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Post-Stroke Rehabilitation: Importance of Neuroplasticity and Sensorimotor Integration Processes

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Questions of the neurorehabilitation of strokes patients are addressed. The importance of the phenomenon of neuroplasticity, which underlies recovery processes after brain lesions, is emphasized. Particular attention is paid to the question of sensorimotor integration in health and CNS pathology, as well as to the role of afferentation in the processes underlying the recovery of motor impairments. The principles of rehabilitation therapy for stroke patients are discussed.

Keywords: neurorehabilitation, stroke, neuroplasticity, sensorimotor integration.

Stroke remains one of the leading causes of disability and social maladaptation of patients, residual signs of stroke of different severities being seen in 65% of patients [1, 2]. Data from the National Stroke Register provide evidence that only about 20% of patients surviving stroke are able to return to their former work [3]. Correctly planned rehabilitation measures are very important for this group of patients, these being effective to some extent or other in 80% of stroke patients, with spontaneous complete recovery of impaired functions in 10%; rehabilitation is ineffective in only 10% of patients [4, 5]. Recent years have seen significant progress in the rehabilitation of poststroke patients. The mechanisms of compensatory processes in the central nervous system (CNS) have been actively studied with the aim of creating new methods with improved rehabilitation efficacy [6]. Use of neuroimaging and neurophysiological methods provides for studies of the processes of reorganization and plastic changes in the CNS which are accompanied by clinical functional improvements.

Neuroplasticity and Sensorimotor Integration. CNS recovery after injury is built on the phenomenon of neuroplasticity, which is the ability of various CNS components to undergo reorganization due to structural changes in brain matter [7], including qualitative and quantitative neuronal rearrangements [8], and because of functional systems of the CNS, changes in the glia, and the development of new interneuronal connections [9]. Brain areas which prior to injury were not involved or had smaller roles in a particular function acquire involvement, and this reorganization is directed to compensating for the injured areas or those with which the injured areas had functional connections [10, 11]. Neuroplasticity processes in the CNS operate at different levels – molecular, cellular, synaptic, and tissue, with the involvement of large groups of neurons in cortical and subcortical structures. The pattern of activation in the brain of each patient at any given moment reflects the state of reorganization of motor neural networks [12]. Performance of tasks is associated with activation of neural networks directly proportional to the complexity of the task, due to recruitment of existing but inactive elements of the functional system [13, 14]; after injury, there is activation of "non-standard" primary and secondary areas of both cerebral hemispheres, these being able to carry out the functions of the injured structures [15]. These processes can occur because of a degree of multifunctionality, including the polysensory functions of CNS neurons [11], which allow them to perceive afferent stimuli of different modalities, and also because of axon growth, formation of new synapses, and increases in the activity of new parts of neural networks [7, 14].

Investigation of stroke patients by positron emission tomography (PET) and functional MRI scans (fMRI) have

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demonstrated excess activation of secondary areas in both hemispheres – the accessory motor and nonmotor zones: the premotor area (PMA) and accessory motor area (AMA), the dorsolateral prefrontal cortex, the cerebellum, the insula, the inferior temporal cortex, and the cingulate gyrus [12, 16–18]. Formation of an activation pattern depends on the severity of damage to the cortical motor areas and fibers in the white matter, as well as the lateralization of the focal lesion.

Injury to the primary motor cortex (PMC), PMA, and AMA in one hemisphere, which are parallel and independent motor subsystems, can be partially compensated for by the activity of the homologous motor areas in the other hemisphere, connected by fibers running through the corpus callosum and involved in functional integration processes during the reorganization of the brain's motor networks [19]. Decreases in the excitability of the PMC in one hemisphere have been shown to lead to rapid disinhibition and activation of the homologous contralateral motor area [20]. An inverse relationship has been identified between clinical recovery and the level of excitability of the secondary motor areas, especially in the healthy hemisphere, along with a direct relationship with the level of activation of the primary sensorimotor cortex of the lesioned hemisphere [17, 18], which is evidence for recovery of the activation pattern to the physiological circuitry for the contralateral control of limb function, i.e., normalization of the interhemisphere balance present before illness [13]. However, some studies have reported results demonstrating the important role of the motor areas of the intact hemisphere in performing difficult and complex tasks with the impaired limb (for example, complex finger movements in patients with almost complete recovery of motor functions [21, 22]. This applies to the PMC, the dorsal PMA, and the superior parietal cortex. Excessive bilateral activation of the PMA is most commonly noted in subcortical [13] and cortical-subcortical lesions [23], only occasional studies showing that premotor activation is not dominant in the lesioned hemisphere [24]. The phenomenon of hyperexcitability of the PMA on the infarcted side is believed to reflect its high level of involvement in attempts to perform tasks despite injuries to the corticospinal tract [11]. This is partly linked with the regulatory influences of the PMA on the PMC operating in the healthy brain, as confirmed by fMRI data in health and pathology [25, 26].

Different parts of the CNS have different levels of neuroplastic potential. The cerebral cortex has the greatest adaptive resource. This is associated with the multiplicity of its cellular elements and the existence of parallel reciprocal connections and overlapping zones, which allows them to use and/or form supplementary pathways and which can carry signals [8]. Changes in intact brain matter are believed to be based on processes such as imbalance of excitation and inhibition, deafferentation, and realization of previously unused connections and/or the formation of new connections [25].

Any injury to the CNS leads to activation of neuroplasticity processes and the application of rehabilitation methods can undoubtedly promote better compensation of the resulting defects [7, 25]. However, extremely active stimulation in conditions of neurorehabilitation may in some cases (particularly in the early acute period of stroke) lead to various unfavorable consequences, such as delayed recovery of motor functions and enlargement of ischemic foci [8]. Various factors leading to this phenomenon have been discussed – additional glutamate and catecholamine release, hyperexcitability of neurons in the perifocal zone, and imbalance of excitation and inhibition processes, though the exact pathophysiological processes of this phenomenon have not been fully clarified.

There is a tight link between the afferent and motor components of neuroplasticity: reorganization of the sensory cortex occurs in response to injury to the motor zones of the brain, while limited pathological processes in the somatosensory cortex can induce changes in the motor areas of the representation zones of, for example, the fingers [6]. The ability of the somatosensory cortex to undergo rearrangement has been demonstrated, with a variety of structural-functional changes occurring in parallel with recovery of motor functions, which is not surprising given the tight afferent-efferent interaction at all levels of the CNS [25, 27, 28]. Highly specific projections have been observed from the sensory cortex to the motor cortex, where each sensory column projects to only a few motor areas [15]. There are continuous interactions between all cortical fields, in turn controlled by the afferent influx, as noted by Anokhin [29] in his description of CNS functional systems, and the dynamic nature of cerebral processes is to a significant extent determined by the afferent component. The cortical representation zones can change depending on the incoming sensory information. In stroke patients, motor derangements are combined with sensory impairments in 40–65% of cases [30–32]. Thus, the afferent system plays an important role in central motor control, which must be considered when organizing rehabilitation methods.

The principles of rehabilitation of motor impairments in cerebral injury include modulation of cortical excitability and peripheral sensorimotor stimulation. Increases in the activity or excitability of the injured hemisphere can be achieved by rhythmic transcranial magnetic stimulation (TMS) in an activation regime using sequential magnetic stimuli separate by identical intervals, while inhibition of the activity of the uninjured hemisphere can be produced using rhythmic TMS in an inhibitory regime with simultaneous restriction of the use of the healthy hand and activation of afferentation from the impaired limb [33, 34]. The latter includes neuromuscular electrostimulation, whose effects are associated with both excitation of large α motoneurons and the facilitatory action of skin afferents [7], therapeutic gymnastics with stimulation of voluntary movements in the impaired limb, and the use of robotic systems to assist movements in the paralyzed limbs [9, 35]. In severe afferent deficit, large numbers of sensory stimuli should be

used, and these should be included in the current level of control of sensorimotor behavior, for example, the combination of electrostimulation and biological feedback during the rehabilitation process.

Repetition of movements is known to form the basis for motor learning and the ability to reproduce them. One possible mechanism of this is the phenomenon of long-term potentiation and the structural transformation of synapses, which depend on the frequency of activation of the corresponding pathways to the sensorimotor cortex [32]. Repeated performance of exercises by stroke patients leads to activation of the sensorimotor cortex of the injured hemisphere and increases corticospinal excitability [23, 36]. Enlargement of the activation zone of cortical areas in the injured hemisphere using paired TMS impulses after movement therapy as described generally correlates with significant clinical improvement in the paralyzed limbs [23]. This effect can be explained by an increase in the number of functioning synapses in the central areas of the motor analyzer and a dynamic rearrangement of the functional systems of the brain using controlled motor loads regulated by feedback, increasing active involvement in the rehabilitation process: the patient is given information on changes in some biological parameter and is able to influence the results of the training undertaken [37].

The bottom-up afferent stream has activatory influences on central structures, determining the level of their tonic state. Proprioceptive stimuli alter the functional properties of neurons, helping them to become polymodal and supporting their sensitivity to stimuli of different modalities [38]. The involvement of proprioceptive afferentation in controlling voluntary movements and the regulation of the ratio of the processes of excitation and inhibition in the CNS have been addressed, as has its triggering role in the development of motor impairments at different levels of the muscle analyzer [39].

One strong source of proprioceptive sensory afferentation arises from the supporting parts of the foot [40]. Hypogravity simulation experiments with mechanical stimulation of the supporting zones of the foot demonstrated the important role of supporting afferentation in controlling the state of the spinal motor systems and regulating postural-tonic reactions, i.e., simultaneous activity of the supporting and muscular afferent systems in controlling locomotion [39, 41].

Stimulation of neuroplasticity processes occurs under the influence of supporting afferentation [42]. Activation of supporting afferentation leads to decreases in muscle spasticity and restoration of movement coordination, which is linked with the development of new functional connections in the brain, promoting recovery of impaired motor stereotypes [39]. Impairments to these processes occur in conditions of prolonged immobilization (for example, after stroke, craniocerebral or spinal trauma), which are apparent clinically as subsequent development of abnormal posture and locomotion. Mechanical stimulation of the supporting zones of the feet activates supporting afferentation and, thus, the system of late synergies, reversing pathologically elevated tone of the muscles involved in organizing posture and gait [41, 43]. Simulation of the sensory pattern of gait in physiological cyclogram conditions with the formation of a novel and strong stream of proprioceptive spike activity in patients with juvenile cerebral palsy (JCP) leads to decreases in the severity of imbalances in reflexes [40].

Use of a dynamic proprioception correction method based on therapeutic costumes in stroke patients produces reductions in the severity of postural-tonic impairments, pathological synkinesias, and clonus, with normalization of complex locomotor acts supporting gait, and restoration of motor stereotypes [43]. This method is based on the creation of an afferent stream acting not only on stroke-damaged neurons, but also on neighboring structures. Thus, actions on different afferent modalities in neurorehabilitation have favorable influences when foci are located in the CNS.

Neurorehabilitation in Stroke Patients. Despite advances in rehabilitation and the existence of a wide spectrum of differently directed restorative methods, a significant proportion of stroke patients have stable motor impairments. This can be explained by the lack of clarity in our understanding of the mechanisms of recovery of motor functions, the contradictory nature of data on the effects of various factors on rehabilitation processes, and the failure when designing rehabilitation programs to consider the main mechanisms by which motor functions are organized, including interhemisphere asymmetry, difficulties defining rehabilitation regimes (methods, optimum duration, intensity of treatments), and contradictions in reports of long-term treatment results in patients in the late recovery and residual periods [9, 44–48].

The period at 3–6 months from onset of stroke is regarded as the most active time for the recovery of motor functions [4]. Functional improvement occurs mainly during the first year after stroke, while recovery of complex motor skills can continue for several years [7, 8]. The existence of compensatory processes has been demonstrated to persist for several years after stroke [46]. A multicenter randomized controlled trial including 127 patients with moderate and severe hemiparesis showed long-term effects with intense rehabilitation even several years after disease onset [45]. Some patients during this period showed normalization of intracortical inhibition in the injured hemisphere, apparent as improvements in the motor domain, which are not produced by analogous processes in the intact hemisphere, which is evidence that hyperexcitability of the motor cortex in the uninjured hemisphere lacks functional significance [48].

In patients with hemiparesis for 4–15 years, intense training of the impaired hand with restraint of the healthy can lead to decreases in the severity of paresis, and significant changes in synaptic activity in the ipsilateral cerebral cortex are also seen [49]. Use of this rehabilitation method is only regarded as appropriate six months after disease onset [7]. It is emphasized that active rehabilitation must continue

until objective improvement in neurological functioning is seen [50]. Further clinical and neurophysiological studies of such patients are therefore required, to progress existing concepts of the mechanisms of motor impairments and to develop pathogenetically based rehabilitation schemes.

Neuroimaging on the background of rehabilitation measures is widely used to study the reorganization of the white matter after brain lesions. fMRI approaches are based on assessment of changes in the level of blood oxygenation. The spatial resolution of this method approaches the submillimeter level, and this is the most effective method for neuroimaging diagnosis, such that it can be used to study changes in the brain due to injury and for dynamic monitoring of rearrangements of activation zones and remodeling of the white matter in response to treatment [51, 52]. The use of fMRI allows the prognostic significance of different types of functional rearrangement of the cortex to be assessed in relation to restoring impaired functions and developing optimum treatment algorithms. The structural integrity of the conducting pathways can be assessed using standard MRI regimes and diffusion-weighted MRI scans and magnetic resonance tractography (MRIt) [53]. However, this is not always possible, for example in minor brain injuries [54]. MRIt provides quantitative assessments of the integrity of the corticospinal tract with in-life visualization of the conducting tracts and interpretation of the three-dimensional picture in relation to the infarct zone [53–55].

fMRI studies of CNS activity because in patients during the late recovery period after a month of treadmill training showed a correlation between increases in endurance on walking and increased activity in the primary sensorimotor cortex, the motor zone of the cingulate gyrus, and the caudate nucleus of both hemispheres, as well as the thalamus of the injured hemisphere [6].

Studies using tractography of the PMC, AMA, dorsal and ventral PMA, and the corresponding descending tracts in patients in the later recovery period after left-hemisphere strokes analyzed predictors of the efficacy of robot-based treatment conducted to facilitate movements in the impaired hand [47]. The conclusion was that particular levels of damage to the descending motor pathways from the PMC, AMA, and dorsal PMA have prognostic significance. The authors took the view that lesions of particular conducting tracts may be a better predictor of treatment efficacy than infarct focus volume. However, lesions to up to 90% of the conducting pathways from the PMC showed dissociation: some patients had moderate motor deficit and treatment results were good, while other patients had severe hemiparesis and unsatisfactory neurorehabilitation effects. This may be based on the smaller volume of descending pathways from the PMC, the features of the topography, and the fiber density in this tract.

The factors determining the efficacy of rehabilitation therapy also include the integrity of the white matter as assessed by TMS and MRIt data and the predominance of lesions of the descending motor pathways rather than of the motor cortex itself [26, 47, 56, 57]. Recovery does not occur in cases of extensive motor cortex lesions, while functional recovery can occur after severe damage to the descending efferent conductors, evidencing the greater neuroplastic potential of the white matter of the CNS than cortical lesions [47].

The widely used TMS method provides a noninvasive approach to studying the corticospinal tract and intra- and interhemisphere connections and provides evaluation of the excitability of cerebral motoneurons and assessment of the corticotopic representation of different muscles [12, 19, 23, 58, 59]. Standard or single-impulse TMS is used to evaluate the functional integrity of the upper motor neuron system, to assess residual motor functions, and to prognosticate functional recovery [23]. Paired-pulse TMS with short and long interimpulse intervals can be used to study the mechanisms of intracortical inhibition and excitation and interhemisphere inhibition, as well as to clarify the role of the cerebral fields in the reorganization of the brain after injury [48, 58, 59]. TMS is regarded as a reliable method for assessing plastic changes in the brain [23].

A restoration method using functional electrical therapy is based on electrical stimulation combined with intense training of the impaired limb, which induces a powerful central ascending sensory stream. These afferent spikes are integrated into the newly formed sensorimotor scheme, activating pre-existing sensorimotor CNS mechanisms [9]. Other methods for controllable local influences on plastic adaptation of the cortex include paired-pulse TMS, rhythmic TMS, epidural stimulation, and direct current TES or transcranial direct current stimulation [21, 44, 60]. Use of these methods provides differential influences on the cortical activity of key "target structures": decreasing brain activation with unfavorable effects (for example, when pain and dystonic disorders are present) or increasing activation leading to improvements in motor functions, with subsequent individual remodeling of neural networks during the rehabilitation of each patient [53]. Thus, direct current TES increases the excitability of the motor cortex and thus improves hand motor function in patients in the late post-stroke recovery period and facilitates motor learning [44, 61]. Rhythmic TMS, producing positive feedback of excitation (stimulation) within the PMC of the injured hemisphere or negative (inhibition) in the opposite hemisphere, leads to improvements in motor functions [34]. This is presumably linked with the fact that negative feedback regulation of excitability in the intact hemisphere via impairment of transcallosal inhibition can distort anomalously high interhemisphere inhibition in relation to the lesioned hemisphere, inducing paradoxical improvement in the function of the paralyzed hand, though this hypothesis requires further development [6]. Use of noninvasive rhythmic TMS accelerates the process of reorganization and improves responses to traditional treatment, such that this method can be regarded as a potential therapeutic intervention. Direct current stimulation (to inhibit the activity of the intact hemisphere during stimu-

lation of the injured hemisphere for 30 min) combined with peripheral sensorimotor stimulation had a greater clinical effect in terms of restoring motor functions in patients with moderate and severe hemiparesis at five months post-stroke as compared with similar treatment on only one hemisphere with simultaneous activation of the ascending somatosensory stream or rhythmic TMS combined with intense training of the paralyzed arm with restraint of the other [62].

The question of the post-stroke activation of the uninjured hemisphere is ambiguous from the point of view of neuroplasticity processes, in contrast to the current view that the prognosis for recovery is less favorable when cortical activity in the ipsilateral hemisphere is increased [8, 47, 58]. Studies using TMS and fMRI demonstrated increases in the activation patterns in both hemispheres in post-stroke patients [21]. The activation of the intact hemisphere during movements of the paralyzed arm seen at the subacute stage of stroke decreases over time and returns to the baseline level with good recovery, or persistence for several years after stroke if reorganization in the injured hemisphere is insufficient for the performance of particular tasks [18, 21, 22]. The significance of this activation remains unclear: the negative consequences of this process for recovery of the normal movement pattern versus the hyperexcitability of the injured hemisphere has been discussed [10, 18], as has the hypothesis that instability of the sensorimotor system in the injured hemisphere induced by lesions to the PMC can be compensated for by increases in the excitability of the dorsal PMA, PMC, and superior parietal cortex of the intact hemisphere [22]. Studies using functional brain mapping [35, 63] supported the view that many of the effects of neurorehabilitation are mediated not only by the persisting motor system of the stroke-damaged hemisphere (the AMA, dorsal and ventral PMA), but also via the PMC of the ipsilateral intact hemisphere. Thus the causes of the significant variability in the response to treatment in patients, due to different levels of damage to the cellular structures of the efferent system, which may be the defining factor for treatment efficacy, has been discussed [25]. The motor zones of the cortex may define treatment efficacy, given that there are direct corticospinal projections from thee cortical fields [64]. The role of the ipsilateral motor conducting pathways in the restoration of motor functions has been discussed [16]. Despite the variability of the location of cerebral infarcts and the different types of functional reorganization, one of the defining factors is the presence or absence of damage to the PMC of the injured hemisphere [57, 65].

Thus, the technical possibilities of current methods of studying the structural and functional organization of the brain are significantly ahead of their actual employment in increasing the efficacy of rehabilitation. Studies of post-stroke neurorehabilitation are clearly impossible without translation of the results into clinical practice. The high social significance and current relevance of the problem of rehabilitation require the use of scientifically based schemes for restorative treatment built on an evidence-based approach providing significant reductions in the level of post-stroke disability.

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