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ВЛИЯНИЕ ЭСТРОГЕНОВ НА ФУНКЦИИ ГОЛОВНОГО МОЗГА ЖЕНЩИН

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INFLUENCE OF ESTROGEN ON THE FEMALE BRAIN

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Резюме. Эстроген играет важную роль в модуляции функций мозга, влияя на когнитивные способности, нейропластичность и эмоциональную регуляцию, что имеет значение для развития нейродегенеративных заболеваний.

Ключевые слова: эстроген, нейропластичность, когнитивные способности.

Resume. Estrogen plays a critcial role in modulating brain function, influencing cognition, neuroplasticity, and emotional regulation, with implications for neurodegenerative diseases.

Keywords: estrogen, neuroplasticity, cognition.

Relevance. Estrogen significantly influences brain function, impacting cognition, mood, and neuroprotection, making its study crucial for understanding neurodegenerative diseases, mental health disorders, and sex differences in brain aging.

Aim: to investigate the influence of estrogen on the brain and the potential applications of hormone therapy (HT) to counteract neurodegenerative effects.

Objectives:

1. To study the physiological mechanisms by which estrogen regulates brain circuits.
2. To investigate the role of estrogen on cognitive functions.
3. To assess how estrogen fluctuations affect neurological disorder suscepitibility.

Estrogen is a hormone that is not only central to reproduction but is also linked to neural circuits, and therefore linked to neurodegenerative disorders.

Estrogen receptors are found throughout the brain. Estrogen β receptors predominate in the hippocampus, thalamus, cerebral cortex, and claustrum. Estrogen α receptors are more prevalent in areas like the amygdala and hypothalamus. Estrogen receptors are also present in the cerebellum, ventral tegmental area, raphe nuclei of the midbrain, neuronal cells, astrocytes, and oligodendrocytes [2]. Through these receptors, estrogen is able to influence the modulation of brain circuits involved in motivation, emotions, memory, attention, and executive function. Therefore, fluctuating estrogen levels result in memory lapses and brain fog during perimenopause and menopause, which are linked with Alzheimer's disease (AD), dementia, depression, anxiety, and schizophrenia.

Estrogen receptors α and β modulate slow, long-term genomic effects. G protein-coupled estrogen receptor 1 (GPER1/GPR30) can mediate fast non-genomic effects, modulating synaptic plasticity, spine density, and neuroprotection [2,5,6]. Further, the brain synthesizes neuron derived estradiol (NDE2) locally and regulates synaptic plasticity, cognition, and neuroprotection independently of peripheral estrogen levels [4].

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In a study done in 2020, whole-brain 3D maps showed areas where higher regional brain volume in the frontal, temporal, parietal and occipital regions were significantly associated with estrogen usage[2,4].

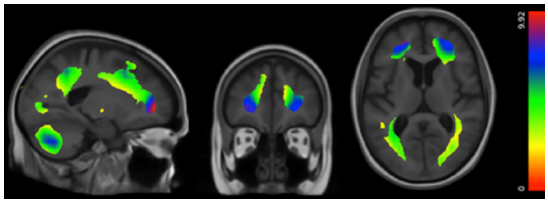

Fig. 1 – 3D brain maps (voxelwise regression) showing brain volume with estrogen use

Upon MRI it was detected that in females there was a significant increase in the volume of grey matter at the time of ovulation, in a study done in 2011. However, no significant changes in male brains were reported[1].

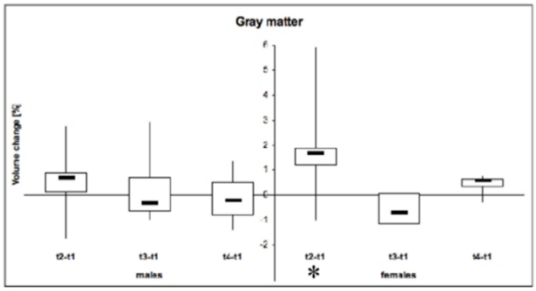

Fig. 2 – Changes in gray matter of the brain during the menstrual cycle

Estrogen increases spine density in the hippocampus, prefrontal cortex, and amygdala. In ovariectomized (OVX) rats, estradiol treatment increased dendritic spine density as well as axospinous synapse density in the hippocampus, as estrogen rapidly modifies the actin cytoskeleton to promote spine formation and maturation[6].

Estrogen also stimulates hippocampal neurogenesis through BDNF and IGF-1 signaling. Further, estrogen modulates long-term potentiation (LTP) via NMDA/AMPA receptor regulation, strengthening synapses, which are sites of excitatory neurotransmission important for learning and memory [6]. Natural menopause is associated with a selective loss of such complex and strong synaptic connections in the hippocampus. According to an experiment done in 2020, administering letrozole which is an aromatase inhibitor, produced dose-dependent cognitive alterations due to a reduction in hippocampal E2 and a decrease in the firing rate of pyramidal neurons. Aromatase inhibition decreases the expression of GPER in the hippocampus, hampering memory formation[7].

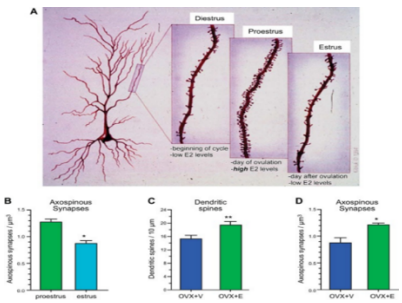

Fig. 3 – Estrogen's influence on modulating hippocampal spine density

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Estrogen influences the mitochondria. In addition to increasing mitochondrial biogenesis and increasing ATP production[5], estradiol increases the expression of the antiapoptotic protein Bcl-2 in mitochondria. Bcl-2 enhances the capacity for mitochondria to sequester cytosolic calcium, providing neurons more resistance from the harmful effects of glutamate-induced excitotoxicity. Further, cyclic estradiol treatment in aged ovariectomized monkeys decreased the incidence of presynaptic donut-shaped mitochondria which is a form that is associated with oxidative stress. Presynaptic boutons with donut-shaped mitochondria affected working memory performance in monkeys and formed abnormally small synaptic contacts[6].

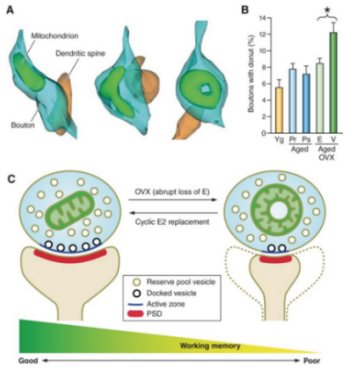

Fig. 4 – Estrogen's role in decreasing the incidence of donut shaped mitochondria

Estrogen influences cerebral blood flow as it is linked to increased nitric oxide production, decreased vascular resistance, and increased angiogenesis. A study was conducted in 2021 with 14 participants, where they were assigned an MRI on two session dates, one in the follicular phase and one in the luteal phase of the menstrual cycle. Afterwards, the immediate and delayed recall of the participants were measured on logical memory tests and resting cerebral blood flow (rCBF) was calculated for four frontal, four temporal, and four limbic regions of interest. There was an increase in rCBF with increasing estrogen levels, and women had better immediate and delayed recall. Greater relative CBF in the left temporal pole was associated with better immediate and delayed recall in women only, suggesting that there are sex differences in verbal episodic memory[8].

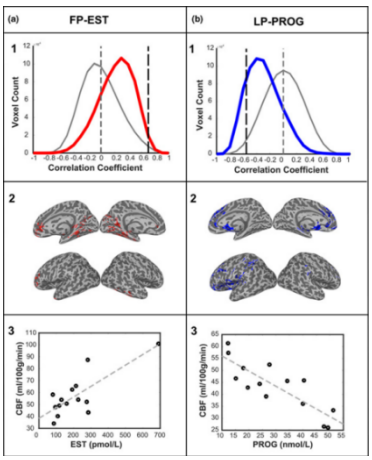

Fig. 5 – Estrogen's influence on cerebral blood flow

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Estradiol treatment after ovariectomy in animals has been shown to decrease choline uptake, choline acetyltransferase (ChAT) activity, and ChAT mRNA levels, thus proving estrogen's influence on the cholingeric system. Estrogen's effect on the cholinergic system was demonstrated by a study which included normal postmenopausal women who received either oral 17β-estradiol or placebo for 3 months. Subjects then took part in five challenge sessions including the cholinergic antagonists scopolamine and mecamylamine or placebo. Results showed that estradiol treatment decreased the effect of cholinergic antagonists and this was reflected in the choice reaction task, which was a measure of attention and psychomotor speed. Estradiol decreased the motor reaction time compared to the placebo[3].

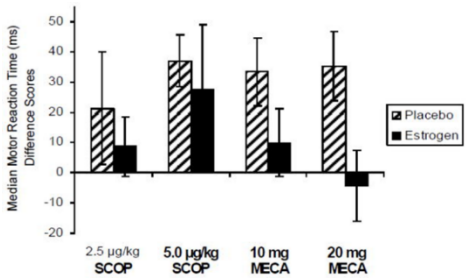

Fig. 6 – Comparison of the effect of placebo and estrogen on median motor reaction time

The dopaminergic system enhances reward, motivation, cognition and may protect against Parkinson's disease. In ovariectomised rats, E2 treatment was implicated in increasing dopamine uptake into dopamine neurons and in preserving nigrostriatal dopaminergic tyrosine hydroxylase positive neurons. Therefore estrogen plays a role in central dopamine function too. Parkinson's symptoms and schizophrenia symptoms in females increase following menopause when endogenous estrogen production decreases. Lastly, addiction is also related to dysfunctional dopamine transmission, and women escalate use of drugs, including psychostimulants, and nicotine more rapidly than men[5].

The onset of depression in women is more common than men, and is a characteristic of times when estrogen levels are relatively low like in early pregnancy, postpartum, and around and following menopause. In women with depression around or following menopause, the effectiveness of treatment with selective serotonin reuptake inhibitors (SSRIs) is enhanced by simultaneous administration of estrogen, and doses of estrogen alone are effective at treating premenstrual, postpartum, and perimenopausal depression. Thus, estrogen influences the serotonergic system too[5].

Abnormal activation and deactivation of the default mode network (DMN) is related to conditions like anxiety, major depressive disorder, schizophrenia, and Alzheimer's disease. Estrogen plays a role in modulating the DMN[4].

Tbl. 1. The role of estrogen in modulating the DMN

Effect	Mechanism	Outcome
Increases DMN coherence and functional connectivity	Estrogen enhances synaptic plasticity (via BDNF, NMDA/AMPA receptors) and cerebral blood flow.	Improved memory integration and self-referential processing.

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Continuation of table 1

Decreases DMN hyperconnectivity (linked to depression & ADHD)	Modulates serotonin (5-HT) and dopamine (DA) signaling in prefrontal cortex (PFC).	Reduces rumination and improves attentional control.
Protection against DMN disruption in Alzheimer's disease	Reduces amyloid-β (Aβ) deposition in DMN hubs (posterior cingulate cortex, medial PFC)	Preserves episodic memory & cognitive reserve.

Conclusions:

1. Estrogen has pleiotropic effects and modulates neurotransmitter systems thus promoting neuroprotection, neuroplasticity and the dynamic reorganization of brain circuits in females.

2. Cyclic and stage dependent variations in estrogen levels are correlated with alterations in memory, cognition and risk of neurodegenerative diseases in females.

3. Utilization of estrogen in hormone therapy, especially administered during the critical window serves as a prophylactic measure and is evidenced by a reduction in symptoms associated with neurodegenerative diseases.

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