დემიის პერიოდში სახელმწიფოთა საერთაშორისო თანამშრომლობის ჭრილში ადამიანის ზემოხსენებული უფლების უზრუნველსაყოფად, ასევე, სახელმწიფო მართვის ორგანოებისა და ადგილობრივი თვითმმართველობის ორგანოების ურთიერთქმედების პირობებში.

ჩატარებული კვლევის მეთოდოლოგიურ საფუძველს წარმოადგენდა სამეცნიერო შემეცნების ზოგადი და სპეციალური მეთოდები: ფორმალურ-ლოგიკური, შედარებით-სამართლებრივი, სტრუქტურულ-ლოგიკური.

დაზუსტდა სახელმწიფოთა საერთაშორისო თანამშრომლობის ცნება ადამიანის უფლებასთან მიმართებით - მიიღოს ხარისხიანი სამედიცინო დახმარება. დამტკიცებულია მისი მიზნის ევოლუცია ისეთი კატალიზატორის გავლენით, როგორიცაა Covid-19-ის პანდემია: ჯანდაცვის სფეროში ძირითად მონაწილეთა შორის ინტერესების ბალანსის მიღწევიდან მდგრადი განვითარების საერთო მიზნების მიღწევამდე.

პირველადაა გამოვლენილი სახელმწიფოთა საერთაშორისო თანამშრომლობის ნორმატიულ-სამართლებრივი მექანიზმის Covid-19-ის პანდემიის პერიოდში აღმოცენებული თავისებურებები ადამიანის უფლების უზრუნველყოფასთან დაკავშირებით მიიღოს ხარისხიანი სამედიცინო დახმარება. არგუმენტირებულია, რომ ასეთი თანამშრომლობის პარადიგმას უნდა წარმოადგენდეს სწორედ მდგრადი განვითარების პარადიგმა.

ხაზგასმულია, რომ გაერთიანებული ერების ორგანიზაციაში მიღებულია ახალი საერთაშორისო-სამართლებრივი მოთხოვნები ჯანდაცვის სისტემების მიმართ, რომელთაც არ შეუცვლიათ პარადიგმა იმის შესახებ,რომ ადამიანის უფლება - მიიღოს ხარისხიანი სამედიცინო დახმარება, წარმოადგენს სახელმწიფოს ძირითად მოვალეობას, თუმცა, საზღვარგარეთის ქვეყნებში შეიცვალა სახელმწიფო მართვის ორგანოებისა და ადგილობრივი თვითმმართველობის ორგანოების ურთიერთქმედების პარადიგმა Covid-19-ის პანდემიის პერიოდში. გამოვლენილია ასეთი ურთიერთქმედების ახლადჩამოყალიბებული მიდგომები.

FINE ARCHITECTURE OF THE HIPPOCAMPUS IN ADOLESCENT, ADULT AND AGED RATS. ELECTRON MICROSCOPIC STUDY

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Aging, the time-related decline of physiological functions, has its consequences on different levels and systems of the organism [1,2]. The brain is especially vulnerable to the aging process. Many neurological and neurodegenerative disorders, such as Parkinson disease, Alzheimer disease, diabetes, or cognitive and emotional disturbances often accompany aging [3,4]. Cognition is important for physical and cognitive well-being across the life span [5,6]. However, sometimes even normal aging, which is not accompanied with age-related pathological states, might be associated with the impairments in cognitive sphere and structural vulnerability of cognitive brain. [7,8]. Due to high significance of this issue, the relationships between aging and cognition is largely evaluated using various approaches. Numerous data, which were gained from task-related functional magnetic resonance imaging and behavioral studies, indicate to different levels of disorders in memory processes, processing speed, decision-making, attention, perception, etc. [9,10]. Morphological studies also indicate to structural modifications in cognitive regions (the decrease of synapse and spine densities, or the changes in grey matter volume) [11,12]. However, there are still many gaps regarding the consequences of aging on cognitive brain. Of special interest should be comparative study of the fine architecture of cognitive areas in experimental animals from different age groups.

Recently, using behavioral and electron-microscopic approaches for studying aged rats, we saw manifestation of anxiety-like behavior and associated alterations in the ultrastructure of the central amygdala, involved in such behavior [13]. In the present electron microscopic research, we are focused on the effects of aging on the ultrastructure of limbic hippocampus – critical area for many cognitive abilities. Specifically, in adult, adolescent and aged male Wistar rats, the ultrastructure of CA1 area, the number of presynaptic and postsynaptic mitochondria, and total number of synaptic vesicles in axo-dendritic synapses of this area were evaluated.

Material and methods. The study included adolescents (P30-36), adult (P125-130) and aged (P330-340) male Wistar rats – 4 animals in each age group. The rats were housed individually, in wire-top polypropylene cages (30-cm width x 30 cm length x 25 cm height) and maintained on a 12-h light/dark cycle. Standard food pellets and tap water were ad libitum. The animal maintenance and electron microscopic procedures were conducted in accordance with European Union Directive on the protection of animals used for scientific research. The Committee of Animal Care at I. Beritashvili Center of Experimental Biomedicine approved the protocols.

Conventional EM technique, described in our earlier studies was used [13,14,15,16]. Specifically, after pentobarbital injection (100 mg/kg), the animals underwent transcardiac perfusion with ice cold heparinized 0.9% NaCl, followed by 500 mL of 4% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, perfusion pressure - 120 mm Hg. The left hemisphere brain tissue blocks containing the CA1 area, were cut into 400 μm thick coronal slices and post-fixed in 1% osmium tetroxide. Then, the area was identified with an optical microscope Leica MM AF, cut out from the coronal slices, dehydrated

in ethanol and acetone and embedded in araldite. From araldite blocks, 70–75 nm thick sections were prepared with an ultramicrotome Leica EM UC7. The sections were placed on 200-mesh copper grids, double-stained with uranyl-acetate and lead-citrate, and examined with JEM 1400 (JEOL, Japan). From each rat, every seventh section – totally 10 sections were evaluated.

Quantitative EM analysis: On EM micrographs, the number and area of pre- and postsynaptic mitochondria, and total number of synaptic vesicles (SVs) were evaluated. The measurements were performed on 240 micrographs (600 dpi tiff files, scale bar – 500 nm): 80 micrographs per group, 20 micrographs from each animal. "Image J" software was used. The approach is described in our previous publications [16,18-20].

Statistical analysis of quantitative data was carried out in a blind manner. The data were processed by Website for Statistical Computation VassarStats (http://vassarstats.net). Two-way ANOVA followed by Tukey HSD test was used, where main effects of two factors "age" and "location" (pre vs post synaptic) and their interaction were analyzed. In the case of mitochondria, multiple comparisons were done to determine the differences in mitochondrial area and their quantity in the pre- and postsynaptic compartments of axo-dendritic hippocampal synapses in adolescent, adult and aged animals. The P-value less than 0.05 was considered as statistically significant. The data are presented as a mean ± standard error of the mean (SEM).

Results and discussion. The ultrastructure of CA1 area in adolescent and adult rats was almost the same: absolute majority of neurons, glial cells and synapses had normal organization, but in a few neurons of adult animals, small concentrations of different types of lipofuscin and lipid granules were observed. However, distinct ultrastructure was observed in about 15% of cells of senescent rats. Thus, the increased number of different types of lysosomes, granules of lipofuscin with vacuoles, and moderately swollen cisterns of Golgi complex and endoplasmic network were detected (Fig. 1A-C). Relatively rare, focal or mild chromatolysis, apoptotic neurons, or partial demyelinated axons were observed. Some astrocytes both proliferate and undergo apoptosis. In parallel, in a number of cells invaginations of the nuclear envelope, and concentrations of normal cellular organelles were seen.

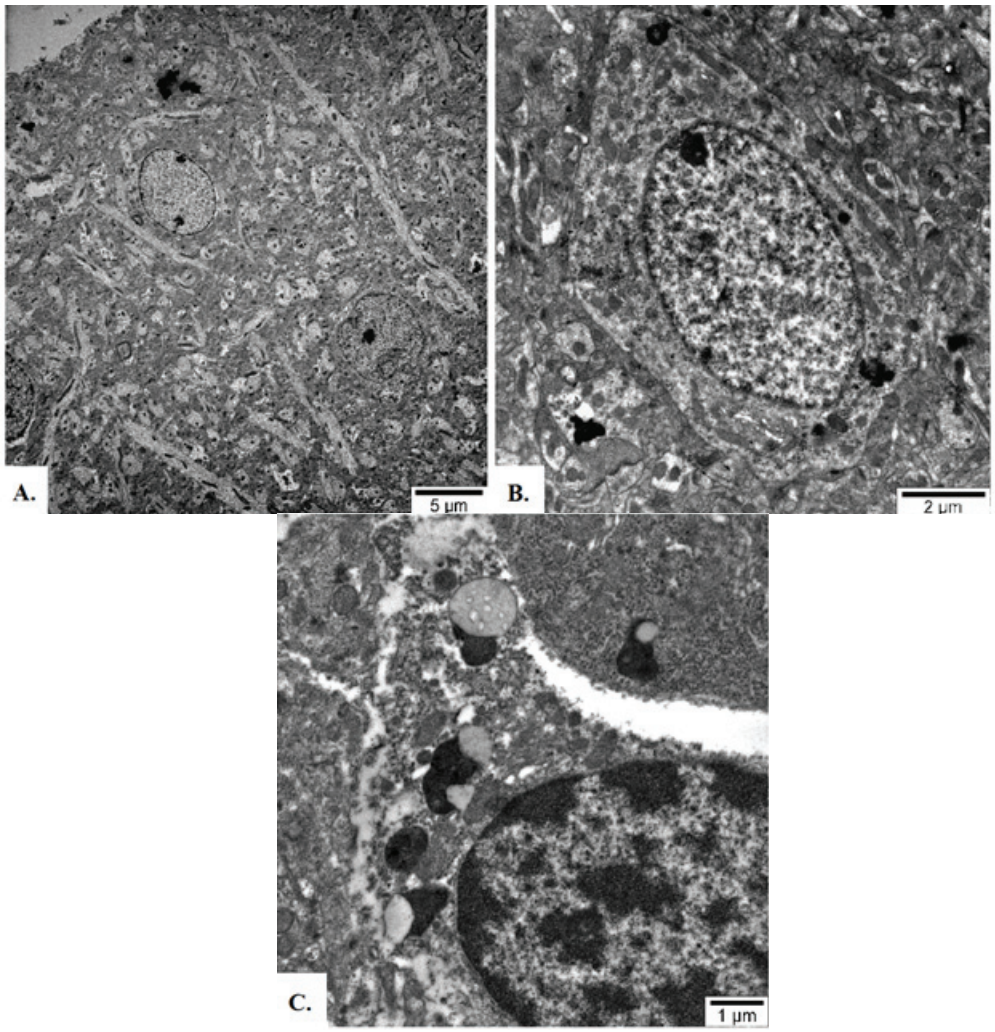

Fig. 1. A - The neuropil of the hippocampus of adolescent male rat. No ultrastructural alterations were observed. B - The neuropil of the hippocampus of adult male rat. Small concentrations of lysosomes were observed. C - The part of damaged cell in the hippocampus of adult male rat. Different types of lysosomes and moderately swelled cisterns of Golgi apparatus were observed

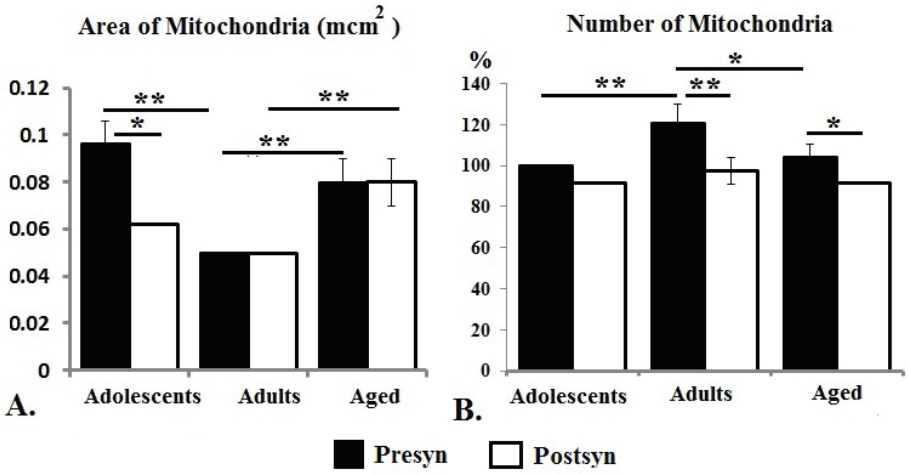

*Fig. 2. The data of EM morphometric analysis of the area of presynaptic and postsynaptic mitochondria in the hippocampus in adolescent, adult and aged animals. Vertical axis - the area in mcm², * - p<0.05, ** - p<0.01*

Quantitative EM analysis. Presynaptic and postsynaptic mitochondria. According to two-way ANOVA, the animal age ($F=3.29$, $p=0.043$) and location of mitochondria ($F=10.16$, $p=0.002$) affect number of mitochondria in pre- and postsynaptic terminals. Particularly, Tukey HSD test has shown that number of presynaptic mitochondria significantly increased in adults than in adolescent animals by 20.65% (1.09±0 vs. 1.32±0.1 $p<0.01$) and decreased in aged animals in comparison with adult animals by16.69% (1.32±0.1 vs. 1.14±0.07, $p<0.05$) (Fig. 2).

Difference in the number of presynaptic mitochondria between adolescent and aged animals is not statistically different (1.09±0 vs. 1.14±0.07, $p>0.05$). Number of postsynaptic mitochondria did not differ between different groups of animals: in adolescent animals - 1±0, adults – 1.07±0.07, aged - 1±0. Pairwise comparisons of the number of pre- and postsynaptic mitochondria in different groups of animals demonstrate significant decrease in the number of postsynaptic mitochondria in axo-dendritic synapses of adult (1.32±0.1 vs. 1.07±0.07, $p<0.01$) and aged animals (1.138±0.1 vs. 1.0±0, $p<0.05$). Difference by 8.6% is not significant in adolescent animals (1.09±0 vs. 1.0±0, $p>0.05$) (Fig.2B).

Total number of synaptic vesicles. One – way ANOVA revealed significant effect of age on the total number of SVs in presynaptic compartment [$F(2,157) = 10.6$, $p<0.0001$]. According to *Tukey HSD* test, a significant difference in total SV counts was observed between adolescent and aged animals (92.76±5.45 vs. 70.66±3.27, $p<0.01$), as well as adults and aged animals (101.87± 5.29 vs. 70.66±3.27, $p<0.01$).

Thus, according our data, the number of synaptic vesicles is significantly lower in aged rats in comparing with adolescent and adult animals. Such significance is more pronounced between aged and adult groups. No difference was detected between adolescent and adult rats (92.76±5.45 vs. 101.87± 5.29, $p>0.05$) (Fig. 3A).

Therefore, in the present experimental study we show that the process of aging affects the ultrastructure of hippocampal CA1, largely involved in different cognitive processes. Such effect is especially significant in aged animals, while adolescent and adult rats show only small dissimilarities. Moreover, the effect of aging is reflected not only on the fine structure of the region, but also on some morphometric parameters of axo-dendritic synapseas – mitochondria and number of synaptic vesicles.

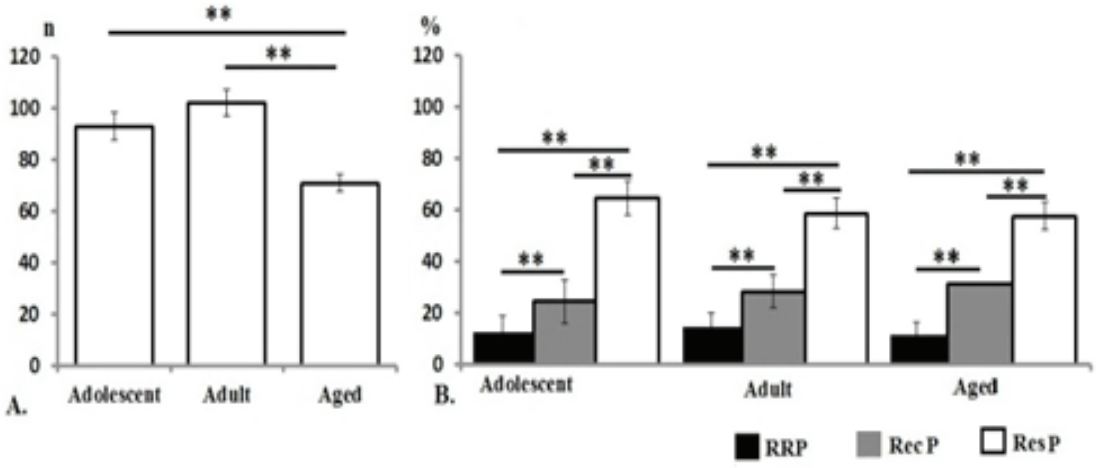

Fig. 3. Number of SVs in presynaptic domains of hippocampal axo-dendritic synapses in adolescent, adult and aged Wistar rats. A - Total number of SVs in presynaptic domains; B - Percentage of SV in different functional pools within different age groups of animals

As expected, the main ultrastructural features of aging rats were the appearance of apoptotic changes and the appearance in a number of hippocampal cells neurons and glial cell of moderate concentrations of lysosomes, granules of lipofuscin and other lipid-containing residues of lysosomal degradation. Such granules, which represent the products of the lipofuscin and lysosome genesis, are directly depending from mitochondrial involvement. With aging, the oxidation and mitochondrial DNA mutations initiate the damaged metabolism of mitochondria which in turn provokes further oxidative stress via oxidative phosphorylation [17,18]. Downregulation of mitochondrial proteases, responsible for the degradation of oxidized proteins, should compromise mitochondrial restoration system [19,20]. Cellular control mechanisms stimulate mitophagy, to remove damaged mitochondria via lysosomes, resulting to the increased number of lysosomes and lysosomal accumulation of mitochondrial hydrophobic ATP-synthases. This additionally provokes increased generation of reactive oxidative species, increased lipofuscinogenesis, lower energy production, and catabolic dysfunction [20-22]. Additionally, because pro-apoptotic proteins do not degrade effectively, the increased concentrations of lipofuscin are often associated with apoptosis [23,24]. Our quantitative data also indicate to significant decrease of the number of mitochondria, the presence of apoptotic cells and increased concentrations of lipofuscin that is reminiscent with this view. It is notable that some of such alterations, in parallel with pathological aggregations of specific proteins, are often observed in such age-related neurological states, as Parkinson's Disease, *Alzheimer's Disease* or Huntington Disease [25]. However, in these cases, such pathologies are numerous and invade large territories of cells. In opposite to it, we observed such alterations only in a few number of cells of aged brain and no abnormal concentrations of age-associated proteins. Therefore, cognitive region of aged animals used in our study is much more saved as cognitive region of individuals with abovementioned age-related diseases. Moreover, we do not exclude at least partial restoration of hippocampal function, as in the number of altered neurons, the ultrastructural peculiarities, such as the invaginations of nuclear membrane, or high concentrations of normal organelles, indicating to high functioning oh these cells were detected. In addition to abovementioned changes, morphometric analysis revealed the decrease of total number of SVs in aged brain. Such changes may indicate to the decrease in neurotransmission or neurotransmitter synthesis.

Earlier, evaluating the ultrastructure of amygdala in Wistar rats of same age groups, we detected more substantial structural pathologies then in present study [16]. Therefore, in our study, in aged Wistar rats cognitive and emotional areas reveal different degree of changes: in comparing with emotional brain. cognitive region remains relatively stable. Such results are in opposite with common misconception, according which aging provokes almost unpreventable loss of all cognitive capabilities [26]. On the contrary, the data support modern view, according which in the case of healthy aging some intervention may slow the changes in learning and probably in emotions that may occur in later stages of life [27].

Conclusion. The results of behavioral study show age-related changes in the process of learning. Such changes are reflected on ultrastructural level of the hippocampus, the part of cognitive brain. The majority of alterations are mild or moderate. Such data, as well as the results of quantitative analysis of different parameters of synapses, give the possibility to suggest that healthy aging does not provoke sustained and progressive loss of cognition: the modifications which develop on aged brain may be stopped or prevented.

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SUMMARY

FINE ARCHITECTURE OF THE HIPPOCAMPUS IN ADOLESCENT, ADULT AND AGED RATS. ELECTRON MICROSCOPIC STUDY

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The study included adolescents (P30-36), adult (P125-130) and aged (P330-340) male Wistar rats – 4 animals in each age group. The rats were housed individually, in wire-top polypropylene cages (30-cm width x 30 cm length x 25 cm height) and maintained on a 12-h light/dark cycle. Standard food pellets and tap water were ad libitum. The animal maintenance and electron microscopic procedures were conducted in accordance with European Union Directive on the protection of animals used for scientific research.

The Ultrastructure of adult and adolescent rats are almost same. However, remarkable changes are expressed between adult and senescent rats. Precisely, in the last one there are following ultrastructural modifications – lipofuscin concentrations, small destructive cytoplasmic organelles, changes in presynaptic vesicular and mitochondrial quantity. Rare apoptotic signs in neurons.

Analysis of all this means that aging in rat’s hippocampus causes selective changes, also it underlines changes in neurotransmission and neuronal developmental pathways.

Keywords: aging, hippocampal C1 field, ultrastructure, rats.

РЕЗЮМЕ

ТОНКОЕ СТРОЕНИЕ ГИППОКАМПА МОЛОДЫХ, ВЗРОСЛЫХ И ПОЖИЛЫХ КРЫС. ЭЛЕКТРОННО-МИКРОСКОПИЧЕСКОЕ ИССЛЕДОВАНИЕ

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Исследование проведено на подростковых (P30-36), взрослых (P125-130) и пожилых (P330-340) крысах-самцах линии Wistar - по 4 животных в каждой возрастной группе. Крыс содержали отдельно, в полипропиленовых клетках с проволочной крышкой 30x30x15 см. В комнатах, где находились клетки, поддерживался 12-часовой световой цикл. Животные имели свободный доступ к стандартным пищевым гранулам и водопроводной воде. Уход за животными и электронно-микроскопические процедуры проводились в соответствии с Директивой Европейского Союза о защите животных, используемых для научных исследований.

Ультраструктура молодых и взрослых крыс была почти одинакова. Заметное отличие выявлено между взрослыми и пожилыми крысами, в частности у последних наблюдались следующие ультраструктурные модификации – концентрации липофусицна, небольшие деструктированные органеллы, количественные изменения пресинаптических везикул и митохондрий. В редких нейронах отмечались признаки апоптоза. Анализ данных указывает, что в гиппокампе крысы возраст вызывает селективные сдвиги, предполагающие изменения в нейротрансмиссии и соответсвующих нейронных сетях.

რეზიუმე

ჰიპოკამპის ნატიფი ულტრასტრუქტურა პატარა, ზრდასრულ და ასაკოვან ვირთაგვებში. ელექტრონულ-მიკროსკოპული კვლევა

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წარმოდგენილ ნაშრომში ტრანსმისიული ელექტრონული მიკროსკოპის გამოყენებით ახალგაზრდა, ზრდასრულ და ასაკოვან მამრ ვირთაგვებში (n=12)

აღწერილია ჰიპოკამპის CA1 ველის ნატიფი აღნაგობა. ახალგაზრდა და ზრდასრული ცხოველების ულტრასტრუქტურა თითქმის მსგავსი იყო. გამოხატული განსხვავება გამოვლინდა ზრდასრულ და ასაკოვან ვირთაგვებს შორის.

ასაკოვანი ვირთაგვების რიგ ნეირონებში აღინიშნა მეტწილად ზომიერი ულტრასტრუქტურული მოდიფიკაციები - ლიპოფუსცინის კონცენტრაციები, ზომიერად დესტრუქტირებული ციტოპლაზმური ორგანელები, ასევე პრესინაფსური მიტოქონდრიების და სინაფსური ვეზიკულების რაოდენობრივი ცვლილებები. იშვიათ ნეირონებში ვლინდებოდა აპოპტოზის ნიშნები. მიღებული მონაცემები მიუთითებს, რომ ასაკი იწვევს სელექციურ ულტრასტრუქტურულ მოდიფიკაციებს CA1 ჰიპოკამპის ველში. სავარაუდოა, რომ დაბერების პერიოდში ეს მოდიფიკაციები მიუთითებენ ნეიროტრანსმისიასა და ჰიპოკამპის რიგ ნეირონულ ქსელებში განვითარებულ ცვლილებებზე.

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