ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (*IJMSIR*)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 4, Issue – 5, September - 2019, Page No. : 210 – 217

Expression Profile of Neuroplasticity During Awake Surgery: Study of The 10 Firsts Low- Grade Gliomas Cases

[1]A.Bouadel, [2]M.Y. Oudrhiri, [3]M. El Hassani, [4]S. Kabbaj, [5]M. Jiddane, [6]A. El Ouahabi

[1]A.BOUADEL, ERNONFOR Neurosciences center, CEDOC SVS, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

[2]M.Y. OUDRHIRI, Department of Neurosurgery, Unit of Pedagogy and Research in Neurosurgery (UPR), Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

[3]M. El Hassani, Department of Neurosurgery, Unit of Pedagogy and Research in Neurosurgery (UPR), Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

[4]S. KABBAJ, Department of Reanimation Anesthesia, Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

[5]M. JIDDANE, Department of Radiology, Unit of Neuroradiology, Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

[6]A. El Ouahabi , Department of Neurosurgery, Unit of Pedagogy and Research in Neurosurgery (UPR), Ibn Sina Hospital University Center, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

Corresponding Author: A.BOUADEL, ERNONFOR, Neurosciences center, CEDOC SVS, Faculty of Medicine and Pharmacy, University of Mohamed 5 RABAT, Morocco.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Classically the functional recovery potential of postoperative neurological deficits has been modest until the emergence of new exploration techniques (fMRI, MRI, PET) and surgical protocols ; such as exeresis in awake conditions allowing an optimization of the total or supra- total low- grade glioma massively infiltrating subcortical connectivities in eloquent regions ; historically not operable with a significantly high functional recovery rate , simultaneously improving quality of life and survival medians. However optimizing the onco-functional balance requires a better understanding of brain activity in a connectionist (hodological) and dynamic (plastic) context, which will be promising to break new research perspectives, on neuroplastic typology and mechanisms neuromodulation of physiological adaptation to the therapeutic concept, including neuroplasticity induced by therapy, transplantation of neural progenitors or the search for pharmacological agents.

Keywords: Peroperative neuroplasticity / Therapeutic neuroplasticity / Functional recovery / Functional brain mapping / Direct electrical stimulation / fMRI

Introduction

The peroperative neuroplasticity remains one of the factors for the success of surgery in an awake condition, allowing for precise maximalist exeresis in functional other than onco-anatomical limits. The objective of this article is to develop the clinical mechanisms and implications on the functional connectivity of networks, both with regard to the identification of the typology and mechanisms of functional recovery, as well as the potential effects of peroperative awake neuroplasticity on the total recovery of postoperative neurological deficits induced by experience neuroplasticity of rehabilitation therapy.

Materials and Methods

This is a retrospective analytical study of a body of existing cases of the first 10 cases of low-grade glioma type II brain tumors, operated by common neurosurgical intervention in awaking mode, under ethical conditions and considerations, in the department of neurosurgery UPR of IBN SINA Rabat University Hospital Center, accredited by the **W**ord **F**ederation of **N**eursurgical **S**ocieties as being **WFNS** Rabat Reference Center since 2002, under ethical conditions and considerations.

The recruitment of patients is done with their consent after detailed explanations; according to the clinical indications objectified by biological, radiological (MRI, fMRI) and an appropriate orthophonic assessment; considering exclusion criteria.

2.1 Functional brain mapping

It is done by direct electrical stimulation (DES) exploiting the neurophysiological effect of a biphasic electrical current on the neuronal membrane potential of an electrical generator checking the following parameters: Rectangular pulses of 1 ms, Frequency 60 Hz, Intensities of 1 to 6 mA (local anaesthesia), and 4 to 18 mA (general anaesthesia), variable in steps of 0.5 mA, Stimulation time: 1 second (sensorimotor), 4 seconds (cognitive functions). It begins by defining the threshold intensity on the premotor or primary sensorimotor cortex whose somatotopy is known and constant, which will allow a negative response from the patient, marked by a temporary functional deficit of the cortex located between the two poles of the bipolar electrode (5 mm spacing probe). The operator applies the bipolar stimulation electrode, regulated at 1 or 1.5 mA, on focused cortex for 2 to 3 seconds. In the absence of a response to stimulation (negative functional cortical mapping), the stimulation intensity should be gradually increased, in steps of 0.5 mA, until a response is obtained **[1]**.

2.2 Information collections

The speech-language therapist must then carefully observe the patient to detect any errors in cognitive task or motor abnormalities that the surgeon can’t detect through the surgical fields. Thus, the performance of a double motor and language task (performing a flexion/extension of the hand elbow while opening and closing the fist and at the same time a language task) is then recommended because it is simple but requires sustained attention, which makes it possible to test the patient's ability to concentrate and his tiredness state during the exeresis procedure. Numbered paper clues are gradually placed on sites that have caused a reproducible deficit (cortical functional mapping) **[1]**.

2.3 Surgery of excision

During deep dissection within the brain white matter, it is possible to stimulate again, either when the surgeon anatomically thinks he will come into contact with a beam essential to the function to be preserved, or when dissection with the ultrasound dissector causes a transient deficit. The stimulation can then be performed at the same intensity as the cortical stimulation. To increase the sensitivity of the stimulation, it’s possible to increase the intensity by 2 mA, which will increase the diffusion of the electrical current around the electrode without causing a convulsive crises **[1]**.

2.4 Pre and postoperative fMRI

fMRI based on functional activation patterns via the study of variations in blood oxygenation rates (BOLD effect, Blood Oxygen Level Dependent), makes it possible to characterize the brain in action and quantify functional connectivity by measuring statistical interdependencies between BOLD signals recorded in spatially remote areas. The Postoperative MRI, performed systematically, makes it possible to evaluate the extent of the resection and to define its different variants. Namely, a complete excision in the case of low-grade gliomas would correspond to removal of all the FLAIR hypersignal regions, verifiable by comparing the pre-surgical MRI and the postoperative MRI control after 48 hours **[2].**

Results

Clinical cases	Recovery Time (s) * Min	Max	Postoperative Neurological Deficit
Patient 1	1	4	Without complications
Patient 2	3	15	Aphasia recovered by Reeducation
Patient 3	2	7	Hemiparesis recovered by Reeducation
Patient 4	1	6	Without complications
Patient 5	2	10	Aphasia recovered by Reeducation
Patient 6	1	5	Memory disorders recovered
Patient 7	3	10	Hemiparesis recovered by Reeducation
Patient 8	3	12	Paraphasia recovered by Reeducation
Patient 9	3	9	Memory disorders recovered
Patient 10	2	8	Hemiparesis out standing recovery

* Recovery Time extremum after peroperative transient neurological deficit by excision in Awake surgery

Figure 1 : Peroperative recovery times of transient neurological deficits due to DES by Stimulation Intensity Threshold SIT or during excision.

Following DES and during tumor removal, transient neurological deficits appear, including partial or total convulsive crises, depending on the stimulation intensity thresholds, location and tumor infiltration. Each patient recovers the inhibited function even in partial convulsive crises in a few seconds; by momentary cessation of exeresis giving the brain time to reorganize itself or reactivate other neurofunctional pathways (peroperative neuroplasticity); until the end of exeresis according to the functional maximalist limit sometimes marked by the occurrence of total convulsive crise.

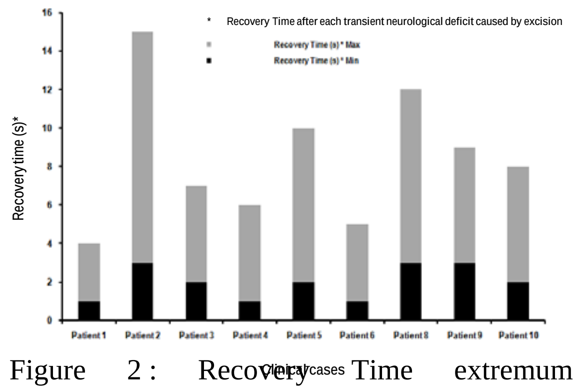

Figure 2 : Recovery Time extremum after intraoperative transient neurological deficit in awake surgery

Recovery time of the inhibited function from cessation of exeresis following the induced transient neurological deficit including partial convulsive crises. It varies from a minimum extremum of 1 s (average of 2.1 s) to 15 s as maximum extremum (average of 8.6 s). Duration of recovery (peroperative neuroplasticity) varies from a minimum of 1 s observed in cortical and subcortical to 15 s most noted during the exeresis in deep eloquent zones. (Optimization of thresholds DES)

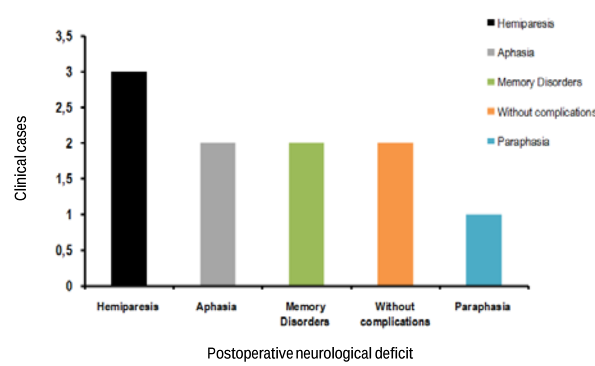

Figure 3 : Postoperative neurological deficits

The study of results reveal that, contrary to the conventional technic of excision surgery, all functions were totally preserved (2 cases without complications) even with transient deficits in peroperative (10 cases) and postoperative neurological deficits after 10 weeks of rehabilitation (8 cases).

The optimization of DES technique shows a fast and higt quality recovery of damaged functions in transient intraoperative deficits during the excision of all cases (peroperative neuroplasticity).

In peroperative care, total convulsive crises (2 cases) were expressed towards the end of exresis surgery in deep eloquent zones marking the functional limit of the tumor.

Discussion

4.1 Peroperative neuroplasticity

In this study, the focus was on peroperative neuroplasticity induced by stimulation and excision in the tumor area. Thus, following exeresis, a neurological deficit **(Figure 1)** due to the disconnection of the extracted portion occurs and several mechanisms are put in place.

Two main types of processes support the neurobiological mechanisms of functional recovery **[3]:**

- Functional reactivation: recovery is done by the perilesional areas of their previous functions, following a period of latency or diaschisis (or functional changes that will remain for a long time) **[4].**
- Functional reorganization: generally occurs when lesions are more massive **[5,6]** and consists of activating noncanonic brain areas for the task; both in the ipsilesional and contralesional hemispheres **[3]**; and areas homologous to the injured areas can be recruited.

Thus, these two processes are carried out according to three main types of morphological changes **[7]:**

- Synaptic remodeling with an implementation time of a few milliseconds to a few minutes: the approximation or removal of existing synapses, the appearance of new synapses, the reinforcement of the interaction between two synapses.
- Pruning or arborization of the branches at the axonal or dendritic branches, with an implementation time of a few minutes to a few days.
- Neurogenesis with a duration of implantation of a few days to a few weeks: mainly in two cerebral regions: the hippocampus region essential to memory mechanisms and which also plays a role in regulating body weight **[8]** and in the olfactory bulb. Data suggest that a third neurogenic "niche" may be located in the parenchyma of the ventral hypothalamus surrounding the 3rd ventricle **[9]**.

In correlation with results of **Figure 2**, the functional recovery time varies from a minimum of 1 s observed in cortical and subcortical to 15 s observed mainly during excision in eloquent deep areas. This recovery marking intraoperative neuroplasticity is mainly done first by synaptic remodelling of all of a functional reactivation and then pruning of the branches consolidating the new neurofunctional interconnectivity as part of a functional reorganization.

4.2 Postlesional neuroplasticity

Hebbian principle brought the notion of response to changes in the environment by remodeling nerve connections and showed the importance of learning in this remodeling **[10, 11]**. Besides the reorganization in response to physiological situations, the adult brain could organize a response to injury situations by reshaping its circuits extremely broad way **[12].**

The Nerve Growth Factor (NGF) became the prototype of molecular families identified by their involvement in neuronal survival and growth but crucial for post-lesional reorganization **[13]**. The evolution of non-invasive investigation methods revealed that the post-lesion reorganization of neuronal circuits did not only concern local connectivity, but extended to whole territories and encompassed tissue responses. like angiogenesis and gliogenesis **[14]**. Thus, in the context of lesions leading to motor deficiency, the functional imaging work made it possible to show that there was a modification of the cortical neuronal activity, with spatial extension of the activation of the primary contralateral motor region of the limb paralyzed and recruitment of ipsilateral sensorimotor regions **[15]**; the involvement of these latter regions being associated with a poorer functional recovery. During language tasks (repetition, name generation) in subjects partially recovered from vascular aphasia, recruitment of distant neurons was also observed with the activation of preserved left temporal frontotemporal regions, as well as symmetric regions from the right hemisphere **[16]**. **(Figure 4).**

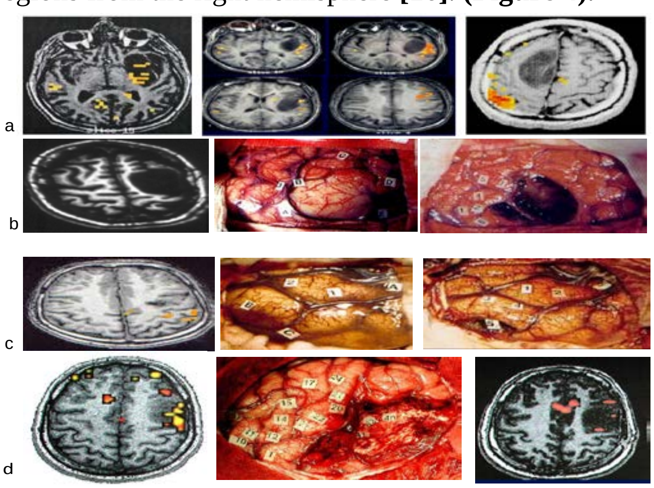

Figure 4 : Study of Neuroplasticity in low grade glioma

a - Preoperative neuroplasticity Intralesional (left), Perilesional (median) and contralateral (right) Duffau et al., Lancet Neurology 2005.

b - Acute peroperative neuroplasticity using stimuli : Local redistribution Duffau et al., Ann Neurology 2000

c - Acute peroperative neuroplasticity using stimuli : Regional redistribution Duffau et al., Ann Neurology 2000

d – Pre, Per and Postoperative neuroplasticity : Expression profil for the same patient Marrelec et al.,

4.3 Molecular Neuroplasticity Modulation Mechanism

The terminal maturation, which gives a neuron its neurochemical identity and its role, is not definitive. Various examples of this ability to modify the molecular content in lesional situation or neuronal versatility according have been described later **[17].** The reworkings of the neuronal circuits are also accompanied by modifications of the vascularization, which adapts to that of the neuronal energy demand.

Among the modalities of neuromodulation allow the neuroplasticity control **(Figure 5)**, The transport of AMPA (α-amino-3-hydroxy-5-methyl-isoxazol) and NMDA (N-methyl-D-aspartat) receptors to and out the synaptic membrane is crucial for the passage of current, which is increased with incorporation into the synapse (Long Term Potentiation LTP), and decreased (Long Term Depression LTD) with diffusion from receptors to the extrasynaptic membrane or internalization **[17,18]**. The phosphorylation of AMPA and NMDA receptors is an important mechanism in internalization/ externalization terms of receptors and current's passage. Multiple phosphorylation sites are responsible for trophic effects, with mechanisms based on cyclic AMP, cyclic GMP, calcium/calmodulin kinase II or protein kinase C. So, the LTP is favoured by the θ rhythm (4.5-8 Hz), which results by phosphorylation of the Y876 residue of the GluR2 subunit of the AMPA receptors. Low frequency stimulation (< 2 Hz) induces LTD and leads to internalization of AMPA receptors.

It has recently been suggested that increases in neurotrophic factors, including BDNF (Brain Derived Neurotrophic Factor), play a critical role in the mode of action of antidepressants **[19]**. Numerous studies have reported the trophic and neuroprotective effect of BDNF, and its role in synaptic plasticity **[20, 21]**. This factor is essential for long-term potentiation, as it is hindered in mice invalidated for its gene. BDNF therefore regulates both the selective survival of neurons during brain development and the experiential regulation of synaptic activation throughout life. The BDNF modulates axonal arborization to promote growth, while neural activity contributes to the stabilization of axonal branches, with both signals converging to shape the shape of axonal dendrites and Increase of calcium in pre and postsynaptic is responsible for the changes in the shape of the dendritic spines.

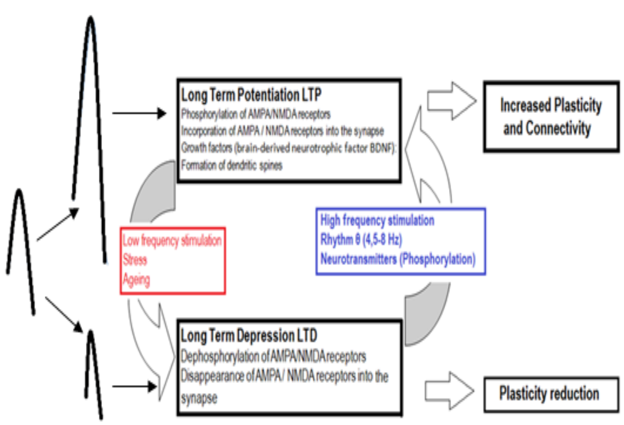

Figure 5: Glutaminergic synapses neuroplasticity: Mechanisms involved in the transition from LTP to LTD

4.4 Neuroplasticity induced by speech therapy

In postoperative care, all neurological deficits were recovered over time during rehabilitation therapy sessions targeted in about 10 weeks **(Figure 3)**, inducing by experience neuroplasticity in favor of speech therapy for aphasia cases. It is expressed by behavioral changes and is decoded by segregation and integration analyses. Thus, following the fMRI data acquisition, it's possible to study the brain areas activations in isolated manner: segregation analyses. It is also possible to study the brain networks activation, or areas sets that act synchronously to accomplish a task: Integration analyses. These dynamic functional networks change their configuration according to the nature and difficulty level of the task. In this case, when two neurons are active simultaneously, they create or strengthen their connection by their synapses, which will facilitate the activation of one another in the future. This principle has been evidenced by Hebb **[22]** and is known as " fire-together-wire-together " **[23]**.

The specificity of a therapy refers to working on a particular deficit by applying targeted therapy. A therapy is specific when it improves a given skill and is built to do so. Specific therapies in turn allow for a higher repetition rate because they target a limited number of behaviors. Thus, since the neurofunctional changes take place thanks to a sufficient repetition rate of the task, it is important to determine this rate which is declined in number of repetitions per session and in number of sessions. Besides, neuroplastic changes require repetitive and concentrated stimulation in a window of time. Finally, salience refers to the fact that the therapy must relate to a task that is useful for the person, capable of capturing all his attention and motivation, with the importance well known by clinicians of proposing personalized intervention items **[23].**

Conclusion

The expression profile of neuroplasticity is extremely complete according to the lesional state, from synaptic remodeling to the connectionist (hodological) and dynamic (plastic) context, allowing excision according to functional other than onco-anatomical limits without permanent postoperative neurological deficits, findings of a synchrony between induced and postlesional therapeutic neuroplasticity.

In the dynamic context, a focus on the continous brain remodeling networks to encode new experiments especially the default mode network, allows to say that the potential of brain plasticity has not yet reached its limit, which opens new perspectives on neuroplasticity research from physiological adaptation to the therapeutic concept, namely the transplantation of progenitors neural or the search for pharmacological agents ensuring the optimization of neuromodulation for instance the allosteric modulators of AMPA receptors.

Data Availability

The data [Exploitation sheet, Clinical informations] used to support the results of this study are available upon request from the corresponding author.

The data used to support the findings of this study are included within the article.

References

1. Duffau H. Peroperative functional mapping using direct electrical stimulations. Methodological considerations. Neurochirurgie 50:474-483, 2004.

2. Berger MS. Functional mapping-guided resection of low-grade gliomas. Clin Neurosurg 1995 ; 42 : 437-452.

3. Grafman J. Conceptualizing functional neuroplasticity. J Commun Disord 2000 ; 33 : 345-56.

4. Murase N, Duque J, Mazzocchio R, et al. Influence of interhemispheric interactions on motor functioning chronic stroke. Ann Neurol 2004 ; 55 : 400-9.

5. Anglade C, Thiel A, Ansaldo AI. The complementary role of thecerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. Brain Inj 2014 ; 28 : 138-45.

6. Crosson B, McGregor K, Kaundinya S, et al. Functional MRI language in aphasia: a review of the literature and the methodological challenges. Neuropsychol Rev 2007 ; 17 : 157-77.

7. Castrén E, Hen R. Neuronal plasticity and antidepressantactions. Trends Neurosci 2013;36:259—67.

8. Davidson TL, Chan K, Jarrard LE, Kanoski SE, Clegg DJ, BenoitSC. Contributions of the hippocampus and medial prefrontalcortex to energy and body weight regulation. Hippocampus 2009;19:235—52.

9. Cheng M-F. Hypothalamic neurogenesis in the adult brain. FrontNeuroendocrinol 2013;34:167—78.

10. Hebb D.O. The effects of early experience on problem solving at maturity. Am Psychol, 1947, 2, 737–745.

11. Weiller C, Isensee C, Rijntjes M et al. Recovery from Wernicke's aphasia: a positron emission tomographic study. Ann Neurol 1995 ; 37 : 723-32.

12. Neves G., Cooke S.F., Bliss T.V. Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nat Rev Neurosci, 2008, 9, 65–75.

13. Levi-Montalcini R. The nerve growth factor and the neuroscience chess board. Prog Brain Res, 2004, 146, 525–527.

14. Rossini P.M,. Calautti C., Pauri F., Baron J.C. Post-stroke plastic reorganization in the adult brain. Lancet Neurol 2003, 2, 493–502.

15. Chollet F, Di Piero V, Wise R et al. The functional anatomy of motor recovery after stroke in humans: a

study with positron emission tomography. Ann Neurol 1991 ; 29 : 63-71.

16. Caramia M, Palmieri M, Giacomini P et al. Ipsilateral activation of the unaffected motor cortex in patients with hemiparetic stroke. Clin Neurophysiol 2000 ; 111 : 1990-6.
17. Barry MF, Ziff EB. Receptor trafficking and the plasticity of excitatory synapses. Curr Opin Neurobiol 2002; 12: 279-86.
18. Tardin C, Cognet L, Bats C, et al. Direct imaging of lateral movements of AMPA receptors inside synapses. EMBO J 2003; 22: 4656-65.
19. Duman RS, Charney DS. Cell atrophy and loss in major depression. Biol Psychiatry 1999; 45: 1083-4.
20. Lauterborn JC, Lynch G, Vanderklish P, et al. Positive modulation of AMPA receptors increases neurotrophin expression by hippocampal and cortical neurons. J Neurosci 2000; 20: 8-21.
21. Dicou E, Rangon CM, Guimiot F, et al. Positive allosteric modulators of AMPA receptors are neuroprotective against lesions induced by an NMDA agonist in neonatal mouse brain. Brain Res 2003; 970: 221-5.
22. Kleim JA, Jones T. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. JSLHR 2008 ; 51 : S225-39.
23. Durand E, Mina D, Vauclare E, et al. Imagerie par résonance magnétique fonctionnelle (IRMf) et orthophonie : quelles applications cliniques ? Rééd Orthe 2014 ; 260 : 151-69.