

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Postoperative Cognitive Dysfunction: Preclinical Highlights and Perspectives on Preventive Strategies

Fabrizio M. Locatelli and Takashi Kawano

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/66574>

Abstract

One of the common complications associated with anaesthesia and surgery in geriatric patients is the postoperative cognitive dysfunction (POCD). This cognitive impairment affects the long-term prognosis and has been shown to be associated with long-term disability, higher health care costs, and even increased mortality. On the other hand, clinical research on POCD is in its infancy, the condition has not been clarified, and since no strategy for management is currently available, it is imperative to develop specific methods for prevention and management. Although its pathogenesis involves various factors, accumulating evidence suggests that surgery elicits an inflammatory response in the hippocampus, a brain area closely related to cognitive function, playing a key role in the development of POCD. Several studies suggest that age-related phenotypic change of microglia is associated with pathogenic neuroinflammation, and more importantly it may be modifiable. In this chapter, we discuss the current overview and preclinical highlights regarding POCD. We further discuss some perspectives on preventive strategies for POCD, based on the findings of our preclinical research and the available literature.

Keywords: POCD, neuroinflammation, microglia

1. Introduction

Sixty years ago, an article entitled *Adverse cerebral effects of anaesthesia on old people* by Dr. Bedfor was published in which he reported for the first time that general anaesthesia and surgery led to cognitive dysfunction in elderly patients [1]. This decline, known as postoperative cognitive dysfunction (POCD), typically persists for several weeks, sometimes a year, but in some people is permanent. Since then, the number of publications assessing POCD has been growing year by year, reflecting the increasing importance and the still remaining controversies over this condition [2].

One of the greatest achievements of modern medicine is the increase in life expectancy; however, as a consequence the world population is today ageing fast, with over 12.3% of the total being over 60 years old [3]. Moreover, life expectancy increased by 5 years between 2000 and 2015, the fastest growth since the 1960s [4]. Though it is one of our greatest achievements, it also poses big challenges as the ageing process is associated with biological and cognitive degeneration [5]. Recent advances in surgical, anaesthetic management and intensive care techniques are associated with a growing number of elderly people undergoing surgical procedures [6]. Consequently, complications associated with geriatric surgery, such as POCD, will become an increasingly common worldwide problem [7, 8]. Furthermore, POCD has been shown to be associated with long-term disability and higher health care costs. In addition, three-month POCD has been statistically associated with increased mortality [9].

POCD is difficult to define; in general it refers to a deterioration in cognition that occurs in the time period after surgery. To truly diagnose POCD, it is necessary to have tested the patient preoperatively (baseline) and determined how much of a decline occurred after surgery. As can be expected, in normal clinical contexts, patients do not usually undergo neuropsychological testing pre- and post-surgery [2, 10]. In consequence, there is a lack of accurate data and even the exact incidence of this condition is unknown [10]. Besides, behavioral responses to cognitive tests not only vary considerably in aged individuals compared with younger individuals, but also an enormous variability of cognitive decline exists across individuals [6, 11]. Additionally, the changes produced by the effects of ageing on cognitive function vary substantially through the different cognitive domains [11]. Likewise, different cognitive domains must be evaluated by specific tests [2]. Hence in order to diagnose and characterize POCD cases, it becomes necessary to carry out neuropsychological tests that assess different domains involved in cognitive function such as learning and memory, attention, psychomotor function and flexibility cognition [2, 10]. In addition, POCD is sometimes characterized by slight declines in cognitive function, making it essential that these tests should be sensitive enough to allow an accurate diagnosis based on the results of pre- and postoperative tests [10]. As a consequence, incidence rates reported may vary considerably according to the cognitive domains explored by different tests and timing [12].

POCD was initially associated with cardiac surgery and indeed was recognized as the most common complication in this intervention, presenting a high incidence [13, 14], although the incidence values vary considerably between different reports, ranging from approximately 30% to 80% at the time of discharge, 10–60% after 3–6 months and 20–60% after 6 months to 1 year [12–20]. This fact may be related to microembolic events that may cause focal cerebral infarcts during the use of the cardiopulmonary bypass pump [12, 21–24].

In recent times, in correlation with the continually increasing number of patients undergoing geriatric surgery, the interest in POCD has expanded to noncardiac surgery as well. So far, the major study assessing this condition was carried out by the International Study of Postoperative Cognitive Dysfunction and included 1218 patients older than 60 years old undergoing elective, noncardiac surgery [7]. Neuropsychological tests were administered

before surgery and at 7 days and 3 months after intervention. This study reported a POCD incidence of 25% 1 week after surgery and 10% after 3 months. Additionally, the probability of POCD incidence in patients aged 70 and over at 3 months (14%) was two times higher than those aged 60 to 69 (7%). Hovens and collaborators [25] reported that the cognitive domains affected by cardiac surgery compared with noncardiac surgery seem to be different. While abdominal surgery affects hippocampal neuronal functioning and in consequence spatial memory, cardiac surgery seems to cause a more general change in inflammation and neuronal function [25].

Furthermore, there appears to exist an association between postoperative pain and cognitive impairment, exerting an influence over the patients' performance on certain cognitive tests [26–28]. Apart from the effect of the pain, the influence of postoperative analgesics should not be ruled out. In fact, successful postoperative pain management may be important in preventing POCD in elderly patients [35]. Additionally, cognitive impairment in elderly patients may also be influenced by stress produced by the hospitalization itself, the postoperative fatigue state, the unfamiliar environment and sleep deprivation [12, 28, 29].

The contribution of the anaesthesia to the development of POCD seems to be subject to discrepancies. When Silbert and colleagues [30] assessed general anaesthesia compared with spinal anaesthesia, no significant difference in the rates of POCD was found. In agreement with this, a meta-analysis carried on by Guay [31] did not find differences between general anaesthesia and regional anaesthesia with spontaneous breathing and sedation only in the development of permanent POCD after noncardiac surgery. Otherwise, another meta-analysis concluded that general anaesthesia, compared to other types of anaesthesia, may increase the risk of developing POCD [32]. These findings are supported by preclinical studies, which suggest that isoflurane anaesthesia administered at clinically relevant doses causes long-term cognitive impairment in unoperated animals [33–35]. However, other studies point towards an enhancement of the cognitive functions after anaesthesia inhalation [36–38].

Although major surgery is frequently associated with the development of POCD, minor surgery proved to decrease the cognitive function in the first postoperative week in elderly patients [39]. Moreover, independently from the nature of the surgical procedure, the only consistent risk factor that has been identified for POCD is advanced age [7, 9, 15, 39–41]. Apart from increasing age as a risk factor for POCD, other factors that can be enumerated are lower level of education, a history of previous cerebral vascular accident, a history of alcohol dependence, preoperative history of post-traumatic stress disorder, poor cognitive health, preceding development of POCD, respiratory complications, infectious complications and a second operation [9, 12, 41–43].

2. Mechanisms of POCD

One of the most challenging problems connected with POCD is the lack of evidence-based preventative strategies. This is due to the fact that the mechanisms that cause POCD in

elderly patients are largely unknown. In fact, surgery induces peripheral immune challenges, leading to an exaggerated neuroinflammatory response. More recently, several studies have demonstrated that neuroinflammation in the hippocampus is most likely to be involved in the pathogenesis of POCD [35, 44–51]. Neuroinflammation is a complex response to brain injury characterized by maladaptive microglial activation mainly involving the activation of glia and increased levels of pro-inflammatory cytokines, including interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α) [52–54]. As the primary source for pro-inflammatory cytokines, microglia are implicated as pivotal mediators of neuroinflammation. In particular, the hippocampus is known to be a region important to cognition and highly vulnerable to ageing. Pro-inflammatory cytokines TNF- α and IL-1 β released from microglia within the hippocampus are reported to inhibit the long-term potentiation that is important in the formation of memory, as well as inducing apoptosis, and thus play a pathogenic role in cognitive disorders in neurodegenerative diseases [48, 52–58]. Based on these findings, it can be hypothesized that age-related microglial priming in the hippocampus, and subsequent overproduction of inflammatory cytokines, plays a critical role in the development of POCD in the elderly population. Therefore, it becomes necessary to understand the roles of neuroinflammation in the pathogenesis of POCD and its potential as a therapeutic target.

Preclinical evidence has shown that microglia in a normal-aged brain are shifted towards the inflammatory phenotype (**Figure 1**). This age-related phenotype change is consistent with the microglial priming, implying that age-related microglia priming could make elderly surgical patients more susceptible to the development of POCD. Neurogenic neuroinflammation is the inflammatory reaction in the central nervous system in response to neuronal activity [59]. Peripheral immune challenges, such as surgical trauma, may lead neurogenic neuroinflammation to become maladaptive [60]. It has been postulated that the inflammatory response may be transmitted through humoral and neural pathways, leading to neuroinflammation. Parabolic experiments in rat models have revealed that the neural pathway may play a dominant role in the development of neuroinflammation after abdominal surgery [60]. These findings seem to confirm the neurogenic neuroinflammatory origin of POCD in aged rats. Though rodents are useful in providing hypothetical models for understanding some of the memory deficits seen in human POCD, it still remains unclear how much can be extrapolated to simulate the neuroinflammatory mechanisms involved in human POCD [2].

While several studies have concentrated on protein regulating inflammation (cytokines), recent evidence points to a critical role of microRNAs (miRNAs) in controlling the inflammatory process [61–64]. A subset of miRNAs notably affects both immune and neuronal functions in particular in the central nervous system. It has been hypothesized that miRNAs regulate neuro-immune functions through alterations of neuron-glia and/or brain-to-body signalling [65]. Moreover, miR-572 has been implicated in the development and restoration of POCD and identified as a possible biological marker for early diagnosis of POCD [61]. In fact, modulating miRNAs using agonist or antagonist miRNAs is a promising approach to treating human neuroinflammatory disorders including POCD.

Lipopolysaccharide (LPS)

(0.1, 1, 10, or 100 ng/ml)

TNF α

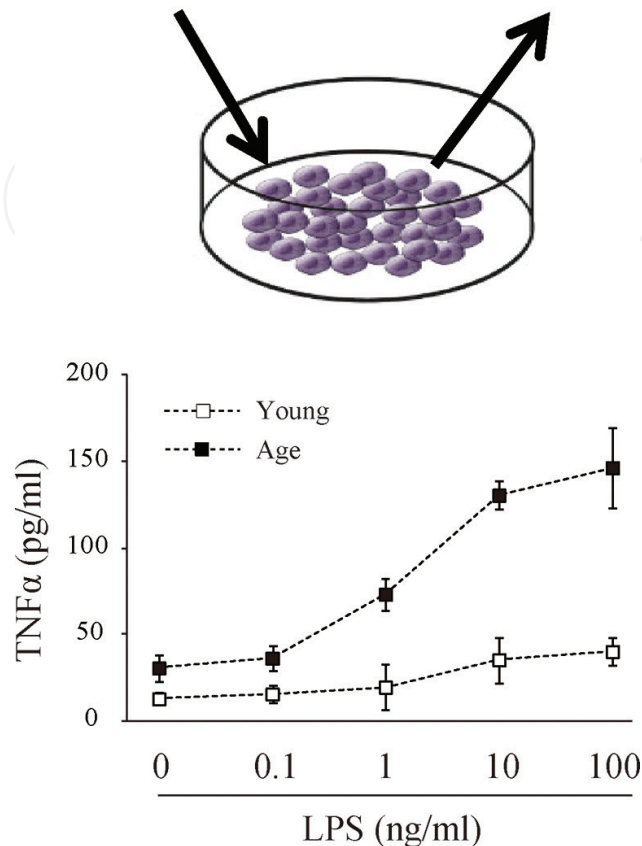


Figure 1. Microglial priming. Effects of ex vivo stimulation with lipopolysaccharide (LPS) on the cultured microglia were shown. Hippocampal microglia were isolated from either young or aged rats. Primary microglia were stimulated with 0.1, 1, 10 and 100 ng/ml or media alone, and levels of TNF- α were determined from supernatants collected 24 h later. The LPS-induced increase in TNF- α was greater in the microglia of aged rats than young. These results indicate that normal ageing may prime microglia for an exaggerated responsiveness to pro-inflammatory stimuli.

3. Treatment and prevention

Notwithstanding the fact that POCD is a common complication for geriatric patients, currently there is not any available statement after general anaesthesia [66]. Additionally, due to the challenging nature of POCD, examples of randomized controlled studies assessing possible intervention for treating or improving POCD are scarce [2]. However, this can be addressed by studies assessing the effects of drugs on cognitive impairment after general anaesthesia. Aminophylline reduced the time necessary for postoperative cognitive recovery from sevoflurane anaesthesia, improving the ventilatory elimination of sevoflurane [67]. Meanwhile, low-dose haloperidol prophylactic treatment did not prove effective in decreasing the incidence of postoperative delirium but had a positive effect on the severity and duration [68]. A pilot, phase 2a study to evaluate the feasibility, safety and efficacy of donepezil in preventing

postoperative delirium did not find significant changes in the incidence of delirium or in the days patients stayed in the hospital, although it did not rule out possible benefits [69]. In agreement with these results, Doraiswamy and collaborators [70] evaluated the effect of donepezil in treating patients with cognitive decline following coronary artery bypass graft surgery, reporting that donepezil did not improve composite cognitive performance but had enhancing effects on some aspects of memory. Meanwhile, the use of gabapentin in the treatment of postoperative pain reduced the occurrence of postoperative delirium [71].

Therefore, the lack of an effective treatment for POCD highlights the importance of the prevention. Over the past years, research efforts have been directed to identifying new strategies for preventing POCD [2]. While lidocaine administered during and after cardiac surgery failed to reduce POCD incidence, some protective effects of lower-dose lidocaine in nondiabetic subjects were found [72]. Moreover, due the anti-inflammatory action of ketamine, POCD incidence was reduced one week after cardiac surgery [73]. Meanwhile, intraoperatively intravenous administration of magnesium in cardiac surgery did not have any preventive effect over POCD [74]. Furthermore, administration of a post-cardiac surgery high dose of dexamethasone failed to reduce the risk of POCD [75], while in another study, a higher dose of dexamethasone actually increased the incidence of POCD in the early postoperative period after microvascular decompression under general anaesthesia [76]. Furthermore, resveratrol showed anti-neuroinflammation and anti-apoptosis effects attenuating the hippocampus-dependent cognitive impairment induced by isoflurane in aged mice [77]. Also, ondansetron administered postoperatively appears to have analgesic and protective effects, additionally seeming to improve the cognitive function in patients undergoing surgery under general anaesthesia [78]. When the effects of postoperative analgesia with ketoprofen on cognitive functions were investigated in aged animals, the results suggested that ketoprofen can prevent the development of surgery-associated memory deficits via its pain-relieving effects [79]. Chronic pretreatment with low doses of candesartan may elicit blood pressure-independent neuroprotective effects in POCD by decreasing hippocampal blood-brain barrier permeability and promoting resolution of neuroinflammation [47]. Further, dexmedetomidine provided neurocognitive protection, attenuating isoflurane-induced injury in rats developing brain [80]. Atorvastatin preserved the hippocampal-dependent fear response and also protected spatial memory on day seven after surgery in a mouse model of postoperative cognitive decline [81]. Aspirin-triggered resolvin D1 prevented neuronal dysfunction and cognitive decline after peripheral orthopaedic surgery in the mouse model [82].

There is considerable evidence that cognitive interventions, such as physical activity and cognitive activity, have positive effects on age-related cognitive changes as well as early-stage dementia in humans [83–89]. In addition, animal models mimicking these interventions, in which rodents were exposed to voluntary wheel running and an enriched environment, showed improvement in cognitive performance (**Figure 2**) [48, 90]. Although the mechanism of these benefits has been debated, both interventions are reported to have common positive effects on microglial number, proliferation and phenotype in the brain. In fact, preoperative cognitive intervention, a combination of physical activity and cognitive activity, has been shown to prevent the development of POCD via restoration of the pro-inflammatory phenotype in aged microglia [48]. In addition, evidence suggests

that an enriched environment attenuated the surgery effects in reduction of brain-derived neurotrophic factor (BDNF) expression and neurogenesis in the hippocampus [90]. Recent time-course analysis using a rat abdominal surgery model revealed that hippocampal neuroinflammation and related microglial activation were found at 7 days after surgery, which resolved to normal levels by 14 days after surgery [48]. Therefore, the effects of pre-operative cognitive intervention may persist long enough to encompass the critical period of POCD development [48].

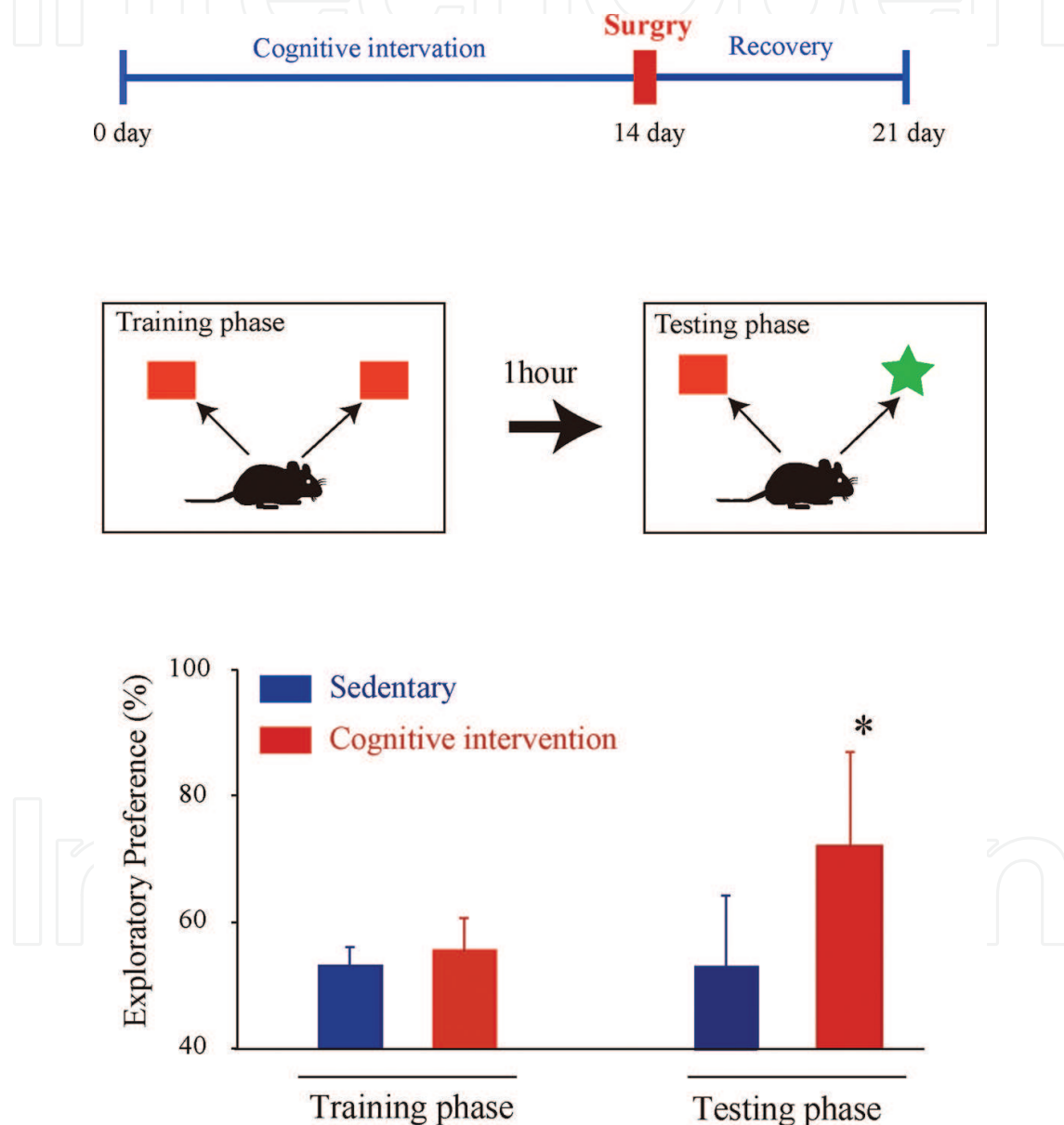


Figure 2. Effects of preoperative cognitive intervention on cognitive function assessed by novel object recognition test in aged rats. All rats were exposed to preoperative cognitive intervention or sedentary condition for 14 days following surgery (laparotomy and small intestinal manipulation) or non-surgery and allowed 7 days of recovery. Seven days after surgery, the effects of cognitive intervention on hippocampal-mediated working memory were assessed by a novel object recognition task. The sedentary rats in the aged group exhibited significantly impaired novel object recognition performance as shown by the similar amount of time spent in exploring the two objects. However, such impairment was not observed in the preoperative cognitive intervention group.

4. Concluding remarks

POCD is increasingly recognized as one of the common complications in geriatric patients despite the lack of strategy for prevention and management. Due to these limitations, preoperative management should be focused on promoting an early recognition of the patients at risk, and preventative measures should be taken from a multimodal approach comprising collaboration between the anaesthesiologist, surgeon, geriatricians and inclusion of family in the postoperative care plan in order to improve overall recovery and avoid long-term sequelae of POCD [2, 6, 10, 66]. Furthermore, it is recommended that patients at high risk for POCD should get preoperative discussion of this issue, allowing patients to make cognitively demanding decisions before surgery [2]. In addition, in line with the positive effects of cognitive interventions in both human and animal models, “pre-surgical rehabilitation” must be encouraged when possible in order to minimize the risk of POCD occurrence and its effects on overall recovery after surgery [2]. Moreover, promising new approaches such as the utilization of the relationship between neuroinflammation and miRNA expression should not be overlooked, in order to understand and discover new treatments. Deregulation of certain miRNAs may be associated with POCD development.

While both cardiac surgery and noncardiac surgery have been associated with POCD, the effects of each seem to affect different cognitive domains and in consequence may originate from different causes or mechanisms [25]. Moreover, the difficulty extrapolating the knowledge gathered through preclinical studies and animal models to human cases and the translation of these findings into therapeutic treatment for POCD points to the need for further work is needed. So far, the surgery-induced neuroinflammation processes including the microglial activation pathways seem to be the most promising therapeutic targets in the management of POCD.

Author details

Fabrizio M. Locatelli and Takashi Kawano*

*Address all correspondence to: takashika@kochi-u.ac.jp

Department of Anesthesiology and Intensive Care Medicine, Kōchi Medical School, Kōchi, Japan

References

- [1] Bedford PD: Adverse cerebral effects of anaesthesia on old people. *Lancet*. 1955; 269(6884): 259-63. doi: 10.1016/S0140-6736(55)92689-1
- [2] Berger M, Nadler JW, Browndyke J, Terrando N, Ponnusamy V, Cohen HJ, Whitson HE, Mathew JP: Postoperative cognitive dysfunction: minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiol Clin*. 2015; 33(3): 517-50. doi: 10.1016/j.anclin.2015.05.008

- [3] Ageing in the Twenty-First Century. A Celebration and A Challenge New York and London. 2012. UNFPA and Help Age International. ISBN: 978-0-89714-981-5
- [4] World Health Organization. World Health Statistics – Life Expectancy Increased by 5 years Since 2000, but Health Inequalities Persist [Internet] 2016. Available from: <http://www.who.int/mediacentre/news/releases/2016/health-inequalities-persist/en/>
- [5] Jin K, James WS, Xunming J, Miriam L, Stambler I: The critical need to promote research of aging and aging-related diseases to improve health and longevity of the elderly population. *Aging Dis.* 2014; 6(1): 1-5. doi: 10.14336/AD.2014.1210.
- [6] Yang R, Wolfson M, Lewis MC: Unique aspects of the elderly surgical population an anesthesiologist's perspective. *Geriatr Orthop Surg Rehabil.* 2011; 2(2): 56-64. doi: 10.1177/2151458510394606
- [7] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O: Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet.* 1998; 351(9106): 857-61. doi: 10.1016/S0140-6736(97)07382-0
- [8] Deiner S and Silverstein JH: Postoperative delirium and cognitive dysfunction. *Br J Anaesth.* 2009; 103(Suppl. 1):i41-6. doi: 10.1093/bja/aep291
- [9] Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology.* 2008; 108(1): 18-30. doi: 10.1097/01.anes.0000296071.19434.1e
- [10] De Cosmo G, Sessa F, Fiorini F, Congedo E: Postoperative cognitive disfunction in elderly patients: a frequent complication. *J Anesth Crit Care Open Access.* 2015; 2(2): 00048. doi: 10.15406/jaccoa.2015.02.00048
- [11] Glisky EL: Changes in cognitive function in human aging. In: *Brain Aging: Models, Methods, and Mechanisms.* CRC Press/Taylor & Francis Boca Raton (FL) USA. 2007; 19:3-20.
- [12] Wang W, Wang Y, Wu H, Lei L, Xu S, Shen X, Guo X, Shen R, Xia X, Liu Y, Wang F: Postoperative cognitive dysfunction: current developments in mechanism and prevention. *Med Sci Monit.* 2014; 20: 1908-12. doi: 10.12659/MSM.892485
- [13] Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM: Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol.* 2008; 63(5): 581-90. doi: 10.1002/ana.21382
- [14] Van Harten AE, Scheeren TW, Absalom AR: A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. *Anaesthesia.* 2012; 67(3): 280-93. doi: 10.1111/j.1365-2044.2011.07008.x
- [15] Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med.* 2001; 344(6): 395-402. doi: 10.1056/NEJM200102083440601

- [16] Knipp SC, Matatko N, Wilhelm H, Schlamann M, Thielmann M, Lösch C, Diener HC, Jakob H: Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. *Ann Thorac Surg.* 2008; 85(3): 872-9. doi: 10.1016/j.athoracsur.2007.10.083
- [17] Evered L, Scott DA, Silbert B, Maruff P: Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg.* 2011; 112(5): 1179-85. doi: 10.1213/ANE.0b013e318215217e
- [18] Shaw PJ, Bates D, Cartlidge NE, French JM, Heaviside D, Julian DG, Shaw DA: Long-term intellectual dysfunction following coronary artery bypass graft surgery: a six month follow-up study. *Q J Med.* 1987; 62(239): 259-68. doi: <http://dx.doi.org/259-268>
- [19] Savageau JA, Stanton BA, Jenkins CD, Frater RW: Neuropsychological dysfunction following elective cardiac operation. II. A six-month reassessment. *J Thorac Cardiovasc Surg.* 1982; 84(4): 595-600.
- [20] Dijk D, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R: Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. *J Thorac Cardiovasc Surg.* 2000; 120(4): 632-9. doi: 10.1067/mtc.2000.108901
- [21] Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S: The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke.* 1994; (7): 1393-9.
- [22] Cox G, Tzioupis C, Calori GM, Green J, Seligson D, Giannoudis PV: Cerebral fat emboli: a trigger of post-operative delirium. *Injury.* 2011; 42(Suppl. 4): S6-10. doi: 10.1016/S0020-1383(11)70005-5
- [23] Leiendecker J, Höcker J, Meybohm P, Fudickar A, Bein B: Postoperative neurocognitive function and microembolus detection in patients undergoing neck dissection: a pilot study. *Eur J Anaesthesiol.* 2010; 27(5): 417-24. doi: 10.1097/EJA.0b013e328336c633
- [24] Qing M, Shim JK, Grocott HP, Sheng H, Mathew JP, Mackensen GB: The effect of blood pressure on cerebral outcome in a rat model of cerebral air embolism during cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 2011; 142(2): 424-9. doi: 10.1016/j.jtcvs.2010.11.036
- [25] Hovens IB, van Leeuwen BL, Mariani MA, Kraneveld AD, Schoemaker RG: Postoperative cognitive dysfunction and neuroinflammation; Cardiac surgery and abdominal surgery are not the same. *Brain Behav Immun.* 2016; 54:178-93. doi: 10.1016/j.bbi.2016.02.003
- [26] Fong HK, Sands LP, Leung JM: The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg.* 2006; 102(4): 1255-66. doi: 10.1213/01.ane.0000198602.29716.53
- [27] Mc Connolly EJ: Severe pain confounds neuropsychological test performance. *J Clin Exp Neuropsychol.* 2000; 22(5): 633-9. doi: 10.1076/1380-3395(200010)22:5;1-9;FT633

- [28] Zywiell MG, Prabhu A, Perruccio AV, Gandhi R: The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. *Clin Orthop Relat Res.* 2014; 472(5): 1453-66. doi: 10.1007/s11999-013-3363-2
- [29] Kaneko T, Takahashi S, Naka T, Hirooka Y, Inoue Y, Kaibara N: Postoperative delirium following gastrointestinal surgery in elderly patients. *Surg Today.* 1997; 27(2): 107-11. doi: 10.1007/BF02385897
- [30] Silbert BS, Evered LA, Scott DA: Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy. *Br J Anaesth.* 2014; 113(5): 784-91. doi: 10.1093/bja/aeu163
- [31] Guay J: General anaesthesia does not contribute to long-term post-operative cognitive dysfunction in adults: a meta-analysis. *Indian J Anaesth.* 2011; 55(4): 358-63. doi: 10.4103/0019-5049.84850
- [32] Mason SE, Noel-Storr A, Ritchie CW: The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. *J Alzheimers Dis.* 2010;22(Suppl. 3): 67-79. doi: 10.3233/JAD-2010-101086
- [33] Culley DJ, Baxter MG, Yukhananov R, Crosby G: Long-term impairment of acquisition of a spatial memory task following isoflurane-nitrous oxide anesthesia in rats. *Anesthesiology.* 2004; 100(2): 309-14.
- [34] Cao L, Li L, Lin D, Zuo Z: Isoflurane induces learning impairment that is mediated by interleukin 1 β in rodents. *PLoS One.* 2012; 7(12): e51431. doi: 10.1371/journal.pone.0051431
- [35] Lin D, Zuo Z: Isoflurane induces hippocampal cell injury and cognitive impairments in adult rats. *Neuropharmacology.* 2011;61(8):1354-9. doi:10.1016/j.neuropharm.2011.08.011
- [36] Komatsu H, Nogaya J, Anabuki D, Yokono S, Kinoshita H, Shirakawa Y, Ogli K: Memory facilitation by posttraining exposure to halothane, enflurane, and isoflurane in ddN mice. *Anesth Analg.* 1993; 76(3): 609-12.
- [37] Callaway JK, Jones NC, Royse AG, Royse CF: Sevoflurane anesthesia does not impair acquisition learning or memory in the Morris water maze in young adult and aged rats. *Anesthesiology.* 2012; 117(5): 1091-101. doi: 10.1097/ALN.0b013e31826cb228
- [38] Parsons CG, Rammes G, Danysz W: Pharmacodynamics of memantine: an update. *Curr Neuropharmacol.* 2008; 6(1): 55-78. doi: 10.2174/157015908783769671
- [39] Canet J, Raeder J, Rasmussen LS, Enlund M, Kuipers HM, Hanning CD, Jolles J, Korttila K, Siersma VD, Dodds C, Abildstrom H: Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand.* 2003; 47(10):1204-10. doi: 10.1046/j.1399-6576.2003.00238.x
- [40] Scott DA, Evered LA, Silbert BSJ: Cardiac surgery, the brain, and inflammation. *Extra Corpor Technol.* 2014; 46(1): 15-22.

- [41] McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, Newman MF: Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. *Anesthesiology*. 2010; 112(4): 852-9. doi: 10.1097/ALN.0b013e3181d31fd7
- [42] Hudetz JA, Patterson KM, Byrne AJ: A history of alcohol dependence increases the incidence and severity of postoperative cognitive dysfunction in cardiac surgical patients. *Int J Environ Res Public Health*. 2009; 6(11): 2725-39. doi: 10.3390/ijerph6112725
- [43] Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Byrne AJ, Warltier DC, Pagel PS: History of post-traumatic stress disorder is associated with impaired neuropsychometric performance after coronary artery surgery. *J Cardiothorac Vasc Anesth*. 2010; 24(6): 964-8. doi: 10.1053/j.jvca.2010.02.019
- [44] Kalb A, von Haefen C, Sifringer M, Tegethoff A, Paeschke N, Kostova M, Feldheiser A, Spies CD: Acetylcholinesterase inhibitors reduce neuroinflammation and -degeneration in the cortex and hippocampus of a surgery stress rat model. *PLoS One*. 2013; 8(5): e62679. doi: 10.1371/journal.pone.0062679
- [45] Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, Takata M, Lever IJ, Nanchahal J, Fanselow MS, Maze M: Role of interleukin-1beta in postoperative cognitive dysfunction. *Ann Neurol*. 2010; 68(3):360-8. doi: 10.1002/ana.22082
- [46] Chi H, Kawano T, Tamura T, Iwata H, Takahashi Y, Eguchi S, Yamazaki F, Kumagai N, Yokoyama M: Postoperative pain impairs subsequent performance on a spatial memory task via effects on N-methyl-D-aspartate receptor in aged rats. *Life Sci*. 2013; 93(25-26): 986-93. doi: 10.1016/j.lfs.2013.10.028
- [47] Li Z, Cao Y, Li L, Liang Y, Tian X, Mo N, Liu Y, Li M, Chui D, Guo X: Prophylactic angiotensin type 1 receptor antagonism confers neuroprotection in an aged rat model of postoperative cognitive dysfunction. *Biochem Biophys Res Commun*. 2014; 449(1): 74-80. doi: 10.1016/j.bbrc.2014.04.153
- [48] Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M: Impact of preoperative environmental enrichment on prevention of development of cognitive impairment following abdominal surgery in a rat model. *Anesthesiology*. 2015; 123(1): 160-70. doi: 10.1097/ALN.0000000000000697
- [49] Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL: Postoperative cognitive dysfunction: involvement of neuroinflammation and neuronal functioning. *Brain Behav Immun*. 2014; 38: 202-10. doi: 10.1016/j.bbi.2014.02.002
- [50] Hovens IB, van Leeuwen BL, Nyakas C, Heineman E, van der Zee EA, Schoemaker RG: Postoperative cognitive dysfunction and microglial activation in associated

- brain regions in old rats. *Neurobiol Learn Mem.* 2015; 118: 74-9. doi: 10.1016/j.nlm.2014.11.009
- [51] Rosczyk HA, Sparkman NL, Johnson RW: Neuroinflammation and cognitive function in aged mice following minor surgery. *Exp Gerontol.* 2008; 43(9): 840-6. doi: 10.1016/j.exger.2008.06.004; doi: 10.1016%2Fj.exger.2008.06.004#pmc_ext
- [52] Bluthé RM, Pawlowski M, Suarez S, Parnet P, Pittman Q, Kelley KW, Dantzer R: Synergy between tumor necrosis factor α and interleukin-1 in the induction of sickness behavior in mice. *Psychoneuroendocrinology.* 1994; 19(2): 197-207. doi: 10.1016/0306-4530(94)90009-4
- [53] Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M: Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A.* 2010; 107(47):20518-22. doi: 10.1073/pnas.1014557107
- [54] Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition—the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc.* 2002; 50(12): 2041-56. doi: 10.1046/j.1532-5415.2002.50619.x
- [55] Pugh CR, Fleshner M, Watkins LR, Maier SF, Rudy JW: The immune system and memory consolidation: a role for the cytokine IL-1 β . *Neurosci Biobehav Rev.* 2001; 25(1): 29-41. doi: 10.1016/S0149-7634(00)00048-8
- [56] Murray CA, Lynch MA: Evidence that increased hippocampal expression of the cytokine interleukin-1 β is a common trigger for age- and stress-induced impairments in long-term potentiation. *J Neurosci.* 1998;18(8): 2974-81.
- [57] Jang S, Dilger RN, Johnson RW: Luteolin inhibits microglia and alters hippocampal-dependent spatial working memory in aged mice. *J Nutr.* 2010; 140(10): 1892-8. doi: 10.3945/jn.110.123273
- [58] McAfoose J, Baune BT: Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev.* 2009; 33(3): 355-66. doi: 10.1016/j.neubiorev.2008.10.005
- [59] Xanthos DN, Sandkühler J: Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. *Nat Rev Neurosci.* 2014; 15(1): 43-53. doi: 10.1038/nrn3617
- [60] Kawano T, Eguchi S, Iwata H, Yamanaka D, Tateiwa H, Locatelli FM, Yokoyama M: Pregabalin can prevent, but not treat, cognitive dysfunction following abdominal surgery in aged rats. *Life Sci.* 2016; 148: 211-9. doi: 10.1016/j.lfs.2016.02.021
- [61] Yu X, Liu S, Li J, Fan X, Chen Y, Bi X, Liu S, Deng X: MicroRNA-572 improves early postoperative cognitive dysfunction by down-regulating neural cell adhesion molecule 1. *PLoS One.* 2015; 10(2): e0118511. doi: 10.1371/journal.pone.0118511

- [62] Raisch J, Darfeuille-Michaud A, Nguyen HT: Role of microRNAs in the immune system, inflammation and cancer. *World J Gastroenterol.* 2013; 19(20): 2985-96. doi: 10.3748/wjg.v19.i20.2985
- [63] Davidson-Moncada J, Papavasiliou FN, Tam W: MiRNAs of the immune system: roles in inflammation and cancer. *Ann N Y Acad Sci.* 2010; 1183: 183-94. doi: 10.1111/j.1749-6632.2009.05121.x
- [64] Sonkoly E, Pivarcsi A: microRNAs in inflammation. *Int Rev Immunol.* 2009; 28(6): 535-61. doi: 10.3109/08830180903208303
- [65] Soreq H, Wolf Y: NeurimmiRs: microRNAs in the neuroimmune interface. *Trends Mol Med.* 2011; 17(10): 548-55. doi: 10.1016/j.molmed.2011.06.009
- [66] Saito S: Management of cognition as reported in Japanese historical documents and modern anesthesiology research papers. *J Anesth.* 2016. doi: 10.1007/s00540-016-2219-9
- [67] El Tahan MR: Effects of aminophylline on cognitive recovery after sevoflurane anesthesia. *J Anesth.* 2011; 25(5): 648-56. doi: 10.1007/s00540-011-1190-8
- [68] Kalisvaart KJ, De Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, Eikelenboom P, Van Gool WA: Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized k-controlled study. *J Am Geriatr Soc.* 2005; 53(10): 1658-66. doi: 10.1111/j.1532-5415.2005.53503.x
- [69] Sampson EL, Raven PR, Ndhlovu PN, Vallance A, Garlick N, Watts J, Blanchard MR, Bruce A, Blizzard R, Ritchie CW: A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry.* 2007; 22(4): 343-9. doi: 10.1002/gps.1679
- [70] Doraiswamy PM, Babyak MA, Hennig T, Trivedi R, White WD, Mathew JP, Newman MF, Blumenthal JA: Donepezil for cognitive decline following coronary artery bypass surgery: a pilot randomized controlled trial. *Psychopharmacol Bull.* 2007; 40(2): 54-62.
- [71] Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, Ames C, Chou D, Weinstein P: Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. *Neurology.* 2006; 67(7): 1251-3. doi: 10.1212/01.wnl.0000233831.87781.a9
- [72] Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, Blumenthal JA, Newman MF, Neurologic Outcome Research Group: Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke.* 2009; 40(3): 880-7. doi: 10.1161/STROKEAHA.108.531236
- [73] Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, Pagel PS, Warltier DC: Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiol Scand.* 2009; 53(7): 864-72. doi: 10.1111/j.1399-6576.2009.01978.x

- [74] Mathew JP, White WD, Schinderle DB, Podgoreanu MV, Berger M, Milano CA, Laskowitz DT, Stafford-Smith M, Blumenthal JA, Newman MF, Fontes MA: Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. *Stroke*. 2013; 44(12): 3407-13. doi: 10.1161/STROKEAHA.113.002703
- [75] Ottens TH, Dieleman JM, Sauër AM, Peelen LM, Nierich AP, de Groot WJ, Nathoe HM, Buijsrogge MP, Kalkman CJ, van Dijk D: Effects of dexamethasone on cognitive decline after cardiac surgery a randomized clinical trial. *Anesthesiology*. 2014; 121(3): 492-500. doi: 10.1097/ALN.0000000000000336
- [76] Fang Q, Qian X, An J, Wen H, Cope DK, Williams JP: Higher dose dexamethasone increases early postoperative cognitive dysfunction. *J Mol Neurosci*. 2014; 52(2): 286-93. doi: 10.1007/s12031-013-0141-2
- [77] Li XM, Zhou MT, Wang XM, Ji MH, Zhou ZQ, Yang JJ: Resveratrol pretreatment attenuates the isoflurane-induced cognitive impairment through its anti-inflammation and-apoptosis actions in aged mice. *J Mol Neurosci*. 2014; 52(2): 286-93. doi: 10.1007/s12031-013-0141-2
- [78] Papadopoulos G, Pouangare M, Papathanakos G, Arnaoutoglou E, Petrou A, Tzimas P: The effect of ondansetron on postoperative delirium and cognitive function in aged orthopedic patients. *Minerva Anesthesiol*. 2014; 80(4):444-51
- [79] Kawano T, Takahashi T, Iwata H, Morikawa A, Imori S, Waki S, Tamura T, Yamazaki F, Eguchi S, Kumagai N, Yokoyama M: Effects of ketoprofen for prevention of postoperative cognitive dysfunction in aged rats. *J Anesth*. 2014; 28(6): 932-6. doi: 10.1007/s00540-014-1821-y
- [80] Sanders RD, Xu J, Shu Y, Januszewski A, Halder S, Fidalgo A, Sun P, Hossain M, Ma D, Maze M: Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. *Anesthesiology*. 2009; 110(5):1077-85. doi: 10.1097/ALN.0b013e31819daedd
- [81] Vizcaychipi MP, Watts HR, O'Dea KP, Lloyd DG, Penn JW, Wan Y, Pac-Soo C, Takata M, Ma D: The therapeutic potential of atorvastatin in a mouse model of postoperative cognitive decline. *Ann Surg*. 2014; 259(6): 1235-44. doi: 10.1097/SLA.0000000000000257
- [82] Terrando N, Gómez-Galán M, Yang T, Carlström M, Gustavsson D, Harding RE, Lindskog M, Eriksson LI: Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. *FASEB J*. 2013; 27(9): 3564-71. doi: 10.1096/fj.13-230276
- [83] Etnier JL, Nowell PM, Landers DM, Sibley BA: A meta-regression to examine the relationship between aerobic fitness and cognitive performance. *Brain Res Rev*. 2006; 52(1): 119-30. doi: 10.1016/j.brainresrev.2006.01.002

- [84] Williams KN: Exploring interventions to reduce cognitive decline in aging. *J Psychosoc Nurs Ment Health Serv.* 2010; 48(5): 42-51. doi: 10.3928/02793695-20100331-03 doi: 10.3928%2F02793695-20100331-03#pmc_ext
- [85] Bherer L, Erickson KI, Liu-Ambrose T: A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *J Aging Res.* 2013; 2013:657508. doi: 10.1155/2013/657508
- [86] Kirk-Sanchez NJ, McGough EL: Physical exercise and cognitive performance in the elderly: current perspectives. *Clin Interv Aging.* 2014; 9: 51-62. doi: 10.2147/CIA.S39506
- [87] Van Gelder BM, Tijhuis MA, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D: Physical activity in relation to cognitive decline in elderly men The FINE Study. *Neurology.* 2004; 63(12): 2316-21. doi: 10.1212/01.WNL.0000147474.29994.35
- [88] Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M: Exercise level and cognitive decline: the MoVIES project. *Alzheimer Dis Assoc Disord.* 2004; 18(2): 57-64. doi: 10.1097/01.wad.0000126614.87955.79
- [89] Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F: Physical activity, including walking, and cognitive function in older women. *JAMA.* 2004; 292(12): 1454-61. doi: 10.1001/jama.292.12.1454
- [90] Fan D, Li J, Zheng B, Hua L, Zuo Z: Enriched environment attenuates surgery-induced impairment of learning, memory, and neurogenesis possibly by preserving BDNF expression. *Mol Neurobiol.* 2016; 53(1): 344-54. doi: 10.1007/s12035-014-9013-1