR = 0s delay). After 3 blocks (30 trials), the majority of rats continued to select the HR arm and therefore had received very little exposure to the new contingencies in the LR arm (i.e., that the delay had been removed from this arm). The rats were therefore given only forced trials for two days (20 forced trials in total, 10 to HR arm, 10 to LR arm) to expose them fully to the change in delay/reward contingencies in the LR arm. Thereafter, a further 6 blocks (60 trials) of choice trials were run. Over the nine blocks of stage 3, all animals reduced their preference for the HR but this reduction was more apparent in all three of the lesion groups compared to the shams. The nine blocks were collapsed into three 'triple-blocks' and analyzed with a repeated-measures ANOVA [model: $\text{Group}_4 \times (\text{Triple-block}_3 \times \text{S}_{39})$]. The ANOVA found no main effect of group, $F(3, 35) = 2.14$; $p = .11$, but there was a main effect of triple-block, $F(2, 70) = 7.79$; $p < .001$ and a group \times triple-block interaction, $F(6, 70) = 2.25$; $p < .05$. Analysis of simple main effects and subsequent pairwise comparisons (Fisher's LSD) revealed an effect of block within the cHPC group, $F(2, 34) = 6.33$; $p = .01$, in that they chose the HR significantly less often in the third triple-block, compared to the first ($p < .001$) and second triple-blocks ($p < .05$). In contrast, there was no change in HR arm choices across this stage of testing in the sham animals (no effect of triple-block; $p > .2$). Pairwise comparisons (Fisher's LSD) of the effect of lesion group within triple-block also revealed that the sham group chose the HR significantly more often than the vHPC group during the first and second triple-blocks (both $p < .05$). The shams also chose the HR significantly more often than the dHPC group during the second triple-block ($p < .05$). There was a trend toward the

shams choosing the HR more than the cHPC group during the third triple-block ($p = .07$).

In summary, combining the results of stages 1 and 3, rats with dorsal, ventral, or complete hippocampal lesions exhibited a reduced preference for a higher reward that was subject to a 10s delay when the alternative was a low reward that was available immediately. In contrast, when the delay to reinforcement was equivalent (stage 2), all groups showed a consistent preference for the higher reward.

Experiment 2: Effortful reward. With no barrier in place, all groups chose the HR arm on more than 90% of trials, further demonstrating that the HPC is not required for simple reward discrimination (Figure 2a). When the 15 cm barrier was first introduced (Figure 2b), the sham and vHPC groups dramatically reduced their preference for the HR arm in the first block but increased their HR choices in subsequent blocks. In contrast, the dHPC and cHPC groups did not show this dramatic reduction in HR choices following the introduction of the barrier. After the first three blocks with the 15 cm barrier in place, 20 forced trials were given to ensure that all groups had adequate exposure to the reward contingencies. Upon retesting, there were no clear differences between the groups (Figure 2, c-h). Preference for the HR arm remained over 80% for all groups over the first four barrier heights (15–30 cm) but declined over the last two barrier heights (35 cm and 40 cm).

To analyze the effect of introducing the barrier, the three blocks with no barrier in place were compared to the first three blocks with the 15 cm barrier in the HR arm [model: $\text{Group}_4 \times (\text{Barrier}_2 \times \text{Block}_3 \times \text{S}_{38})$]. The ANOVA found significant main effects of lesion group, $F(3, 34) = 3.99$; $p < .05$, barrier, $F(1, 34) = 23.34$; $p < .001$, and block, $F(2, 68) = 8.71$; $p < .001$. In addition, there was a barrier \times lesion group interaction, $F(3, 34) = 6.74$; $p < .001$. Simple main effects analysis and subsequent pairwise comparisons (Fisher's LSD) revealed that group differences were only present following the introduction of the 15 cm barrier, $F(3, 34) = 5.75$; $p < .01$. The cHPC group chose the HR arm significantly more than the sham ($p < .001$) and vHPC groups ($p < .01$). The dHPC group also chose the HR arm more often than the shams ($p < .05$) and there was a trend toward the dHPC group choosing the HR arm more than the vHPC group ($p = .08$).

A separate analysis examined the remaining testing blocks (Figure 2c-h) with the barrier height increasing by 5 cm every 3 blocks (15 cm (after forced trials), 20 cm, 25 cm, 30 cm, 35 cm, and 40 cm). The three blocks at each height were collapsed into one triple-block (designated "barrier height") and analyzed with a repeated-measures ANOVA [model: $\text{Group}_4 \times (\text{Barrier Height}_6 \times \text{S}_{37})$]. The ANOVA revealed a main effect of barrier height, $F(5, 165) = 10.88$; $p < .001$, but no effect of lesion group, $F(3, 33) = 0.83$; $p = .49$, and no group \times barrier height interaction, $F(15, 165) = 0.85$; $p = .62$.

In summary, without the barrier in the HR arm there were no differences in HR choices between the groups. In contrast, when the 15 cm barrier was first introduced, the sham and vHPC groups significantly reduced their choice of the HR arm compared to the cHPC and dHPC groups. In subsequent blocks the vHPC and sham groups increased their HR choices and after the 20 forced trials the groups did not differ at any of the barrier heights.

Discussion

Complete (cHPC), dorsal (dHPC), and ventral (vHPC) cytotoxic hippocampal lesions all led to reduced choice of a delayed high reward (HR) in favor of an immediately available low reward (LR) (Expt 1). The combined results of postoperative stages 1 and 3 suggest deficits in the complete and both partial lesion groups. The deficits were not due to a complete inability to remember which reward size was associated with which arm of the maze. When an equivalent 10s delay was introduced in both goal arms, all rats chose the HR arm on nearly all trials (stage 2). The deficit was, however, reinstated when the inequality was reintroduced (stage 3). In contrast, when the HR-cost was in terms of physical effort required to climb a barrier, the HPC lesioned animals' HR choices, for the most part, resembled controls, although initially both cHPC and dHPC lesioned rats were in fact more inclined to climb the barrier for the HR.

This study extends the findings of Rawlins et al. (1985) in demonstrating hippocampal lesion effects on a delay based, cost-benefit decision making T maze task, using more selective, fiber sparing, cytotoxic lesions. These effects are therefore clearly hippocampal in origin and are not due to damage to fibers of passage. Furthermore, the present study used the same experimental paradigm that has previously revealed effects with OFC lesions (Rudebeck et al., 2006). The impulsivity displayed by the hippocampal lesioned animals in postoperative stage 1 appeared similar, at least in some respects, to that seen with orbitofrontal lesions (Rudebeck et al., 2006). The present results also extend the findings of Rawlins et al. (1985) in showing that when an equivalent delay was associated with both the high and low rewards, then all the lesioned rats chose the larger reward on the majority of trials. Therefore, the effect of hippocampal damage was not due to a complete inability to use short- or intermediate-term memory to bridge the spatiotemporal discontinuity between what the animal did at the choice point and the size of the reward obtained.

Furthermore, the present results suggest that the HPC is involved in delay but not effort-based decision making tasks. However, they should be interpreted cautiously as training for the delay task was carried out preoperatively whereas all training for the effort task was postoperative, and occurred after postoperative testing on the delay task. Further experiments, in which separate groups of rats are trained preoperatively on the effort task and then given hippocampal lesions, are required to fully resolve this issue (Rudebeck et al., 2006; Walton et al., 2002). Furthermore, it is interesting to note that both the cHPC and dHPC groups were in fact initially more willing to climb the barrier than controls and vHPC lesioned rats. In fact, rats in the cHPC group chose to climb the barrier on 97% of trials during the first three blocks after the barrier was first introduced compared to 53% in the sham group. The reason for this effect is not immediately obvious. One possible account is that rats exhibit a neophobia toward the barrier when it is first introduced, and that this neophobia is reduced in animals with hippocampal lesions (Bannerman, Deacon, Offen, Friswell, Grubb, & Rawlins, 2002). However, reduced neophobia is associated with ventral but not dorsal hippocampal damage, and therefore this explanation seems unlikely. Alternatively, it is possible that the initial barrier performance of the cHPC and dHPC rats was due to perseveration. Both of these groups of rats continued to choose the HR arm, as in the previous, no-barrier condition, whereas both sham and vHPC rats shifted their behavior and

increased their number of LR arm choices. However, a general increase in perseveration in HPC lesioned animals cannot account for the dataset as a whole; for example, in the delay task it is the lesioned animals (cHPC, dHPC and vHPC) and not the shams that shift their behavior (Expt 1, stages 1 and 3). Therefore, an account based on increased perseveration also seems unlikely. Interestingly, there is previous evidence that rats with HPC lesions are willing to work harder for food reward (Schmelzeis & Mittleman, 1996). HPC lesioned rats showed a profound increase in the breakpoint when trained on an operant progressive ratio 10 schedule of reinforcement, in which they were required to exert progressively more effort (increased number of lever presses) to obtain successive reinforcers. The present results suggest that this effect may be attributable to cell loss in the dorsal subregion of the HPC.

The present results also suggest an important role for both dorsal and ventral hippocampus in the neural circuitry that underlies decision making on the intertemporal choice (delay) task. This result is consistent with our prediction that the vHPC is a critical subregion for performance on the delay based, cost-benefit decision making task. However, the effect of dHPC lesions on this task was not necessarily as predicted on the basis of the anatomical segregation of HPC-OFC connections.

Previous studies have suggested a preferential role for dHPC in spatial memory tasks, whereas the vHPC has been implicated in aspects of fear and/or anxiety (Bannerman et al., 2004). Both of those findings are entirely consistent with the anatomical connections of the hippocampus along the septotemporal axis (Witter & Amaral, 2004). The present demonstration that vHPC lesions disrupt performance on an intertemporal choice task, is also consistent with the anatomical connectivity between vHPC and OFC (Jay & Witter, 1991), and the recent demonstration that OFC lesioned rats also choose impulsively on the same T maze task (Rudebeck et al., 2006). However, the present results also suggest a role for the dorsal hippocampus, which although possibly less pronounced initially (Expt 1, stage 1), is clearly apparent when the original reward contingencies were later reinstated in Expt 1, stage 3. Collectively, these results suggest that the OFC and HPC contribute to an extended neural circuitry underlying intertemporal choice, cost-benefit decision making, which presumably also includes brain areas such as the nucleus accumbens and basolateral amygdala (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Pothuizen, Jongen-Relo, Feldon, & Yee, 2005; Winstanley, Theobald, Cardinal, & Robbins, 2004).

Importantly, the effects of vHPC lesions on the intertemporal choice T maze task in the present study are in contrast to the lack of effects on classical spatial memory tests, such as the Morris watermaze (Moser et al., 1995), and also the spatial working memory version of the T maze paradigm (Bannerman et al., 1999; Hock & Bunsey, 1998). We have argued previously for a preferential role for vHPC on tasks which have a potential defensive component (Bannerman et al., 2004). For example, vHPC lesions reduce freezing during fear conditioning (Maren & Holt, 2004; Richmond et al., 1999) and have anxiolytic effects on unconditioned tests of anxiety (Bannerman et al., 2002; Kjelstrup et al., 2002; McHugh et al., 2004). The present results suggest that the effects of ventral lesions go beyond tasks with a defensive component. However, it is still possible that the vHPC lesion effect on the present task reflects an aversive component associated with the frustration of the delay to reinforcement in the HR arm. Normal

animals might form an association between the aversiveness of the delay period and the larger reward (“counterconditioning”). If the vHPC lesioned rats do not perceive the delay as aversive in the same way as controls then this counterconditioning may not occur.

Alternatively, the effects of complete and partial HPC lesions on the delay task could still be explained by a subtle memory deficit. As pointed out previously, HPC lesioned rats were not completely unable to remember which reward size was associated with which arm of the maze: in the second stage of postoperative testing in Experiment 1, all groups preferred the HR arm when the 10s delay was present on both the HR and LR arms. Nevertheless, an account in which the memory trace is merely attenuated in HPC lesioned rats might still suffice. It is thus possible that the failure of HPC lesioned animals to choose the delayed HR option during stage 1 and stage 3 reflects a reduced (rather than completely impaired) ability to bridge the delay and associate the HR outcome with the appropriate memory of what happened at the choice point. Such an account might still be consistent with the view that the hippocampus acts as a temporary or intermediate memory store for information, allowing animals to form associations across temporal discontinuities (Rawlins, 1985; Schmitt et al., 2004). Furthermore, this might also explain why HPC lesioned rats shift to choosing the HR when the 10s delay is present on both arms (Expt 1, stage 2): the memory trace attenuation then applies equally to either choice but is associated with rewards of different sizes.

A further alternative explanation is that the change in responding in HPC lesioned rats could reflect a specific impairment in the processing of temporal information associated with the delay to reinforcement following the response choice. In this respect, the performance of the vHPC rats on the classical, rewarded alternation T maze paradigm might be informative. Ventral HPC lesioned rats display absolutely no impairment on this spatial working memory task (Hock & Bunsey, 1998; Bannerman et al., 1999), even when there is a substantial delay (600s) between the sample run and the choice run of each trial (Bannerman et al., 2002). This suggests intact short term memory in the vHPC rats. In contrast, there is a clear ventral HPC lesion effect in the present intertemporal choice T maze task. Consequently, it may be that an impairment in processing information about the delay to reinforcement is the crucial factor in revealing a ventral HPC lesion effect. A proposed role for the hippocampus in temporal information processing has been suggested previously. For example, studies using the peak interval procedure suggest that HPC lesions lead to an inconsistency in time estimation (Buhusi, Mocanu, & Meck, 2005; Meck, Church, & Olton, 1984). Furthermore, in many respects, the pattern of results obtained with complete and partial HPC lesions in the present study resembles the effects seen during the differential reinforcement of low rates of responding (DRL) task (Bannerman et al., 1999). Performance on the DRL task requires the animal to withhold from responding until some minimum period of time (the DRL requirement) has elapsed. As in the present study, complete, dorsal, and ventral HPC lesioned rats were impulsive, in that they were less able to withhold from lever-pressing until the prescribed delay period had passed. Interestingly, similar parallels between a delay-based decision making task and the operant DRL task have also been observed for lesions of the nucleus accumbens (Pothuizen et al., 2005). It is possible, therefore, that the effects of vHPC lesions, at least, are due to deficits in temporal information processing.

In view of our original hypothesis, and the segregation of anatomical connections between the HPC and OFC along the septo-temporal axis, the effect of dHPC lesions on the intertemporal choice T maze task might be considered surprising, although it is worth pointing out that during postoperative stage 1, the performance of the dHPC group did appear to recover to control levels by the fourth block of testing. Nevertheless, there is a clear and lasting change in behavior in the dHPC group during postoperative stage 3 in which the animals are again choosing between a delayed HR and an immediate LR, suggesting that the dHPC does make an important contribution to intertemporal choice behavior on this T maze task. One possible explanation for the dHPC lesion effects is that the task might involve integrating spatial information about the two goal arms with information about the different delays and reward sizes, and that the deficit with dHPC lesions therefore reflects the role of this subregion in spatial memory (e.g., Bannerman et al., 1999). Against this, there is no actual requirement for the animals to use an allocentric spatial solution. It is sufficient for the animals to use an egocentric strategy (turn left or turn right) when choosing a particular goal arm. Indeed, both the dHPC and cHPC lesioned rats were perfectly capable of choosing the HR when there was an equivalent delay to reinforcement in both arms (postoperative stage 2), and when there was no delay in either arm (Expt 2, no barrier condition). An alternative explanation is that both the dorsal and ventral hippocampus contribute to temporal information processing, a suggestion which is also consistent with the effects of both dHPC and vHPC lesions on the nonspatial, DRL task. It would therefore be of interest to examine the effects of lesions of both hippocampal subregions on a definitively nonspatial, intertemporal choice task (Cheung & Cardinal, 2005).

Of course, it is possible that both dHPC and vHPC lesions affect performance on the intertemporal choice task, but for different reasons. For example, there is the intriguing possibility that both lesions result in impulsivity, but that dHPC lesions do so through an inability to withhold from executing an inappropriate response (behavioral disinhibition), whereas vHPC lesioned animals are unable to properly value delayed rewards, possibly as a consequence of disrupting HPC-OFC connections. A lack of behavioral inhibition and thus an inability to withhold from responding might also of course explain the initial increased preference of dHPC and cHPC rats to climb the barrier, and is also consistent with the observation that dHPC but not vHPC lesioned rats display locomotor hyperactivity (e.g., McHugh et al., 2004). It has been suggested previously that the impulsivity construct can be fractionated into (i) impulsive action, an increase in action production and/or a failure to inhibit action execution (behavioral inhibition), and (ii) impulsive choice or decision making, which may be the result of being unable to properly value delayed rewards (Evenden, 1999; Winstanley et al., 2004). However, it is important to note that an increase in impulsive action does not necessarily lead to an increase in impulsive choice (Winstanley et al., 2004). For example, whereas OFC but not ACC lesioned rats display impulsive choice or decision making, as exemplified by their impaired performance on the T maze intertemporal choice task, ACC but not OFC lesioned rats exhibit impulsive action (Rudebeck et al., 2006). ACC rats exhibit premature motor responses (Passetti, Chudasama, & Robbins, 2002) and display locomotor hyperactivity (Rudebeck et al., 2006), but importantly they do not demonstrate impulsive choice during testing on the intertemporal choice, T maze task (Rudebeck et al., 2006). It remains uncertain, there-

fore, whether the effects of dHPC lesions in the present study can be fully explained by an increase in impulsive action.

Conclusions

To conclude, any account of HPC function has to explain the effects on spatial memory, anxiety, impulsive choice, and behavioral disinhibition observed after HPC damage. The present results argue that both the dorsal and ventral HPC are involved in intertemporal choice, delayed-based decision making tasks, and also support the hypothesis that the HPC plays a fundamental role in the integration of different aspects of contextual information to guide response selection (Gray & McNaughton, 2000).

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