

Modeling the influence of heavy ion beams on neurogenesis and functioning of hippocampal neural networks

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Abstract. Radiation-induced impairment of hippocampal neurogenesis is one of serious factors associated with cognitive detriments after radiation therapy of brain cancers and realization of long-term manned space flights. The goal of this study is to develop a mathematical model describing radiation-induced changes in cellular populations participating in neurogenesis and how these alterations worsen the processing of information by hippocampus. Modeling results have demonstrated that heavy ions may cause non-reversible suppression of neurogenesis, which is followed by failure of pattern encoding and retrieval by hippocampal neural networks.

1 Introduction

Radiation-induced cognitive disfunction becomes a serious concern in hadron therapy and long-term manned space flights [1, 2]. In recent years a number of neurocognitive detriments have been reported, including progressive deficits in short- and long-term memory loss, spatial orientation, visual motor processing and impaired learning. As it is well-known, hippocampus plays a key role in a short-term and long-term memory, integrating processes and plasticity of the brain. The analysis of recent experimental studies at particle accelerators with energetic protons and heavy ions suggests that the hippocampus is one of the most sensitive regions of the central nervous system (CNS) under irradiation. The subgranular zone (SGZ) of hippocampus contains radiosensitive population of dividing cells participating in neurogenesis, therefore, a detailed study of related phenomena is a very important task. However, in order to predict any cognitive dysfunction, the existing models of neurogenesis need to be supplemented with functional models of neural networks reflecting the actual performance of neural cells in the process of cognition. This is the goal of the present study.

2 Methods

In our work we have used two mathematical models: for dynamics of neuronal cell population and hippocampal neural network activity after irradiation.

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2.1 Hippocampal neurogenesis after acute irradiation

For describing hippocampal neurogenesis a mathematical model by E. Cacao and F.A. Cucinotta [3, 4] was used. Cellular population in SGZ is represented by four compartments: neural stem cells, NSC (n_1), neuroblasts, NB (n_2), immature neurons, ImN (n_3) and glioblasts, GB (n_4). NSCs are regulated by their proliferation (p_1) and differentiation into NBs and GBs. In turn NBs differentiate into ImNs. Furthermore losses of all cell populations by apoptosis due to irradiation have been considered (n_5). Moreover, we have categorized radiosensitive cells as undamaged (n_j), weakly damaged (n_{jW}) and heavily damaged (n_{jH}), based on the extent of radiation-induced damage, where $j = 1 - 4$), which represents the four neuronal cells populations in the model. We imply that weakly damaged cells can undergo repair with rates α_{jR} , while heavily damaged cells and misrepaired weakly damaged cells, both lead to apoptosis with rates ν_j and α_{jM} , respectively.

Dynamics of the neuronal cell population after acute irradiation is described by the following ordinary differential equations, Eqs. (1) – (6b):

$$\frac{dn_1(t)}{dt} = (p - d_1)n_1(t) + \alpha_{1R}n_{1W}(t), \quad (1)$$

$$\frac{dn_2(t)}{dt} = 2x_a d_1 n_1(t) - (d_2 + a_2)n_2(t) + \alpha_{2R}n_{2W}(t), \quad (2)$$

$$\frac{dn_3(t)}{dt} = d_2 n_2(t) - a_3 n_3(t) + \alpha_{3R}n_{3W}(t). \quad (3)$$

$$\frac{dn_4(t)}{dt} = x_b d_1 n_1(t) - a_4 n_4(t) + \alpha_{4R}n_{4W}(t). \quad (4)$$

$$\frac{dn_5(t)}{dt} = \alpha_{2M}n_{2W}(t) + \nu_2 n_{2H}(t) + \alpha_{3M}n_{3W}(t) + \nu_3 n_{3H}(t) - \nu_5 n_5(t), \quad (5)$$

$$\frac{dn_{jW}(t)}{dt} = -\alpha_j n_{jW}(t), \quad (6a)$$

$$\frac{dn_{jH}(t)}{dt} = -\nu_j n_{jH}(t), \quad (6b)$$

where $j = 1 - 4$, which means four neuronal cell populations in the model; d_1 and d_2 are rates of differentiation from NSC to NB and NB to ImN, respectively; a_2, a_3, a_4 are apoptosis rates of NB, ImN and GB, respectively; x_a, x_b are the fraction of NSC differentiating into NB and GB, respectively.

NSC proliferation p in Eq. (1) considers the feedback of radiation damage on proliferation, contributions of weakly and heavily damaged cells expressed by dimensionless multipliers Φ and Γ , respectively. NSC proliferation is manifested by $\Theta_{mg} \mu$, where μ describes the increase in newly born activated microglia relative to a nonirradiated condition and Θ_{mg} accounts for the contribution of this feedback on proliferation:

$$p = \frac{\Psi}{1 + \Theta_2(n_2 + \Phi n_{2W} + \Gamma n_{2H}) + \Theta_3(n_3 + \Phi n_{3W} + \Gamma n_{3H}) + \Theta_{mg}\mu}, \quad (7)$$

where Ψ is the maximum proliferation rate and multipliers Θ_2 and Θ_3 represent the dissimilar contribution of NB and ImN in the negative feedback on NSC proliferation.

Initial conditions for cell population after acute irradiation of dose D are given by [4]:

$$n_j(0) = N_j e^{-D/D_{0j}}, \quad n_{jW}(0) = \gamma_j N_j (1 - e^{-D/D_{0j}}), \quad n_{jH}(0) = (1 - \gamma_j) N_j (1 - e^{-D/D_{0j}}), \quad (8)$$

where γ_j is a fraction of weakly damaged cells, N_j are the cell counts without irradiation, and D_{0j} is a characteristic dose, when 37% of cells are undamaged.

Parameters for hippocampal neurogenesis of the mouse were taken from Cacao and Cucinotta [3, 4] and modified according to experimental data [7–9]. Particularly, we have used different from [4] dose-related parameters for 600 MeV/u ^{56}Fe ion beams: $D_{01} = 7.5\text{Gy}$, $D_{02} = 1.3\text{Gy}$, $D_{03} = 2\text{Gy}$.

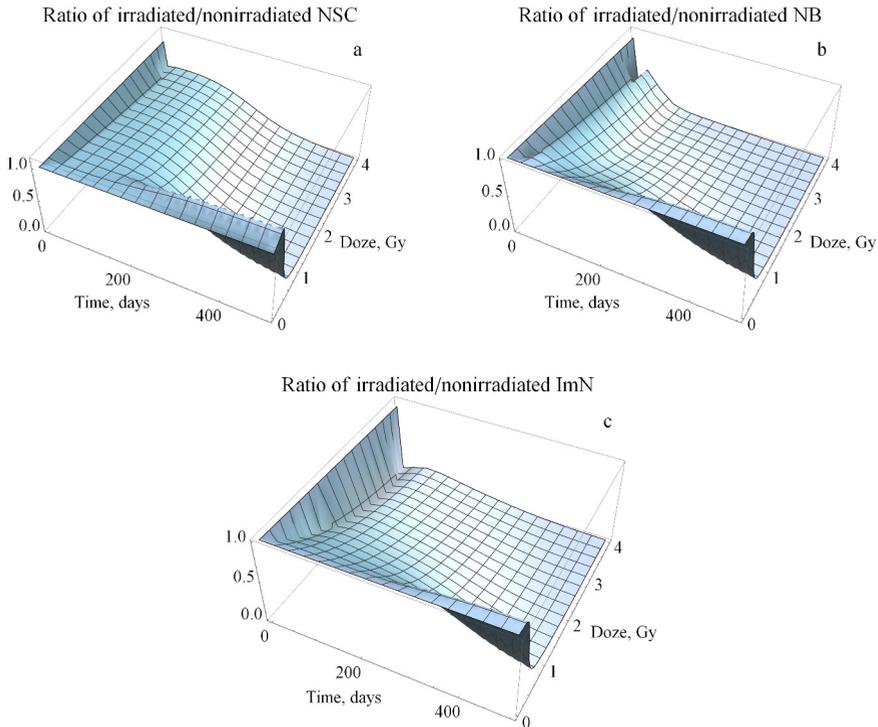


Figure 1. Modeling dynamics of hippocampal neurogenesis after acute exposure to different doses of 600 MeV/u iron ion radiation for neuronal cell populations: a) neural stem cells, b) neuroblasts, c) immature neurons

2.2 Hippocampal neural networks

The hippocampal neurons organized in various neural networks play an important role in learning, memory consolidation as well as in integration of the received information. Hippocampus consists of two main regions: dentate gyrus (DG) and cornu ammonis (CA3/CA1). The cells in different hippocampal regions compute information differently. DG has been implicated in pattern separation, CA3 in pattern completion and CA1 in novelty detection and mismatch of expectations.

In order to study the influence of neurogenesis on cognitive functions we have applied a modified version of hippocampal microcircuits model by Cutsuridis et al. [5]. The model uses biophysical representations of the major cell types including both the new-born and mature granule cells of DG, CA3 and CA1 pyramidal cells and six types of interneurons: basket cells, axo-axonic cells, bistratified cells, oriens lacunosum-moleculare cells, mossy cells and hilar perforant path associated cells. Inputs to the network have come from the entorhinal cortex (EC) and the medial septum (MS). The model simulates accurately the timing of firing different hippocampal cells with respect to the theta rhythm.

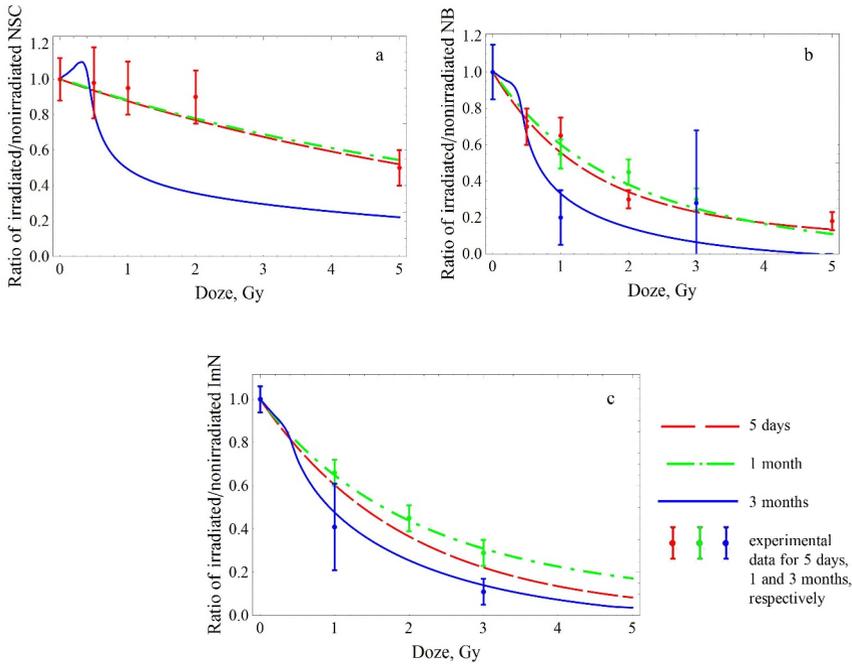


Figure 2. Dose-dependent response of hippocampal neurogenesis to acute exposure of iron radiation in comparison with experimental data [7–9] after 5 days, 1 and 3 month postirradiation: a) neural stem cells, b) neuroblasts, c) immature neurons

In the SGZ, newly born neurons migrate into the DG granule cell layer and mature, connecting it with the CA3 region of the hippocampus. The influence of immature granular cells (ImN) on network performance was implemented according to the model of posttraumatic DG activity [6]. It follows that the increase of the number of newborn granular neurons enhances network excitability, and, thus, newborn neuron loss following irradiation will likely suppress the network activity.

During the computation in the NEURON software toolkit we studied the patterns of voltage spikes produced by neural network. Theta modulated inputs at alternate phases and strengths to the network came from the EC and the MS. The retrieval of information have been observed when DG, CA3 and CA1 cells experience collective discharge at different phases of theta oscillations. The retrieval success was calculated according to the simulation procedure described in [5].

3 Results

Dynamics of hippocampal neurogenesis up to 500 days after acute exposure to 600 MeV/u ^{56}Fe ions in different doses is presented in Fig. 1. Severe radiation-induced cell loss occurs on the first few days of postirradiation followed by a recovery until 30-90 days of postirradiation, at which the point activated microglial cells modulate responses. Recovery to normal condition is more evident for NBs than ImNs, and the negative feedback regulation by the inflammatory response on proliferation begins to manifest at 30 days of postirradiation in NBs and at 60-90 days of postirradiation in ImNs. At 300 days of postirradiation, the population

dynamics has shown that the recovery of impaired neurogenesis can occur at $D < 0.4$ Gy of 600 MeV/u iron ion irradiation. Neuroblasts have been found to be more sensitive to radiation treatment than NSC and ImN, however, the radiation-induced loss of ImN is observed at higher doses.

The radiation-induced cell losses have been estimated at various postirradiation periods of time and doses. The dose-dependent response of hippocampal neurogenesis to acute exposure of iron at a specified postirradiation time, was compared to their respective experimental data. As follows from Fig. 2 the biophysical model agrees well with heavy-ion experiments.

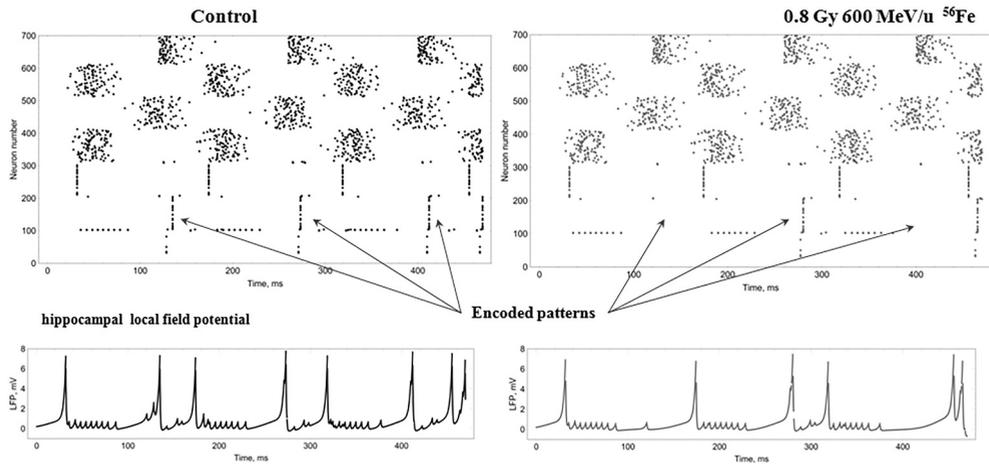


Figure 3. Neural network activity in normal conditions (left) and after 1 month of 0.8 Gy 600 MeV/u iron ion irradiation (right). Cue patterns modulating theta-rhythm (neurons numbers from 300 to 700) result in synchronized spiking activity of hippocampal neurons (0-300) on rastergramms. Voltage traces corresponding to the hippocampal local field potential are presented at the bottom of the picture. After irradiation two of three possible patterns in DG granule cells (neurons 0-100) and CA3 pyramidal cells (neurons 100-200) are lost

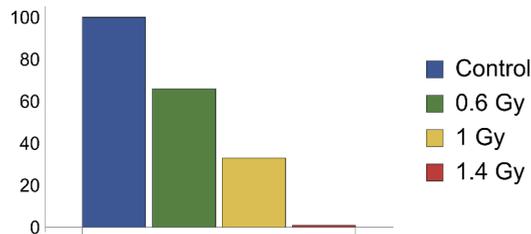


Figure 4. Percentage of the pattern retrieval success calculated from network activity after radiation-induced damage caused by 600 MeV/u iron ions with different doses

In this way, when neurogenesis is suppressed by the irradiation, the population of DG cells loss highly excitable immature neurons, and this path of information processing becomes partially disrupted. The results of neural network activity computation (Fig. 3) suggest that the success of information encoding and retrieval during at least three theta cycles becomes disrupted in DG and CA3 circuits. Dose dependences taken at 1 month after irradiation

tion (Fig. 4) clearly correlate with the previously shown pictures of neurogenesis simulation. Heavy ions such as 600 MeV/u iron ions will likely produce cognitive deficits at very low doses less than 1 Gy, which is in agreement with the known animal experiments [10–12].

4 Conclusion

Impairment of neurogenesis is known to be a critical factor in cognitive detriments and disease. The understanding the role of dose, radiation type and dose rate is extremely important for these investigation. However, to predict any radiation-induced deficits in CNS, the knowledge of biological pathways and their outputs need to be organized into a hierarchy of mathematical models. Using only two levels of hierarchy this work has shown that heavy ions may cause non-reversible suppression of neurogenesis. Models linking a specific cell loss and network structure suggest that radiation-induced suppression of neurogenesis worsens information processing in dentate gyrus neural networks perturbing the normal activity of hippocampus.

In summary, comprehensive modeling techniques now make it possible to interpret perturbations in the neuronal number and function at the network level, which can link selected biological effects to their impact on the network performance. Studies on how the accelerated charged particles affect the brain structures are very limited by the complexity of animal experiments on accelerator complexes, and therefore further development of the computer modeling methods becomes especially important.

Acknowledgements. The work was supported by Russian Foundation for Basic Research (grant No.17-29-01007).

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