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Research Report

Synaptic plasticity and experimental autoimmune encephalomyelitis: implications for multiple sclerosis

Massimiliano Di Filippo[a,*], Antonio de Iure[a], Valentina Durante[a], Lorenzo Gaetani[a], Andrea Mancini[a], Paola Sarchielli[a], Paolo Calabresi[a,b]

[a]Clinica Neurologica, Dipartimento di Medicina, Università degli Studi di Perugia, Perugia, Italy
[b]IRCCS Fondazione S Lucia, Rome, Italy

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ABSTRACT

Structural and functional neuronal plasticity could play a crucial role during the course of multiple sclerosis (MS). The immune system and the central nervous system (CNS) strictly interact in physiologic conditions and during inflammation to modulate neuroplasticity and in particular the ability of the synapses to undergo long-term changes in the efficacy of synaptic transmission, such as long-term potentiation (LTP). During MS, neuroinflammation might deeply influence the ability of neuronal networks to express physiologic plasticity, reducing the plastic reserve of the brain, with a negative impact on symptoms progression and cognitive performances. In this manuscript we review the evidence on synaptic plasticity alterations in experimental autoimmune encephalomyelitis (EAE), the most diffuse and widely utilized experimental model of MS, together with their potential underlying mechanisms and clinical relevance.

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1. Introduction

Multiple sclerosis (MS) is a chronic, worldwide diffused, inflammatory and neurodegenerative disease that affects the central nervous system (CNS) (Compston and Coles, 2008). The disease usually starts with a relapsing-remitting course but over time most patients start to develop progressive neurological deficits occurring independently of relapses (Compston and Coles, 2008).

MS, and in particular its relapsing-remitting phase, appears to be mediated by immunological mechanisms (McFarland and Martin, 2007). However, even in the earliest phases of the disease, pathogenic aspects involving neurons, axons and synapses coexist. To date, the pathogenesis of disease progression and neuro-axonal involvement in MS is still complex and far from being completely elucidated (Imitola et al., 2006).

Synaptic plasticity represents one of the most fascinating properties of the brain since it reflects CNS ability to retain memories, to learn, and to cope with injuries in an adaptive or maladaptive manner. Structural and functional neuronal plasticity, and in particular the ability of the synapses to undergo long-term changes in the efficacy of synaptic

*Corresponding to.Clinica Neurologica, Dipartimento di Medicina, Università degli Studi di Perugia, Ospedale S. Maria della Misericordia, 06132, Perugia, Italy. Tel.: +39 075 5784228; fax: +39 075 5784229.
E-mail address: massimiliano.difilippo@unipg.it (M. Di Filippo).

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transmission, named long-term potentiation (LTP) and long-term depression (LTD) (Malenka and Bear, 2004) may play a crucial role during the course of multiple sclerosis (Pelletier et al., 2009). Since the immune system and the CNS strictly interact in physiologic conditions and during inflammation to modulate neuroplasticity, it is possible to conceive that plastic synaptic processes might be altered in the MS brain (Di Filippo et al., 2008). In particular, the neuroinflammatory environment that characterizes MS may deeply influence the ability of neuronal networks to express physiologic plasticity, leading to the progressive exhaustion of the plastic reserve of the brain, with negative effects on symptoms progression and cognitive performances.

The aim of the present work is to review the available evidence on synaptic plasticity alterations in experimental autoimmune encephalomyelitis (EAE), the most diffuse and widely accepted experimental model of MS, together with their potential underlying mechanisms and clinical relevance.

2. The importance of brain plasticity in MS

During MS, brain plastic process might try to cope with the diffuse white and grey matter damage that characterizes the disease, in order to preserve neurological functions. Accordingly, it has been raised the hypothesis that long-term preservation of brain functional adaptive mechanisms might contribute to a more favorable course of the disease (Rocca et al., 2010). Different MS functional domains are influenced by plastic processes. For example, it has been shown that early neuroplasticity in higher visual areas plays a pivotal role in mediating recovery from optic neuritis (Jenkins et al., 2010). In particular, baseline fMRI responses in the lateral occipital complex were found to be associated with a better visual outcome at 12 months (Jenkins et al., 2010) independently from demyelination or neuroaxonal tissue damage in the anterior or posterior visual pathway (Jenkins et al., 2010). This evidence points to the fact that early and effective brain plasticity might ameliorate the long-term consequences of disease relapses, suggesting that pharmacological or neurophysiological strategies able to drive adaptive plasticity in the initial stages of the disease might counteract future disability.

Sensorimotor reorganization also characterizes MS, depending on the disease phases and stages and on the extent of CNS damage (Tomassini et al., 2012). Indeed, as the disease progresses, functional reorganization evolves into a pattern of bihemispheric activation (Rocca et al., 2005) with involvement of higher control sensorimotor areas even for simple motor tasks (Rocca et al., 2005; Tomassini et al., 2012). In particular, as the disease evolves from the initial stages to the progressive phases, the functional reorganization of the motor system leads to the sequential involvement of primary sensorimotor regions (Rocca et al., 2005), secondary motor areas (Rocca et al., 2003) and multimodal non-motor areas (Rocca et al., 2002), with a hierarchical distribution (Tomassini et al., 2012).

Cognition is another functional domain that is very frequently involved in MS (Chiaravalloti and DeLuca, 2008) and for which brain plasticity may exert an important role. It has been shown that specific cognitive tasks such as memory, information processing and executive functions may require the activation of wider and more bilateral networks in patients with MS than in healthy individuals (Audoin et al., 2003; Chiaravalloti and DeLuca, 2008; Chiaravalloti et al., 2005; Tomassini et al., 2012). Interestingly, however, it has also been reported by some studies a lower magnitude of activation of task-specific networks in patients with MS compared with healthy subjects (Cader et al., 2006) suggesting that, although cognitive processing in the task appears to be performed using similar brain regions in patients and controls, the patients could have a reduced functional reserve for cognition relevant to memory (Cader et al., 2006).

In conclusion, it appears evident that brain networks underlying very relevant functional domains such as vision, sensorimotor function and cognition are progressively modified by the MS-associated pathologic process in a way that can be adaptive or maladaptive in nature. In particular, the observed functional reorganization can be interpreted as an adaptive form of plasticity in which compensatory activation might enable patients to efficiently perform simple tasks, but recruiting more complex brain systems than normal subjects (Pelletier et al., 2009). At the same time, it is not possible to exclude that functional changes might also reflect forms of maladaptive plasticity. In particular, it has been shown that brain activity changes directly related to disability may reflect responses to altered patterns of use (Reddy et al., 2002).

An interesting observation is that the ability of the brain to express LTP-like changes, explored through transcranial magnetic stimulation (TMS) seems to counteract disability progression in MS (Weiss et al., 2014). For example, it has been shown that paired associative stimulation (PAS)-induced LTP is a predictor of symptoms recovery from relapses (Mori et al., 2014a) and that LTP, explored over the primary motor cortex is possible and even enhanced in the initial, relapsing-remitting phases of the disease, while it is absent is subjects suffering from a progressive form of MS (Mori et al., 2013).

Thus, it is possible to conceive that, in the first years after MS onset, a patient may be able to cope with the focal and diffuse brain damage associated with the disease by exploiting the ability of brain networks to adapt themselves in a plastic manner. Conversely, after the exhaustion of its plastic reserve the disease could enter in its progressive, more disabling phases. These considerations increase the interest in understanding the basic mechanisms of neuronal plasticity applied to MS and, in particular, the bidirectional interaction between the immune and the nervous system in the modulation of neuronal function, in order to hypothesize the use of plasticity as a target for therapeutic and rehabilitative strategies.

3. Synaptic plasticity and the neuro-immune interaction

One of the most important features of the brain is represented by its ability to store vast amounts of information and to dynamically modify the strength of synaptic connections between neurons and neuronal networks. Synaptic plasticity,