

# MICROGLIAL PLASTICITY

**Natalia Alina Topor**

Department of Life Sciences, Faculty of Medicine, "Vasile Goldis" Western University of Arad

2.Dana Olar Department of Life Sciences, Faculty of Medicine, "Vasile Goldis" Western University of Arad

3.Cecilia Avram ,Department of Life Sciences, Faculty of Medicine, "Vasile Goldis" Western University of Arad,

4.Ramona Burlacu, Department of Life Sciences, Faculty of Medicine, "Vasile Goldis" Western University of Arad

\*Correspondence: Natalia Alina Topor, "Vasile Goldis" Western University Arad, Faculty of Medicine, Department of Life Science, no. 1 Constitution St., 310396, Arad, Romania, Tel. +40-(257)-222222, Fax. +40-(257)-222222, email [alinatopor@gmail.com](mailto:alinatopor@gmail.com)

**Abstract.** Epistemological concept of plasticity makes links between the unconscious and the conscious, the expression of the future systems is now centered on the perception and representation of brain plasticity. The plasticity of spirit., as knowledge and consciousness of the world, concept that touches art, cross exchange and continuous flow between people, languages and knowledge, and transdisciplinarity approach to human plasticity. Neurobiological plasticity concept showing that experience leaves structural and functional neural networks, also shatter classical opposition between a psychic etiology and organic etiology of mental phenomena. Associations between neuropsychiatric and immunological disorders might involve disruption of microglial activity.

**Keywords:** brain, microglia, neural, plasticity, unconscious.

## INTRODUCTION

Microglia, the immune-competent brain cell is now the main player in the neurosciences, being impossible to talk about the physiology and pathology of the brain without involving this cell, known until yesterday only to support immune function of central nervous system, the microglia is at the interface of biological, medical and psychological sciences(Kato,2013).

Interdisciplinarity, which makes possible to escape from the dogma of a single science, is based on the concept of plasticity, which is the fundamental characteristics of the world at all levels (starting with the first level of matter, continuing with the plasticity of the living/ brain, of the subject, then of the mind/ spirit and ending with the metaplasticity that there is at all previous levels and includes them.Dobono,2012).

Conceptual axis connecting interdisciplinarity is plasticity of the biophysical systems, something that could be seen as a plastic code enabling extension and durability of living, matter, mind and spirit.

Neuroscience, behavioral physiology, neurophysiology, all begin with the relation mind -

brain, which caused many debates in all fields of knowledge, including philosophy and culture.

In the same manner, we can not discuss about the mind-brain interface without the concept of plasticity. Only plasticity is able to provide the joint interface between unformed and formed, between matter and form, between content and container, between nature and acquired, from the contents of consciousness and emotions; plasticity interfacing being and human behavior, transformations of matter and form and their cosignification in living universe.

On the biological level we can talk about the neuronal plasticity and recently, the discovery of the interaction between microglia and neurons question microglia involvement in neuronal plasticity.Ketteman,2011

## THE UBIQUITOUS PLASTICITY

Starting from plasticity, as the fundamental characteristics of matter, at all levels of the organization, interaction and reality, the concept of plasticity has wide recognition in every field of knowledge. Epistemological there are described several

interfaces the plasticity, including interface mind - brain.

## **THE MIND-BRAIN INTERFACE. BRAIN PLASTICITY**

The second level of plasticity is described by referring to the plasticity of the living / brain, the first level being the material. Describing adaptation, movement and coherence observable beginning with organelles and finishing to body/organism, plasticity is expressed at all levels of life: phylogeny, epigenesis, ontogenesis. In animals and humans, brain plasticity is inextricably linked to the representation of the surrounding world.

Plasticity is expressed in brain restless, always on the move, which is now recognized by neurosciences as the place of permanent reorganization, directly linked to subjective experience immediate or last translated by modulating gene expression during embryogenesis, by increased neuroplasticity to adolescence and by adult neurogenesis in certain brain structures, through the perceptions and cognitive systems implied in memory processes, emotion, and unconscious.

This world of the brain involves the paradox of being both the structured and orderly living organ system, as well as the most sensitive to the environment, and to the particular experience of the subject. Homeostasis is finely regulated to primates and humans. Innate plasticity of the brain and consciousness are integral and grow together, in an area of plastic expression that leads to unity of action as an expression of living systems in the ecosystem. These positions illustrate the role of plasticity in information theory and especially in the brain-spirit interface. Indeed many authors talk about the limits of phenotypic disorders autism and schizophrenia. Recently microglia is involved in nervous system disorders as well as in brain physiology in homeostatic conditions. Dobono, 2010

## **INTERFACE MICROGLIA-NEURON. MICROGLIAL PLASTICITY. MICROGLIA IN NEURONAL PLASTICITY**

The microglia senses synaptic activity through their extended complement of neurotransmitter receptors. Microglia in the state of surveillance scans synaptic contact in its territory through contacts (4-5 min) with synaptic structures. Wake, 2009 In conditions

of ischemia this contact is prolonged (an hour and more) and these extended links between microglial processes and synapses lead to disappearance of the latter.

This plastic behavior indicates constant monitoring of the status of synaptic resting microglia, through secretion of NCAM, integrins / adhesion molecules / transient contact between microglia and neurons.

The change of synapse can trigger local response of glial cells with consequences in remodeling synaptic architecture, process called "synaptic stripping", produced for example from the cortex neuroinflammation and probably mediated by ATP / adenosine release from microglial cells in early stages of activation. Yamada, 2008

The synaptic stripping removes excitatory synapses glutamergic thus limiting neuronal excitability and glutamate toxicity. Linda, 2000, the specificity of action is associated with MHC class F present in neurons and microglia receptors.

Microglial surgical removal may decrease the effectiveness of synaptic and interfere with neuronal communication. In conclusion, microglial cells have a plastic role in the ability to remove and shape the synapses from their territorial areas. Cullheim, 2007

The same time, the microglia may potentially be involved in the reverse creation of new synapses. Evidence indicates involvement of microglia in regulating synaptogenesis in early postnatal brain. Microglia can stimulate the synaptogenesis of the secretory thrombospondins (TSPs) forming part of the extracellular matrix proteins critical for synapse formation, produced by astrocytes. Chamak, 2007. TSP1 interacts with the integrin-associated protein CD47, which receives signals from regulatory protein (SIRP)  $\alpha$ , a transmembranar protein expressed by neurons and macrophages. Christopherson, 2005

SIRP $\alpha$ -CD47 system is involved in regulating migration and phagocytosis, immune homeostasis and neural networks. CD47 and the two ligands, SIRP $\alpha$  and TSP1, a homeostatic role in the immune system, and participate in synaptic structure involving CNS innate immune system cells such as microglia. thrombin, the blood coagulation factor II(a) and name-giving inducer of TSP in platelets, which has been associated with synapse elimination and plasticity (Turgeon, 1997, Zoubine, 1996), has its receptors expressed on microglia (Balcaitis, 2003).

Microglia appears as an important factor in restoring neuronal connectivity by controlling reactive synaptogenesis at CNS (Luo, 2006). Plastic regenerative potential of microglia is well documented, the importance of microglia recovery and repair neuronal (Batchelor 1999, Bruce-Keller 1999, Moller, 1996). Synaptic connectivity was demonstrated in transplantation microglia / macrophages in the lesioned optic nerve or spinal cord improves posttraumatic regeneration (Lazarov, 1996, Rabchevsky, 1997).

The contributions of microglia, and in particular of certain phenotypes (Butovsky, 2006, McPherson, in press) to CNS plasticity may include the support of neurogenesis. Some studies show the role of T cells and microglia in the maintenance of neurogenesis in the hippocampus as well as spatial learning ability.

Adaptive immune system and innate immunity keeps cell renewal capacity and supportive CNS (it suggests that TLRs may modulate neurogenesis in hippocampus). TLR2 and TLR4 have been identified in the neural stem cells with opposite effects on their proliferation and differentiation (Rolls, 2007). These TLRs agonists affect microglia. Importance of microglial normal functions has been demonstrated in mice with a homozygous loss of function mutation in *Hoxb8*, having developed a syndrome similar to an obsessive-compulsive disorder in humans. *Hoxb8* lineage was associated in CNS with a subpopulation microglia and bone marrow transplantation has been saving (Chen, 2010). Thus has been demonstrated that synaptic contacts and neural elements could benefit from the action of microglia. Associations between neuropsychiatric and immunological disorders might involve disruption of microglial activity.

Microglial-derived factors may affect also direct synaptic transmission. This, for example, has been observed in bone marrow, which stimulating microglia with ATP to trigger the release of BDNF, thereby converting the glycine- and GABA-mediated inhibitors of the excitatory postsynaptic responses of. This type of interaction - microglia / neuron have been discussed in the context of neuropathic pain, although similar mechanism could be active in the absence of pathological insult. Direct microglia to synaptic plasticity in the hippocampus was also observed treated with Ap1-42. This treatment inhibits the induction of LTP (Wu, 2008), which in turn was mediated by NO

released by microglia. Activated microglial cells have the potential to influence the homeostatic synaptic scaling, which requires uniform adjustment to all synapses via a mechanism distinct from long-term synaptic potentiation or depression (Wang, 2004).

Studies have founded synaptic scaling in response to prolonged blockade of activity mediated by proinflammatory cytokines  $\text{TNF-}\alpha$  from glial cells (Stellwagen, 2006). They conclude that glial cells actively participate in regulating activity-dependent homeostatic regulation of synaptic connectivity by modulating the levels of  $\text{TNF-}\alpha$ . In the central nervous system, the NO is first of all a neuromodulator factor. And also a toxic gas in the cytotoxic attack used by immune cells, such as microglia, which can release NO - and thus integrating endocrine activities with activities of the immune system in response to infection and injury when NO is induced as part of a reactive phenotype.

Microglial cells, based on their state of activation, may have a trophic role (Elkabes, 2006), indicated by neurotrophin expression, secretory proteases (Kohsaka, 1996) secreted by microglia nutrition of neural circuits that regulate growth, differentiation, and the formation of neural circuits. Elkabes (2006) keeping perspective of the developmental potential of microglia in the CNS, numerous inflammatory cytokines are associated with immune response and have a role in the maturation of the CNS, such as astroglial growth factor IL-1 (Giulian, 1998).

Microglial cells are involved in nervous system development based on well-controlled balance between neurogenesis and neuronal death. Microglia has dual action on neurogenesis, supportive and negative, probably related mechanisms for differences in the activation status of microglia, and therefore the difference in the secretion of cytotoxic factors or protective / instructive (Ekdahl, 2009). Microglia-derived factors are involved in directing the migration and final training of neural cells. If ever microglial cells can give rise to other cells, including neuronal phenotype is an interesting question.

Even if microglia express stem cell markers and therefore was considered as an immature cell trans-differentiation of this type of transition for neural guidance will challenge mesodermal origin of microglia (Aarum, 2003).

Microglial cells have the potential to regulate the development, structure, and function of neural networks. They permanently monitor the synaptic contacts and receive information from neural networks. In theory, at least, microglial cells are also able to remodel the neuronal connectivity of and thus participate to physiologic processes in common with those of neurons.

Multiple states of activation of microglial cells allow the existence of "active resting" microglia, or even "active" compartments in the microglial surveillance processes that interact dynamically with neural circuits and provide additional plastic cover.

In pathological situations with blood-derived monocytes/macrophages infiltrating the CNS, features and functions of resident microglia and the invading cells may overlap or complement each other, with both detrimental and beneficial consequences (Shechter, 2009, Simard, 2006)

What is needed for recruitment of peripheral macrophages when microglia could perform all tasks? Responses are expected to understand microglia in health and disease and to evaluate the therapeutic potential of their irregularity correction. kettemann

## **PERSPECTIVES AND FUTURE DIRECTIONS REGARDING MICROGLIAL PLASTICITY**

The cerebral pathology is correlated with the activation of microglial cells recognized by the morphological transition from one form branched amoeboid type. In the last two decades, microglial cells have emerged as an essential component for understanding cellular brain disease. Battery microglial cells can release a signal molecule which serve in the cross-talk with brain cells, for example, macroglial cells and neurons, as well as infiltration of immune cells such as T lymphocytes. There have been studies focus on the motility cells that led to the conclusion that microglial cells are active even in normal brain. Further studies will produce a more heterogeneous microglial cell diversity based on the development of the brain region or pathological condition. It also remains an interesting and unresolved question under what conditions and through what mechanisms prevent or contrary microglial cells facilitates the progression of brain disease.

## **INTERFACE MATER - PSYCHIC**

Indeed, the plastic approach enrolls in the plurality of memories, conscious and possible unconscious, indicating common subjects with current neuropsychanalytic developed by Solms, 1998, 2002 Damasio, 2008, 2013 and Ansermet and Magistretti, which recognizes the key role of plasticity in linking synapses by psychic, situating in the biological approach of the Freudian unconscious, but conceptually differentiating interpretation that converges to the individuation and Jungian archetypes. Plastic interface psychic - material, plasticity complex, so named by analogy, is the only process capable of interfacing the brain and mind, the subject and object, experience - awareness, innate processes - the acquired ones, unconscious - conscious, without losing our identity.

It is the privileged place for the expression of plasticity memories. A place where the thoughtful being can plasticity will, where complexity becomes irreversible for those who evolve the material world, where plasticity of the spirit lead to the unique evolution of each individual.

## **INTERDISCIPLINARY AND TRANSDISCIPLINARY**

Transdisciplinarity involves the concept of plasticity - that, at the third level, described by Debono, 2012 refers to the subject plasticity located at ontological, epistemic and transdisciplinary intersections which found human society.

Mind / spirit plasticity involves upstream states of receptivity (systems of consciousness, perceptions without representations noncognitive) and downstream states of consciousness (neuroplasticity, cognition, phenomenology, etc.). By extension, the plasticity of the mind / spirit is the generic term chosen to describe this approach which refers to knowledge and consciousness of the world.

Introducing the subject in the world plasticity record the human experience. This experience leads to a specific dimension: that of a project, an otherness, a possible transcendence also the birth of conscious and unconscious processes themselves.

## **CONCLUSIONS**

Neurobiological plasticity concept showing that experience leaves a structural and functional neural networks, also shatter classical opposition

between a psychic etiology and organic etiology of mental phenomena.

This plasticity introduces designation of a mental causality able to modify the synaptic organization. Plasticity involves thinking of neural networks as open to change; therefore the brain is seen as a highly dynamic organ in permanent interaction with the environment and the psychic life of the subject. Plasticity can always change what was, and keep the subject open to unpredictability in the construction of individuality. Therefore, plasticity has introduced a new paradigm for thinking about the connection between psychological and the biological. If the neural network is determined biologically programmed to change and the subject participate in its emergence, neuroscience and psychology / psychoanalysis meet in new manner to issue of emerging the singularity, in which they can train each other.

Interdisciplinarity and transdisciplinarity of neuroscience and psychology can focus on the consequences of changing the knowledge paradigm, change that is itself evidence of plasticity, which reveals potential given by the contingent experience, towards becoming each subject, each with his brain.

Epistemological concept of plasticity makes links between the unconscious and the conscious, between the genetic and epigenetic, which alone fully reveals the expression of the future systems is now centered on the perception and representation of brain plasticity shows its relevance and minuses. The plasticity of spirit, as knowledge and consciousness of the world, concept that touches art, cross exchange and continuous flow between people, languages and knowledge, and transdisciplinarity approach to human plasticity. An approach that emphasizes methadynamics aware systems, infinite plasticity of the spirit, from the universal character of plasticity inherent in the basic material, the shape and the surrounding reality. The plasticity of spirit articulates his experience with the matter that thinks, self empowerment targets crossing the collective unconscious of humanity.

## REFERENCES

Aarum J, Migration and differentiation of neural precursor cells can be directed by microglia. *Proc Natl Acad Sci USA* 100: 15983–15988, 2003

Balcitis S, Xie Y, Weinstein JR, Andersen H, Hanisch UK, Ransom BR, Moller T. Expression of proteinase-activated receptors in mouse microglial cells. *Neuroreport* 14: 2373–2377, 2003.

Batchelor PE, Liberatore GT, Wong JY, Porritt MJ, Frerichs F, Donnan GA, Howells DW. Activated macrophages and microglia induce dopaminergic sprouting in the injured striatum and express brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. *J Neurosci* 19: 1708–1716, 1999.

Bruce-Keller AJ. Microglial-neuronal interactions in synaptic damage and recovery. *J Neurosci Res* 58: 191–201, 1999.

Butovsky O, Ziv Y, Schwartz A, Landa G, Talpalar AE, Pluchino S, Martino G, Schwartz M. Microglia activated by IL-4 or IFN- $\gamma$  differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Mol Cell Neurosci* 31: 149–160, 2006.

Chamak B, Dobbertin A, Mallat M. Immunohistochemical detection of thrombospondin in microglia in the developing rat brain. *Neuroscience* 69: 177–187, 1995.

Chen SK, Tvrdik P, Peden E, Cho S, Wu S, Spangrude G, Capecchi MR. Hematopoietic origin of pathological grooming in Hoxb8 mutant mice. *Cell* 141: 775–785, 2010.

Christopherson KS, Ullian EM, Stokes CC, Mullen CE, Hell JW, Agah A, Lawler J, Mosher DF, Bornstein P, Barres BA. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. *Cell* 120: 421–433, 2005.

Cullheim S, Thams S. The microglial networks of the brain and their role in neuronal network plasticity after lesion. *Brain Res Rev* 55: 89–96, 2007

Damasio A, Meyer K. "Behind the looking glass". *Nature* 454 (7201): 167–168. doi:2008

Damasio, A; Carvalho, J. "The nature of feelings: Evolutionary and neurobiological origins". *Nature reviews. Neuroscience* 14 (2): 143–52. doi:2013

Debono, Marc Williams, "Condition of plasticity" in the journal *Implications Philosophiques*, 2012

Debono, Marc Williams, "The complex of Plasticity : progress achieved and immersion", in *PLASTIR* n°18, 03/2010.

Ekdahl CT, Kokaia Z, Lindvall O. Brain inflammation and adult neurogenesis: the dual role of microglia. *Neuroscience* 158: 1021–1029, 2009.



Elkabes S, DiCicco-Bloom EM, Black IB. Brain microglia/macrophages express neurotrophins that selectively regulate microglial proliferation and function. *J Neurosci* 16: 2508–2521, 1996.

Giulian D, Young DG, Woodward J, Brown DC, Lachman LB. Interleukin-1 is an astroglial growth factor in the developing brain. *J Neurosci* 8: 709–714, 1988.

Kato TA and Kanba S (2013) Are microglia minding us? Digging up the unconscious mind-brain relationship from a neuropsychanalytic approach. *Front. Hum. Neurosci.* 2013.

Kettenmann Helmut, Uwe-Karsten Hanisch, Mami Noda, and Alexei Verkhratsky, *Physiology of Microglia*,

*Physiol Rev* vol. 91 no. 2 461-553, 2011

Kohsaka S, Hamanoue M, Nakajima K. Functional implication of secretory proteases derived from microglia in the central nervous system. *Keio J Med* 45: 263–269, 1996.

Lazarov-Spiegler O, Solomon AS, Zeev-Brann AB, Hirschberg DL, Lavie V, Schwartz M. Transplantation of activated macrophages overcomes central nervous system regrowth failure. *FASEB J* 10: 1296–1302, 1996.

Linda H, Shupliakov O, Ornung G, Ottersen OP, Storm-Mathisen J, Risling M, Cullheim S. Ultrastructural evidence for a preferential elimination of glutamate-immunoreactive synaptic terminals from spinal motoneurons after intramedullary axotomy. *J Comp Neurol* 425: 10–23, 2000.

Luo C, Clark JW Jr., Heming TA, Bidani A. A macrophage cell model for pH and volume regulation. *J Theor Biol* 238: 449–463, 2006.

Magistretti PJ, Ansermet F. Neuronal plasticity: a new paradigm for resilience. *Schweiz Arch Neurol Psychiatr.*;159:475–9., 2008

McPherson CA, Kraft AD, Harry GJ. Injury-induced neurogenesis: consideration of resident microglia as supportive of neural progenitor cells. *Neurotox Res.* In press.

Moller JC, Klein MA, Haas S, Jones LL, Kreutzberg GW, Raivich G. Regulation of thrombospondin in the regenerating mouse facial motor nucleus. *Glia* 17: 121–132, 1996.

Rabchevsky AG, Streit WJ. Grafting of cultured microglial cells into the lesioned spinal cord of adult rats enhances neurite outgrowth. *J Neurosci Res* 47: 34–48, 1997.

Rolls A, Shechter R, London A, Ziv Y, Ronen A, Levy R, Schwartz M. Toll-like receptors modulate adult hippocampal neurogenesis. *Nat Cell Biol* 9: 1081–1088, 2007.

Shechter R, London A, Varol C, Raposo C, Cusimano M, Yovel G, Rolls A, Mack M, Pluchino S, Martino G, Jung S, Schwartz M. Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. *PLoS Med* 6: e1000113, 2009.

Simard AR, Soulet D, Gowing G, Julien JP, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron* 49: 489–502, 2006.

Solms, M. Preliminaries for an integration of psychoanalysis and neuroscience. Presented at a meeting of the Contemporary Freudian Group of the British Psycho-Analytical Society, 1998

Solms, M. & Turnbull, O.) *The Brain and the Inner World: An Introduction to the Neuroscience of Subjective Experience.* London & New York: Other/Karnac., 2002

Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF- $\alpha$ . *Nature* 440: 1054–1059, 2006.

Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *J Neurosci* 29: 3974–3980, 2009.

Wang Q, Rowan MJ, Anwyl R.  $\beta$ -Amyloid-mediated inhibition of NMDA receptor-dependent long-term potentiation induction involves activation of microglia and stimulation of inducible nitric oxide synthase and superoxide. *J Neurosci* 24: 6049–6056, 2004.

Wu LJ, Zhuo M. Resting microglial motility is independent of synaptic plasticity in mammalian brain. *J Neurophysiol* 99: 2026–2032, 2008.

Yamada J, Hayashi Y, Jinno S, Wu Z, Inoue K, Kohsaka S, Nakanishi H. Reduced synaptic activity precedes synaptic stripping in vagal motoneurons after axotomy. *Glia* 56: 1448–1462, 2008.

Zoubine MN, Ma JY, Smirnova IV, Citron BA, Festoff BW. A molecular mechanism for synapse elimination: novel inhibition of locally generated thrombin delays synapse loss in neonatal mouse muscle. *Dev Biol* 179: 447–457, 1996.

