Available online at www.sciencedirect.com
ScienceDirect
Journal of Clinical Neuroscience 13 (2006) 885–897
Journal of Clinical Neuroscience
www.elsevier.com/locate/jocn

Review

Brain plasticity: From pathophysiological mechanisms to therapeutic applications

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Received 8 August 2005; accepted 10 November 2005

Abstract

Cerebral plasticity, which is the dynamic potential of the brain to reorganize itself during ontogeny, learning, or following damage, has been widely studied in the last decade, in vitro, in animals, and also in humans since the development of functional neuroimaging. In the first part of this review, the main hypotheses about the pathophysiological mechanisms underlying plasticity are presented. At a microscopic level, modulations of synaptic efficacy, unmasking of latent connections, phenotypic modifications and neurogenesis have been identified. At a macroscopic level, diaschisis, functional redundancies, sensory substitution and morphological changes have been described. In the second part, the behavioral consequences of such cerebral phenomena in physiology, namely the ''natural'' plasticity, are analyzed in humans. The review concludes on the therapeutic implications provided by a better understanding of these mechanisms of brain reshaping. Indeed, this plastic potential might be 'guided' in neurological diseases, using rehabilitation, pharmacological drugs, transcranial magnetic stimulation, neurosurgical methods, and even new techniques of brain–computer interface – in order to improve the quality of life of patients with damaged nervous systems.

Keywords: Brain plasticity; Sensorimotor; Language; Functional neuroimaging; Electrical stimulation mapping; Brain diseases treatment

1. Introduction

For a long time, based on anatomo-functional correlations in patients with cerebral injury, and despite the description by some pioneers of post-lesional recovery,[1] the dogma of a static functional organization of the brain was widespread, that is, the inability to compensate any damage involving the so-called eloquent areas. However, through regular reports of functional improvement following insult of cortical or subcortical structures considered 'critical', this view of a 'fixed' organization of the central nervous system (CNS) has been called in to question in the past decades. Many investigations have been carried out, initially in vitro and in animals, then in humans since the development of non-invasive neuroimaging, to study the mechanisms underlying these compensatory phenomena: the concept of brain plasticity was born.

This review is aimed to link the better understanding of the pathophysiology of cerebral plasticity (at sub-cellular, cellular, and synaptic map level) and the possible use of this dynamic potential for clinical applications, namely a 'guided-plasticity' applied to therapy.

1.1. The concept of brain plasticity

Cerebral plasticity is a continuous process allowing short-term, middle-term and long-term remodelling of neuronosynaptic maps, to optimise the functioning of brain networks.[2] Plasticity plays a critical role:

- during phylogenesis;
- during ontogeny, with the elaboration of new circuits induced by learning, and the maintenance of neural networks in adults, then in elderly people:[3] 'natural plasticity';[4]

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doi:10.1016/j.jocn.2005.11.045

- after damage to the peripheral or central nervous system, with functional reshaping underlying a partial or complete clinical recovery: 'post-lesional plasticity'.[5]

Moreover, these dynamic phenomena must be stabilized to enable functioning of the system: 'homeostatic plasticity'.[6]

2. Neurophysiological basis of cerebral plasticity

2.1. Preliminary animal experimentations

For the past 20 years, numerous animal studies have shown that functional cortical organization may be modulated by experience, and by lesions of the peripheral or central nervous system.

2.1.1. Peripheral lesions

Somatosensory map reshaping has been elicited by peripheral sensory deprivation, such as deafferentation induced by local anesthesia, transecting or ligating peripheral nerves, digit or hand amputation.[5,7] The cortical area corresponding to the injured cutaneous receptive fields becomes responsive to stimuli originating from the adjacent cutaneous fields. Thus, the cortical regions adjacent to the deprived cortex expand at its expense. When the reorganization is acute (minutes), the mechanism suggested is a likely unmasking of latent intracortical connections.[8] This reorganization could be either: (i) reversible, raising the question of the real adaptative value of such dynamic phenomena; (ii) stabilized within hours; and even (iii) strengthened via the occurrence of additional remodelling during the following months.[5,7]

Such reshaping was also observed in the primary motor cortex (M1), with the expansion of the cortical areas adjacent to the representation of the part of the body injuried, after a lesion of a peripheral nerve.[9,10]

2.1.2. Central lesions

After cortical lesions within the primary somatosensory area, redistribution of the damaged representations has been demonstrated both in the vicinity of the injury, and in remote regions.[11] Indeed, following stroke involving the representations in cortical area 3b of specific skin surfaces in monkeys, a post-lesional re-emergence of the representation of the fingertips engaged in behavior was observed in novel locations in area 3b. Additionally, an enlargement of the representation of the fingers in cortical area 1 was also reported, as well as a striking emergence of a new representation of the cutaneous fingertips in area 3a, predominantly within zones that were previously excited only by proprioceptive inputs – in monkeys who had reacquired sensorimotor skill after retraining.[12] These data support the existence of an experience-dependent post-lesional plasticity.

The same observations were reported for motor function.[13,14] Following an early lesion of M1 of the 'hand' in monkeys, a new cortical representation of this hand was found, with expansion into a medial territory previously occupied by representations of the elbow and shoulder.[15] The essential role of this new displaced representation was proved by its reversible functional inactivation with the gamma-aminobutyric acid (GABA)-agonist muscimol. Indeed, this inactivation dramatically impaired dexterity of the opposite hand without affecting the ipsilateral hand – converse to the inactivation of the ipsilesional premotor cortex and both supplementary motor area cortices, which did not interfere with manipulative behavior.[15] After an equivalent M1 lesion in adult monkeys, inhibition of the premotor cortex in the damaged hemisphere suppressed the recovered manual dexterity of the affected hand, suggesting that the mechanisms of post-lesional plasticity were different depending on the timing of the injury during development.[16]

In addition to studies showing that skill acquisition can modulate motor maps, with specific learning-dependent enlargement of cortical representation,[17] animal experimentations also suggested that, after focal M1 damage, rehabilitative training such as constraint-therapy could shape reorganization in the adjacent intact cortex. This reshaping could favor the recruitment of the undamaged motor cortex, which might play an important role in motor recovery.[14]

Potentiation of post-lesional plasticity using pharmacological agents was tested, with evidence of a neuroprotective effect on the somatotopic map of chronic treatment with piracetam.[18]

Finally, transgenic mice models enabled modulation of plasticity.[19–22]

2.2. Pathophysiological mechanisms underlying brain plasticity

Several hypotheses underlying plasticity have been suggested, from ultrastuctural to synaptic map levels.[1,23–25]

2.2.1. Microscopic level

2.2.1.1. Development. 'Natural plasticity' takes place in several stages:[26] (i) cyto- and histogenesis, with proliferation and elaboration of dendritic and axonal branches; (ii) period of migration, formation of synapses and cellular differentiation; and (iii) precise organization of the circuitry, through apoptotic phenomena, axonal regression and elimination of cells and synapses. This final remodelling allows the removal of superfluous networks, increases the specificity of each circuit – particularly by learning, based on task repetition, according to Hebbian's concept[27,28] – and increases the plastic potential of the system.

2.2.1.2. Modulation of synaptic strength. Beyond structural modifications such as an increase in the size and number of synapses during learning,[29] the synapse itself should not be considered as a 'static', but as a 'dynamic' connection, with plastic properties[30] underlying functional map reshaping at

a macroscopic level.[9,31] Repeated nerve impulses alter the processes of synaptic transmission: subsequent stimulations of the presynaptic membrane generate an increase (or a decrease) in the influence on the postsynaptic neuron. This activity-dependent synaptic plasticity is induced at the level of appropriate synapses during memory formation, and seems both necessary and sufficient for the information storage underlying the type of memory mediated by the area in which that plasticity is observed.[32] Such process allows a dynamic control of the flow of information within the neuronal networks, and explains the phenomena:

- of long-term potentiation (LTP), that is, a durable increase in the synaptic strength following a brief high-frequency stimulation, when such stimulation otherwise induces a short-term potentiation, with rapid return to the baseline – a mechanism discovered in the hippocampus, and demonstrated in M1;[33]
- of long-term depression (the opposite), with an essential role in learning and memory.[34]

Furthermore, some synapses can auto-regulate themselves: this is called 'metaplasticity'.[35]

According to Hebbian's rule, which states that learning and memory are based on modifications of synaptic strength among neurons that are simultaneously active, due to task repetition, it was demonstrated that motor skill learning strengthened horizontal connections in M1 through long-term potentiation – but not in M1 ipsilateral to the trained limb.[36] However, despite numerous data supporting plasticity as necessary for learning and memory, little data currently supports the notion of sufficiency.[32]

Finally, the mechanisms of synaptic stabilization, especially through a regulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, constitute 'homeostatic' plasticity,[6] essential to balance the processes of Hebbian plasticity.[27,28]

2.2.1.3. Synchrony. Synchrony within the functional network is crucial. For instance, precise synchrony between the temporal parameters of episodic electrostimulation of the nucleus basalis and of an auditory stimulus are required to generate a massive reorganization of the primary auditory cortex.[37]

Plasticity may be considered as changes of the activity of isolated neurons,[38] of synaptic efficacy, and of the temporal relations between ensembles of neurons in specific oscillation bands.[39] Combination of these mechanisms could lead to a modulation of the behavior through a reorganization of the eloquent networks, and through the elaboration of actual 'neo-networks'.

Recent biomathematical modelling has tried to measure such 'effective' connectivity, using partial coherence analyses of fMRI data.[40] Such concepts are also studied in silico, using neural network models of cortical functions based on the computational properties of the cortex.[41]

2.2.1.4. Unmasking of latent connections and networks. Due to the dynamic organization of functional maps, stabilization of cortical representations is maintained by a network of inhibitor GABA interneurons.[8] In normal conditions, these interneurons block horizontal connections, particularly between pyramidal cells. However, if this inhibition is suppressed, following sensory deprivation or learning, these intracortical connections become functional.[42] Therefore, this 'unmasking' of latent connections, allowing the transformation of silent synapses to functional synapses,[43] represents a major mechanism of short-term plasticity.[44] This process is facilitated by the organizational properties of the connectivity of the thalamo-cortical networks,[45] and by mechanisms able to rapidly change the level of excitability of neurons and synaptic transmission – via a decrease in GABA inhibition.

2.2.1.5. Modulation of neuronal activity by glia. Glia play a major role in modulation of neuronal activity.[46]

Due to their anatomical location between synapses and vessels, astrocytes represent an essential interface in the neuro-vascular coupling through regulation of energy metabolism.[47] By releasing neurotransmitters and other extracellular signaling molecules, glia can affect neuronal excitability and synaptic transmission, and co-ordinate activity across networks of neurons.[48] Glia can also communicate with other glial cells through intracellular waves of calcium, via gap-junction,[49] and via intercellular diffusion of chemical messengers, constituting an actual glial network able to both listen and talk to neuronosynaptic circuits.[50]

Moreover, in developmental plasticity,[51] radial glia play a fundamental role in the co-ordination of neuronal migration from the subventricular zone to the cortex.[52]

2.2.1.6. Modulation of neuronal activity by the extracellular matrix. The extracellular matrix seems equally involved in the regulation of neuronal activity and synaptic plasticity.[53–55]

2.2.1.7. Structural modifications. Numerous neuronal and glial phenotypic modifications have been demonstrated.

At the neuronal level, dendritic spine and axonal sprouting or neosynaptogenesis have been observed in vitro and in animals.[29] Experience-dependent plasticity of cortical receptive fields is accompanied by an increased synapse turnover, suggesting that experience drives the formation and elimination of synapses and that these changes may underlie adaptive remodelling of neural circuits.[56] Morphological synaptic plasticity may also be induced by brain damage.[57] Rapid structural changes (number, size and shape of dendritic spines) have been observed rapidly after damage, possibly due to the synthesis of a new protein.[58] The participation of growth factors and neurotrophins has also been suggested.[59] The role of the AMPA receptors and integrins in the stabilization of morphological changes has been underlined[29] as another mechanism of 'homeostatic' plasticity.[6]

Moreover, axons can undergo spontaneous regeneration and elongation.[60] However, in injury, molecules in the extracellular environment, or those associated with myelin, can inhibit such axonal growth.[61]

Glia are involved in the control of the number of synapses.[62] Additionally, astrocytes exhibit a high degree of plasticity of phenotype. Their morphology changes markedly during neuronal migration, maturation, and degeneration, suggesting that astrocytes must constantly adjust to meet changes in brain environment.[63] Modifications in the size of glia have been demonstrated, sometimes rapidly (hours), in physiology[64] and following injury.[56] These phenotypic changes may be transmitted between glial cells through connexin.[65]

2.2.1.8. Neurogenesis. Against the dogma that new neurons cannot be added to the adult mammalian brain, neurogenesis within the olfactory bulb, the dentatus gyrus,[66] and even the neocortex of adult primates,[67] has been recently reported. This phenomenon has also been demonstrated in the adult human brain.[68,69] Neurogenesis occured in vitro, from multipotential progenitor cells isolated from the adult human epileptic temporal neocortex,[70] hippocampus,[71] and subcortical white matter.[72] These new neurons may play a role in learning and memory, through the modulation of neuronosynaptic circuits, the elaboration of new connections between them, and the development of new networks.[73] Neurogenesis could also be involved in post-lesional plasticity. Following cortical injury in adult mice, endogenous neural precursors can be generated in situ, to differentiate into mature neurons, in neocortical areas that do not normally undergo neurogenesis.[74] Thus, it may become possible to manipulate endogenous multipotent precursors in situ to replace damaged neurons, allowing the development of neuronal replacement therapies for brain injuries that do not require transplantation of exogenous cells.[75]

2.2.1.9. Other factors. The influence of neurotrophins, gene expression[76], social environment[77], stress and exercise[78] on neural and behavioural plasticity have been studied, with possible interactions between these factors.

2.2.2. Macroscopic level

These ultrastructural changes may lead to a functional reorganization at a macroscopic scale, through the mechanisms described hereafter.

2.2.2.1. Diaschisis. Diaschisis, that is, functional (electrophysiological, metabolical, hemodynamic) changes in structures remote from the site of focal brain damage, was conceptualized as underlying initial worsening of function after injury.[79–81] Its secondary resolution may participate in spontaneous functional recovery.[82]

2.2.2.2. Intrinsic reorganization within eloquent areas: functional redundancies. Due to a dynamic organization of the eloquent areas, with multiple cortical representations of the same function within the same region, ('functional redundancies'[83]) a lesion involving a discrete eloquent site can be compensated by the recruitment of adjacent redundant sites. These functional redundancies, located within the same region as the area damaged, can be 'unmasked' following injury, which generates a local hyperexcitability.[8,84]

2.2.2.3. Reorganization within functional network. In wide lesions, within-area redistribution cannot be sufficient to restore the function. Other regions belonging to the same functional network may be recruited: first, perilesional areas; then, if the functional compensation is still insufficient, remote ipsi-hemispheric structures.[85,86] Finally, due to the suppression of transcallosal inhibition, functional homologous structures in the controlateral hemisphere may also be recruited.[87]

2.2.2.4. Cross-modal plasticity. When the lesion involves many epicenters within a functional network, recruitment of structures initially not belonging to this eloquent circuit is possible: "cross-modal plasticity".[88–91] Congenitally blind patients have an improved auditory spatial tuning due to an additional recruitment of the visual cortex,[92] while congenitally deaf adults recruit the auditory cortex during visual stimuli.[93] Both have better tactile discrimination, with visual cortex and auditory cortex activation during somatosensory tasks, in blind[94] and deaf humans[95] respectively. Moreover, interactions between sensory deprivation and cognitive functions such as language, have been reported,[96,97] likely due to an exuberant functional connectivity.[98] Another finding supporting the functional adaptative value of sensory substitution was reduced tactile discrimination when transcranial magnetic stimulation was applied to the visual cortex of blind patients – but not healthy volunteers.[99]

Such knowledge may help to predict the success of sensory implants: deaf individuals in whom cross-modal plasticity is extensive are the least likely to benefit from cochlear implants.[100]

2.2.2.5. Compensatory strategies. When the unimodal association areas able to participate in functional restoration are also damaged, heteromodal association areas such as the dorso-lateral prefontal or intraparietal cortices may be recruited. This is not an actual recovery of the function, but rather the elaboration of compensatory cognitive strategies.[101]

2.2.2.6. Macroscopic morphological changes. Ultrastructural modifications and neurogenesis may generate macroscopic morphological changes, detectable by voxel-based morphometry.[102]

The size of the left planum temporale may be an anatomical marker of left hemispheric specialization for language comprehension.[103] The volume of the cerebellum[104]

and Broca's area[105] is increased in musicians. The volume of mesio-temporal structures can be correlated to face recognition[106], and the volume of the hippocampi is increased in taxi drivers.[107]

Furthermore, an increase in the density of white matter tracts constituting frontotemporal pathways is found predominantly in the left speech-dominant hemisphere in children: such results support a gradual and asymmetric maturation during childhood.[108] Also, asymmetry between volumes of left and right white matter has been demonstrated in adults, proportional to language lateralization.[109] This asymmetry supports an increased intrahemispheric connectivity in subjets with more lateralized functions, according to Ringo's theory.[110]

Finally, transient morphological changes in grey matter can be induced by training.[111]

3. Natural plasticity in humans

Despite a static 'point-by-point' view of the somatotopic organization of the Penfeldian homunculus,[112] recent studies in healthy volunteers demonstrate the existence of multiple represention of movements within the primary sensorimotor cortex,[113] with an overlap and a hierarchical organization of the functional redundancies.[114]

M1 is subdivided into two regions (4 anterior and 4 posterior), according to anatomical, neurochemical and functional criteria, with the posterior area more recruited when a higher attentional control is required during movement.[115] Some cortical sites within M1 may correspond to a representation of muscle, while other sites may correspond to representation of postures and more complex movements, in particular bimanual,[116] versing on an actual action.[117] The debate concerning the parameters of movements that are really coded by M1 neurons is still open,[118] but is moving toward a likely control of the kinetic and dynamic parameters of voluntary movement.[119] Therefore, the cortical representation of muscles and movements may be organized as a 'mosaic',[120] facilitating an intrinsic reshaping of M1 during learning.

This is in accordance with functional neuroimaging studies[121–123] performed during skill learning. An extension of activation was observed as a recruitment of adjacent sites to facilitate the acquisition of new motor sequences. This phenomenon may be transient or durable,[124] particularly in musicians.[125,126] These observations support a more complex role for the primary sensorimotor area than control of movement, namely involvement in cognitive functions – motor skill learning,[127] mental imagery,[128] and calculation.[129]

Temporal organization of this mosaic is essential. Numerous electrophysiological studies show changes both in the activity of isolated neurons in the sensorimotor cortex following skill learning,[38,130] and in the oscillations of neural activity in this same region during movement.[131,132] These oscillations may reflect the synchronous cortical activity of many neurons, and may enable rapid modification of the ensemble of neurons involved in the execution of a movement, through a modulation of the relationships between their time-course.[39,132]

Plasticity also implies changes in activity within the 'non-primary' structures of the sensorimotor network,[133] such as the supplementary motor area and lateral premotor cortex,[134] cingulum,[135] insula, posterior parietal cortex,[136] cerebellum,[137] deep grey nuclei and thalamus.[138] Plasticity equally implies changes in the effective connectivity within the whole functional network[139] – as revealed by measuring the coherence of the activity between the distinct areas involved in sensorimotor function.[140]

Concerning language and cognition, the current view is of a spatio-temporal functioning of parallel distributed cortico-cortical and cortico-subcortical networks,[141–143] with both simultaneous and successive participation of mosaics of hierarchically organized areas, some of them being essential while others being compensable – with an interindividual variability.[144]

4. Therapeutic perspectives based on plasticity-guidance

4.1. Rehabilitation

Rehabilitation is actual retraining based on task repetition, to facilitate plasticity phenomena, leading to a positive reinforcement of one task while inhibiting others.[145]

Concerning sensorimotor rehabilitation, functional neuroimaging shows that re-activation of brain structures may be induced by mental imagery of the movement,[146] its observation,[147] or passive training.[148] A single session can produce a use-dependent enlargement of M1 representations paralleled by an improvement in motor function in stroke patients, nevertheless with a variable long-term stabilization.[149] Moreover, constraint-induced movement therapy is extensively used.[150] This method generates a re-expansion of cortical motor areas,[151] correlated to functional recovery,[152–154] if this therapy is performed 6 h per day.[155] Conversely, immobilization induces a decrease of motor area size.[156] Finally, the timing of rehabilitation is still controversial, as it has been suggested that early physiotherapy might generate exacerbation of brain injury – due to an early post-lesional vulnerable period.[157,158]

Concerning aphasia therapy, while some randomized trials have not demonstrated significant impact,[159,160] other trials show a favorable effect from language therapy,[161–164] including in children.[165] This discrepancy may be due to differences in the intensity of training. Aphasia therapy seems efficacious if the program comprises at least one hour of training per day in the 3 months following lesion (90 h minimum 'constraint-induced therapy').[166] Furthermore, neurofunctional imaging performed before and after training shows a reshaping of the language map,[167] particularly with a re-activation of Broca's area and the left supramarginal gyrus,[168] with a possible recruitment of the right non-dominant hemisphere.[167] Current perspectives consist

of intensive, individual language therapy specifically adapted to each aphasic symptom.[164]

Finally, robotic devices[169] and other prostheses may facilitate plasticity, particularly sensory substitution,[170] even following many years of deficit.[171]

4.2. Pharmacology

Beneficial effects of pharmacological agents on brain reshaping have been studied after stroke and traumatic injury.[172] Cortical motor plasticity can be modulated by norepinephrine,[173] paroxetine,[174] fluoxetine,[175] scopolamine[176] or lorazepam,[177] that is, substances that influence the mechanisms of LTP.[178,179] Concerning language, several trials demonstrated the efficacy of drugs in the recovery of aphasia, especially amphetamine,[180] bromocriptine,[181] and piracetam[182] – which facilitates the reactivation of structures within the left hemisphere, as shown using positron emission tomography.[182]

A combination of rehabilitation and pharmacologic agents has been suggested.[181,183] However, very few patients currently benefit from these medications,[184] for which the indications must be better evaluated.

4.3. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is another approach to modulate cortical functional representations.[185] This method induces, depending on the frequency of stimulations, either a facilitation or an inhibition of the cortical area, through influence on LTP.[186] TMS can rapidly increase M1 excitability, with a durable effect.[187] This potentiation may facilitate motor learning and rehabilitation.[188] Conversely, in dystonic patients with writer's cramp, repetitive inhibitory low-frequency TMS applied to M1 allowed a transient normalization of the cortical representation of the hand.[189] TMS is also able to modulate sensory maps, and has been used to improve contralesional visuospatial hemineglect.[190,191]

Concerning higher functions, TMS may facilitate picture-naming,[192] learning and memory,[193] analogic reasoning[194] and decision-making.[195] Therefore, TMS may be used for neurocognitive rehabilitation.[188] It can modulate both the function of the area stimulated and links between this region and the other structures involved in the functional network; that is, it may induce an actual reorganization through a modulation of the effective connectivity.[196] Recent works suggest synchronizing repetitive the TMS and the EEG rhythm, particularly in the frequencies underlying cognition (gamma-band),[197] to strengthen the connectivity within the functional network to enhance cognitive performance.[198]

Transcranial magnetic stimulation can be combined with rehabilitation or pharmacologic drugs, to potentiate effects on plasticity.[199] TMS can also be considered for other therapeutic applications:[200] depression,[201] tic and obsessive-compulsive disorders in Tourette's syndrome,[202] acute[203] and chronic[204] pain, posttraumatic stress disorder[205] and epilepsy.[206,207]

4.4. Surgery

4.4.1. Chronic stimulation

Chronic electrical stimulation has undergone considerable development, particularly in movement disorders. High-frequency stimulation of the deep grey nuclei can modulate function of the subcortico-cortical loops, with an improvement in the motor (and even cognitive and behavioral) symptoms in Parkinson's disease,[208,209] dystonia,[210] and essential tremor.[211] Moreover, deep brain stimulation has been proposed in chronic intractable cluster headaches,[212] psychiatric diseases,[213] especially obsessive-compulsive disorder,[214] and medically intractable epilepsy.[215]

Chronic cortical stimulation may also modulate functional networks, especially in movement disorders[216] and chronic pain,[217,218] via extradural electrodes implanted over the central region. However, the mechanism of action remains unclear.[219,220]

Chronic stimulation will continue to develop and improve, due to its 'reversible' nature. Moreover, it will benefit from better understanding of the oscillatory dynamics of functional networks.

4.4.2. Surgical resection

Brain surgical resections are common in intractable epilepsy and neuro-oncology. This is particularly true in low-grade gliomas, which frequently involve eloquent areas, possibly due to developmental factors and to the glio-neuronal interactions previously described.[221,222] Induction of a functional redistribution due to the surgical procedure was recently reported, through an unmasking of latent intracortical connections.[83,84] Moreover, this acute remapping observed during resection can be durably stabilized, possibly leading to a long-term remodelling of the functional maps both in the ispi- and contro-lesional hemispheres, as shown by comparing pre- and post-operative functional MRIs.[87] This compensatory redistribution, surgically-induced, was observed for sensorimotor and cognitive functions such as language, in resections involving the primary eloquent areas, and also associative unimodal and plurimodal regions, for example the insular lobe, left inferior frontal gyrus, dorso-lateral prefrontal cortex or left posterior temporal areas,[223–228] without inducing sequelae.

Additionally, as surgery induces compensatory mechanisms that recruit latent networks, this functional reorganization has been reported as a basis for a second surgery, which could extend the initial resection without sequelae. For instance, in some patients, incomplete tumor removals were performed in an initial operation, due to the involvement of eloquent areas. A few years later, the tumor started to grow back and second surgery was done using intraoperative functional mapping. This mapping showed a clear reshaping of the eloquent (sensory, motor and language)

maps. Functional sites corresponded to new adjacent areas, unmasked as a result of the first surgery. This reshaping allowed a total removal of the tumor without deficit.[229]

Therefore, the use of this plastic potential may enable optimal surgical impact in neuro-oncology.[230] A better understanding of these mechanisms should be integrated into surgical indications and dynamic surgical planning. Such a strategy, taking into account the plastic potential and its variability among patients, may help to extend the possibility of resections in so-called 'non-operable eloquent areas', while preserving quality of life.[231,232]

Nevertheless, cortical plasticity is possible only if subcortical connectivity is preserved. Indeed, stroke studies have taught that damage involving the white matter induces severe permanent deficit, supporting the essential role of subcortical pathways.[233] Similarly, in neuro-oncological surgery, many patients display sequelae due to an interruption of the white matter fibers.[234,235] Consequently, during surgery in eloquent areas, the systematic use of intraoperative subcortical stimulation seems mandatory, to better understand underlying anatomo-functional connectivity[141,142,236] and to avoid postsurgical sequelae, which will always be possible despite cortical plastic potential.[237]

4.4.3. Grafts

Modulation of brain function may be considered through neural grafts, influenced by the environment and experience.[238] Although transplantation has remained for a long time at the experimental phase in animals,[239] recent studies have shown applications in humans. The best example is intrastriatal transplantation of fetal striatal neuroblasts in Huntington's disease, which induces motor and cognitive improvement, due to restoration of the function of striato-cortical loops,[240] as suggested using PET, as opposed to continued hypometabolism in patients with failed grafts.[241] Also, transplantation of dopaminergic neural cells has been advocated in Parkinson's disease, particularly within the putamen, with encouraging results,[242] with metabolic changes correlated with the amount of grafted tissue.[243]

Moreover, transplantation of cultured human neuronal cells has been proposed for motor deficit after stroke involving the basal ganglia.[244] Functional improvement was observed in half the patients, with a correlation between clinical results and changes of regional metabolism of glucose measured by PET.[245,246]

The use of pluripotent stem cells has also been suggested,[68,247] including hematopoietic progenitors, able to differentiate in to glial or neural cells depending on the environment.[248] Stem cells can be specifically 'attracted' following brain damage[249] or by tumor.[250] The promotion of axonal guidance, the blocking of factors playing a role in regeneration failure (particularly glial scar),[251] the use of growth factors[252] and even modulation of the immune response,[24] have been considered to facilitate graft efficacy.

4.4.4. Brain-computer interface

Brain-computer interface (BCI)[253] is based on: (i) self-regulation of electroencephalographic activity registered on the scalp,[254] or an electrode implanted on the brain surface, within M1[255] or in the subcortical structures;[256] or (ii) self-regulation of the blood oxygen level dependent (BOLD) signal provided by a real-time fMRI.[257] The goal is to control the movement of a cursor on a computer screen, to select letters or icons, or to command a neuroprosthetic device.[258] BCI is possible through an adapted algorithm of information processing, allowing the conversion of electrophysiological or hemodynamic input into an output that is able to control an external device, ideally with visual, somesthetic and even auditory feedback.[259]

This technique can partly restore communication in severely paralyzed patients, particularly after stroke generating a 'locked-in syndrome'.[260,261] BCI improvement via better recording, processing and feedback of the information in real-time, could increase its applications.[262]

5. Conclusions

Recently, concepts of the spatio-temporal functioning of the nervous system have been dramatically modified. Indeed, the brain is now considered a morphologically and functionally dynamic structure, influenced by the environment, and constituted by interactive distributed glio-neuro-synaptic networks. Each of these comprises several essential and/or modulatory epicenters, with behavioral consequences that depend on their effective spatio-temporal connectivity. Moreover, this whole system is stabilized by a homeostatic plasticity.

Better understanding of these phenomena will enable us to guide cerebral plastic potential, and thus regulate the dynamics of eloquent networks and facilitate functional recovery following brain damage. Such linkage between an improved knowledge of the pathophysiological (microscopic and macroscopic) mechanisms underlying cerebral plasticity, and constraints in its use, opens a large field of new therapeutic perspectives applicable to the functional restoration and optimization of quality of life in patients with nervous system diseases.

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