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Sex differences in neuroplasticity and functional recovery after neurosurgical interventions

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ABSTRACT

Objective. To analyze modern data on the influence of biological sex and gender factors on mechanisms of neuroplasticity and functional recovery after neurosurgical interventions.

Material and methods. We reviewed the databases (PubMed, Scopus, Russian Science Citation Index (RSCI) and Google Scholar) over the past 10 years. The review covers clinical trials, prospective and retrospective cohort studies and animal models of traumatic brain injury, surgery for brain cancer, vascular accidents and spinal cord injury. The main parameters were diffusion tensor imaging data, functional MRI, hormonal profile and standardized clinical scales including the modified Rankin scale, Barthel index, ASIA and FIM scales.

Results. Female brain has better interhemispheric connectivity that provides adaptive advantage in focal lesions of dominant hemisphere. Male brain is optimized for intrahemispheric signaling promoting faster motor coordination. Estrogens and progesterone have neuroprotective effect through modulation of inflammatory response and support of myelination, but this effect depends on age and phase of reproductive cycle. In clinical practice, women often demonstrate lower rates of functional independence at discharge after stroke due to comorbidity and social factors, despite equal or superior potential for neurological recovery compared to men.

Conclusion. Biological sex is a critical determinant of neurosurgical outcomes. Discrepancy between biological recovery potential (higher in women) and actual functional outcomes (often better in men) highlights the need to develop personalized, gender-specific rehabilitation protocols taking into account specifics of connectome and hormonal backgrounds.

Keywords: *neuroplasticity, neurosurgery, gender differences, sexual dimorphism, functional recovery, estrogens, neuroimaging, connectome, rehabilitation, neuroprotection.*

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Introduction

Neuroplasticity is a fundamental property of nervous system defined as capacity for structural and functional reorganization in response to injury or external environmental changes [1]. In modern neurosurgery with preferable QoL preservation in addition to correct technical procedure per se, understanding individual mechanisms of plasticity is essential. In recent years, various researchers considered biological sex as a key variable [2, 3] determining cerebral response to surgical trauma and subsequent recovery [4].

Historically, neuroscience and neurosurgery evolved with bias towards research of male models. This led to underestimation of women's specific needs and insufficient data on sexually dimorphic pathophysiological mechanisms [4, 5]. However, data accumulated over the past decade indicate that biological differences between men and women (from gene expression and serum hormones to neural network architecture) result in unique recovery trajectories following central nervous system (CNS) injury [4—7].

In this review, the concept of "sex" encompasses biological attributes such as chromosomes, hormonal profile and anatomical features. "Gender" implies a set of socially constructed roles and behavioral patterns that also influence access to medical care and efficacy of rehabilitation [8, 9]. Interaction of these factors determines how a patient's brain compensates for functional deficits after tumor resection, vascular event or trauma.

Modern neuroimaging techniques, such as resting-state functional MRI and DTI tractography, enable visualization of these differences in real time. According to connectome studies, male and female brains employ different strategies for the same objectives. This has direct impli-

cations for planning neurosurgical approaches and predicting postoperative outcomes [10]. This report presents a comprehensive synthesis of data on how sexual dimorphism modulates neuroplasticity and functional recovery across various clinical scenarios.

Sex hormones (estrogens, progesterone and testosterone) are potent modulators of neuroplasticity with effects on genomic and non-genomic levels. Estrogens, particularly 17β-estradiol, are recognized as critical factors for neuronal survival. Their antioxidant effect is realized through neutralization of free radicals. Moreover, estrogens modulate apoptotic pathways preventing perifocal cell death [11].

Experimental models of traumatic brain injury demonstrate that estrogens reduce neuroinflammation by suppressing microglial activation and release of pro-inflammatory cytokines [12]. Furthermore, estrogens stimulate synthesis of brain-derived neurotrophic factor (BDNF) promoting axonal growth and formation of new synapses [13]. Notably, decline in serum estrogens following menopause or surgical oophorectomy is associated with accelerated neurodegeneration and reduced cognitive reserve. This underscores the role of hormonal status in neurosurgical practice.

Progesterone and its metabolites are also important for recovery, particularly in processes of myelination. They stimulate oligodendrocyte proliferation and myelin protein synthesis. This is critical for restoring nerve impulse conduction after traumatic or surgical injury of white matter [12, 13]. In clinical studies of TBI, women often demonstrate better survival rates in acute phase. This phenomenon is associated with endogenous neuroprotective environment [14].

Testosterone also contributes to plasticity in men, though its role is more complex. On one hand, testosterone can undergo aromatization into estrogens in cerebral structures providing local protection [15]. On the other hand, high testosterone can exacerbate oxidative stress-related damage under certain conditions. This factor sometimes correlates with more severe cerebral edema in men in acute phase of injury [15].

Molecular-genetic factors

In addition to hormonal influences, genetic variation is important for plasticity. The 5-HTTLPR polymorphism in serotonin transporter gene (SLC6A4) affects stress vulnerability and incidence of postoperative depression (strong negative predictor of functional recovery) [16]. Researches indicate that carriers of "short" allele have less effective serotonergic transmission. This is more common in women and may explain their susceptibility to emotional disturbances after neurosurgical interventions [16].

The Val66Met polymorphism in the BDNF gene is another important genetic factor. The Met allele is associated with reduced BDNF secretion leading to smaller hippocampal volumes and slower recovery of motor and cognitive functions [16]. This effect may be different in men and women interacting with menstrual cycle phases or hormonal therapy.

Connectome characteristics

One of the most significant neuroimaging breakthroughs in recent years is characterization of fundamental differences in brain "wiring". Analysis of large cohorts (> 900 individuals) using diffusion MRI revealed predominant intra-hemispheric connections in males and higher inter-hemispheric connectivity in women [17].

These differences hold clear evolutionary and functional significance. Male architecture is optimized for association between perception and coordinated action (front-to-back connectivity within a single hemisphere), whereas female architecture facilitates integration of analytical and intuitive information processing modes (interhemispheric connectivity) [17].

In neurosurgical context, this implies that women possess a more substantial structural substrate for recruiting homologous regions in contralateral hemisphere to aid compensation after damage to one hemisphere (tumor resection or stroke). Men can more effectively recover function if intact areas remain within the same hemisphere.

Rehabilitation process is essentially a form of motor learning. Researches of microstructural white matter changes during intensive training revealed sex-specific trajectories [18]. In a study where participants learned a complex visuomotor objective, women demonstrate significantly higher fractional anisotropy within the middle part of the corticospinal tract (nodes 38—51). This is interpreted as enhanced fiber organization or myelination [18]. There were no such changes in men despite similar behavioral outcomes.

These findings suggest that men and women achieve comparable functional results through distinct neuroplastic mechanisms. Women may rely on more focal and intense structural changes within primary motor pathways. Men may use broader recruitment of cortical resources or alternative patterns of reorganization [19]. Consequently, pooling data from both sexes in rehabilitation studies may "dilute" statistical significance of results and mask specific recovery mechanisms [18, 19].

Sex differences in neuro-oncology

Sex significantly influences epidemiological profile and biological behavior of brain tumors. Malignant gliomas, including glioblastomas, are more common in men, while meningiomas and neuromas are predominantly "female" tumors [20].

Analysis of patients after resection of intracranial neoplasms revealed interesting perioperative differences [20]:

1) men have a higher rate of redo surgeries (5.8% vs. 3.0%) and higher overall complication rate, although these

differences do not always reach statistical significance after adjustment for age [20];
2) women more frequently require admission to intensive care units (22.1% vs. 17.4%); this may be attributed to clinical characteristics and more cautious management of female patients in certain clinics [20].

Preoperative planning for tumors near functionally significant areas requires a comprehensive mapping. Functional MRI revealed that men and women employ different neural strategies to perform speech tasks [21].

Women demonstrate higher reliance on specialized linguistic areas, such as the left inferior frontal gyrus. Men demonstrate broader activation extending beyond the classic speech network to include supplementary motor area and precentral gyrus [21].

Interestingly, functional connectivity of these areas also differs. In women, supplementary motor area is more strongly connected to temporal regions responsible for semantic processing. In men, supplementary motor area is linked to cognitive control areas within midline brain structures [21]. Thus, neurosurgeons should consider the patient's sex when assessing risks. Indeed, damage to "non-classic" areas in men may result in more severe speech deficits than would be predicted by traditional localization models.

In low-grade gliomas, slow growth of tumor allows the brain to undergo extensive functional reorganization. There are 2 patterns of longitudinal speech reorganization [22]:

1. Type 1: a shift from left-hemisphere dominance to co-dominance after surgery through activation of homologous areas in the right hemisphere.
2. Type 2: atypical (right-hemisphere or mixed) speech representation established prior to surgery under the influence of tumor.

In both instances, the brain's default mode network has a pivotal role. Increased intra-network functional connectivity after glioma resection correlates with better cognitive performance. These processes are more pronounced in patients with tumors in the right hemisphere [23].

Despite importance of this area, the impact of neurosurgery on sexual health has long been overlooked. Analysis of patients with diffuse low-grade gliomas revealed that 53% experience postoperative sexual changes [24].

Women are more likely to suffer from objective sexual dysfunction (60% vs. 29% in men). However, men usually report lower sexual desire and arousal, particularly after temporal lobe resections [24]. This underscores the need to incorporate sexual health assessments into standard rehabilitation protocols for both sexes.

Neuroplasticity in TBI

There is a so-called "gender paradox" in research of TBI. Experimental data consistently indicate a female advantage regarding survival and recovery, attributed to neuroprotective effects of progesterone and estrogens. However, clinical data in human populations often show the opposite: women report more severe and prolonged symptoms after mild TBI compared to men [25].

Women more frequently complain of headaches, dizziness and loss of confidence. Men more often report difficulties in setting realistic goals and experience anxiety [26]. Neuroimaging data confirm biological basis for these differences. After acute mild TBI, men demonstrate higher intrinsic functional connectivity within motor networks, executive function networks and cerebellum. This phenomenon may be a mechanism for rapid compensation [27]. In women, these changes take a different form and often affect connections between limbic system and visual areas. This correlates with more pronounced emotional symptoms [28].

Despite neuroprotective potential demonstrated in experimental studies, large-scale clinical trials (ProTECT III and SYNAPSE) found no significant benefits of administering progesterone or estrogens in acute phase of severe TBI compared to placebo [29, 30].

Spinal cord recovery after injury also demonstrates sexually dimorphic patterns. Interestingly, women with complete and incomplete spinal cord injuries show significantly greater improvement in motor scores (ASIA scale) one year after injury compared to men [29]. This "natural" advantage in neurological recovery is attributed to protective effect of estrogens on spinal cord neurons [29].

However, this picture changes when analyzing functional independence (FIM). Despite better muscle strength, women often have lower FIM scores at discharge, particularly in domains such as bladder management and transfers [29]. This points to a complex relationship between biological recovery (neuroplasticity) and actual functional outcomes. In women, these outcomes may be constrained by physiological factors (lower muscle mass) or social expectations during rehabilitation [30].

Specifics of neuroplasticity and rehabilitation in stroke

Stroke is still a leading cause of disability, and gender differences are particularly pronounced in this area. Women have poorer functional outcomes (mRS score >2) after 3 months and 1 year [31]. According to recent studies, this disparity persists even after adjusting for age and severity of baseline stroke [31].

One of the causes of poorer recovery in women is higher incidence of pre-stroke depression and dementia, as well as more severe oxidative stress and nutritional deficiencies in acute phase [32]. Malnutrition affects 52% of women and 33% of men after stroke reducing resources available for cerebral plastic reorganization [33].

After aneurysmal subarachnoid hemorrhage, women also demonstrate poorer prognosis (mRS score ⩾2 at discharge). This is attributed to higher susceptibility to delayed cerebral ischemia and vasospasm [34, 35].

Neurorehabilitation technologies (virtual reality, robotics and brain-computer interfaces) offer new tools for stimulating plasticity. To date, most studies found no need for radically different technological approaches for men and women regarding recovery of upper limb motor functions.

Nevertheless, gender-related factors may be critical in other functional domains, such as cognitive recovery and psychological well-being. For instance, telerehabilitation platforms (such as the Guttmann Neuro Personal Trainer—GNPT) enables creation of personalized cognitive profiles incorporating the patient's sociodemographic data [36, 37]. This is crucial, as efficacy of cognitive training depends on baseline education and specific characteristics of affected neural networks. As previously noted, these networks demonstrate sexual dimorphism.

Conclusion

Analysis of literature data provides a comprehensive picture of how biological sex influences success of neurosurgical interventions and subsequent rehabilitation. Neuroplasticity is not a uniform process. It is profoundly determined by sexual dimorphism in brain at all levels (from molecular to systemic one).

Female brain possesses a unique "neuroprotective reserve" driven by hormonal profiles and high interhemispheric connectivity. This creates potential for more effective neurological recovery. This phenomenon particularly evident in spinal cord injury and focal cortical lesions. However, this potential is often not fully realized in actual clinical practice. Social factors, delayed manifestation of cardiovascular diseases and CNS tumors in women, as well as high incidence of psycho-emotional complications often result in poorer functional outcomes.

Men, conversely, demonstrate greater vulnerability in acute phase (more frequent complications and redo interventions), but they utilize rehabilitation resources more effectively to achieve functional independence. This may be attributed to optimization of their connectome for highly specialized motor tasks and lesser impact of depressive states on motivation for recovery.

For modern neurosurgery, this implies a shift towards "gender-sensitive medicine" model:

1. At the stage of diagnosis and planning, it is necessary to account for differences in functional representation (particularly speech) to minimize iatrogenic damage ("atypical" zones for men and areas of high interhemispheric integration for women).
2. In early postoperative period, a differentiated approach to monitoring of complications and nutritional support is required (with particular attention to the risk of ischemia in women and surgical complications in men).
3. Regarding rehabilitation, there is a need for protocols converting neurological recovery into functional autonomy for women (intensive physical therapy) and cognitive training for men taking into account their intrahemispheric compensation strategies.

Future researches should focus on longitudinal studies of connectome with mandatory sex-disaggregated data analysis to identify subtle markers of successful plasticity. Only by moving away from "unisex" models in neuroscience, we can ensure maximum efficacy in neurosurgical treatment for every patient regardless of biological sex.

Author contribution:
Concept and design of the study — Yusupov F.A., Abdykadyrov M.Sh.
Collection and analysis of data — Abdykadyrov M.Sh.
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