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Surgery Results in Exaggerated and Persistent Cognitive Decline in a Rat Model of the Metabolic Syndrome

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Abstract

Background—Postoperative cognitive decline can be reproduced in animal models. In a well-validated rat model of the Metabolic Syndrome, we sought to investigate whether surgery induced a more severe and persistent form of cognitive decline similar to that noted in preliminary clinical studies.

Methods—In rats that had been selectively bred for low and high exercise endurance, the low capacity runners (LCR) exhibited features of Metabolic Syndrome (obesity, dyslipidemia, insulin resistance, and hypertension). Tibial fracture surgery was performed under isoflurane anesthesia in LCR and high capacity runner (HCR) rats and cognitive function was assessed postoperatively in a

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trace-fear conditioning paradigm and Morris Water Maze; non-operated rats were exposed to anesthesia and analgesia (sham). Group sizes were n = 6.

Results—On postoperative D7, LCR rats had shorter freezing times than postoperative HCR rats. Five months postoperatively, LCR rats had a flatter learning trajectory and took longer to locate the submerged platform than postoperative HCR rats; dwell-time in the target quadrant in a probe trial was shorter in the postoperative LCR compared to HCR rats. LCR and HCR sham rats did not differ in any test.

Conclusion—Postoperatively, LCR rats diverged from HCR rats exhibiting a greater decline in memory, acutely, with persistent learning and memory decline, remotely; this could not be attributed to changes in locomotor or swimming performance. This Metabolic Syndrome animal model of surgery-induced cognitive decline corroborates, with high fidelity, preliminary findings of postoperative cognitive dysfunction in Metabolic Syndrome patients.

Mild transient cognitive decline after surgery may occur commonly; however, some patients develop a more severe form that meets the Diagnostic and Statistical Manual of Mental Disorders IV classification of delirium or a longer-lasting form, referred to as postoperative cognitive dysfunction. It has been estimated that 11% of patients undergoing elective surgery develop delirium between postoperative days 1–4; surgical patients with this complication require more intensive care and have a higher mortality rate.[1] Because postoperative cognitive dysfunction is not classified in the Diagnostic and Statistical Manual of Mental Disorders IV, it lacks firm diagnostic criteria; if a threshold of “worse than expected” postoperative cognitive decline is used, then postoperative cognitive dysfunction occurs in >10% of non-cardiac surgical patients over the age of 65 years.[2]

With neither standardized cognitive domain testing nor appropriate controls, some have challenged whether the frequency of persistent postoperative cognitive decline is beyond that expected from “natural,” age-dependent deterioration.[3–5] In order to overcome the lack of appropriate controls in clinical studies (*i.e.*, surgical patients who are randomized to a cohort that does not receive surgery), we have set up models of rodents in which to explore the independent effects of surgery and anesthesia, and to address the molecular and cellular mechanisms that contribute to this condition.[6–9] For animal models to be valid, these models need to reproduce salient features of the clinical syndrome. Patient factors, including increasing age, less higher education, postoperative complications (respiratory and infectious), and re-operation, had all been reported to increase the likelihood of developing postoperative cognitive decline.[2,10] We, and others, have shown that more severe and persistent cognitive decline occurs in the settings of perioperative infection[11] and advanced age.[12]

The induction of short-lived neuroinflammation, following the release of damage-associated molecular patterns from traumatized tissue, appears to be necessary for the organism’s central nervous system-mediated “sickness behavior;” this is comprised of a fever, anorexia, somnolence, and cognitive impairment, and injured animals in this state remain sedentary promoting healing rather than risking further injury. Our recent preclinical studies have revealed that the transient cognitive decline that follows aseptic surgical trauma occurs by engaging the innate immune system through nuclear factor-κB-dependent signaling to

release cytokines that disrupt blood brain barrier integrity.[6–9] Through a permeable blood brain barrier, bone marrow-derived macrophages migrate into the brain parenchyma promoting neuroinflammation that is capable of interfering with processes required for learning and memory.[8,13]

Two recent preliminary reports from Hudetz *et al.* have drawn attention to an exacerbation of early postoperative cognitive decline, as well as a greater likelihood of the persistence of postoperative cognitive decline in patients with Metabolic Syndrome (MetaS) who undergo either cardiac or non-cardiac surgery, respectively.[14,15] In order to investigate the possible mechanisms, we reverted to a validated animal model of MetaS.

Most of the mouse models of MetaS are created by the extinction or modification of a single gene ± a dietary perturbation. These gene knock-out/knock-in approaches reveal the dependence on that gene, together with the subsequent adaptations, for the resulting loss or gain of function. These approaches may fail to model the human phenotype because they do not reconstitute complex gene-gene interaction. Amongst the several rat models of MetaS, we have chosen one that not only has the appropriate phenotype but also has been generated in a manner that is “lifestyle-related.” Starting in 1995, Koch and Britton applied divergent artificial selection for intrinsic low and high endurance running capacity starting with a founder population of genetically heterogeneous rats. Thirty generations of selection have produced lines of low capacity runners (LCRs) and high capacity runners (HCRs) that differ by 7-fold in treadmill running capacity.[16] The LCR rats contain features of the MetaS, including elevated low density lipoproteins, cholesterol, blood pressure, triglycerides, fasting glucose, insulin, C-reactive protein, and visceral adiposity being 100 g heavier than the HCR rats at 12 weeks.[17] The LCR rats have a low intrinsic aerobic capacity that results in easy fatigability; this may contribute to their sedentary behavior[18] which is thought to be causally related to the development of the MetaS.[19,20]

Using this rat model of MetaS, we have explored whether cognitive decline is more severe in the early postoperative period and whether it is likely to be more persistent in the LCR rats that have the features of MetaS; establishment of this an abnormal immune response to elective surgery can set the stage for a thorough exploration of the mechanisms that can contribute to these and other inflammation-mediated postoperative complications.

Materials and Methods

Animals

All experimental procedures involving animals were approved by the University of California, San Francisco Institutional Animal Care and Use Committee, and conformed to National Institute of Health guidelines. Animals were handled in strict accordance with good animal practice. LCRs and HCRs were developed by Koch and Britton.[16] The LCR rats are maintained as genetically heterogeneous lines by using a rotational mating paradigm that minimizes inbreeding, thereby maintaining genetic complexity and allowing combinations of allelic variants at multiple interacting loci to be enriched by selection pressure.[16,21]

Only male rats aged between 4 and 5 months were used. All animals were fed standard rodent chow and water ad libitum, and were housed (2 rats per cage) in sawdust-lined cages in an air-conditioned environment with 12-h light/dark cycles. Animals were tagged and randomly allocated to the surgery or sham group before any procedure was undertaken; researchers were blinded to the group assignment during assessments, prior to the analysis phase. Because of the difference in color and weight between the LCR (brown, approximately 400 g) and HCR (white approximately 300 g) rats, it is not possible for the observer to be blinded for the phenotype, but they were blinded for the treatment group. Forty-eight rats were included with no lethality or exclusion.

Surgery

Under general anesthesia with 2.1% isoflurane in 0.30 FiO_2, rats underwent an open tibial fracture of the left hind paw with an intramedullary fixation under aseptic surgical conditions as previously described.[7–9] The surgical field was maintained as sterile throughout the procedure. Briefly, the left hind paw of surgical animals was meticulously shaved and disinfected with povidone iodine. Following a median incision, a 20 G pin was inserted into the intramedullary canal, the periosteum was stripped, and osteotomy was performed. The wound was irrigated, the skin was sutured, and the animals were allowed to recover spontaneously from the anesthetic. During the procedure, temperature was monitored and maintained at 36.5–37.5°C with the aid of warming pads (Harvard Apparatus, Holliston, MA) and a temperature-controlled light. Buprenorphine (0.1 mg/kg) was given subcutaneously to provide analgesia after the induction of anesthesia and before skin incision. The sham rats were exposed to anesthesia and analgesia as above and had the paw shaved.

Twenty-four rats were used for trace-fear conditioning (TFC) assessed 7 days after surgery and an additional 24 rats were used for Morris Water Maze (MWM) assessed 5 months after surgery.

Behavioral Studies

Trace Fear Conditioning—TFC was used to assess hippocampal-dependent memory in rodents as previously described.[7–9] The clear acrylic TFC chamber (Med Associates Inc., St Albans, VT), with dimensions of 32 cm long, 25 cm wide, and 25 cm high, included a floor constructed of stainless steel bars that was connected to a shock delivery system (Med Associates). The chamber was wiped with a pine-scented cleaner (5% Pine Scented Disinfectant; Midland, Inc., Sweetwater, TN) before and after each session, and training and assessment was performed in a room illuminated with overhead fluorescent bulbs with a ventilation fan providing background noise (65 db). During the training, rats were allowed to explore this context for 3 min, after which they were presented with an auditory cue (75–80 dB, 5 kHz, conditional stimulus for 20 s). The unconditional stimulus, a 2-s foot shock (0.8 mAmp), was administered 20 s after termination of the auditory tone. Rats were removed from the chamber after an additional 30 s. Rats anticipate the shock by “freezing,” which is defined as the absence of all movement except for respirations; this defensive posture reflects learned fear. When placed in the same context on a subsequent occasion, the learned fear is recalled, and the amount of learning and recall is measured by the amount of freezing.

Surgery was performed within 30 min after training. Memory of the learned fear was assessed 7 days later by returning the rat into the same chamber in which it was trained, in the absence of tone and shock. Behavior was recorded by a Polaris digital video recorder (Cohu Electronics Division, Poway, CA). Each animal's behavior was scored every 5 s during the 5 min observation period and a percentage was calculated using the formula $100\times f/n$, where f is the number of freezing events per rat and n is the total number of observations per rat.

Open Field—A standardized measure of general motor function is spontaneous activity. At the conclusion of the contextual fear response, rats were placed in a wooden open field apparatus (45" square; 18" high) in which the floor was subdivided into 25 blocks (9" square) with thin white stripes, and activity was recorded by the Polaris digital video recorder (Cohu Electronics Division, Poway, CA). The number of line crossings and rearings performed in a 5 min epoch was scored by an observer that was unaware of group assignment.[22]

Morris Water Maze

Five months after surgery, separate cohorts of rats were investigated in the MWM in the following manner.[23]

Cueing Procedure—A platform (diameter, 10.3 cm) was placed one inch above the level of warm (24°C), opaque water in a circular pool (diameter, 180 cm; depth, 50 cm). The platform was rendered more visible from the surface by marking its edge with bright, yellow tape. For each of the three sessions, the rat was placed in the water and emerged from the water onto the platform within 60 s; if not, the rat was guided towards the raised platform. A different platform site was used for each session. This cueing procedure enables the rat to realize that they can escape the water by locating a platform.

Spatial Reference Memory—The pool is surrounded by visual cues and the platform is submerged below the surface. Daily, two training sessions spaced 7 h apart, were performed; for each session, the rat was released from one of three assigned locations facing the wall of the tank, resulting in one short, one medium, and one long swim per session, in random order. Rats were given 90 s to locate the hidden platform; if the rat failed to locate the hidden platform within the allotted time, the rat was guided to the platform. In either case, the rat was removed from the platform after 15 s. To minimize any bias associated with platform location, equal numbers of rats in each group were assigned one of the four quadrant locations of the platform for the duration of training. The time to reach the platform (latency), path length, swimming speed, and time-integrated distance to the platform were analyzed using an EthoVision video tracking system (Noldus Instruments, Wageningen, Holland) that was set to analyze 10 samples per second. The mean difference of decrease in the escape latency to the submerged platform per session, as well as the escape latency for the final session (session number 10), were analyzed.

Probe Trials—To assess memory retention for the hidden platform location, a probe trial, with the platform removed from the tank, was performed immediately after the last training

session. During the 60-s probe trial, the proportion of time spent in the quadrant in which the platform previously resided ("target quadrant"), as well as each of the other quadrants, was determined for a 60-s interval.

Statistical Analysis

Data are presented as a mean ± SD. We tested for normal distribution of the data with the d'Agostino and Pearson omnibus test and the equality of variances with the F-test. For comparisons of the two independent variables (strain [HCR/LCR] and surgery [fracture/sham]), we performed two-way ANOVA; this was followed by four pairwise student *t* tests with a Bonferroni correction (Bonferroni corrected alpha = 0.05/4 = 0.0125).

For TFC, we performed two-way ANOVA, testing the percentage of freezing time followed by four pairwise *t* tests (Bonferroni corrected alpha = 0.05/4 = 0.0125).

Regarding the MWM test, based on previous data[24] (SD of the percentage of dwell time in target quadrant = 15), we estimated that a sample of 6 rats per group was necessary to find a significant difference between the LCR and the HCR surgery groups, with 80% of power if the difference was 25%. For the spatial reference memory experiments, the escape latency to the submerged platform of the 4 groups in the last session was analyzed with two-way ANOVA followed by four pairwise *t* tests (Bonferroni corrected alpha = 0.05/4 = 0.0125). To analyze the mean difference of decrease per session within the 10 sessions, we used a mixed-effects linear regression model[25] with a three-way interaction involving session number, intervention (surgery or sham), and strain (LCR/HCR) with all lower order terms as predictors. We performed four additional *post hoc* models for pairwise comparisons of groups to determine whether there was a faster improvement in the latency time to platform amongst pairings across sessions; a pairing was deemed significantly different if the interaction term for the session and group was significant in the model (Bonferroni corrected alpha = 0.05/4 or 0.0125). For the probe trial, we compared the proportions of dwell time spent in each of the quadrants for the groups with a two-way ANOVA followed by four pairwise *t* tests (Bonferroni corrected alpha = 0.05/4 or 0.0125).

A two-tailed *P* value < 0.05 was considered statistically significant and data were analyzed using Stata 11.2 software (StataCorp, College Station, TX).

Results

Animals were assessed by open field testing after the contextual fear response on day 7, in order to exclude possible locomotor impairments that could confound the TFC assessment. Spontaneous movement was not different in the LCR *versus* HCR rats with or without surgery (fig. 1). Acute postoperative memory, assessed by the percentage of time spent freezing when the rat was placed in the same context as the pre-operative TFC training, was impaired in both cohorts of postoperative rats on postoperative day 7. Two-way ANOVA revealed a significant interaction between the strain and intervention ($P = 0.02$); the degree of memory impairment, as reflected by the percentage freezing, was greater in the postoperative LCR than the postoperative HCR rats (20 ± 4, *vs.* 33 ± 6, $P = 0.006$, fig. 2).

In the MWM test, the swimming speed was similar in all groups tested at 5 months (fig. 3A). Although the strain of the rats presented a significant effect on the weight recorded one week prior to the MWM ($P < 0.001$), surgery had no significant effect, suggesting that all groups continued to thrive throughout the course of the study (fig. 3B).

LCR surgery rats had significantly less overall improvement with successive tests compared to HCR surgery, as evidenced by a significantly longer time required to locate the submerged platform after the final, 10th session ($P = 0.007$ for two-way ANOVA strain effect). Pairwise *post hoc t* tests revealed that this strain effect was significant in the surgery rats (LCR surgery *vs.* HCR surgery, 34 ± 21 *vs.* 15 ± 6, $P = 0.001$, fig. 4A). A three-way interaction in the mixed-effects model was significant ($P = 0.010$), indicating that the effects of surgery and strain could not be considered in isolation when explaining variation in the rate of change in time to the submerged platform over successive trials. The mean rate of improvement (seconds/per session) was significantly less ($P < 0.001$) for the postoperative LCR rats (2 s/session) than for the sham-LCR rats (6 s/session) in a pairwise comparison of groups (fig. 4B). The difference in improvement per session between postoperative LCR rats and postoperative HCR rats (3 s/session, $P = 0.010$) was also significant after applying a Bonferroni correction. The modeled curves reveal that the improvement in the escape latency *per* session to locate the hidden platform in the LCR surgery group was smaller than the LCR sham group (fig. 4B), whereas the improvements of HCR surgery and HCR sham rats were similar (fig. 4C).

In the probe trial, two-way ANOVA revealed a significant interaction between strain and intervention ($P = 0.02$) for the target quadrant (in which the platform formerly resided); *post hoc* analyses revealed that the percentage of time that the postoperative LCR rats spent in the target quadrant was significantly shorter than for each of the other groups (for example—LCR surgery *vs.* HCR surgery 24 ± 7 *vs.* 40 ± 6, $P = 0.007$, fig. 5). Apart from the postoperative LCR group, groups spent significantly more time in the target quadrant than in each of the others, while the postoperative LCR rats spent equivalent time in each of the four quadrants.

Discussion

Cognitive decline after surgery, whether temporary in the form of Postoperative Delirium or persistent, possibly in the form of Postoperative Cognitive Dysfunction, appears to be associated with long-term adverse outcomes including withdrawal from the workplace, loss of independent living, and an increase in mortality rate.[2,26] Therefore, it is vital to understand the risk factors and pathogenesis that may contribute to these postoperative complications.

In a series of preclinical studies, we had noted that postoperative cognitive decline is due to the engagement of the innate immune system in response to aseptic trauma.[6–9,27,28] The expression of cognitive decline is due to neuroinflammation that produces a constellation of symptoms, referred to as “sickness behavior,” which is thought to protect the traumatized organism from further injury and to facilitate the healing process.[29] This is a short-lived process in which neuroinflammation is curtailed by feedback mechanisms that involve both

neural (especially the parasympathetic nervous system), as well as humoral (including oxygenated and nitrogenated lipid) factors.[30,31] Disruption of these precisely regulated processes may contribute to abnormal quantitative and qualitative responses to aseptic trauma.[8] The existence of a disease that causes either exacerbation of the acute postoperative decline and/or the persistence of cognitive impairment, validates the animal model as one in which to explore pathogenic mechanisms and, thereby, possible therapeutic interventions.[14,15]

MetaS, comprised of insulin resistance (hyperglycemia that can progress to Type 2 diabetes mellitus), visceral obesity, hypertension, and dyslipidemia increases the risk of postoperative complications contributing to a significantly higher mortality rate.[14,15,32] In a recent review of a case series of coronary artery bypass surgical patients, those suffering with MetaS had a longer postoperative stay although overall outcome was not affected.[33] Many of the complications of MetaS (including atherosclerosis) are inflammatory in nature with the pathological adipose stores being the source of pro-inflammatory adipokines.[34] It is estimated that more than a quarter of the American adult population has MetaS; its prevalence is probably over-represented in the surgical population, with half of all patients undergoing cardiac surgery being afflicted by this syndrome.[32] Recent evidence indicates patients suffering from MetaS may be particularly susceptible to postoperative cognitive decline.[14,15]

Starting in 1995, Koch and Britton applied divergent artificial selection for intrinsic low and high endurance running capacity starting with a founder population of genetically heterogeneous rats. Thirty generations of selection have produced lines of LCRs and HCRs that differ 7-fold in treadmill running capacity[16]; the LCR rats contain features of the MetaS, including elevated low density lipoproteins, cholesterol, blood pressure, triglycerides, fasting glucose, insulin, C-reactive protein, and visceral adiposity being approximately100 g heavier than the HCR rats at 12 weeks.[18] The LCR-HCR rats represent polygenic substrate that can be used for exploring medically-relevant features, such as postoperative cognitive decline, that may be associated with the MetaS.[14,15] The major genetic hypothesis is that contrasting alleles, causative of the trait differences, have been enriched or fixed differentially between the lines.

In the behavioral paradigms that we have used to interrogate cognitive domains of learning and memory, non-surgical LCR and HCR rats did not differ in either TFC or in the MWM. For the MWM experiments, we applied a mixed-effects model that took into account the strain, the type of surgery and the repeated measures. This model allowed us to gain power and to capture the rate of learning of the rats. Other tests, which are perhaps more “subtle” than the ones that we employed, do show a behavioral phenotype in nonsurgical rats.[35] Postoperatively, the LCR rats exhibit both an early exacerbation of memory decline as well as a persistent abnormality in both learning and memory. Non-cognitive factors that could have contributed to the behavioral assessments, such as altered spontaneous movement in TFC or the swim speed in MWM, are not different between the LCR and HCR rats.

It is noteworthy that the HCR rats may not represent “normal” rats and are more akin to organisms that are performing at a higher level of efficiency for energy expenditure

compared to “normal” rats. As eight strains of rats formed the original cross-breeding reagents, it is not possible to ascertain which strain of rat is the normal one to be used as a control. Therefore, we can only comment that postoperatively, the LCR rats diverge from the HCR rats and are not able to opine whether this difference relates to deterioration in function from normal for the LCR rats and/or an improvement from normal for the HCR rats. However, it is noteworthy that the HCR rats do not appear to recover from acute postoperative memory decline faster than that noted in our earlier study involving male Sprague Dawley rats in a Y-maze test.[6]

Our findings set the stage for a thorough exploration of the reasons why MetaS induces differences in postoperative cognitive function. Recently, we reported that when the cholinergic neural feedback mechanism for surgery-induced neuroinflammation is disrupted in wild-type mice, an exacerbation of postoperative cognitive decline follows.[8] It is noteworthy that patients with MetaS have a disorder in cholinergic function.[36,37] Further exploration in these rat reagents may reveal the mechanism for this abnormality in cholinergic function and, thereby, reveal targets for interventions.

While we have concentrated on the reasons why the brain is a target for postoperative inflammatory complications, it will be important to consider whether other postoperative complications with a putative inflammatory basis, including conversion from acute to chronic postoperative pain and thrombo-embolic complications, may have a similar propensity to occur in MetaS possibly on the basis of dysregulation of mechanisms involved in the initiation and/or resolution of inflammation.

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What We Already Know about This Topic

- The contributions of surgery, anesthesia and pathophysiological factors in postoperative cognitive decline are difficult to resolve in clinical studies
- Metabolic syndrome might enhance inflammation-mediated postoperative complications, including cognitive dysfunction

What This Article Tells Us That Is New

- Using a rat model, metabolic syndrome produced greater memory impairment and persistent learning and memory decline following tibial fracture surgery under isoflurane anesthesia
- Further studies are necessary to determine the mechanisms of these effects, and how metabolic syndrome exacerbates postoperative cognitive dysfunction

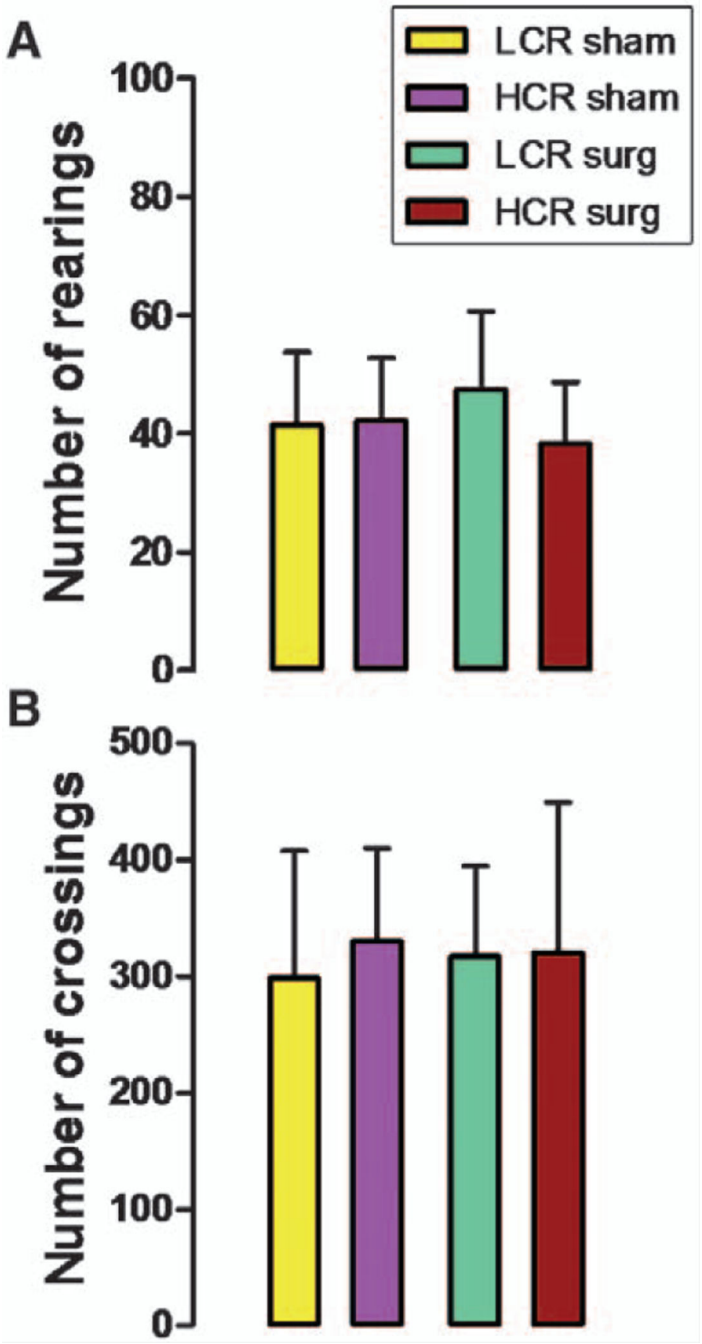

Fig. 1.

Effect of phenotype and surgery on spontaneous mobility in open field test. On postoperative day 7, vertical (number of rearings, *A*) and horizontal (number of grid-crossings, *B*) movement was recorded for 5 min. Data were analyzed with two-way ANOVA with *post hoc* pairwise *t* test comparisons with Bonferroni correction; results are expressed as mean and SD (n = 6). There was no statistically significant difference noted in pairwise comparisons. HCR = high capacity runner phenotype; LCR = low capacity runner phenotype; surg = surgery.

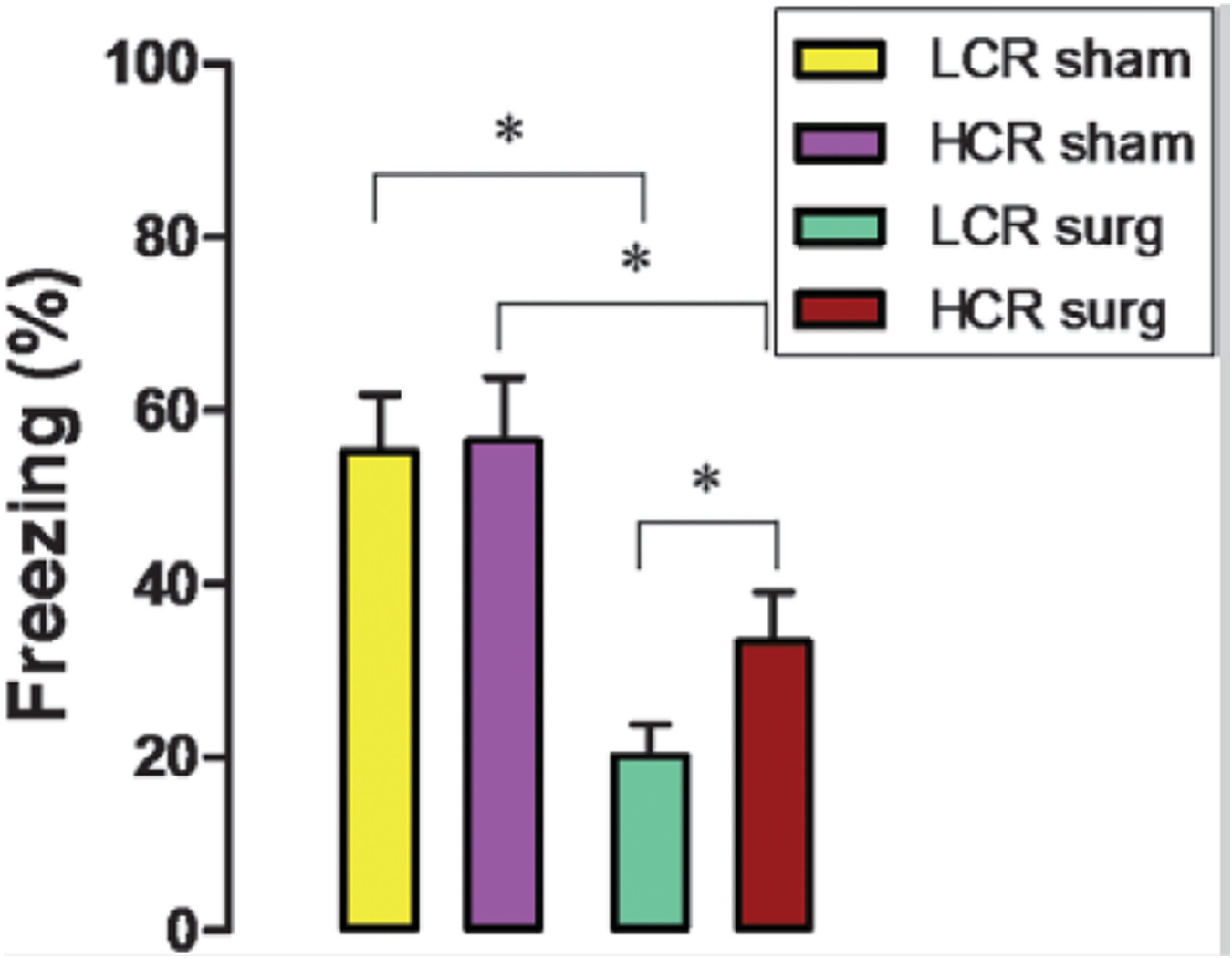

Fig. 2.

Acute effect of surgery and phenotype on hippocampal-dependent memory. After pre-operative training in a trace-fear conditioning paradigm, the percent time that a rat spent freezing during a 5 min epoch was assessed on postoperative day 7 when placed in the same context as the training. Data were analyzed with two-way ANOVA with *post hoc* pairwise *t* test comparisons with Bonferroni correction and results are expressed as mean and SD (n = 6). A significant interaction was noted between strain and surgery ($P = 0.02$). *Post hoc* pairwise comparison revealed that each of the surgical groups exhibited significantly less freezing time than their own sham cohort HCR; furthermore, the LCR surgical group exhibited significantly less freezing time than the HCR surgical group. There was no significant difference between the LCR/sham and HCR/sham groups. * $P < 0.01$. HCR = high capacity runner phenotype; LCR = low capacity runner phenotype; surg = surgery.

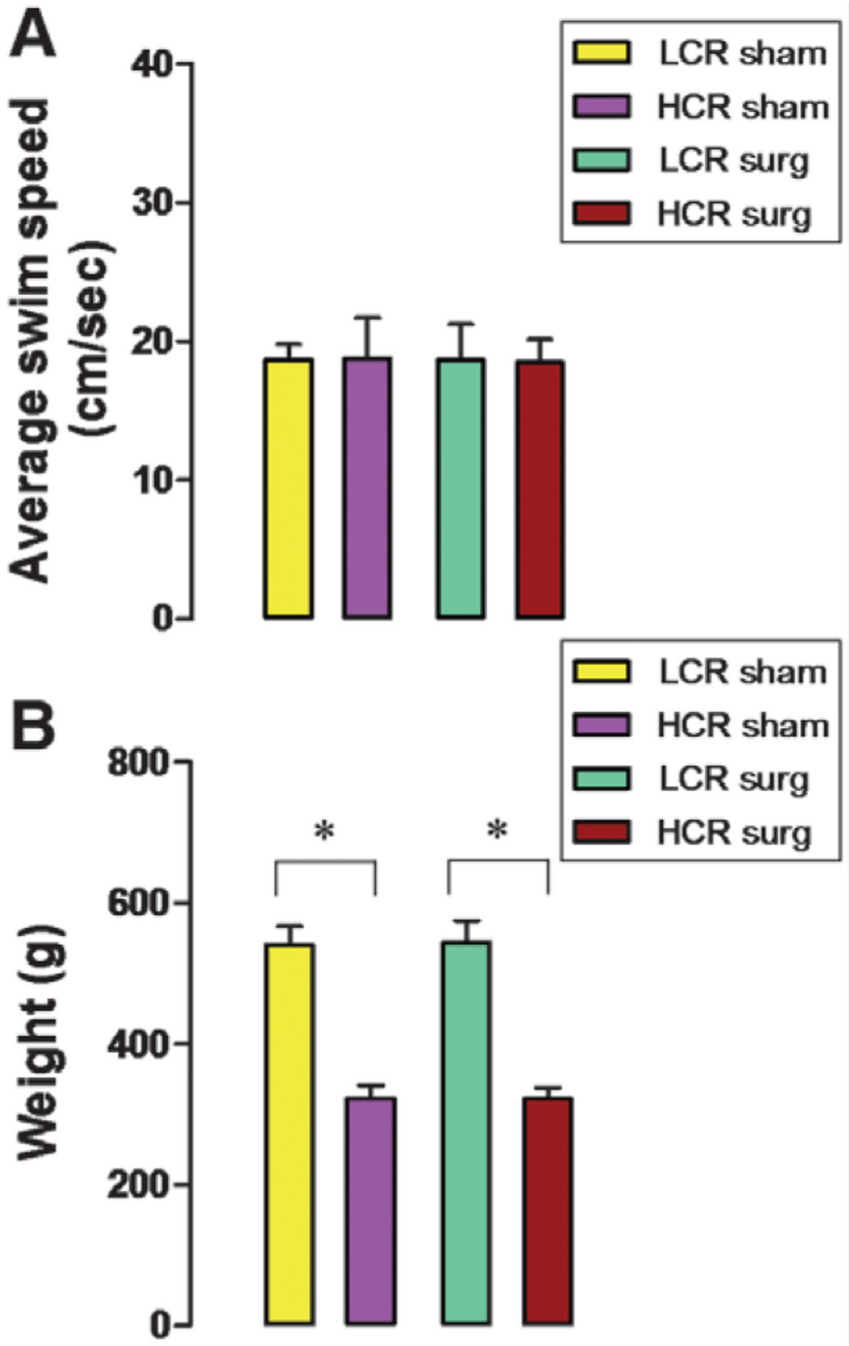

Fig. 3.

Effect of surgery and phenotype on swim speed and thriving. (*A*) Five months after surgery, swimming speed was measured during the spatial reference memory portion of the Morris Water Maze. Data were analyzed with two-way ANOVA with *post hoc* pairwise *t* test comparisons with Bonferroni correction; results are expressed as mean and SD (n = 6). There was no statistically significant difference noted for either interactions or for pair-wise comparisons. (*B*) Weights were measured five months after surgery and data were analyzed with two-way ANOVA; this showed a significant effect of the strain without any effect of the

surgery (n = 6, $P < 0.001$ for strain, $P = 0.93$ for surgery, and $P = 0.81$ for interaction by strain and surgery). HCR = high capacity runner phenotype; LCR = low capacity runner phenotype; surg = surgery.

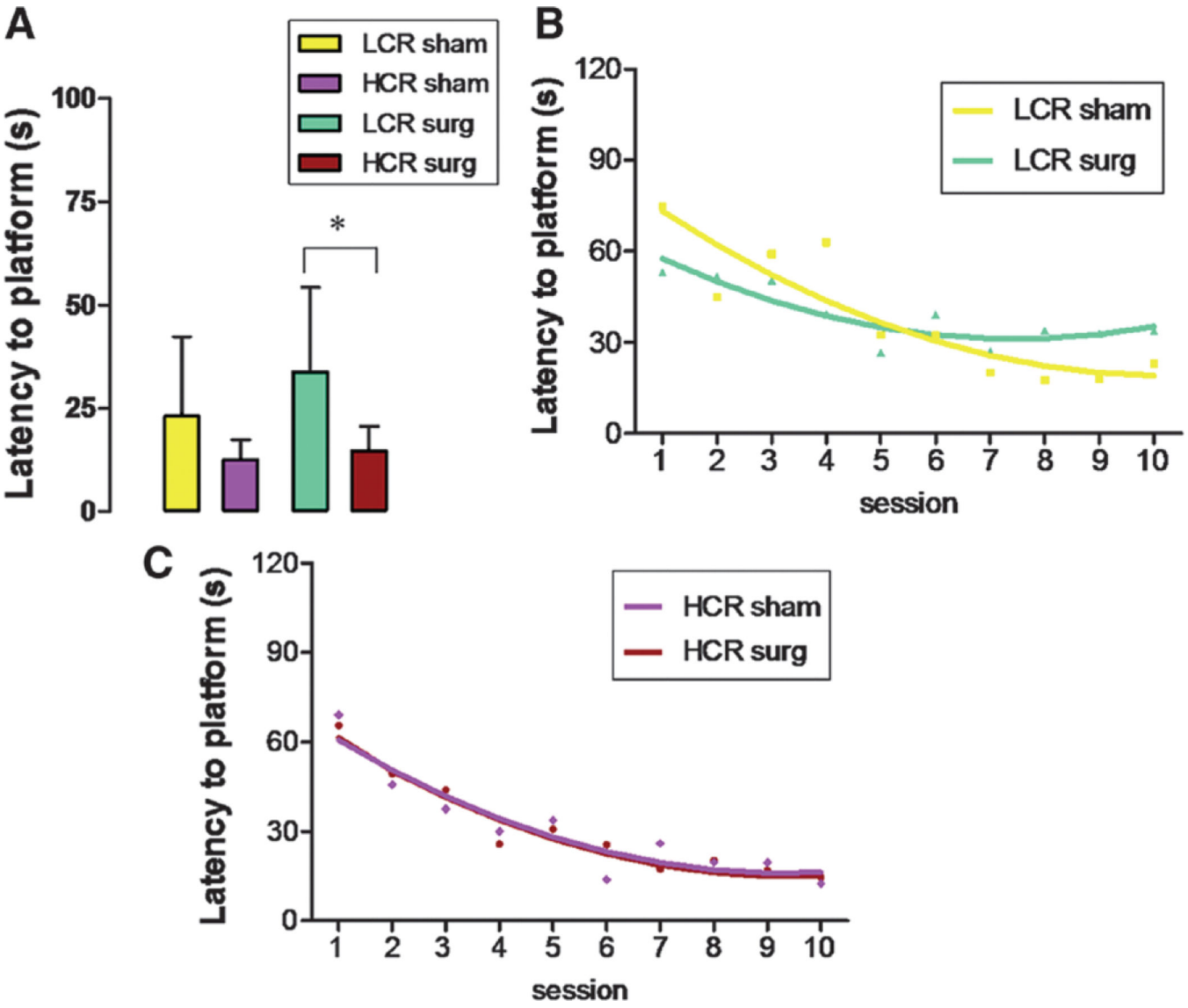

Fig. 4.

Effect of remote surgery and phenotype on learning. (*A*) Five months after surgery, rats were tested twice daily for 5 consecutive days, for their ability to locate a submerged platform in a Morris Water Maze. For each of the ten sessions, the latency (s) to escape the water and find the platform was the average of three scored trials. Data were analyzed at session 10 with two-way ANOVA showing a significant effect of the strain ($P = 0.007$ for strain), but not for surgery, or for the interaction by strain and surgery. *Post hoc* pairwise *t* test comparisons with Bonferroni correction revealed that escape latency to the submerged platform in LCR surgery rats was significantly longer than for the HCR surgery rats (* $P = 0.01$). Mixed-effects linear regression model of the effect of surgery on learning in LCR (*B*) and HCR (*C*) rats. The average raw values for each session from *A* were analyzed, taking into account the three-way interaction involving session number, surgery/sham and a session-squared term. Pair-wise comparisons with Bonferroni correction revealed that the slope was significantly less in LCR surgery rats compared to the LCR sham rats ($P < 0.001$); additionally, there was

a significant difference in slope between LCR surgery rats and HCR surgery rats (P = 0.010). The curves for sham and surgery HCR rats were similar (C). HCR = high capacity runner phenotype; LCR = low capacity runner phenotype; surg = surgery.

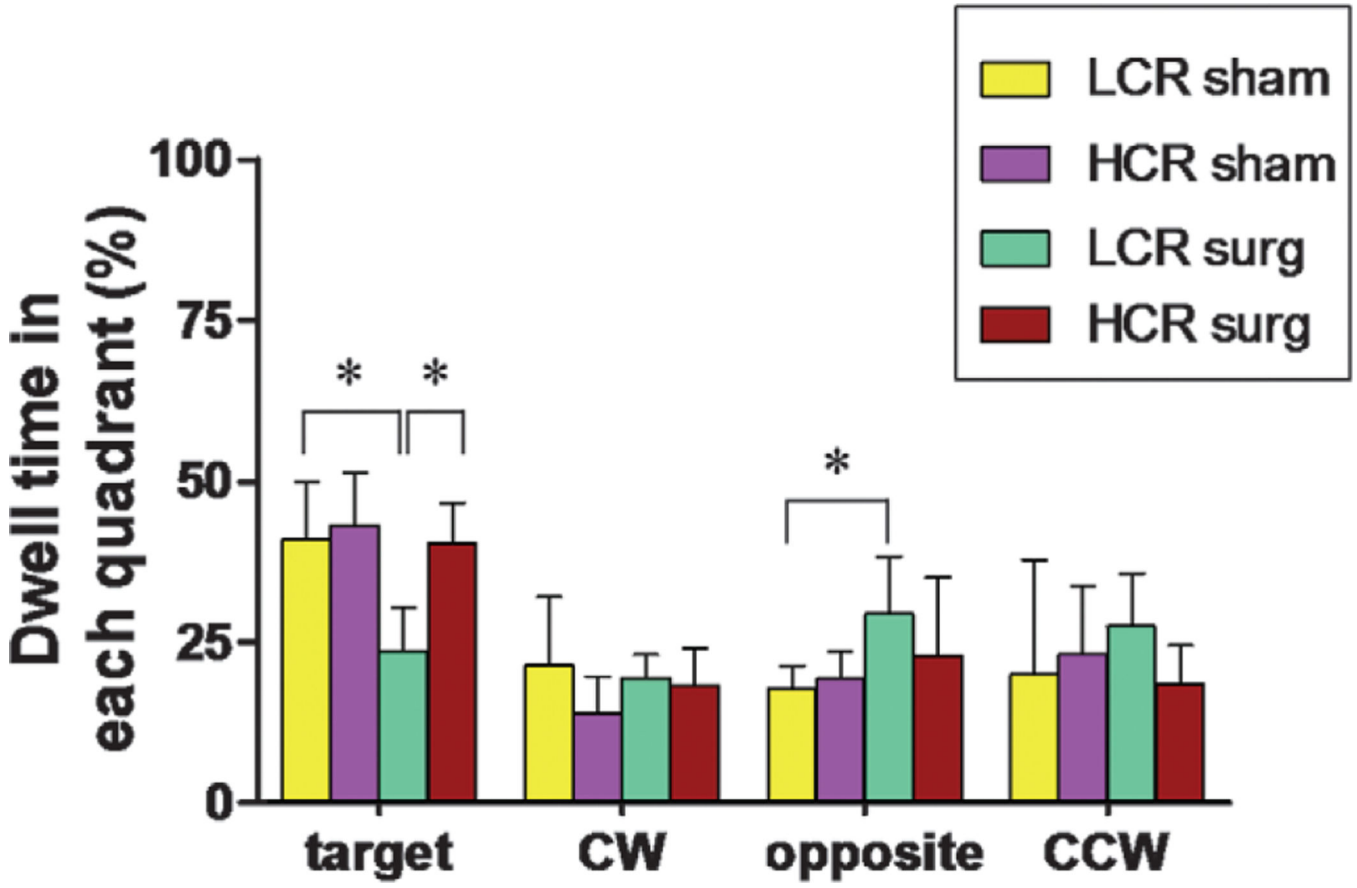

Fig. 5.

Remote effect of surgery and phenotype on memory. Five months after surgery, immediately following the last session in the spatial reference test (described in Figure 4), rats were returned to the Morris Water Maze in which the submerged platform had been removed. The probe trial consisted of measuring the % of time spent within a 60 s epoch, in the quadrant in which the platform formerly resided; this is referred to as dwell time in target quadrant. In addition, the time spent in the opposite quadrant, clockwise quadrant (CW), and counterclockwise (CCW) quadrant were also measured. Each quadrant's data were analyzed separately with two-way ANOVA followed with *post hoc* analyses, and results are expressed as mean and SD (n = 6). For the target quadrant, there was a significant interaction between strain and surgery ($P = 0.04$) and the dwell time was significantly lower (* $P < 0.01$) in the LCR surgery rats than for either the HCR surgery or LCR sham groups. For the opposite quadrant, there was a significant strain and surgery effect ($P = 0.003$ for the surgery, $P = 0.04$ for the strain and $P = 0.12$ for the interaction) and the percent of dwell time in the LCR surgery rats was significantly higher in LCR sham rats (* $P < 0.01$). The four groups spent similar time in CW and CCW quadrants. HCR = high capacity runner phenotype; LCR = low capacity runner phenotype; surg = surgery.