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REVIEW

INTERPLAY BETWEEN INTRA- AND INTERHEMISPHERIC REMODELING OF NEURAL NETWORKS AS A SUBSTRATE OF FUNCTIONAL RECOVERY AFTER STROKE: ADAPTIVE VERSUS MALADAPTIVE REORGANIZATION

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Abstract—Brain injuries such as focal stroke initiate a myriad of neural events leading to local and remote alterations in cerebral networks. The neurochemical and neurophysiological mechanisms underlying these postlesion changes raise the question of their beneficial or adverse effects on functional recovery. In this review, we aim to reconcile findings from animal and patients studies using a ''from cellular- to network-levels'' perspective to gain further insights into the neuroplasticity mechanisms underlying recovery of sensorimotor functions. Ultimately, an integrative view of the multiple facets of poststroke changes should give an impetus to novel neurorehabilitation strategies by providing evidence of how neuroscience findings can be translated and operationalized within the context of restorative stroke.

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Key words: focal stroke, ipsi/contralesional hemisphere, cortical remapping, interhemispheric inhibition, constraint-induced movement therapy.

Contents

INTRODUCTION

Given the highly interconnected nature of the neuronal matrix sustaining sensory, motor and cognitive functions, deficits induced by focal brain damage result from the disorganization of both local and spatially distributed and functionally interconnected neuronal networks in which neural information is processed and integrated in complex representations sustaining every facet of behavior. Distant effect of local brain injury can be assimilated with the diaschisis phenomenon originally described by Von Monakow (1914) as a suppression of function due to reduced metabolism and blood flow, abolition of excitability or long-lasting inhibition in regions adjacent to or remote from, but physiologically connected to, the primary locus of injury. According to this theory a substantial part of recovery takes place as diaschisis dissipates in spared tissue over time. The term diaschisis is now used in a wider sense to cover all remote effects of acute and chronic cerebral injury (see Meyer et al., 1987; Andrews, 1991; Finger, 2009). It is widely held that functional recovery following brain damage can result from this dissipation process as well as repair mechanisms.

Spontaneous reorganization underlying substantial functional recovery usually takes place over time in the perilesion area as well as in more distant regions in the

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Abbreviations: AMPARs, AMPA receptors; BDNF, brain-derived neurotrophic factor; CIMT, constraint-induced movement therapy; CSS, corticospinal system; CSTs, corticospinal tracts; fMRI, functional magnetic resonance imaging; IO, intrinsic optical; M1, primary motor; MCAO, middle cerebral artery occlusion; MEG, magnetoencephalography; MEP, motor-evoked potentials; NMDA, *N*-methyl-D-aspartate; PMd, dorsal premotor cortex; RF, receptive fields; rTMS, repetitive transcranial magnetic stimulation; S1, somatosensory; SMA, supplementary motor area; SMC, sensorimotor cortex; TCI, transcallosal inhibition; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; VSD, voltage-sensitive dye.

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ipsilesional and contralesional hemispheres. Recovery promoted by spontaneous or experience-dependent neural plasticity mechanisms is generally attributed to a greater contribution of neuronal circuits previously involved in the impaired function, i.e. a vicariation process first proposed by Ogden and Franz (1917) or to recruitment of new neuronal networks, i.e. a compensation/substitution process initially stated by Munk (1881) (for reviews, see Finger, 2009; Stein, 2013). Despite the remarkable development of neuroanatomical, neurophysiological and neuroimaging techniques that has yielded a wealth of data, further investigations are required to clarify the temporal and spatial progression of neural changes that may promote or hinder functional recovery. Moreover, the beneficial or detrimental effects of postlesion changes need to be unequivocally determined so as to optimize neuroplasticity-based rehabilitative interventions.

This review examines current ideas and recent advances from animal and human studies that have shed light on the neural changes enabling recovery of function after stroke, known as the leading cause of chronic adult disability, as an attempt to clarify some controversial issues and offer the prospect for improving insight into the neural foundations of rehabilitative practice following brain damage. Animal studies are very useful for exploring neural mechanisms of functional recovery and tracking reorganizational changes from synapse to network level with a spatial and temporal resolution without equivalent in human investigation methods which, on the other hand, provide a large-scale view of widespread alterations in brain structures. In this review, findings are examined from the perspective that unilateral damage to cortical regions leads to both local and distributed changes and gives rise to a disruption of interhemispheric dynamics followed by reorganization. Subsequent alteration of neuronal networks can be viewed as maladaptive changes or as a substrate of functional recovery on which rehabilitative procedures can capitalize. Particular emphasis is placed on changes in structures subserving S1 functions after focal stroke. While loco-regional alterations in the motor areas (reviewed in Dancause and Nudo, 2011 and Nudo, 2013) are not within the scope of the present review, distributed changes in motor-related brain structures are however considered whenever S1 findings are not available and key motor findings shed light on the process of recovery.

FOCAL ISCHEMIC DAMAGE TO S1 CORTEX: PERILESION REMAPPING

After focal stroke targeting the primary motor (M1) and/or somatosensory (S1) cortices, topographic representations have been shown to reorganize in spared neuronal circuits of the peri-infarct cortex (Castro-Alamancos and Borrel, 1995; Nudo and Milliken, 1996; Xerri et al., 1998; Dijkhuizen et al., 2001; Frost et al., 2003; Kleim et al., 2003; Gharbawie et al., 2005; Winship and Murphy, 2008; Brown et al., 2009). This postlesion map reorganization raises intriguing questions about the underlying mechanisms and functional correlates. After a focal ischemic lesion targeting the cutaneous representation of two-digit tips in area 3b of S1 in monkeys, new representational zones serving the deprived skin surfaces emerged after 2 or 3 months in the peri-infarct cortical sectors bordering the infarct (Merzenich et al., 1987; Xerri et al., 1998). This remapping was based on a redistribution of neuronal receptive fields (RF). Similar findings were described 15–17 weeks after infarct to digit 3 representation in raccoons (Doetsch et al., 1990). Electrophysiological recordings performed within the reorganized areas revealed an enlargement of cutaneous RF resulting in reduced spatial selectivity of cortical neurons and thus low spatial resolution of the emergent representations. In rats, a doubling in RF size was observed in hindlimb primary S1 area 7 days after small infarcts damaging parts of this representation (Reinecke et al., 2003). The RF expansion in the peri-infarct cortex was recorded few hours after primary sensorimotor area infarct, suggesting a rapid unmasking of previously unexpressed excitatory connections (Fujioka et al., 2010), similar to that described following peripheral nerve injury (for review, see Calford, 2002).

Unmasking of latent synaptic inputs is attributed to the highly convergent and divergent organization of the thalamocortical networks, widespread intracortical connections and the combination of both excitatory and inhibitory influences that modulate the excitability of cortical neurons. It is generally assumed that the RF of a given layer IV cortical cell reflects only a fraction of its synaptic connections, the others being in a latent state. Using intracellular recordings, Li and Waters (1996) described homotypic convergence of both suprathreshold and subthreshold inputs from several forepaw digits and pads to S1 neurons in rats. Likewise, Zarzecki et al. (1993) reported that, in the region of racoon S1 cortex representing a given digit, neurons also received 'off-focus' afferents from adjacent fingers. Gioanni (1987) observed a high degree of convergence of heterotypic inputs, i.e. cutaneous and proprioceptive, to layer IV neurons in the region of the S1 forepaw representation in rat. Moreover, electrophysiological membrane potential recordings and voltage-sensitive dye (VSD) imaging revealed broad subthreshold RF in L2/3 neurons (Moore and Nelson, 1998; Zhu and Connors, 1999; Brecht et al., 2003; Ferezou et al., 2007).

Using intrinsic optical (IO) imaging in mice, Winship and Murphy (2008, 2009) also described perilesion remapping after photothrombotic lesion to forelimb S1 representation. No clear forelimb activation was recorded in S1 2 weeks after the lesion. However, in animals recovered for 1 and 2 months, forelimb-evoked activity was found in the peri-infarct rim, extending posterior and medial relative to control animals, with significant overlap with the S1 hindlimb region. This extensive remapping may reflect, at least in part, a delayed unmasking of previously latent connections. Using *in vivo* two-photon calcium imaging, Winship and Murphy (2008, 2009) documented stroke-induced changes in S1-evoked response properties of individual and layers 2/3 cortical neurons. They showed that 1 month after stroke, neurons normally