PERSPECTIVE

# Environmental enrichment as a promising strategy for aiding multiple sclerosis treatment

Multiple sclerosis (MS) is a complex chronic disease of the central nervous system (CNS) which includes three main anatomopathological characteristics: inflammation, demyelination, neurodegeneration. This pathology induces many clinical symptoms, depending on the site of the lesions, such as motor, sensitive, visual, urinary and cognitive manifestations. In addition, MS is a very heterogeneous disease that displays different clinical courses or phenotypes (relapsing/remitting MS, primary progressive MS (PPMS) and secondary progressive MS (SPMS). Both neurodegeneration and inflammation are present along the natural history of the disease. However, the balance of both phenomena varies according to the course of the disease. In relapsing/remitting MS form, the acute inflammation, mainly adaptive immunity, predominates over the neurodegeneration, being the main cause of the relapses. In SPMS and PPMS, the neurodegeneration predominates over the inflammation, which appears as chronic inflammation, being innate immunity (microglia and astroglia) the main feature in the neurodegenerative process.

Even though MS was considered as a white matter disease, recently it was demonstrated to affect also the grey matter, observed as neurodegenerative and demyelinating lesions located mostly in the cortex (Silva et al., 2020). These cortical lesions are the main contributors to clinical disability and cognitive impairment and they are mostly found in PPMS and SPMS patients (Lublin et al., 2014). These plaques of primary demyelination in the cortex represent an MS specific key feature and they are not seen in other chronic neuroinflammatory disorders. Even though, the rate of episodes of relapses are unpredictable in relapsing/remitting MS, peripheral inflammation seems to exacerbate these events. Clinical studies revealed an association between infections and relapses, which may lead to the worsening of neurological damage. In the same line of thought, SPMS and PPMS was reclassified as "active" or "inactive" recently, depending on the presence of peripheral acute inflammation, which may exacerbate both central damage and symptoms, such as new relapses or new evidence of CNS lesions, with concomitant neurodegeneration (Lublin et al., 2014). Factors, such as smoking, obesity, limited sun exposures, poor sleep quality, sedentariness, influence the progression of MS (Alfredsson and Olsson, 2019) throughout the increase of peripheral inflammation.

Non-pharmacological treatments such as cognitive rehabilitation, exercise and social support, are being evaluated in patients and animal models of neurodegenerative diseases because they can act synergistically with pharmacological therapeutics agents. As a preclinical approach, "enriched environment (EE)" has been widely used in animal models of neurological diseases, to evaluate the effects of social, physical and cognitive enrichment. The EE consists of large cages, which provides social enrichment (the animals are placed in numerous groups per cage), physical enrichment (the cages contain running wheels for exercise) and cognitive and sensory enrichment (provided with a variety of objects to interact, tunnels and spaces) (**Figure 1**) (Fischer, 2016). Conversely, laboratory animals are placed in impoverished environments, with smaller cages, small animal groups, no elements to interact and no wheels for physical activity. In this perspective, we resumed the latest results obtained from studies related to EE in both MS patients and MS animal experimental models.

The first evidence was described by Hebb in 1947, showing that the laboratory rats that he brought to his home as pet were smarter than the ones that remained at the laboratory conditions. From then on, numerous publication reflected the beneficial effect of EE on the cognitive function, memory, plasticity and neural function in healthy animals. EE experiments in animal models of neurological diseases such as MS, Parkinson's disease, Huntington, Alzheimer's disease, epilepsy, amyotrophic lateral sclerosis, stroke and brain injury (Fischer, 2016; Silva et al., 2020) have been conducted to answer two fundamental questions: does it generate any benefit? Which are the mechanisms that mediate these effects? Regarding the first question, EE has demonstrated to have beneficial effects in a variety of symptoms, such as cognition, physical, emotional and social features, magnetic resonance imaging parameters, blood biomarkers, cerebrospinal fluid and brain tissue in animal models of neurological pathologies (Fischer, 2016; Silva et al., 2020). Several mechanisms, such as decrease of pro-inflammatory cytokines along with an increase of anti-inflammatory cytokines in brain, blood and cerebrospinal fluid, decrease of microglia activation, promotion of neurogenesis, enhance of neural plasticity, increased adult oligodendrogenesis, increased concentration of neurotrophins and modulation of gene expression, have been described as involved in different pathologies (Fischer, 2016; Silva et al., 2020).

Few papers mention the effects of EE in MS models. Briefly, EE alleviated experimental autoimmune encephalomyelitis (EAE) symptoms, inhibited spinal cord inflammation through regulation of type 1 T-helper cells mediated by glucocorticoid receptor signaling. The authors demonstrated that a key molecule such as hypothalamic brain-derived neurotrophic factor is involved in the activation of the hypothalamic-pituitary-adrenal axis, and prevented EAE-induced thymic distress (Xiao et al., 2019). Additionally, both in a focal demyelination model (lysolecithine injection) and in the inflammatory EAE model, subventricular zone mitotic activity and the number of subventricular zone-derived cells in demyelinated areas were significantly increased by EE. Enriched housing conditions also promoted the oligodendrocyte fate of subventricular zone recruited cells in the EAE lesions. Altogether, this result shows that EE provides beneficial conditions to promote the mobilization of neural progenitors into demyelinating lesions and to favour functional recovery (Magalon et al., 2007). Recently, our group demonstrated beneficial effects of EE in a model of focal cortical pathology of MS, among them: improves short-term memory impairment and decreases anxiety and anhedonia, decreases cortical neuroinflammation, glial activation, demyelination and neurodegeneration, shifts microglia phenotype from pro-inflammatory M1 to anti-inflammatory M2 and decreases peripheral inflammation (Silva et al., 2020) (**Figure 1**). This study represents the first one that evaluates the effects of EE on the cortex, which have a high clinical relevance because its correlation with cognitive impairment and physical disability (Silva et al., 2020). EE improved forced swim induced depression by enhancing cognition and motor function in cuprizone model of demyelination. Interestingly, these findings demonstrated that even though most of the MS symptoms cannot be reversal only by EE, the side effect of depression can be ameliorated. The mechanisms involved in the beneficial effects of EE on this model require further investigations (Mohamed et al., 2019).

EE can be also used as preventive treatment. Preventive EE, improves the clinical symptoms, reduces the inflammatory infiltrate in the cortex but not in the spinal cord, diminishes demyelination in the spinal cord along with benefits to ongoing synaptic impairments in the cortex of acute EAE animals, located in the EE previous to the induction of the disease. In addition, it also improves the locomotor activity, anxiety-like symptoms and curiosity (Bonfiglio et al., 2019).

In MS patients, there are no studies addressing the influence of the three EE factors (physical exercise, social and cognitive stimulation) on disease course. Most of the studies analyse the effects of a single component, but very few of them combine at least two factors. The publications that analyzed the beneficial effects of physical activity and cognitive rehabilitation studied both factors as separate strategies and not as a whole. Indeed, the ideal situation, should also include the analysis of social and emotional factors. Physical activity improves MS symptoms, such as, blood biomarkers, reduce of relapse rate, improvement of brain volume (Motl et al., 2018). The combination of exercise and cognitive rehabilitation improved both motor and cognition symptoms in MS patients probably due to the interaction between cognitive and motor pathways (Jimenez-Morales et al., 2017; Barbarulo et al.,

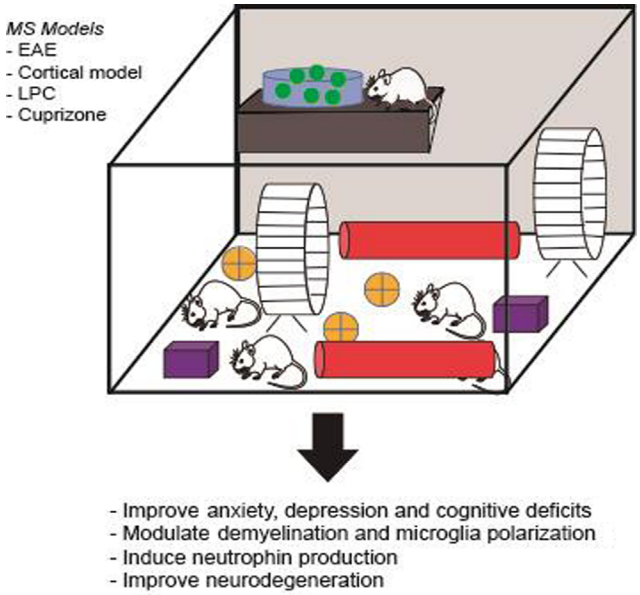


**Figure 1 Schematic diagram of enriched environment where the rodents are allowed to have access to physical exercise (running wheels), social (great number of animals per cage) and cognitive stimulation (access to tunnels, maze, toys).**
EAE: Experimental autoimmune encephalomyelitis; LPC: lysophosphatidylcholine; MS: multiple sclerosis.

2018). However, the clinical evaluation of EE is quite controversial because of the difficulty of maintaining the controlled clinical condition in patients with neurological pathologies, as we can do with laboratory animals. It is technically unmanageable to dissociate the components of EE in humans, making it difficult to study specific key components. There are several limitations for designing a clinical trial in patients which evaluates the effects of exercise, social interaction and cognitive stimulation as a whole: the heterogeneity of the cohorts of patients included, different designs, different definitions, concepts and techniques of cognitive-social and physical enrichment, different parameters to evaluate or endpoints (Motl and Pilutti, 2016). In this way, in 2018, the National MS Society establishes a Wellness Research Working Group and research priorities. The primary mission of this group is to provide scientific evidence supporting the influence of lifestyle, behavioral, and psychosocial approaches in promoting optimal health of mind, body, and spirit (i.e., wellness) in MS people as well as its consequences in managing the disease (Motl et al., 2018).

In conclusion, EE should be considered as an effective complementary therapeutic tool to pharmacological treatments. EE should be viewed as a combination of multiple factors, physical and cognitive rehabilitation and social interaction that create an environment that makes the brain more receptive to pharmacological treatments. EE represents an enjoyable, safe, economic and non-invasive non-pharmacological complementary tool. Evidence from experimental animals demonstrates that exercise and cognitive stimulation alone does not induce the same benefits as the combination of all factors, and these factors should include social interaction. Integrative non-pharmacological interventions in patients with neurological pathologies should become a priority research focus in the future, in the context of well-designed clinical trials for each pathology.

*This work was supported by the National Agency for Scientific and Technological Promotion (ANPCyT), Argentina, PICT-2012-0656 grant (to CCF); the René Baron Foundation and Institute of Translational Medicine and Biomedical Engineerie of the Italian Hospital (IMTIB, CONICET) (to CCF).*

*This information was presented in part in European Committee for Treatment and Research in Multiple Sclerosis ECTRIMS 2019 congress (platform of oral presentation).*

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***Received:** December 11, 2019*
***Peer review started:** December 17, 2019*
***Accepted:** January 9, 2020*
***Published online:** February 28, 2020*

***doi:** 10.4103/1673-5374.276334*


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*C-Editors: Zhao M, Li JY; T-Editor: Jia Y*