Brain, Behavior, and Immunity 54 (2016) 178–193

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Postoperative cognitive dysfunction and neuroinflammation; Cardiac surgery and abdominal surgery are not the same

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ARTICLE INFO

Article history:
Received 15 September 2015
Received in revised form 25 January 2016
Accepted 7 February 2016
Available online 8 February 2016

Keywords:
Postoperative cognitive dysfunction
Surgery
Cardiac
Abdominal
Behavior
Cognition
Neuroinflammation
Neutrophil gelatinase-associated lipocalin
Brain-derived neurotrophic factor
Neurogenesis

ABSTRACT

Postoperative cognitive dysfunction (POCD) is a debilitating surgical complication, with cardiac surgery patients at particular risk. To gain insight in the mechanisms underlying the higher incidence of POCD after cardiac versus non-cardiac surgery, systemic and central inflammatory changes, alterations in intraneuronal pathways, and cognitive performance were studied after cardiac and abdominal surgery in rats.

Male Wistar rats were subjected to ischemia reperfusion of the upper mesenteric artery (abdominal surgery) or the left coronary artery (cardiac surgery). Control rats remained naïve, received anesthesia only, or received thoracic sham surgery. Rats were subjected to affective and cognitive behavioral tests in postoperative week 2. Plasma concentrations of inflammatory factors, and markers for neuroinflammation (NGAL and microglial activity) and the BDNF pathway (BDNF, p38MAPK and DCX) were determined.

Spatial memory was impaired after both abdominal and cardiac surgery, but only cardiac surgery impaired spatial learning and object recognition. While all surgical procedures elicited a pronounced acute systemic inflammatory response, NGAL and TNFα levels were particularly increased after abdominal surgery. Conversely, NGAL in plasma and the paraventricular nucleus of the hypothalamus and microglial activity in hippocampus and prefrontal cortex on postoperative day 14 were increased after cardiac, but not abdominal surgery. Both surgery types induced hippocampal alterations in BDNF signaling.

These results suggest that POCD after cardiac surgery, compared to non-cardiac surgery, affects different cognitive domains and hence may be more extended rather than more severe. Moreover, while abdominal surgery effects seem limited to hippocampal brain regions, cardiac surgery seems associated with more wide spread alterations in the brain.

1. Introduction

The first reports of long-lasting cognitive impairment following surgery in older persons were published 6 decades ago (Bedford, 1955; Boshes et al., 1957). This postoperative cognitive dysfunction (POCD) is characterized by dementia-like symptoms such as memory impairment, loss of concentration, an inability to plan, and difficulty to switch between tasks (Krenk et al., 2010). Since researchers started identifying POCD as a perioperative decline in performance on two or more tests of a broad neuropsychological test battery (Moller et al., 1998), it was shown that POCD can occur after all types of surgery, albeit at a much higher incidence in cardiac- versus non-cardiac surgery (see Rasmussen, 2006; Selnes et al., 2006a for extensive literature reviews). The reported incidence of POCD is 20–50% three months after cardiac surgery (Evered et al., 2011; Fontes et al., 2013; Kok et al., 2014; Liu et al., 2009; Meybohm et al., 2013; Newman et al., 2006, 2001; Patron et al., 2013), compared to 5–20% after non-cardiac surgery (Dijkstra et al., 1999; Evered et al., 2011; Moller et al., 1998; Radtke et al., 2013; Rasmussen et al., 2000). Although much less investigated, postsurgical symptoms of depression have also been

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http://dx.doi.org/10.1016/j.bbi.2016.02.003
0889-1591/

reported and they seem particularly prominent after cardiac surgery (Borsook et al., 2010; Faria et al., 2014; Nickinson et al., 2009; Patron et al., 2014; Tsapakis et al., 2009).

Several mechanisms have been proposed to be involved in the development of POCD. Mounting evidence indicates the involvement of inflammatory processes (see Hovens et al., 2012; van Harten et al., 2012 for literature reviews). In rodent studies postsurgical increases in systemic and hippocampal pro-inflammatory cytokines and microglial activation have been associated with postoperative impairment of spatial and contextual learning and memory (Barrientos et al., 2012; Cibelli et al., 2010; Hovens et al., 2014b; Tang et al., 2011; Wan et al., 2007). Moreover, inhibition of central pro-inflammatory cytokine signaling was shown to attenuate postoperative memory impairment in rodents (Barrientos et al., 2012; Cibelli et al., 2010; Jiang et al., 2015; Terrando et al., 2010). A recent meta-analysis confirmed the association between the peripheral inflammatory response to surgery and POCD in patients (Peng et al., 2013). Inflammatory mediators in the brain may influence learning and memory directly, but also indirectly by inhibiting intraneuronal signaling pathways (Yirmiya and Goshen, 2011). Pro-inflammatory cytokines can for example inhibit brain-derived neurotrophic factor (BDNF)-signaling via activation of p38 mitogen activated protein kinase (p38MAPK) and nuclear factor κB (NF-κB), resulting in reduced neurogenesis and neuronal plasticity (Cortese et al., 2011; Fidalgo et al., 2011; Hovens et al., 2014b; Tong et al., 2012; Yirmiya and Goshen, 2011).

Alternatively, several studies reported spatial memory impairment in rodents subjected to anesthesia and implicated anesthesia-induced neuroinflammation or apoptosis as mediator (Cao et al., 2012; Chen et al., 2013; Kong et al., 2013; Li et al., 2013, 2014; Wang et al., 2015). However, most animal studies on POCD that included anesthesia control groups did not find an effect of anesthesia alone on memory and learning performance (Barrientos et al., 2012; Cao et al., 2010; Cibelli et al., 2010; Hovens et al., 2014b; Rosczyk et al., 2008; Wan et al., 2007; Zhang et al., 2015). Accordingly, clinical research on the relationship between anesthesia and POCD has remained inconclusive (Mason et al., 2010; Monk and Price, 2011; Newman et al., 2007; Radtke et al., 2013; Sauer et al., 2009).

With respect to POCD after cardiac surgery, studies have focused particularly on the potential involvement of cardiopulmonary bypass (CBP) and the associated occurrence of micro-embolisms and cerebral hypoperfusion. While spatial memory performance was shown to be impaired in rats after CPB with and without embolisms (de Lange et al., 2008; Homi et al., 2010; Jungwirth et al., 2006), clinical studies on the association of CPB and microembolism with POCD have remained inconclusive (Barber et al., 2008; Bartels et al., 2013; Fearn et al., 2001; Fontes et al., 2013; Gerriets et al., 2010; Kok et al., 2014; Kruis et al., 2010; Lombard and Mathew, 2010).

Recently, we developed a rat model for POCD after abdominal surgery, confirming the suggested association between cognitive impairment and neuroinflammation (Hovens et al., 2015a, 2014b, 2013). The aim of the current study was to gain insight in the mechanisms underlying the increased risk for POCD after cardiac surgery versus non-cardiac surgery. Therefore, we studied various aspects of affective behavior and learning and memory after cardiac and abdominal surgery in rats. Additionally, in brain areas related to the behavioral parameters, we investigated the systemic inflammatory response and markers for central inflammation, intraneuronal pathways, and neurogenesis. We hypothesized that cardiac surgery would be associated with a more severe behavioral impairment and corresponding alterations in the brain.

2. Materials and methods

2.1. Animals and housing

Male Wistar rats (HsdCpb:WU, Harlan, Venray, NL) weighing 240–300 g were housed in groups of 2–3 rats under controlled environmental conditions (temperature of 20 ± 2 °C and humidity of 50 ± 10%). The rats had ad libitum access to laboratory chow and tap water and were kept on a 12:12 light dark cycle with lights off at 9.00 AM.

Rats were weighed daily at 9.00 AM. Body weight measurements were used to determine the maximum amount of body weight loss compared to the body weight on the intervention day. All behavioral experiments were performed in the first half of the dark phase. All experiments were approved by the local animal experiment and welfare committee (Dier Experimenten Commissie, Groningen, the Netherlands).

2.2. Design

A power analysis was performed to determine the number of animals for the study using G*power 3.1.9. The power analysis indicated that 12 animals per group were needed to significantly detect an effect of 20% with a standard deviation of 15% in a one-way ANOVA of 5 groups with a power of 0.8 and significance level of 0.05. For the main experiment, rats were divided into: abdominal surgery (abdomen, $n = 12$); cardiac surgery (heart, $n = 18$ based on an expected mortality rate of 30%); and thoracic sham surgery (thorax, $n = 12$) as control for the cardiac surgery group. All rats that underwent surgery received a permanent indwelling jugular vein cannula to mimic effects of long term catheterization and allow timed blood-sampling with minimal handling. Control groups remained naïve (control, $n = 13$), received anesthesia and analgesia only (anesthesia, $n = 12$), or were only equipped with a jugular vein catheter under anesthesia (JVC, $n = 10$). To avoid interference of sickness behavior or acute effects of surgery on cognition (delirium), rats were allowed one week recovery before behavioral testing. In the second postoperative week, rats were subjected to a range of behavioral tests measuring various aspects of affective behavior, learning and memory: the sucrose preference test; open field test; novel object and location tests; and training, probe trials, and reversal training in the Morris water maze (MWM).

Rats were sacrificed 90 min after completion of the MWM reversal task on postoperative day 14. Blood was collected 6 h and 14 days after surgery and analyzed for tumor necrosis factor α (TNFα), interleukin (IL)-1β, IL-6, IL-10, IL-17, vascular endothelial growth factor (VEGF) and the inflammatory damage marker neutrophil gelatinase-associated lipocalin (NGAL). Brains were collected and areas with an expected association with the behavioral parameters were analyzed: the hippocampus for spatial and context related learning and mood; the prefrontal cortex for object recognition and mood; the striatum for cognitive flexibility; and the amygdala for mood-related behavior. Additionally, we included the paraventricular nucleus as this brain region is thought to be involved in regulating neuroendocrine and autonomic responses to inflammatory stimuli and was shown to have a neuroinflammatory response to myocardial infarction (Dworak et al., 2012; Rana et al., 2010; Xia and Krukoff, 2003). Immunohistochemical staining was performed to determine the levels of NGAL and to visualize microglia using ionized calcium-binding adapter molecule 1 (IBA-1) as markers for neuroinflammation. Additionally, as potential link between inflammation and the BDNF-pathway, immunohistochemical staining was performed for phosphorylated

p38 mitogen-activated protein kinase (p38MAPK), brain-derived neurotrophic factor (BDNF), and young maturing neurons using doublecortin-X (DCX).

Since heart and sham surgery, but not abdominal surgery, required artificial respiration the respiration method could have contributed to the observed differences in the compared surgical procedures. Therefore, an additional control experiment was performed to assess the influence of artificial respiration. A power analysis with G*Power 3.1.9. was performed based on plasma NGAL data from the main experiment and showed that 5 animals per group were needed for an ANOVA with a power of 0.8 and significance level of 0.05. In this experiment we compared plasma NGAL concentrations and microglial staining of rats that underwent anesthesia only (anesthesia, $n = 5$), anesthesia + artificial respiration (respiration, $n = 5$) and anesthesia + artificial respiration + thoracic sham surgery (thorax, $n = 5$).

2.3. Surgical procedures

Rats were anesthetized using 3% sevoflurane anesthesia in a mixture of 30% oxygen and 70% medical air (0.8 L/min), and placed on a heating pad to prevent hypothermia. Analgesia consisted of local application of Marcaine (intercostal block) around the surgical wounds and a single injection of buprenorphine (0.003 mg/kg s.c.), a partial opioid receptor agonist with limited immunomodulatory effects, one hour after closure.

Abdominal surgery was performed as described before (Hovens et al., 2014b). An incision was made along the linea alba. The intestines were exteriorized and the superior mesenteric artery (SMA) was dissected and clamped for 45 min, leading to hypoperfusion of the mesenteric vascular bed. After clamp removal, reperfusion was checked visually, the intestines were placed back in the abdominal cavity, and the muscle and skin were sutured separately.

For the cardiac surgery, rats were intubated directly following induction. As described previously (Schoemaker and Smits, 1994), an incision was made between the third and fourth left rib. The lung was gently pushed aside and the pericardium was torn to expose the left ventricle. A ligature was tightened around the left coronary artery for 45 min. After removal of the ligature, reperfusion was checked visually and the muscle and skin were sutured separately. The thoracic sham surgery was identical to the cardiac surgery, except for the ligation.

In addition to the surgical procedures described above, all animals that underwent surgery where equipped with a jugular vein catheter during the 45 min waiting period (Steffens, 1969). This procedure was performed as it was part of our previous abdominal surgery model (Hovens et al., 2014b), mimics the effects of long-term catheterization, and allows timed blood-sampling with minimal handling. The right jugular vein was dissected free and a silicon heart catheter (0.95 mm OD) was inserted in the jugular vein with the tip extending into the right atrium. The other end was fixed to the skull and attached to a metal bow. The catheter was filled with a Polyvinylpyrrolidone/heparin solution to prevent clot formation.

JVC controls were only equipped with a jugular vein catheter whereas anesthesia controls only underwent 1 h and 15 min of anesthesia, equal to the duration of the surgical procedures. Artificial respiration controls underwent 1 h and 15 min of artificial respiration under anesthesia. Anesthesia and analgesia in these groups was equal to that of the surgery groups. Naïve control animals did not receive any analgesia or anesthesia.

In the control experiment for artificial respiration, blood oxygen saturation ($[O^2]$) and heart rate (HR) were recorded (Pulse Oximeter, Uno BV, Zevenaar, the Netherlands) 3 times during the procedure: immediately after induction, intubation, or opening of the thorax; halfway through the procedure; and immediately before the end of the procedure.

2.4. Behavior

2.4.1. Affective behavior: Sucrose preference test and open field

Since depressive-symptoms have been reported after surgery and may influence cognitive test performance, affective behaviors were studies. The affective behaviors anhedonia, loss of interest, and anxiety may largely depend on the hippocampus, medial prefrontal cortex, and amygdala (Russo and Nestler, 2013). To investigate anhedonia, the sucrose preference test was used. Rats were habituated to a 1% sucrose solution in their home cage, first for 24 h and a day later for a 3 h period, in the week before the intervention. Sucrose preference was determined on postoperative day 9. Rats were housed individually for 7 h with ad libitum access to chow, a bottle of tap water, and a bottle with 1% sucrose solution. The bottles were weighed before and after the test to determine the amount of water and sucrose solution consumed. The amount of sucrose solution consumed as percentage of the total amount of fluid intake was used as measure of sucrose preference and thus anhedonia. The open field test was performed to assess interest and anxiety in a novel environment, 10 days following the intervention (Schoemaker and Smits, 1994). A square arena (100 * 100 * 40 cm) was divided in a center (60 * 60 cm) and border zone. The rat was placed in the center of the field. Behavior was recorded for 5 min and analyzed for the percentage of time spent in each zone and the total distance moved using Ethovision software (Noldus Information technology, Wageningen).

2.4.2. Novel location and novel object test

To determine short-term spatial memory, the novel location test was performed on postoperative day 11. This spatial task is considered to depend largely on hippocampal functioning (Dere et al., 2007). The rat was placed in the center of a square test box (60 * 50 * 50 cm) and presented with two identical objects for three minutes (exploration phase). The objects were removed and cleaned to remove smell cues. After 45 s, one object was placed back at its original location, whereas the other was moved to a novel location (location recognition phase).

One hour following the novel location test, the novel object test was performed to determine short-term object memory. This task, performed with a short latency between the exploration and novel object phase, is thought to be independent of hippocampal function, but rather depend on attentional functions related to the prefrontal cortex (Dere et al., 2007). The exploration phase of the novel object test was identical to the novel location test. Only now, after 45 s, one of the previously used familiar objects and a novel object were placed in the test box.

Behavior was recorded and analyzed using Eline software to determine the time the rats spent exploring both objects. The time the rats spent exploring the left object (in the exploration phase), the relocated object, or the novel object was expressed as percentage of the total object exploration time and used as measure of place preference, short-term spatial memory, and short-term object memory, respectively.

While in the present study we always performed the novel location test prior to the novel object test, pilot data from another study (unpublished) indicate that the order of testing does not influence the outcome of these tests.

2.4.3. Morris water maze test

Spatial learning, spatial memory and cognitive flexibility were assessed using a MWM protocol as described before (Hovens et al., 2014b). A round pool (140 cm ID) was filled with water

(26 ± 1 °C) and divided in 4 quadrants. A platform was invisibly located in the center of the target quadrant. On day 12 following the intervention, rats underwent 3 training sessions in the MWM with a one hour interval. The training sessions consisted of 3 consecutive trials. Each trial, the rat was placed in the center of one of the non-target quadrants using a pseudo-random protocol. The rat was allowed to search for the platform for 60 s. If the rat did not find the platform, it was guided there manually. Once on the platform, the rat was left there for 10 s. After completion of the three trials the rat was towel dried and returned to the home cage. The average escape latency per training session was recorded and taken as measure for spatial learning, considered to depend mainly on hippocampal function (D'Hooge and De Deyn, 2001).

On postoperative day 13, spatial memory was assessed in a probe trial. The platform was removed from the pool and the rat was placed randomly in the center of one of the non-target quadrants. Behavior was recorded for 60 s and analyzed using Ethovision (Noldus Information technology, Wageningen) for time spent in each quadrant and distance moved. Time spent in the target quadrant was taken as measure for spatial memory, considered to depend mainly on hippocampal function (D'Hooge and De Deyn, 2001). This protocol, consisting of a short training and probe trial 24 h later, was designed to measure the relatively subtle memory problems that may be present following surgery. We previously showed that adult control rats spend significantly more time in the target quadrant compared to the time in the opposing quadrant and compared to the 25% time in the target quadrant that would be expected if the rats explored randomly (Hovens et al., 2014b, 2015b). However, compared to the more extensive training protocols that are often used in literature, the preference for the target quadrant is still relatively low, around 35%.

One hour after the probe trial, rats were subjected to two more training sessions to ensure all the animals would learn the platform location. This was confirmed with a second probe trial on postoperative day 14. One hour after this second probe trial, animals were subjected to two reversal training sessions, each consisting of 3 trials, in which the platform was located in the quadrant opposing the target quadrant. The area under the curve (AUC) of the average escape latencies of the two reversal training sessions was taken as measure of cognitive flexibility, considered to be largely mediated by the dorsomedial striatum (D'Hooge and De Deyn, 2001).

2.5. Biochemical analysis

2.5.1. Histochemistry

Myocardial ischemia reperfusion can lead to myocardial damage ranging from small focal necrotic lesions to a full transmural myocardial infarction. To check for the presence of a transmural infarction a Sirius red staining was performed (van der Meer et al., 2005; Van Kerckhoven et al., 2000). After sacrifice, hearts were excised and fixed in 4% paraformaldehyde (PFA). Heart tissue was paraffinized, sliced into 4 μm thick transversal sections and fixed on glass. The sections were deparaffinized in xylol and hydrated through a decreasing gradient of ethanol in ultrapure water. The sections were stained with 0.1% Sirius red (Sigma-Aldrich) in saturated picric acid for 30 min and 0.1% Fast green (Sigma-Aldrich) in saturated picric acid for 30 min. Both staining steps were followed by rinsing in 0.01M HCl (2×), tap water (2×) and ultrapure water (2×). The sections were dehydrated through gradients of ethanol and xylol and coverslipped. Transmural infarct size was determined as the percentage of scar length to total left ventricular circumference. Presence of small focal necrotic lesions was checked for, but could not be properly quantified.

2.5.2. Immunohistochemistry

Ninety minutes following the last MWM reversal training, rats were anesthetized with 6% pentobarbital (2 ml/kg i.p.) and transcardially perfused with cold saline containing 0.1% EDTA followed by 4% PFA. Brains were collected and post fixed for 2 days in 4% PFA. The brains were dehydrated using 30% sucrose in PBS, frozen, and cut into 30 μm thick sections. To visualize microglia, sections were pre-treated with 0.3% H_2O_2 for 30 min, incubated for 3 nights at 4 °C with 1:2500 rabbit-anti-IBA1 (Wako, Neuss, Germany) in 0.01M PBS containing 1% bovine serum albumin (BSA) and 0.1% TX, and incubated for 2 h at room temperature (RT) with 1:500 goat-anti-rabbit (Jackson, Wet Grove, USA) in 0.01M PBS containing 1% BSA. For NGAL staining, sections were pre-treated with 0.3% H_2O_2 for 10 min, incubated for 4 nights at 4 °C with 1:200 goat-anti-Lipocalin-2 (R&D systems, Minneapolis, USA) in 0.01M PBS, and incubated for 2 h at RT with 1:500 rabbit-anti-goat (Jackson, Wet Grove, USA) in 0.01M PBS. For p38MAPK staining, sections were pre-treated with 0.01M TBS containing 0.2% TX for 30 min followed by 3% H_2O_2 for 20 min at RT, blocked for 1 h at RT with 1% BSA and 1% normal goat serum (NGS) in 0.01M TBS, incubated with 1:250 rabbit-anti-Phospho-p38MAPK (Thr180/Tyr182) (Cell Signaling Technology) in 0.01M TBS containing 1% BSA and 1% NGS for 2 h at 37 °C, overnight at RT, and 3 nights at 4 °C, and incubated with 1:500 goat-anti-rabbit (Jackson, Wet Grove, USA) in 0.01M TBS overnight at 4 °C. For BDNF staining, sections were pre-treated with 3% H_2O_2 for 20 min, blocked for 1 h at RT with 5% NGS in 0.01M PBS, incubated with 1:1000 rabbit-anti-BDNF (Alomone labs, Jerusalem, Israel) in 0.01M PBS containing 1% BSA and 1% NGS for 3 h at 37 °C, overnight at RT, and 3 nights at 4 °C, and incubated overnight at 4 °C with 1:500 goat-anti-rabbit (Jackson, Wet Grove, USA) in 0.01M PBS. To visualize young maturing neurons, sections were pre-treated with 3% H_2O_2 for 20 min, blocked for 1 h at RT with 5% normal rabbit serum (NRS) in 0.01M PBS, incubated with 1:1000 goat-anti-DCX (Santa Cruz, Dallas, USA) in 0.01M PBS containing 1% BSA and 1% NRS for 3 h at 37 °C, overnight at RT, and 3 nights at 4 °C, and incubated with 1:500 rabbit-anti-goat (Jackson, Wet Grove, USA) overnight at 4 °C in 0.01M PBS. After these first staining steps, all sections were incubated at RT for 2 h with avidin-biotin peroxidase complex (Vectastain ABCkit, Vector, Burlingame, USA) and DAB-stained using a 0.075 mg/ml DAB solution activated with 0.1% H_2O_2. Sections were mounted on glass slides, dehydrated through gradients of ethanol and xylol, and coverslipped.

Stainings were analyzed by a researcher blinded to the treatment in 3 sections per area per rat. NGAL levels were determined in the Dentate Gyrus inner blade (DGib) and hilus of the hippocampus, Zilles Cg1 region of the prefrontal cortex (PFC), and the magnocellular and parvocellular part of the paraventricular nucleus (PVN). Pictures were taken at 50× magnification. NGAL staining in the hippocampus, characterized by a light gray staining throughout the molecular layer, was analyzed by optical density measurement corrected for the background staining in the molecular layer. NGAL staining in the PFC and PVN, characterized by darkly stained NGAL-positive cells, was analyzed by measuring area coverage.

Microglial activity was determined as described before (Hovens et al., 2014a). Briefly, using Image Pro (Image Pro Plus 6.0, Media Cybernetic Inc. Rockville, USA), the number of microglia, total cell size and total cell body size was determined at 100× magnification in the molecular layer of the DGib, the hilus, the radial layer of the CA1 and CA3 region, the dorsomedial (DMS) and dorsolateral striatum (DLS), basolateral amygdala (BLA), PVN, and PFC. The cell body to cell size ratio was determined as measure for microglial activity.

The optical density (OD) of BDNF staining and p38MAPK staining (100× magnification) was determined and corrected for background staining using quantimet software (Leica QWin, Leica

Microsystems). The OD for BDNF staining was determined in the granular layer of the DGib, CA1, and CA3 and the PFC. The OD for p38MAPK staining was determined in the granular layer of the the DGib, CA1, and CA3, the radial layer of the CA1 and CA3, and the hilus.

The number of young maturing neurons was determined by counting the number of DCX positive cells in the DG (50× magnification). The length of the granular cell layer of the DG was measured using Image Pro Plus software. The number of young maturing neurons per mm of the DG was used as measure for neurogenesis.

All stainings were first performed in the control, abdomen, thorax, and heart group. Subsequently NGAL and BDNF stainings were repeated in JVC and anesthesia groups and a sample of the control group. To allow comparison, the outcomes of these stainings were converted to percentage of the control values in the respective staining sessions.

2.5.3. ELISA

Blood samples were taken 6 h following the intervention from the jugular vein catheter and at sacrifice via cardiac puncture. Blood was centrifuged for 10 min at 2600 G and plasma was collected and stored at −80 °C until further analysis. Plasma TNFα, IL-1β, IL-6, IL-10, IL-17, and VEGF concentrations at 6 h following the intervention were determined in 1.25 × dilution using the Bio-Plex Pro Rat 6-plex cytokine assay (Bio-Rad Laboratories BV, Veenendaal, the Netherlands) for 10 animals per group. Plasma NGAL concentrations at 6 h and 14 d following the interventions were determined using the Rat NGAL ELISA kit (Bioporto Diagnostics, Gentofte, Denmark) according to manufacturer's instruction for 10 animals per group and for 5 animals in the anesthesia, respiration, and thorax group. Plasma IL-6 and TNFα concentrations 14 d following the intervention were determined in 4 animals per surgery group as a pilot using the Rat IL-6 ELISA kit (Invitrogen, Frederick, USA) and Rat TNF-α LEGEND MAX™ ELISA (BioLegend, San Diego, USA) following manufacturer's instructions.

2.6. Statistical analysis

Group means (±SEM) were calculated. Statistical analysis was performed using SPSS (version 22, IBM). First, statistical analysis was performed to assess group differences between the control groups of the main experiment (control, anesthesia, and JVC). For further analysis control and anesthesia groups were compared with the surgical interventions. MWM spatial learning and object exploration time in the novel object and location test were analyzed by repeated-measures ANOVA and Tukey post hoc analysis. The time in the target and opposing quadrant during the MWM probe trials was assessed with a 2 * 2 ANOVA with quadrant and experimental group as independent variables. Post-hoc analysis consisted of a paired *t*-test between the time in the target and opposing quadrant during the probe trials. All other outcomes were compared with a one-way ANOVA and Tukey post hoc analysis. The outcomes of the control experiment were analyzed separately. A significance level of $p \leqslant 0.05$ was used.

3. Results

3.1. Mortality and body weight loss

One of the rats that underwent thoracic surgery and five of the rats that underwent heart surgery died during the surgical procedure, leading to 11 rats in the thorax group and 13 rats in the heart group. In the other experimental groups none of the animals died.

Baseline body weight was 311 ± 17 g. There was a significant difference in weight loss between groups ($F_{4,55} = 19.19$, $p < 0.001$, Fig. 1). All surgery groups lost significantly more body weight than control rats. Weight loss after heart surgery was significantly higher than after abdominal surgery.

3.2. Influence of anesthesia and jugular vein catheterization

Weight loss differed significantly between the control groups (control = 1.4 ± 2.0%; anesthesia = −0.4 ± 2.8%; JVC = −1.3 ± 1.5%, $F_{2,34} = 15.44$, $p = <0.001$) with increased weight loss of JVC compared to control ($p < 0.001$). Control groups also differed significantly in plasma NGAL ($F_{2,19} = 22.22$, $p < 0.001$), IL-1β ($F_{2,25} = 3.39$, $p = 0.050$), IL-10 ($F_{2,24} = 5.82$, $p = 0.009$), and VEGF ($F_{2,25} = 3.46$, $p = 0.047$) concentrations 6 h postoperatively, and NGAL concentrations 14 d postoperatively ($F_{2,32} = 3.57$, $p = 0.040$). However, post hoc analysis only showed a significant increase in IL-10 ($p = 0.013$) concentrations at 6 h and NGAL concentrations at 6 h ($p = 0.000$) and 14 d ($p = 0.013$) in the JVD compared to the control group. The control groups did not differ in behavioral test outcomes except for the time in the center of the open field ($F_{2,34} = 3,75$, $p = 0.035$), which was higher in the JVC group compared to controls ($p = 0.048$).

3.3. Presence of transmural infarction

Of the 13 rats that underwent cardiac surgery 6 rats had a transmural infarction. Average infarct size was 29 ± 9%, with 3 rats displaying an infarcted area larger than 20% (35%, 38% and 55%). Ischemia reperfusion injury in the heart may also lead to development of focal infarctions (Lipsic et al., 2004), which can't be quantified with the standard methods. There were no significant differences in weight loss, behavioral test outcomes or biochemical measurements between the rats with and without transmural

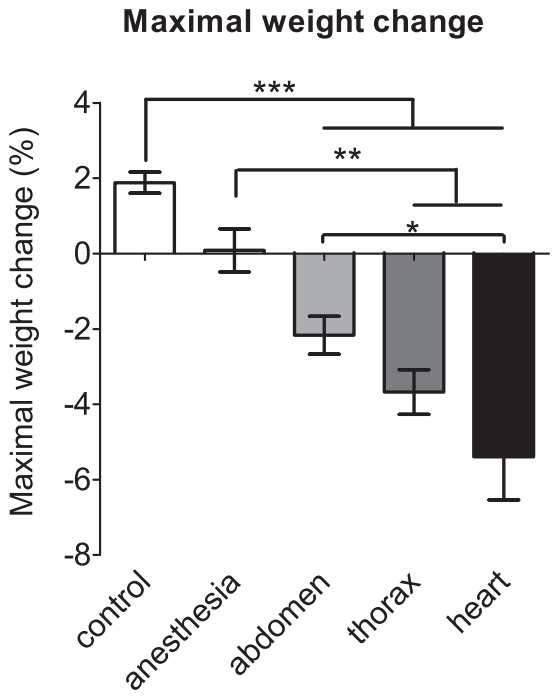


Fig. 1. Maximal weight change following the intervention (mean ± SEM). Weight change is expressed as percentage compared to the body weight prior to surgery. Control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

infarction. This is illustrated in the supplementary data. In view of these outcomes, all cardiac surgery rats were combined into one group for further analysis.

3.4. Affective behavior

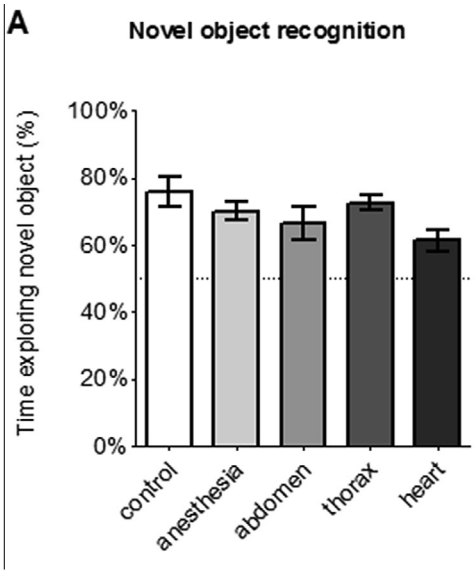
There was no significant influence of surgery on behavioral test outcomes in sucrose preference ($F_{4,53} = 1.68$, $p = 0.169$), the time spent in the center of the open field ($F_{4,56} = 0.19$, $p = 0.945$) or the distance moved in the open field ($F_{4,456} = 0.54$, $p = 0.708$).

3.5. Learning and memory

The experimental groups did not display a preference for either the left or the right object during the exploration phases of the novel object and novel location test ($F_{4,57} = 0.63$, $p = 0.664$). In the novel object test, 3 rats were removed from further analysis due to anxious/agitated behavior, displaying vocalization while being transported to and/or in the test environment (1 control, 2 thorax). There was a strong trend for a difference in object recognition ($F_{4,53} = 2.54$, $p = 0.051$, Fig. 2A) with heart surgery rats displaying decreased object recognition compared to control rats ($p = 0.035$). Object exploration in the novel object test (Fig. 2B) was not significantly affected by test phase ($F_{1,53} = 2.48$, $p = 0.121$) or surgery ($F_{3,53} = 1.22$, $p = 0.315$).

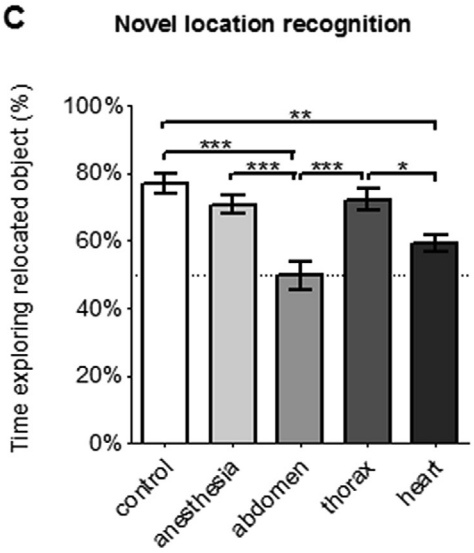
There was a significant group difference in location recognition ($F_{4,57} = 11.78$, $p < 0.001$, Fig. 2C). Location recognition was decreased after abdominal surgery compared to control, anesthesia, and thoracic surgery. Heart surgery led to decreased location recognition compared to control and thoracic surgery. Moreover, abdominal surgery rats performed significantly worse than heart surgery rats. Object exploration in the novel location test (Fig. 2D) was not significantly affected by test phase ($F_{1,57} = 0.07$, $p = 0.790$) or surgery ($F = {}_{3,57} = 0.70$, $p = 0.593$).

All experimental groups showed a significant decline in escape latencies over the training sessions in the MWM ($F_{4,228} = 68{,}22$, $p < 0.001$), indicating that all groups were able to learn the platform location (Fig. 3A). Overall, the learning curve did not differ significantly between groups ($F_{16,228} = 0.73$, $p = 0.766$). However, separate analysis of training sessions showed a significant difference



B Novel object recognition

Total object exploration time		
	Exploration phase	NO phase
Control	19±2%	20±3%
Anesthesia	26±3%	22±1%
Abdomen	26±2%	27±4%
Thorax	26±3%	23±3%
Heart	29±3%	23±2%



D Novel location recognition

Total object exploration time		
	Exploration phase	NL Phase
Control	18±2%	17±2%
Anesthesia	20±2%	20±2%
Abdomen	16±1%	15±2%
Thorax	17±2%	20±3%
Heart	16±1%	15±1%

Fig. 2. Novel object and novel location test (mean ± SEM). (A) Novel object recognition in the novel object test. (B) Total time spent on object exploration (%) during the exploration phase and novel object phase of the novel object test. (C) Spatial recognition in the novel location test. (D) Total time spent on object exploration (%) during the exploration phase and novel location phase of the novel location test. Dotted line = reference line for expected exploration time (50%) if rats explore randomly. Control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

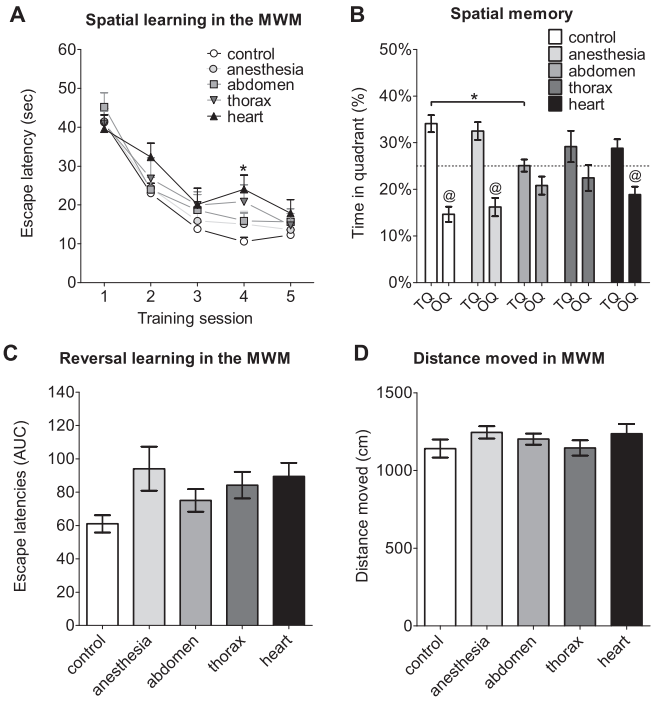


Fig. 3. Morris water maze (mean ± SEM). (A) Spatial learning. Average escape latency (sec) is shown for the 5 training sessions. (B) Spatial memory after a short training period (3 training sessions). The time spent in the target quadrant (TQ) and opposing quadrant (OQ) during the probe trial is depicted. Dotted line = reference line for time in target quadrant (25%) if rats explore randomly. (C) Cognitive flexibility. The area under the curve (AUC) for the escape latencies during the two reversal training sessions is shown. (D) Distance moved (cm) during the MWM probe trial. Control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$ compared to control, $^{@}p < 0.05$ compared to TQ.

between groups in training session 4, the first training session of the second training day ($F_{5,57} = 3{,}04$, $p = 0.024$), with a significant difference between heart surgery and control rats only ($p = 0.019$). In the first probe trial, after a relatively short training period of three training sessions (Fig. 3B), there was a significant effect of quadrant ($F_{1,106} = 69.32$, $p < 0.001$) and quadrant * intervention ($F_{4,106} = 5{,}70$, $p < 0.001$), but not of intervention alone ($F_{3,92} = 0.28$, $p = 0.892$). This indicates that there was a group difference in the preference for the target versus the opposing quadrant. The abdominal surgery group, but not the other surgery groups, spent significantly less time in the target quadrant compared to control and the time spent in the target quadrant was significantly higher than the time spent in the opposing quadrant in the control, anesthesia, and heart groups, but not in the abdomen and thorax groups. In the second probe trial, after a training period of five training sessions (data not shown), there was a significant effect of quadrant ($F_{1,92} = 72.13$, $p < 0.001$) only and all rats spent significantly more time in the target quadrant compared to the opposing quadrant. Thus all surgery groups were able to learn the location of the platform, but the abdominal surgery group required more training sessions to do so. There was no difference between groups in the AUC of the reversal learning trials ($F_{5,54} = 1.93$, $p = 0.119$, Fig. 3C) or the distance moved during the probe trials (after 3 training sessions: $F_{4,53} = 1.03$, $p = 0.401$, Fig. 3D; after 5 training sessions: $F_{4,53} = 0.68$, $p = 0.611$).

3.6. Systemic and central inflammatory response

Plasma concentrations of main pro- and anti-inflammatory cytokines indicated a pronounced systemic inflammatory response 6 h following the surgical interventions. There was a significant difference between groups in the plasma concentrations of NGAL ($F_{4,34} = 41.03$, $p < 0.001$, Fig. 4A), TNFα ($F_{4,35} = 8.74$, $p < 0.001$, Fig. 4B), IL-1β ($F_{4,45} = 18.42$, $p < 0.001$, Fig. 4C), IL-6 ($F_{4,45} = 5.84$, $p = 0.001$, Fig. 4D), and IL-10 ($F_{4,44} = 13.06$, $p < 0.001$, Fig. 4E). NGAL and TNFα were particularly increased in the abdominal surgery group compared to the other surgical and control procedures. NGAL was also increased in all surgical groups compared to control and anesthesia only, but TNFα was not. IL-1β and IL-10 were increased to a similar extent in all surgical groups, while IL-6 was increased only after abdominal and cardiac surgery. Plasma concentrations of VEGF did not differ between groups ($F_{4,45} = 1.18$, $p = 0.335$) and IL-17 concentrations were below the detection level of the used assay (1.0 pg/ml) in all experimental groups.

Pilot analysis showed that plasma IL-6 and TNFα levels on postoperative day 14 were below the detection level of the ELISA kit (23.5 pg/ml and 7.8 pg/ml respectively) in all experimental groups. Outcomes of NGAL measurement on day 14 are displayed in Fig. 5, with representative pictures of NGAL staining in Fig. 5D and E. Plasma NGAL concentrations on postoperative day 14 differed significantly between groups ($F_{4,42} = 10.34$, $p < 0.001$, Fig. 5A), with increased NGAL concentrations in the thorax and heart group compared to the abdomen, anesthesia, and control groups, but no difference between thorax and heart. NGAL staining in the DG differed significantly between groups ($F_{4,56} = 6.42$, $p < 0.001$, Fig. 5B), with significantly higher concentrations of NGAL in all surgery groups compared to the anesthesia group and a trend for increased NGAL after abdominal ($p = 0.094$) and cardiac surgery ($p = 0.078$) compared to control. NGAL staining in the hilus was not affected by surgery. NGAL staining in the magnocellular part of the PVN was significantly affected by surgery ($F_{4,55} = 8.01$, $p < 0.001$, Fig. 5C), with a significantly increased area coverage after thoracic and cardiac surgery compared to control and anesthesia rats. NGAL staining in the parvocellular part of the PVN ($F_{4,55} = 0.67$, $p = 0.604$) and PFC (control: 100 ± 6%, anesthesia: 88 ± 3%, abdomen: 107 ± 6%, thorax: 117 ± 5%, heart: 91 ± 14%, $F_{4,55} = 2.25$, $p = 0.075$) did not differ between groups.

Microglial activity determined by the cell body to cell size ratio of microglia in hippocampal and non-hippocampal brain regions is depicted in Fig. 6. In the hippocampus, microglial activity differed between groups in the hilus only ($F_{3,48} = 10.72$, $p < 0.001$). Microglial activity in the hilus was significantly increased after thoracic and cardiac surgery. Additionally, cardiac surgery rats displayed increased microglial activity in the hilus compared to abdominal surgery rats. The number of microglia in the hilus followed a similar pattern (control: 105 ± 5, abdomen: 114 ± 14, thorax 122 ± 10, heart: 119 ± 16, $F_{3,48} = 3.90$, $p = 0.015$). In the PFC microglial activity differed significantly between groups ($F_{3,47} = 6.62$, $p = 0.001$), with a significantly increased activity after thoracic and cardiac surgery and a trend for increased activity after abdominal surgery ($p = 0.063$). In the BLA, DMS, DLS, and PVN microglial activity did not differ between groups.

3.7. Effects of artificial respiration

To our surprise, plasma NGAL levels on postoperative day 14 were increased almost 3-fold in both the heart and thorax group compared to the other experimental groups, Therefore we further examined in a separate experiment which part of the interventions may have contributed to these elevated levels: artificial respiration or opening of the thorax and pericardium.

Rats that underwent anesthesia, artificial respiration, or thoracic surgery differed significantly in their maximal weight loss following the intervention ($F_{2,14} = 6.40$, $p = 0.003$, Fig. 7A), with a significantly higher weight loss following thoracic surgery compared to the other interventions. The groups showed a significant

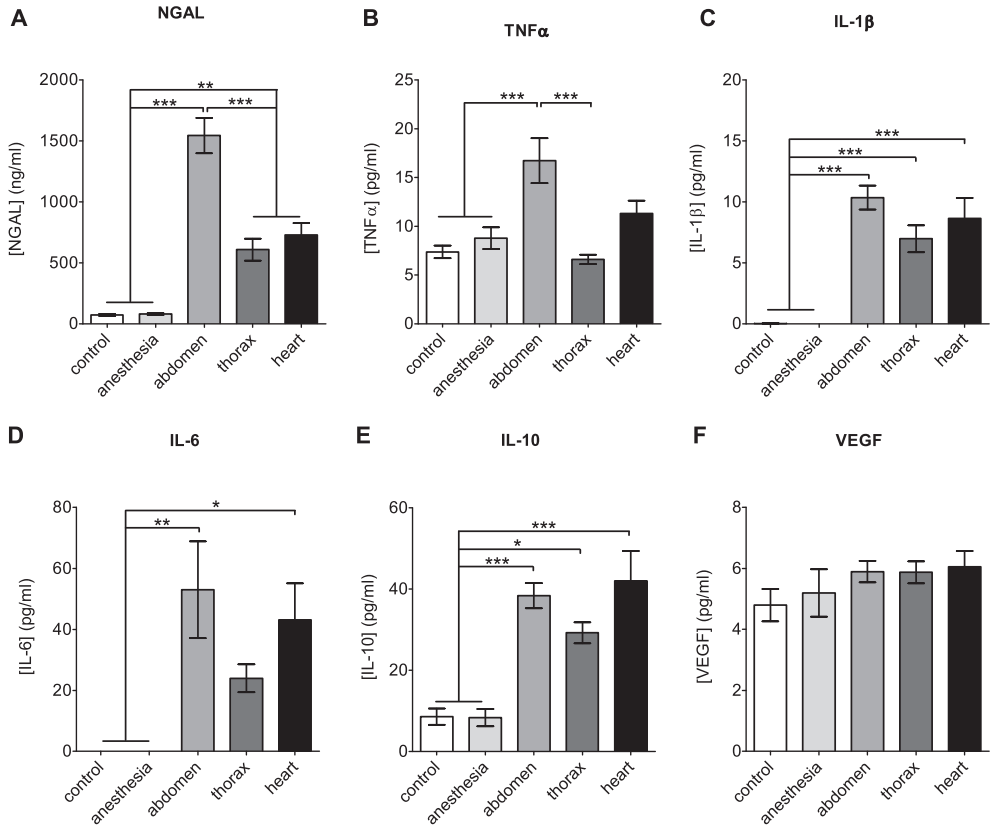


Fig. 4. Systemic inflammatory response 6 h following the interventions. (A) Plasma neutrophil gelatinase-associated lipocalin (NGAL) concentrations (ng/ml). (B) Plasma tumor necrosis factor α (TNFα) concentrations (pg/ml). (C) Plasma interleukin-1β (IL-1β) concentrations (pg/ml). (D) Plasma interleukin-6 (IL-6) concentrations (pg/ml). (E) Plasma interleukin-10 (IL-10) concentrations (pg/ml). (F) Plasma vascular endothelial growth factor (VEGF) concentrations (pg/ml). Control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

difference in plasma NGAL ($F_{2,14} = 10.40$, $p = 0.002$, Fig. 7B), with significantly elevated NGAL after thoracic surgery compared to the other interventions. Oxygen saturation was not influenced by artificial respiration or thoracic surgery at any time point (average outcomes: anesthesia: 98.5 ± 1.0%, respiration: 98.3 ± 0.7%, thorax: 97.9 ± 0.5%). HR was significantly reduced immediately after opening of the thorax, which was normalized at the later time points (immediately after induction: anesthesia = 412 ± 30 bpm, respiration = 366 ± 36 bpm, thorax = 327 ± 22 bpm, $F_{2,14} = 10.39$, $p = 0.002$; halfway through intervention: anesthesia = 408 ± 3 3 bpm, respiration = 404 ± 11 bpm, thorax = 379 ± 27 bpm; end of intervention: anesthesia = 39 6 ± 27 bpm, respiration = 371 ± 3 3 bpm, thorax = 376 ± 34 bpm).

3.8. Intraneuronal pathways and neurogenesis

The level of p38MAPK (Fig. 8A) differed significantly between groups in the granular layer of the CA3 ($F_{3,45} = 3.00$, $p = 0.040$) and DGib ($F_{3,45} = 3.13$, $p = 0.035$) and the hilus (control: 0.078 ± 0.020, abdominal: 0.055 ± 0.016, thoracic: 0.059 ± 0.025, heart: 0.073 ± 0.036, $F_{3,45} = 2.83$, $p = 0.049$), but did not differ significantly in the granular layer of the CA1 ($F_{3,45} = 1.78$, $p = 0.164$). In the DGib and CA3 p38MAPK was significantly decreased compared to control in the abdominal surgery group only. BDNF levels as percentage of control (Fig. 8B) differed significantly between groups in the granular layer of the CA1 ($F_{4,55} = 4.21$, $p = 0.005$) and CA3 region ($F_{4,55} = 4.36$, $p = 0.004$), but not in the DGib ($F_{4,52} = 1.88$, $p = 0.128$). In the CA1 both the abdominal and cardiac surgery groups showed significantly decreased BDNF levels compared to control. In the CA3 only the cardiac surgery rats displayed significantly decreased BDNF level compared to the anesthesia group. The number of DCX positive cells (Fig. 8C) in the DG, indicative of the number of early maturing neurons, differed significantly between groups ($F_{3,47} = 5.74$, $p = 0.002$), with a significant decrease in DCX in both abdominal and cardiac surgery rats compared to control animals.

4. Discussion

To gain insight in the mechanisms underlying the higher incidence of POCD after cardiac versus non-cardiac surgery, we compared behavioral outcomes and parameters for inflammation, intraneuronal pathways, and neurogenesis after major abdominal and major cardiac surgery. We hypothesized that cardiac surgery would be associated with more severe cognitive dysfunction, neuroinflammation, and alterations in intraneuronal pathways.

4.1. Cognition and behavior after cardiac versus abdominal surgery

In concurrence with previous studies, we observed a selective impairment of spatial memory and recognition in rats that underwent abdominal surgery, as these rats only showed impaired performance in the MWM probe trial and novel location recognition test (Barrientos et al., 2012; Cibelli et al., 2010; Fan et al., 2014; Hovens et al., 2015b, 2014b; Terrando et al., 2010; Vacas et al., 2014). Interestingly, cardiac surgery seemed to be associated with another pattern of cognitive impairment rather than a more severe impairment of spatial memory performance. While decreased spatial learning and a trend towards decreased object recognition were observed in rats that underwent cardiac surgery, the decrease

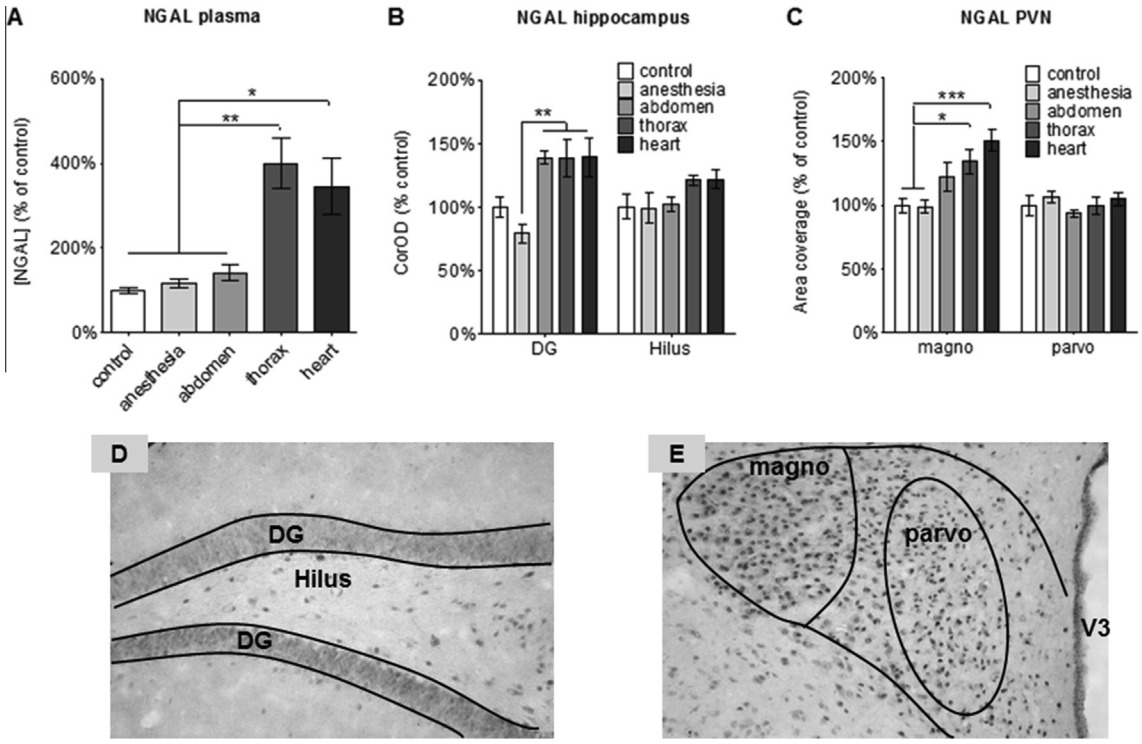


Fig. 5. Neutrophil gelatinase-associated lipocalin (NGAL) in plasma and brain areas on postoperative day 14 (mean ± SEM). (A) Plasma NGAL concentrations (ng/ml) as percentage of control levels. (B) The optical density (OD) of NGAL staining in the hilus and granular layer of the dentate gurys (DG) of the hippocampus, corrected for the OD in the molecular layer of the DG (corOD) as percentage of control levels). (C) The area coverage of NGAL positive cells in the magnocellular and parvocellular region of the paraventricular nucleus (PVN) as percentage of control levels. (D+E) Rsepresentative photographs of NGAL staining in the hippocampus (D) and PVN (E). DG = dentate gyrus, magno = magnocellular region, parvo = parvocellular region, V3 = third ventricle, control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

in performance in the spatial memory tasks was less severe in these animals compared to the rats that underwent abdominal surgery.

To our knowledge, we are the first to directly compare cardiac and non-cardiac surgery in an animal model for POCD and include behavioral tests for several cognitive domains. One previous study reported the effects of myocardial ischemia-reperfusion on spatial memory in the first postoperative week (Yuan et al., 2014). In concurrence with our findings, they showed that spatial memory was impaired after cardiac surgery. Additionally, several recent studies using myocardial infarction models to study the effect of heart failure on cognitive function, indicate that myocardial infarction may lead to long-term spatial memory impairment (Frey et al., 2014; Hong et al., 2013; Ito et al., 2013). Of note is that all of these studies only included cognitive tests for spatial learning and memory.

Although caution should be taken with inference of pre-clinical findings to clinical practice, the behavioral results of our study provide food for thought. In clinical studies, POCD is generally defined as a significant impairment in at least two neuropsychological tests (Newman et al., 2007; Rasmussen, 2006). Using this definition, a more generalized cognitive impairment, as observed in our cardiac surgery group, may be more readily diagnosed as POCD than isolated spatial memory impairment. It has indeed been noted that subjective cognitive complaints are reported more frequently than POCD is diagnosed. Johnson et al. (2002) for example found that 29% of middle-aged surgical patients reported memory complaints three months following major non-cardiac surgery, whereas POCD was diagnosed in only 6% of these patients.

Rats that underwent thoracic (sham) surgery or jugular vein catheterization alone did not display any signs of cognitive impairment in the second postoperative week. This may reflect the relative mild nature of the surgical procedure, which may not lead to postoperative cognitive dysfunction for more than a few days (Barrientos et al., 2012).

Depressive symptoms have been reported after both general and cardiac surgery. Exploratory behavior and sucrose preference were not affected by any of the surgical interventions in our study. This is in accordance with previous studies that showed altered open field behavior during the first postoperative days, but not thereafter (Feng et al., 2013; Hovens et al., 2014b; Lu et al., 2015). After myocardial infarction, lasting alterations in affective behavior have been reported (Frey et al., 2014; Ito et al., 2013; Schoemaker and Smits, 1994). These conflicting results may be explained by the milder ischemia-reperfusion model used in our study.

4.2. Systemic and neuroinflammation after cardiac versus abdominal surgery

The abdominal, thoracic, and cardiac surgeries all elicited a pronounced acute systemic inflammatory response with increased levels of NGAL, IL-1β, IL-6, and IL-10 6 h after the procedures. Interestingly, NGAL and TNFα concentrations were particularly elevated 6 h after abdominal surgery. In contrast, two weeks after thoracic and cardiac surgery systemic NGAL concentrations were still increased three fold, while NGAL had returned to control levels in the abdominal surgery group at that time.

NGAL is classically used as a marker for renal damage. However, it is now known to be produced under inflammatory conditions by a variety of cell types including endothelial cells, cardiomyocytes, astrocytes, and microglia (Gouweleeuw et al., 2015; Lee et al., 2007; Naudé et al., 2012). NGAL is rapidly expressed upon stimulation with various inflammatory mediators, including TNFα (Gouweleeuw et al., 2015). NGAL plays a prominent role in the

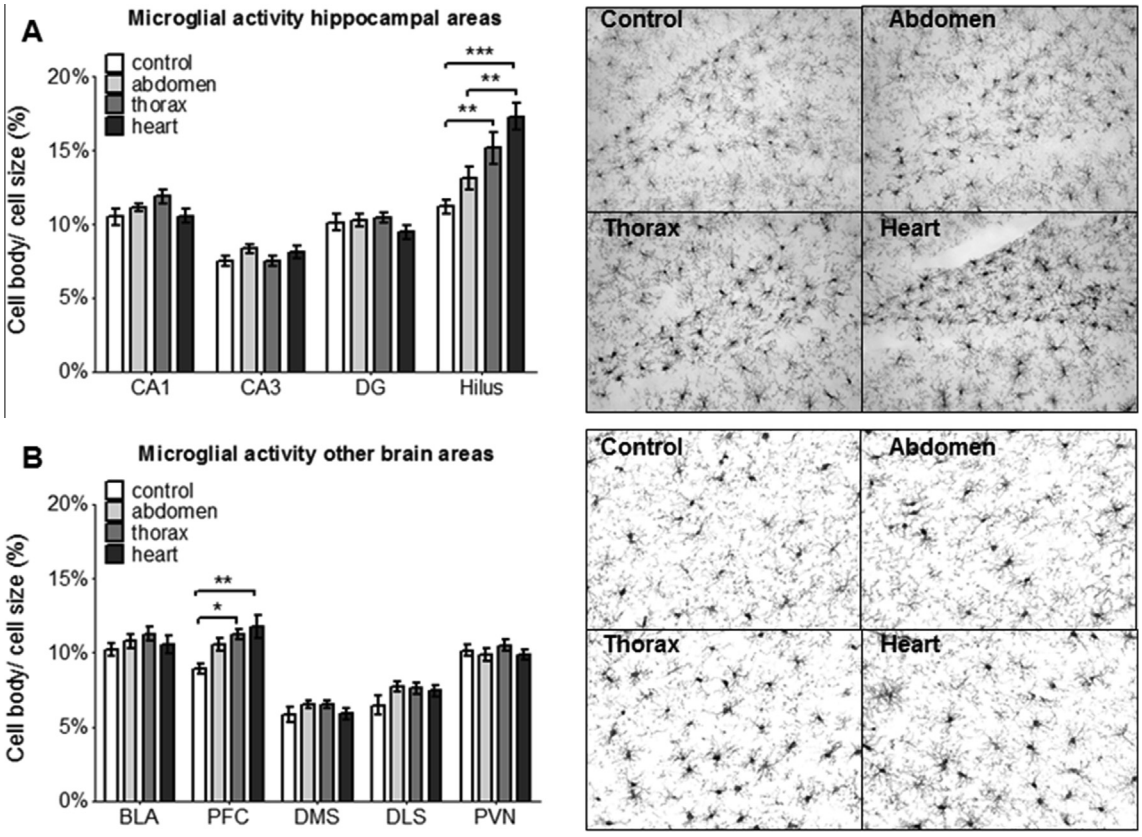


Fig. 6. Microglial activity determined as the cell body to cell size ratio (%) of IBA-1 stained microglia (mean ± SEM). (A) Left: Microglial activity in hippocampal brain areas Right: representative pictures of IBA-1 staining in the hippocampal hilus. (B) Left: Microglial activity in non-hippocampal brain areas. Right: representative pictures of IBA-1 staining in the PFC. DG = dentate gyrus, BLA = basolateral amygdala, PFC = prefrontal cortex, DMS = dorsomedial striatum, DLS = dorsolateral striatum, PVN = paraventricular nucleus, control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

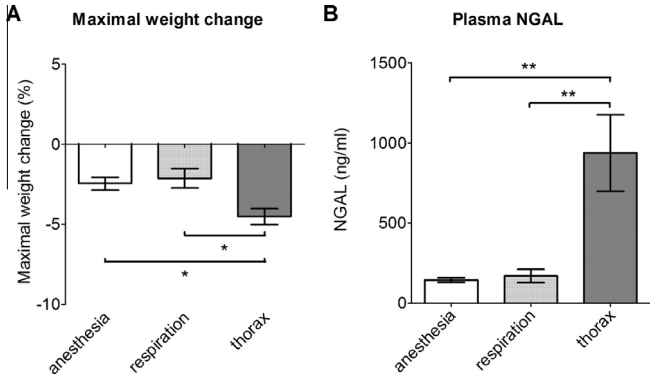


Fig. 7. Influence of artificial respiration (mean ± SEM) investigated in a separate control experiment. (A) Maximal weight change following the intervention expressed as percentage compared to the weight prior to the intervention. (B) Plasma neutrophil gelatinase-associated lipocalin (NGAL) concentrations (ng/ml). Control = naïve control, anesthesia = anesthesia for ¼ h, respiration = artificial respiration under anesthesia for 1¼ h, thorax = thoracic surgery. $^{*}p < 0.05$, $^{**}p < 0.01$.

innate immune response (Borregaard and Cowland, 2006; Schroll et al., 2012). The extensive bacterial-host interaction in the intestines may therefore have contributed to the more pronounced acute inflammatory response after abdominal surgery. Notably, NGAL was also shown to have important immunomodulatory and chemotactic properties (Borregaard and Cowland, 2006; Schroll et al., 2012) and as such may be essential for the controlled initiation and resolution of inflammatory processes (Shashidharamurthy et al., 2013). Therefore the pronounced TNFα and NGAL concentrations after abdominal surgery may have contributed to a faster resolution of inflammation compared to the other surgical groups.

Chronic systemic elevations of NGAL have been associated with inflammatory tissue damage in a variety of organs including the heart and brain (Gouweleeuw et al., 2015; Lee et al., 2007; Naudé et al., 2012). Moreover, NGAL has been associated with cognitive impairment in chronic inflammatory conditions (Naudé et al., 2014, 2012) and has recently received attention as a potential marker linking heart failure and mental dysfunction (Gouweleeuw et al., 2015).

Regarding its known role as marker for renal damage, it can be questioned whether the observed increased NGAL levels are due to renal side-effects of the surgical procedures. Indeed many patients with chronic heart failure suffer from renal dysfunction (Heywood et al., 2007). However, as in a previous study even permanent coronary artery ligation in rats did not cause or exaggerate renal dysfunction (Szymanski et al., 2012), it does not seem likely that renal side-effects were present in the current study.

The plasma concentrations of IL-6 and TNFα on postoperative day 14 were below the detection level of the used ELISA kits in all the experimental groups. These outcomes are in concordance with previous studies showing that the plasma levels of these pro-inflammatory cytokines return to baseline within the first postoperative week (Barrientos et al., 2012; Cibelli et al., 2010; Hovens et al., 2014b; Terrando et al., 2010). Since NGAL is present in relatively high concentrations in plasma and tissue, it may provide a more readily measurable marker for inflammatory tissue damage.

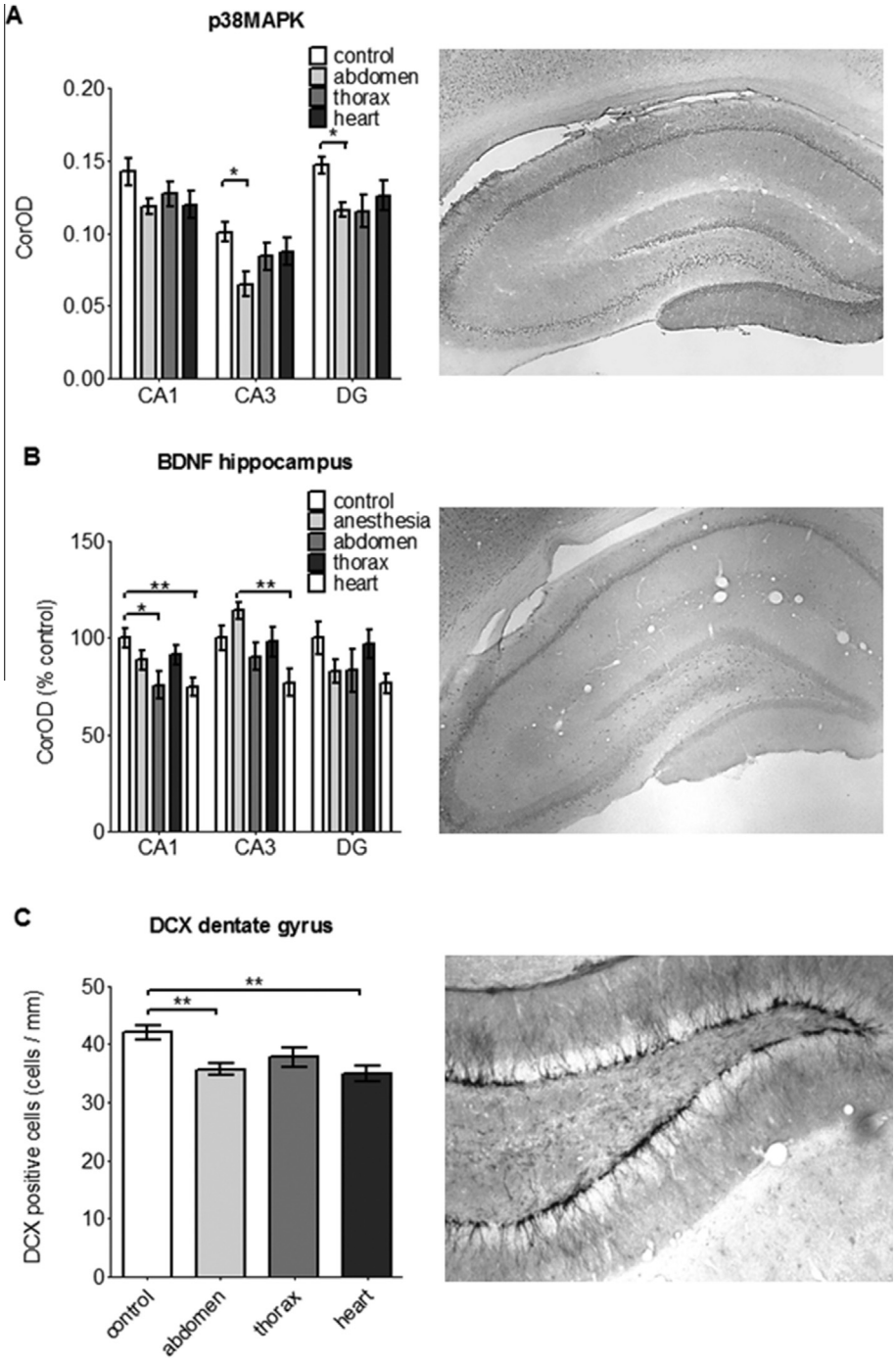


Fig. 8. Markers for intraneuronal pathways and neurogenesis in the hippocampus (mean ± SEM). (A) Left: The optical density (OD) of phosphorylated p38 mitogen activated protein kinase (p38MAPK) staining the CA1, CA3, and DG. Right: representative picture of p38MAPK-staining in the hippocampus. (B) Left: The optical density (OD) of brain-derived neurotrophic factor (BDNF) staining in the CA1, CA3, and DG. Right: representative picture of BDNF-staining in the hippocampus. (C) Left: The number of doublecortin X (DCX) positive cells in the granular cell layer of the DG corrected for the length (mm) of this cell layer. Right: representative pictures of DCX-staining in the DG. DG = dentate gyrus, control = naïve control, anesthesia = anesthesia for 1¼ h, abdomen = abdominal surgery, thorax = thoracic surgery, heart = cardiac surgery. $^{*}p < 0.05$, $^{**}p < 0.01$.

We measured NGAL and microglial activity in various brain regions to gain insight in the neuroinflammatory changes associated with abdominal and cardiac surgery. In accordance with previous research, two weeks after abdominal surgery there were no significant alterations in microglial activity compared to control levels (Barrientos et al., 2012; Chu et al., 2013; Cibelli et al., 2010; Hovens et al., 2014b; Jiang et al., 2015; Lu et al., 2015; Terrando et al., 2010; Wan et al., 2007). However, we did measure increased NGAL staining in the dentate gyrus two weeks after abdominal surgery, indicating that hippocampal neuroinflammation might not have been totally resolved. In contrast to the abdominal surgery group, the cardiac surgery rats showed a more extensive pattern of neuroinflammatory changes, with increased NGAL levels in the dentate gyrus and magnocellular part of the PVN and increased microglial activity in the hippocampal hilus and PFC. These results suggest that cardiac surgery is associated with increased or prolonged inflammatory activity in several brain regions. The difference in regenerative capacity of cardiac muscle

tissue (Frangogiannis, 2006) compared to the intestines (Blikslager et al., 2007; Derikx et al., 2008a; Grootjans et al., 2012, 2010a) may provide an explanation.

Next to an important role in regulating neuroendocrine and autonomic responses to peripheral inflammation (Quan, 2014; Xia and Krukoff, 2003), the PVN is involved in the regulation of cardiovascular homeostasis, with the parvocellular part regulating sympathetic outflow and the magnocellular part producing both vasopressin and oxytocin (Badoer, 2001). Therefore it might be possible that the observed increase in NGAL in the magnocellular neurons is a response to surgery-induced alterations in cardiovascular function, e.g. blood pressure. However, we previously showed that 60 min of myocardial ischemia had no effect on blood pressure during the procedure and up to three hours thereafter (Schoemaker and van Heijningen, 2000) and Xia and Krukoff (2003) reported that activation of neurons in the magnocellular part of the PVN due to peripheral inflammation did not cause changes in blood pressure. Moreover, myocardial infarcts smaller than 30% of the left ventricular circumference, did not affect cardiac output measurements, suggesting complete hemodynamic compensation (Schoemaker and Smits, 1990). We did observe a temporary decrease in HR immediately after opening of the thorax in the thoracic surgery group, which may be due to the sudden change in thoracic pressure. However, already halfway through the surgical procedure HR had recovered to the level of anesthesia controls. Hence, long-lasting alterations in cardiovascular functioning seem unlikely to have contributed to the outcomes of the current experiment.

To our surprise, we also observed increased plasma NGAL and increased microglial activity in the hilus and PFC in the rats that had undergone (sham) thoracic surgery. Artificial respiration has been reported to induce neuroinflammation (Chen et al., 2015). As both the thoracic and cardiac surgical procedures, but not the abdominal surgery, were performed using artificial respiration, this could have induced the inflammatory response. The outcomes of our control experiment however indicate that artificial respiration alone was not sufficient to cause the rise in plasma NGAL levels. This suggests that opening of the thoracic cavity and/or the pericardium in itself may have triggered the long lasting inflammatory response.

4.3. Intraneuronal pathways and neurogenesis after cardiac vs abdominal surgery

As potential link between neuroinflammation and cognitive deterioration, we investigated the level of phosphorylated p38MAPK, BDNF, and neurogenesis (DCX). Previous studies have implicated reduced levels of BDNF and (consequently) neurogenesis and neuronal plasticity as mediator between neuroinflammation and cognitive impairment (Barrientos et al., 2006; Cortese et al., 2011; Fan et al., 2014; Fidalgo et al., 2011; Lu et al., 2008; Tian et al., 2015; Tong et al., 2012). Our previous research suggest that alterations in BDNF-mediated neuronal signaling outlasts the neuroinflammatory response to surgery (Hovens et al., 2015b, 2014b). Increased production of p38MAPK may be a key factor in the initiation of neuronal dysfunction through inhibition of BDNF signaling (Liu et al., 2011; Tong et al., 2012; Wang et al., 2010; Xing et al., 2008).

In the current study, we observed a reduction in the levels of BDNF and the number of young maturing neurons in hippocampal regions of both the abdominal and cardiac surgery rats. Surprisingly, we found hippocampal levels of phosphorylated p38MAPK to be decreased after abdominal surgery and unchanged in the cardiac surgery rats. Hypothetically, this might reflect a compensatory mechanism that will eventually counteract the BDNF reduction in the late postoperative phase. As we previously described, the isolated hippocampal alterations in markers for neuronal pathways and neurogenesis after abdominal surgery are in concurrence with the observed isolated spatial (hippocampal dependent) memory impairment in this group (Hovens et al., 2015b, 2014b).

4.4. Effects of anesthesia and catheterization

In accordance with most POCD studies we did not observe an effect of anesthesia alone on behavioral test performance, nor inflammation or BDNF levels. In contrast, rodent studies that specifically investigated the effects of anesthesia reported long-lasting cognitive impairment after anesthesia, anesthesia-induced neuroinflammation and neuronal damage (Cao et al., 2012; Kong et al., 2013; Li et al., 2013, 2014; Wang et al., 2015). Possibly, differences in dose and duration of anesthesia cause these contrasting findings (Liu et al., 2014; Peng et al., 2011). Our findings indicate that the anesthesia and analgesia applied in this study was in itself not responsible for the behavioral and inflammatory changes observed after surgery. However, we cannot exclude that the anesthesia and/or analgesia may have contributed to the effects of surgery or may have modulated these effects. Likewise, although our results indicate that jugular vein catheterization alone did not influence behavior, we observed minor effects of the catheterization on the plasma concentrations of inflammatory factors that may have contributed to the overall effect of the surgical procedures in our study.

Considering these outcomes, it is impossible to conclude whether potential influences of anesthesia and catheterization differ depending on the type of surgery or application method of anesthesia (nose cap vs intubation). Moreover, both anesthesia and long-term catheterization are integrative parts of major surgical procedures in patients. Therefore, we chose to use the naïve control animals as main control for the surgical procedures.

4.5. Influence of cardiac and abdominal ischemia-reperfusion

In this experiment we used cardiac and mesenteric ischemia-reperfusion to model the effects of major cardiac and abdominal surgery. Ischemia-reperfusion injury of the heart invariably occurs during cardiac surgery, either globally due to temporary cardiac arrest and CBP or locally due to various surgical techniques (Habertheuer et al., 2014; Turer and Hill, 2010). Myocardial ischemia-reperfusion contributes substantially to the local and systemic inflammatory response and postoperative myocardial damage (McGuinness et al., 2008; Raivio et al., 2006). Vice versa the inflammatory response to cardiac and thoracic tissue injury and contact to foreign materials (CBP) may contribute to myocardial ischemia-reperfusion injury (Gu et al., 1999).

Hypoperfusion of the mesenteric vascular bed is associated with temporal ischemic damage to the intestinal villi and loss of intestinal barrier function leading to increases in systemic endotoxin levels and greatly contributing to the local and systemic inflammatory response (Grootjans et al., 2010a, 2010b; Petrat et al., 2010; Sandek et al., 2008). After reperfusion intestinal barrier function is quickly restored (Derikx et al., 2008a).

Notably, non-abdominal surgical procedures, including cardiac surgery, have also been associated with reduced mesenteric perfusion and loss of intestinal barrier function (Derikx et al., 2008b; McGuinness et al., 2008). Therefore, alterations in gut barrier function might have contributed to the effects of the cardiac surgery in the current study. Conversely, chronic or intermittent ischemia of the mesenteric vasculature is thought to contribute to the development of cardiovascular pathology due to the chronic translocation of endotoxins and/or the resulting chronic systemic inflammatory response (see Krack et al., 2005; Sandek et al., 2008 for literature reviews). However, as to our knowledge one episode of mesenteric

hypoperfusion does not substantially affect cardiac function, we do not expect an effect of the currently used abdominal surgery model on cardiac perfusion or function.

4.6. Role of cardiovascular pathology

It has been suggested that the increased incidence of POCD after cardiac surgery is a consequence of the underlying pathology rather than a surgery effect (Keizer et al., 2005; Rosengart et al., 2005; Selnes et al., 2006b). As the rats in our study were all healthy before undergoing the surgical procedure, our results indicate that independent of previous pathology, cardiac surgery seems associated with exacerbated postoperative inflammation and cognitive dysfunction. Still, as common cardiovascular pathologies such as renal failure and metabolic disease have been associated with inflammation and cognitive impairment (Feng et al., 2013; Hudetz et al., 2011a, 2011b; Kadoi and Goto, 2006; Su et al., 2012), in practice cardiovascular pathology may very well contribute to the increased incidence and severity of POCD after cardiac surgery.

5. Conclusions

Our findings indicate that the effects of abdominal surgery seem limited to hippocampal dependent tasks and hippocampal brain regions. In contrast, cardiac surgery seems associated with another pattern of cognitive impairment, including spatial memory, learning and object recognition, a prolonged increase in systemic NGAL levels, and more wide spread alterations in the brain involving the hippocampus, hypothalamus, and prefrontal cortex. The exact relation between the observed increases in inflammatory and neuronal markers and the decline in cognitive performance needs to be clarified in future research. However, these results suggest that POCD after cardiac surgery, compared to non-cardiac surgery, may be more extended rather than more severe.

Conflict of interest

Dr. Hovens, Dr. van Leeuwen, Prof. Dr. Mariani, Dr. Kraneveld, and Dr. Schoemaker report no biomedical financial interests or other potential conflicts of interest. The study was funded by the University of Groningen. Funding sources had no influence on the experimental design, experimental procedures, analysis or interpretation of the data.

Acknowledgments

Many thanks to Jan Bruggink, Wanda Douwenga, Jan Keijser, Kunja, Slopsema, and Suzan Thijssen for their technical assistance, Leonie Gouweleeuw for proofreading, and Steffen van Heijningen, Wouter Vranckx, and Priscilla Slagter for their work as undergraduate students on this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbi.2016.02.003.

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