Environmental enrichment improves the MS trajectory by reducing inflammation and increasing BNDF levels

Anne de Boer (S3383504)
01/07/2022
Supervised by prof. Dr. Jocelien Olivier

Abstract

Multiple sclerosis (MS) is a chronic inflammatory neurological disease that attacks myelinated axons in the central nervous system and causes widespread lesions in the brain and spinal cord. Although treatments exist for this disease, currently there are none that improve cognitive impairments. Environmental enrichment (EE) is the modification of the standard laboratory conditions to improve the intensity and quality of environmental stimulation. It consists of social enrichment, physical exercise and cognitive activity and it has therapeutic potential for MS patients as it is known to improve cognition in other disorders. The aim of this essay is to investigate the mechanism of how EE can improve three pathophysiological features of MS: cognitive impairment, inflammation and demyelination. Individually, physical exercise and social enrichment are beneficial for MS patients as they cause decreased pro-inflammatory cytokine levels and elevated BDNF levels in rodents and humans. This is beneficial for cognition, inflammation and myelination. Cognitive training is beneficial by activating the dopamine D1 receptor or by increasing 3-hydroxykynurenine and increasing neuronal activity in rodents. The components combined as EE, is shown to be beneficial for MS patients since it increases myelination, decreases inflammation and improves cognition primarily by decreasing inflammation and increasing BDNF levels.

Content

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurological disease that attacks myelinated axons in the central nervous system (CNS) and causes widespread lesions in the brain and spinal cord (Olek, 2011; Calabresi, 2004; Trapp et al., 1998). Typically, the onset of this disease is between the years 20 to 45 and the development can be subtle or sudden (Calabresi, 2004). In 2007 in Europe, it was found that almost 400 000 patients were afflicted with an estimated cost of thirteen billion per year (Sobocki et al., 2007). Symptoms of MS include visual impairment with pain, paresthesia (burning or prickling sensation), weakness, impaired coordination, and cognitive impairment (Dobson & Giovannoni, 2019; Chiaravalloti & DeLuc, 2008). Furthermore, MS patients suffer from depression and fatigue which severely impacts their quality of life (Janardhan & Bakshi, 2002). The available MS therapies aim to either slow down the disease or aim to decrease symptoms. However, there are currently no specific pharmacological treatments that improve cognitive deficits (Amato et al., 2013).

Figure 1. An environmentally enriched cage vs a standard cage (Taken from Silva et al., 2020)

Environmental enrichment (EE) has gotten increasingly more attention in the last years for its therapeutic potential in animals. EE has been proven beneficial for both healthy animals and animal models of neurodegenerative and psychiatric diseases (Silva et al., 2020). EE is the modification of the standard laboratory conditions to improve quality and intensity of environmental stimulation (Baroncelli et al., 2010). Although enrichment paradigms vary, they broadly include, but are not limited to, one or more of these three pathological features: cognitive enrichment, physical activity, and social stimulation (Guillén, J., 2017). Animals live in an enriched environment when they are able to interact with other animals, in large cages that contain running wheels for exercise and items that can provide cognitive enrichment such as tunnels and toys. This provides a more complex environment compared to normal housing where they are kept in smaller cages, without other animals to interact with and that do not contain toys or running wheels (Figure 1) (Fischer, 2016). As said before, environmental enrichment can have beneficial effect on cognitive function, memory, and plasticity in healthy animals, but also in animal models of neurological diseases (Baroncelli et al., 2010). For example, in Alzheimer disease animal models, EE is able to normalize the cognitive performance and revives adult neurogenesis (Jankowsky et al., 2005). Additionally, several studies show that EE also can have neuroprotective effects in models of Parkinson's disease and Huntington's disease (Faherty et al., 2005; Lazic et al., 2006).

Next to improving cognition in animal model of neurodegenerative and psychiatric diseases, EE can also provide health benefits for humans. However, there is a big difference between the average complexity of the environment of animals and humans. This is because standard laboratory rodents live in small cages while, others suggest, the standard human already lives in an 'enriched environment' compared to animals. However, EE can be applied in humans. Human environmental enrichment consists of social enrichment (e.g. social support), sensory enrichment (e.g. tactile, auditory, or visual

facilitation), cognitive enrichment (e.g. brain games) and motor enrichment (e.g. exercise) (Singhal et al., 2014; Janssen et al., 2012; Clemenson et al., 2015). Applying these enrichment components has also been proven to be beneficial for humans as it was proven that EE improves cognition in children with autism, although no studies have yet been performed with MS patients (Clemenson et al., 2015).

Environmental enrichment could provide a good therapy strategy for MS patients as it is already known to alleviate cognitive impairments while it can also offer other health benefits. However, because this is such a recent topic of interest, only a few studies have been published that investigate the beneficial effects of EE on different pathophysiological features of MS. Furthermore, the mechanisms underlying the health benefits of EE have not been investigated yet. For this reason, the aim of this article is to investigate how environmental enrichment can provide a therapy strategy for patients with multiple sclerosis. To do this, first the pathology of MS will be explained. Following, the effect on and possible pathways of the three different components of EE (social enrichment, physical exercise and cognitive activity) on three pathophysiological features of MS (inflammation, demyelination and cognitive deficits) will be explored. Lastly, the mechanisms that contribute to the beneficial effect of the combined components of EE on MS patients will be described. The findings will subsequently be discussed in the light of MS treatment.

Multiple sclerosis

Multiple sclerosis (MS) is a complex disease for which the underlying cause has not yet been determined, although some environmental factors that combined with the genetic background can play a role in developing MS. A few examples of these environmental factors are sunshine, smoking and vitamin D. (Ramagopalan et al., 2010). While the direct cause of MS is unclear, a lot of research is performed investigating the pathology of MS as this is important for developing new treatments for MS patients.

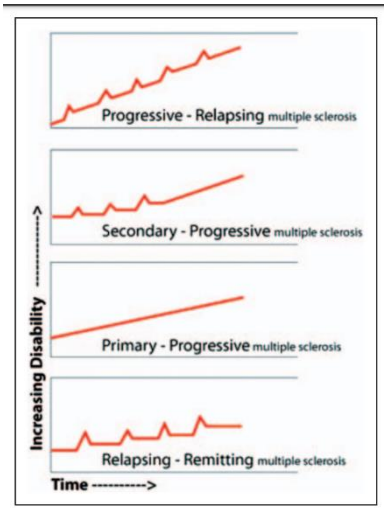

Figure 2. Clinical categories of MS (Taken from Brombin & Serio, 2016)

MS patients can be grouped into four categories based on the course of their disease (reviewed by Goldenberg, 2012). These categories are relapsing-remitting MS, secondary progressive MS, primary progressive MS, progressive-relapsing MS (Figure 2). The first category is marked by its periods of relapses of symptoms followed by periods of remission, where these symptoms improve or disappear. The patients that have relapsing-remitting MS can develop secondary progressive MS where the disease worsens with or without the periods of remission. Treatment with disease-modifying agents can delay the progression to this stage. Patients with primary progressive MS do not have periods of remission. For them, the disease continuously worsens over time. Progressive-relapsing MS is the categories of MS that is progressive from the beginning with flare-ups of worsening symptoms without periods of remission.

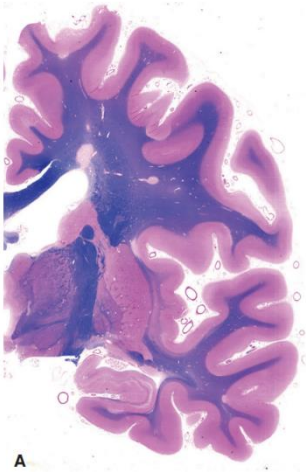

Figure 3. Large confluent focal demyelinated lesions in the white matter (Taken from Lassmann, 2013)

Inflammation is one of the main characteristics of MS. During the course of the disease, demyelinated inflammatory lesions arise in the white and gray matter of the central nervous system (CNS) (Figure 3). These lesions are composed of areas of oligodendrocyte- and myelin loss combined with inflammatory cell infiltrates (Bendszus & Storch-Hagenlocher, 2013). Lesions contain T-lymphocytes but are dominated by MHC class I restricted CD8+ T-cells (Lassmann, 2013). Mainly, increased pro-inflammatory cytokines such as interleukin-17 (IL-17), IL-22, IL-1, IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) together with a decreased level of anti-inflammatory cytokines IL-4 and IL-10 are thought to cause MS (Figure 4) (Wang et al., 2018). Because of this inflammation, demyelination and oligodendrocyte damage occurs. This damage subsequently causes myelin to be almost completely lost (Babinski 1885; Prineas 1985). Although remyelination occurs during all stages of the disease and axons are largely preserved during the early stages of the disease, irreversible axonal damage will develop as the disease progresses (Lassmann, 2013; Trapp et al., 1998). The amount of axonal loss varies a lot between patients and between different lesions within the same patient (Ferguson et al. 1997; Trapp et al. 1998).

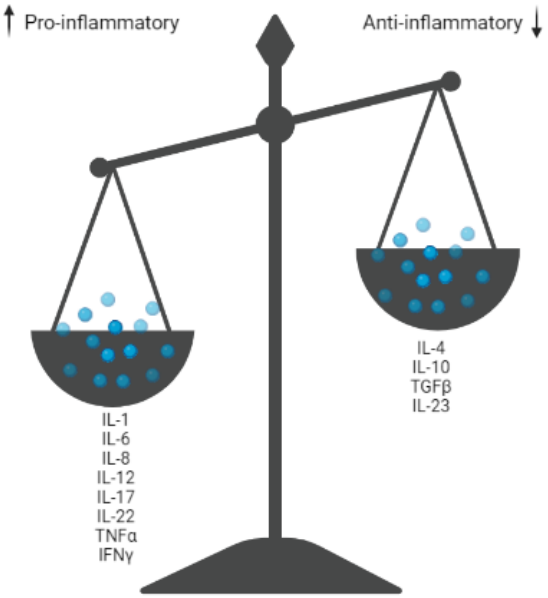

Figure 4. The pro- and anti-inflammatory cytokine imbalance in MS

The symptoms of patients with MS are the consequences of the focal inflammatory plaques that can interrupt critical axonal tracts and cause the loss of neuronal functional areas. These inflammatory plaques form either intermittently or acutely with periods of relapses. The development of these plaques can occur over the course of hours or days, and it can last for weeks or months before they improve, if they improve (Olek, 2021). Early MS shows recovery, but most relapses leave behind some damage that cannot be salvaged. During the progression of the disease, these damaged areas lead to neurological deficits that can eventually cause sustained disability (Goldenberg, (2012). The actual symptoms of the patients can vary based on the part of the central nervous system (CNS) that is affected. The most common presentations are optic neuritis, brainstem, and spinal cord syndromes (Miller et al., 1989).

Optical neuritis is a symptom of MS where vision is affected. Patients experience vision changes that range from blind spots to complete blindness changes and this optical neuritis is caused by lesions in the optic nerve (De la Cruz & Kupersmith, 2006). Inflammation resulting in lesions in the spinal cord can cause motoric or sensory symptoms. These symptoms include weakness of the muscles and a reduced sensation in focal areas. Next to this, inflammation of the vestibular or cerebellar pathways can lead to ataxia and vertigo (Olek, 2021). This entails impaired coordination of voluntary muscle movement and a subtype of dizziness respectively (Ashizawa & Xia, 2016). Next to these symptoms, MS patients can also suffer from cognitive impairment such as deficits in complex attention, deficiency of information processing, executive functioning, processing speed, and long-term memory (Chiaravalloti & DeLuca, 2008).

The current therapies for this disease are MS-specific disease-modifying therapies and symptomatic therapies that can help with managing neurological dysfunction related symptoms. Disease-modifying therapies are usually focused on early treatment which aim to prevent long-term disability. These therapies are focused on suppressing inflammation and are therefore often immunosuppressing or immunomodulatory drugs and that are administered during the relapsing phase of MS. They reduce the rate of relapses, reduce accumulation of lesions, and stabilize, delay, and sometimes improve disability (Galetta et al., 2002). In contrary to disease-modifying therapies, symptomatic treatments are not MS-specific but aim to target the symptoms that arise from CNS damage (reviewed by Henze et al., 2006). However, as stated before, there are currently no therapy strategies that can help MS patients with the cognitive impairment. This is where EE can possibly help combat different symptoms as it might reduce cognitive dysfunction and inflammation.

In summary, inflammation is a big factor in MS. Because of this inflammation, inflammatory lesions are formed in the CNS which causes demyelination and eventually axonal loss. The location of this axonal damage influences the symptoms that MS patients face. The current treatment strategy is slowing down the development of the disease and treating the symptoms.

Physical exercise

Physical exercise (PE) is well known for its health benefits for many diseases and disorders. It can alleviate mental health problems, reduce risk of all-cause mortality, cardiovascular disease, diabetes, cancer and can improve cognition (Chekroud et al., 2018; Lee et al., 2012). As PE has such a wide range of beneficial effects, it might come as no surprise that it also has beneficial effects for MS patients.

PE and cognition

First of all, PE can be beneficial for cognition as PE is able to increase cognitive ability in both animal studies and human studies. One study looked at a pharmacological animal model of Parkinson's disease which uses reserpine to induce cognitive and motor deficits. They found that these deficits could be improved by running wheel and treadmill exercise in rats (Aguiar et al., 2009). Furthermore, human adults that are exposed to chronical aerobic exercise performed better with visual pattern separation tasks (Déry et al., 2013). One study wanted to study the effect of PE on cognition of the elderly and used resistance training. This is a form of physical activity that exercises a muscle or muscle group against external resistance. They concluded that this kind of training improves short- and long-term spatial memory in the elderly (Cassilhas et al., 2007).

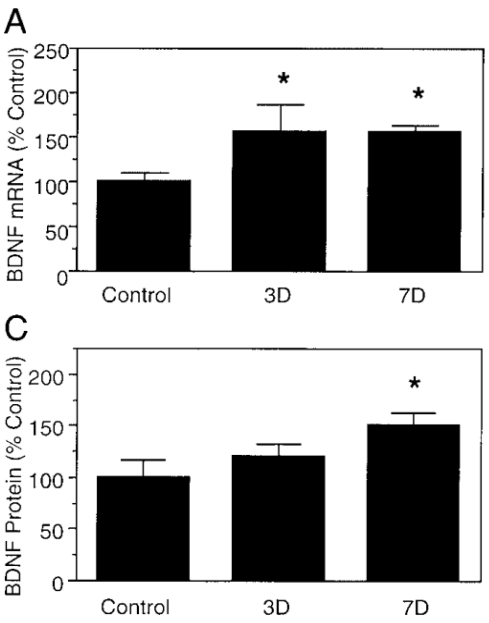

Figure 5. spinal cord lumbar levels of brain derived neurotrophic factor (BDNF) mRNA (A) and protein (B) levels after 3 and 7 consecutive days of voluntary running wheel exercise relative to sedentary control (Taken from Gómez-Pinilla et al., 2002)

Factors that could underlie the beneficial effect of physical exercise are the BDNF and the IGF-1 pathways. BDNF is released during exercise and is thought to promote changes in neuronal plasticity via modulation of multiple neurotrophins (Figure 5) (Gómez-Pinilla et al., 2002). Additionally, BDNF is known to be a marker for cognitive function in ageing women and individuals with cognitive impairment (Komulainen et al., 2008; Siuda et al., 2017). Furthermore, the study of Küster et al. (2017) found a trend for an increase of BDNF after physical training in older adults at a risk of dementia. They also investigated whether there was a correlation between BDNF levels and cognitive performance in these older adults and observed a significant positive association between BDNF and memory (Figure 6). This further suggests that BDNF could be part of a pathway between physical exercise and cognition. In another study, the same positive association between PE, BDNF and cognition has been found, but in young adults. Here, it was concluded that endurance-trained athletes have higher concentrations of BDNF and that there is a positive correlation between cognition and BDNF levels (Belviranli et al., 2016). In addition, a study investigating MS patients found that 9 weeks of endurance training strongly increased BDNF levels in these patients. However, long term effects were much less pronounced (Briken et al., 2016).

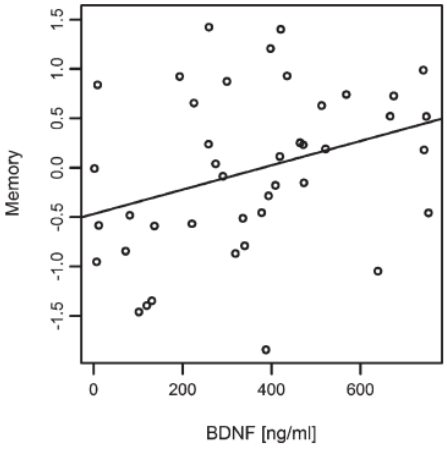

Figure 6. Higher brain-derived neurotrophic factor (BDNF) and irisin serum levels were significantly associated with better memory performance (Taken from Küster et al., 2017)

PE and myelination

Physical exercise has also been proven to be beneficial for myelination. The general beneficial effect of PE on myelination is supported by the fact that PE helps neurogenesis and has a beneficial effect on neuroplasticity through the release of brain-derived neurotrophic factor (BDNF) (Gómez-Pinilla et al., 2002; Cheng et al., 2020). In addition, different types of exercise can improve motor function and increase motor nerve conduction velocity which could indicate an enhanced myelin thickness (van Meeteren et al., 1997). With respect to myelination and MS, many studies have been performed to investigate the effect of physical exercise on sheath regeneration. A meta-analysis by Feter et al. (2018) concluded that physical exercise was positively associated with myelin sheath thickness (Figure 7). Other studies showed that low-to-moderate continuous physical exercise could increase myelin sheath thickness and decreases progression of demyelination (Bobinski et al., 2011; Bernardes et al., 2013). However, studies with different physical training protocols did not find the same results (reviewed by Feter et al., 2018).

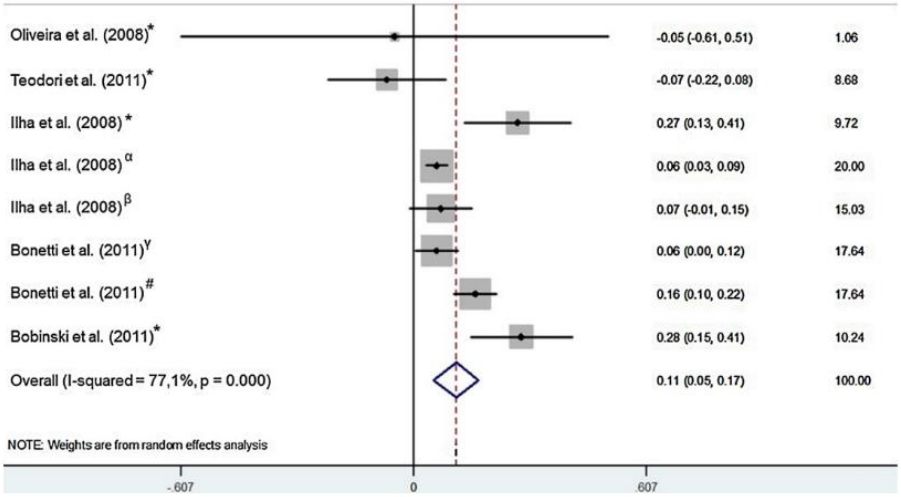

Figure 7. Metanalysis showing the association of physical exercise with the myelin sheath thickness, compared with the control non-exercise group. *: endurance training; α: resistance training; β: concurrent training; γ: motor control training; #: balance training (Taken from Feter et al., 2018)

A few of the suspected underlying factors of this beneficial effect of PE is BDNF. The study of Ahn et al. (2016) investigated the effect of therapeutic exercise on memory recovery of aged gerbils after an ischemic stroke. They found that four weeks of exercise helped with memory recovery and that long-term exercise ameliorated myelin damage that was caused by the ischemic stroke. This improvement was correlated with increased BDNF levels. This indicates that PE can help MS patients by improving myelination which might be mediated by elevated BDNF levels.

PE and inflammation

PE has an anti-inflammatory effect in central organs and peripherally. PE generates reactive oxygen species (ROS) and activates the immune system which can have both positive and negative health effects depending on the type and degree of activated immune system response (Finsterer, 2012). First of all, it was found that PE had an anti-inflammatory effect in coronary heart or artery disease patients. This was achieved by reducing the levels of pro-inflammatory cytokines IL-6, IL-8, TNF-α, and IFN-γ and by increasing the anti-inflammatory IL-10 levels (Figure 8) (Goldhammer et al., 2005; Niessner et al., 2006). The same anti-inflammatory effect was found in women with MS since plasma IFN-γ and IL-17 levels were reduced after exercise (Golzari et al., 2010). This anti-inflammatory effect of PE has been

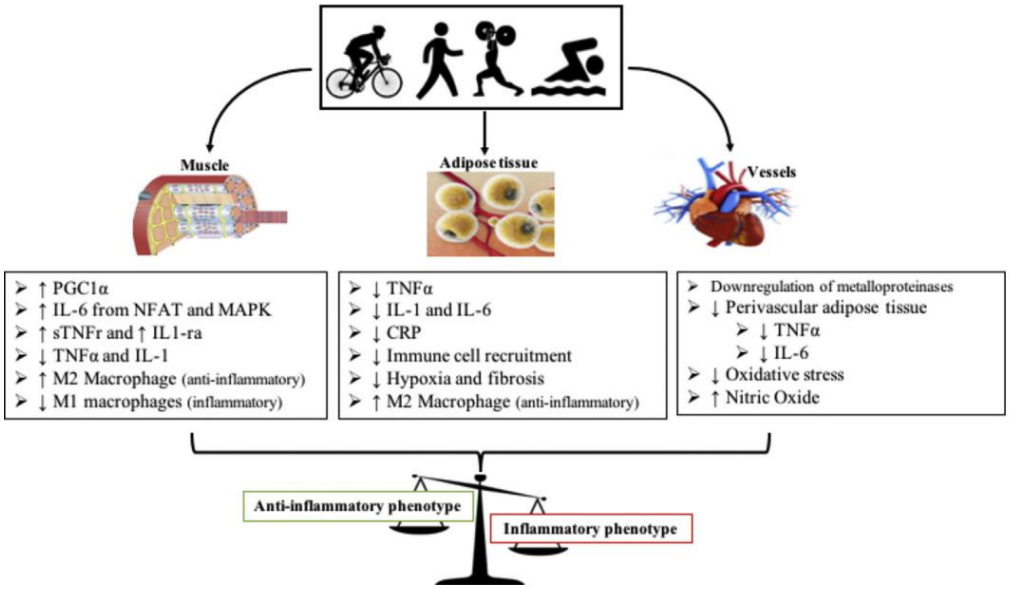

Figure 8. Overview of how exercise can promote anti-inflammatory phenotype in different tissues. PGC1a: peroxisome proliferator-activated receptor g co-activator 1a, IL-6: interleukin 6, NFAT: nuclear factor of activated T-cells, MAPK: mitogen-activated protein kinase, sTNFr: soluble tumor necrosis factor receptors, IL-1ra: interleukin 1 receptor antagonist, TNFa: tumor necrosis factor alpha, IL-1: interleukin 1, CRP: C-reactive protein (Taken from Metsios et al., 2020).

proven valuable for MS patients. One study found that clinically stable MS patients have higher IL-10 levels than clinically unstable patients (Hu et al., 2017). Furthermore, MS patients who received IFN-γ antibodies showed a significant decrease of multiple pro-inflammatory cytokines which were associated with an improved disease course (Skurkovich et al., 2001).

Proliferator-activated receptor g co-activator 1α (PGC-1α) could potentially exert the anti-inflammatory effects of PE (Handschin et al., 2007). PGC-1α is activated during exercise by the AMP-activated protein kinase and PGC-1α knockout animals show an increased expression of TNF-α and IL-6 (Benatti & Pedersen, 2015; Handschin et al., 2007). This shows that PE can help MS patients by decreasing inflammation.

In summary, physical exercise is beneficial for myelination and cognition and reduces inflammation. The anti-inflammatory effect of PE is achieved by decreasing the pro-inflammatory cytokines IL-6, IL-8, TNF-α, and IFN-γ and by increasing the anti-inflammatory cytokine IL-10 possibly through the release of PGC-1α. PE also has beneficial effects on cognition and myelin by releasing BDNF. All in all, physical exercise can be very beneficial for MS patients.

Social enrichment

Social enrichment is one of the main additions that are made to the habitats of animals in rodent studies to make it more complex and increase environmental stimulation. It is mostly studied in combination with toys and other cognitive enriching objects. To investigate the effect of social enrichment on cognition, inflammation and myelination, animals that are socially housed will be studied in comparison to animals that are housed in social isolation. Animals that are socially housed are in an enclosure with one or more companions are able to have social interactions while socially isolated animals cannot interact with other animals. By comparing these living situations, the effect of social enrichment on cognition, myelination and inflammation can be seen.

Social enrichment and cognition

Social interaction can influence cognitive performance. First of all, this can be seen as animals who experience a lack in social interaction show decreased cognitive performance. For example, one study showed that mice that are socially isolated had cognitive deficits compared to control animals. However, re-socialization could recover these deficits (An et al., 2017). The same is true for rhesus monkeys that are raised in a social isolation paradigm as they exhibit cognitive deficits in the object learning task (Sanchez et al., 1998). Furthermore, in an Alzheimer transgenic mouse model, isolation resulted in impaired spatial working memory (Huang et al., 2011). Secondly, that social interaction can influence cognitive performance can be seen in humans, where it is observed that social enrichment can benefit cognition. One study looked at social interaction in late life and found beneficial effects for cognition as individuals who are more socially integrated showed less cognitive decline with ageing. Moreover, a socially integrated lifestyle in late life was proven protective against AD and dementia (Menec, 2003; reviewed by Fratiglioni et al., 2004). Thirdly, social enrichment in animals produces similar beneficial effects on cognition. A study by Templer et al. (2019) showed that social housing was protective against age-related working memory deficits in rats (Figure 9). In this study, it was hypothesized that social housing preserves prefrontal function by enhancing long-term potentiation.

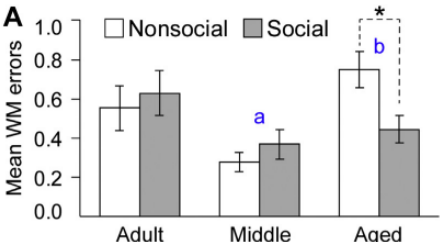

Figure 9. Performance on the radial arm maze across ages showing mean working memory errors (Taken from Templer et al., 2019)

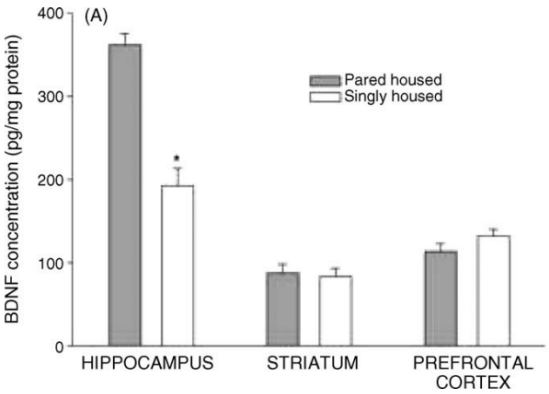

Figure 10. BDNF protein concentrations in various brain region in male rats singly or paired housed (Taken from Scaccianoce et al., 2006)

A possible mechanism for the beneficial effect of social enrichment on cognition is BDNF. A study showed that 8 weeks of pair-housed social enrichment is enough to increase BDNF levels in the hippocampus significantly in comparison to socially isolated rats (Figure 10) (Scaccianoce et al., 2006). The same effect of social enrichment on BDNF levels has been observed in other two studies. Both O'Keefe et al. (2014) and Venna et al. (2014) investigated rats that after experiencing a stroke, were housed either in pairs, or in isolation. O'Keefe et al. (2014) found a significant increase of BDNF levels at day 49 post-stroke in pair-housed rats in comparison to socially isolated rats. Venna et al. (2014) found an increase of BDNF levels at 90 in pair-housed rats compared to socially isolated rats. The results from these studies are not completely translatable to MS patients as they look at animals that have experienced a stroke. However, it does indicate that BDNF might be a possible mediator of the beneficial effects of social enrichment on cognition as BDNF has often been associated with cognition. For example, in

the elderly, decreased BDNF serum levels are associated with lower cognitive test scores (Shimada et al., 2014). Additionally, in subjects that suffer from neurodegenerative diseases, lower BDNF serum levels correspond to higher cognitive impairment (Siuda et al., 2017). Furthermore, in subjects with bipolar disorder, high BDNF serum levels are associated to good cognitive functioning (Mora et al., 2019). In Alzheimer's disease patients, high serum BDNF levels predict a slower cognitive decline (Laske et al., 2011). Because of this connection between BDNF serum levels and cognition, higher BDNF levels could be a possible mechanism of how social enrichment can benefit cognition.

Social enrichment and myelination

The beneficial effect of social enrichment on myelin has not been widely studied. Because of this, the effects of social enrichment will mostly be inferred by studying the effects of social isolation.

The effect of social isolation on myelination was investigated by Makinodan et al. (2012). They found that mice that were socially isolated for two weeks after weaning, showed alterations in myelination as myelin thickness. This paper also investigated myelin-associated glycoprotein (MAG) and myelin basic protein (MBP). These are key myelin specific proteins where MAG is a minor constituent for myelin sheath and MAG plays a key role in the early stages of myelination and the maintenance of myelin (Gupta et al., 2005). The study found that the levels of these proteins in the medial prefrontal cortex was reduced due to social isolation (Makinodan et al., 2012). This suggests that the decreased MAG and MBP expression caused by social isolation could contribute to the decreased myelin thickness. The same effect was found in the study of Liu et al. (2012). Here, that social isolation in mice caused hypomyelination in the prefrontal cortex (Figure 11). These changes could be reversed by exposing the mice to socially enriched environments (Liu et al., 2012).

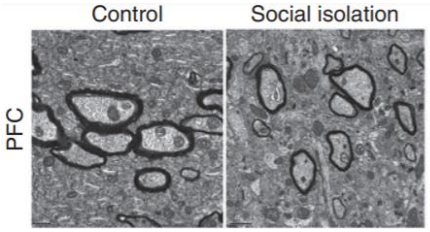

Figure 11. Electron micrographs of axons in the PFC (Taken from Liu et al., 2012)

Multiple mechanisms have been suggested to underly the beneficial effects of social enrichment on myelin. One example of such an underlying mechanism is the ErbB3 ligand neuregulin-1 (NRG1). ErbB3 is a member of the epidermal growth factor receptor family, which is activated by, among others, neuregulins and other ErbBs (Sithanandam & Anderson, 2008). Neuregulin-ErbB signaling is essential for the onset of myelination and inhibition of ErbB3 results in reduced myelination (Lyons et al., 2005; Adilakshmi et al., 2011). As explained before, the study of Makinodan et al. (2012) found that social isolation caused reduced myelin thickness and they concluded that reduced ErbB3 ligand NRG1 expression could contribute to the molecular mechanism for this effect. This was concluded as social isolation leads to reduced ErbB3 ligand NRG1 expression levels in the prefrontal cortex. However, in a later publication the same authors determined that NRG1-ErbB3 was not involved in remyelination in mice (Makinodan et al., 2016). In this later study, they found that although social isolation reduced myelin thickness, NRG1 mRNA levels did not differ between socially isolated animals and group housed animals. They also investigated BDNF as a possible mediator, but also did not find altered serum BDNF levels between socially isolated and group housed animals. Alternatively, they investigated if IL-6 levels

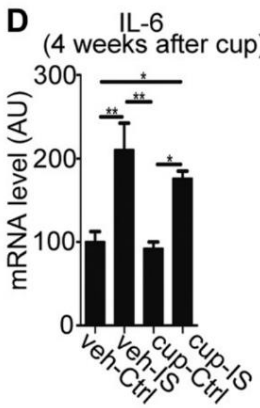

Figure 12. IL-6 mRNA levels in the mPFC of socially isolated mice and control mice (Taken from Makinodan et al., 2016)

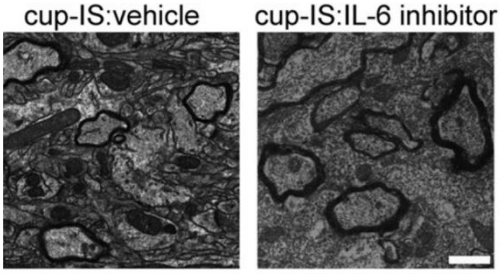

Figure 13. Images of myelinated axons in the mPFC of veh-IS and cup-IS mice that were treated with an IL-6 inhibitor (taken from Makinodan et al., 2016)

could be involved as they thought stress related cytokines, such as IL-6, could differ between the two group. Because they showed that socially isolated mice have increased IL-6 expression, they concluded that social isolation might disturb remyelination through regulation of IL-6 (Figure 12). Furthermore, they also found that IL-6 administration inhibited remyelination while blocking IL-6 function facilitated remyelination (Figure 13). IL-6 influences remyelination by blocking the NMDA receptor which is important for neuronal activity and activity-dependent myelination (Fang et al., 2013; Qiu et al., 1998; McLennan, 1983; Wake et al., 2011; Lundgaard et al., 2013). Stress could be an underlying factor of the increased IL-6 expression in socially isolated mice, as studies have shown that psychosocial stress can increase IL-6 levels (Ganança et al., 2016; Lovera & Reza, 2013; Simpson et al., 2014). The IL-6 cytokine family members are crucially involved in the immunoregulation of MS patients and blocking IL-6 signaling in MS patients limits immune-mediated tissue injury (Janssens et al., 2015). As this blocked IL-6 signaling is beneficial for MS patients, decreased IL-6 levels might be the underlying mechanism of the beneficial effects of social enrichment.

Social enrichment and the immune system

The social environment of animals can influence the immune system. As described in the previous paragraph, social isolation is associated with increased IL-6 levels which causes decreased remyelination, possibly because of increased social stress. This relationship was also confirmed in a meta-analysis where a significant association was found in adults. The analysis showed that if adults are lonelier, they also have higher IL-6 levels (Figure 14). Furthermore, there was a correlation between the solitude and more downstream inflammatory markers. This was concluded as social isolation was associated with increased levels of the acute phase proteins CRP and fibrinogen (Smith et al., 2020). These amplified levels of IL-6, CRP and fibrinogen could be bad for MS patients as high levels of IL-6 are reported with delayed treatment of MS and worse future disease course high levels of these fibrinogen and CRP are seen during MS relapses and (Stampanoni Bassi et al., 2018; Acuña et al., 2017; Doi et al., 2009). As social enrichment is the opposite of social isolation and might prevent feelings of loneliness, it can be suggested that social enrichment can decrease or prevent the increase the levels

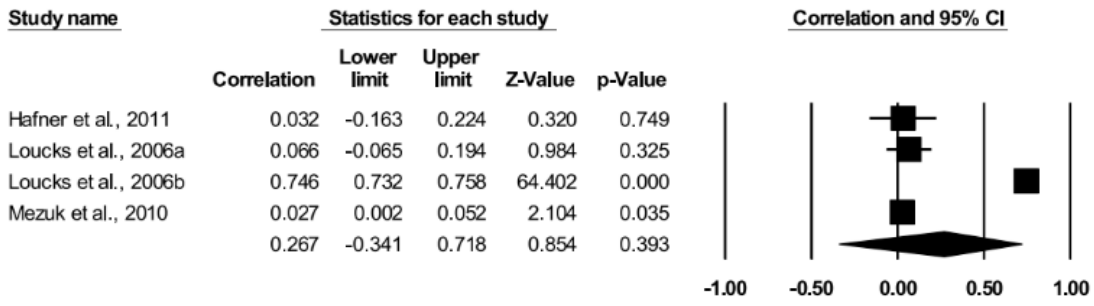

Figure 14. Forest plot of association between social isolation with IL-6 (taken from Smith et al., 2020)

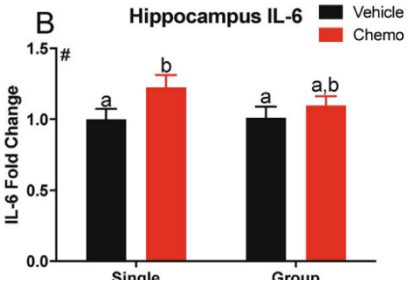

Figure 15. IL-6 mRNA expression in the hippocampus of single or group housed mice receiving vehicle or a chemotherapeutic injection. Graph bars that do not share a letter are statistically significant different at $p < 0.05$ (Taken from Walker et al., 2020)

of inflammatory substances. This in end could prove beneficial for MS patients. Eisenberger & Cole (2012) aimed to investigate the neural mechanisms that can translate social experiences into health-relevant physiological responses and concluded that loneliness can influence inflammation through activation of the stress pathway. Some other studies have also shown that social influences on health can cause reduced inflammation. For example, Walker et al. (2020) investigated the effect of social enrichment on several inflammatory cytokines that were heightened because of chemotherapy. They examined two groups of mice that received chemotherapy. One group was socially housed, and the other was housed in social isolation. This study found that the group housing animals show lower inflammatory cytokine signaling as IL-6 levels were attenuated (Figure 15). Additionally, a study that investigated healthy human participants showed that if social networks are broader, serum IL-6 levels are lower (Loucks et al., 2006). However, some articles discovered the opposite. One study compared the immune responses in rhesus monkeys that were housed singly, in pairs or in groups. They concluded that the ratios of CD4+ and CD8+ were significantly lower in singly housed monkeys than socially housed monkeys, suggesting that immune activation is lower when there is no social enrichment. Furthermore, in this study, group housing was also associated with higher levels of the pro-inflammatory cytokine IFN-γ and lower levels of anti-inflammatory cytokine IL-10 (Table 1) (Schapiro et al., 2000). This increase of these pro-inflammatory cytokines points towards a heightened immune activity which could have negative effects on the course of the disease of MS patients (Dinarello, 2000). Overall, most studies indicate that social isolation can increase immune activity and social enrichment can decrease it. This decrease in immune activity could be helpful for MS patients.

Table 1. Cytokine production comparing housing situations at baseline and at 12 months (taken from Schapiro et al., 2000)

	Baseline	12 months
IFN-γ[a,b,c,d,e]		
Single	18.0 ± 12.9	28.2 ± 16.7
Pair	25.2 ± 13.4	32.5 ± 19.0
Group	190. ± 67.5	75.3 ± 29.0
IL-2[a,b]		
Single	20.0 ± 8.67	4.74 ± 6.86
Pair	22.4 ± 5.78	2.69 ± 4.82
Group	25.2 ± 3.86	8.75 ± 5.37
IL-4[f]		
Single	0.78 ± 1.47	1.40 ± 2.37
Pair	0.42 ± 0.97	1.59 ± 2.11
Group	0.23 ± 0.79	2.24 ± 2.13
IL-10[a,b,c,d]		
Single	20.5 ± 5.68	10.7 ± 6.02
Pair	19.6 ± 5.25	12.1 ± 6.43
Group	40.5 ± 6.40	10.0 ± 3.72

In summary, social enrichment may have beneficial effects on both myelination and cognitive performance. This is mostly based on studies that show that social isolation has detrimental effects on these pathophysiological features of MS. Some publications showed beneficial effects of social enrichment on inflammation; however, some publications concluded the opposite. The beneficial effect of social enrichment on myelination could be caused by decreased IL-6 levels and the beneficial effect on cognition has been connected to increased BNDF levels. As these results are mostly based on studies investigating social isolation, the effect of social enrichment on the myelination, cognitive performance and inflammation cannot be concluded with absolute certainty.

Cognitive enhancement

As MS patients suffer from cognitive impairment, it might not be surprising that cognitive training could be beneficial for them. A beneficial effect of cognitive training on cognition is to be expected, but does this also work for MS patients and through what mechanism does this happen? Next to this, can cognitive training also help combat the loss of myelin and can it perhaps help attenuate the inflammation that happens during the MS trajectory?

Cognitive enhancement and cognition

Cognition decline is one of the more debilitating symptoms of MS for which cognitive training would be an obvious solution. It will come as no surprise that cognitive training is known to increase cognitive performance. There are different types of memory that can be targeted by different types of cognitive training. The working memory is a capacity limited system that can hold information temporary, and its size is thought to be a key determinant of one's ability to complete cognitive tasks (Engle et al., 1999). Cognitive training that is designed to target working memory capacity has a wide range of cognitive benefits (reviewed by Morrison & Chein, 2011). For example, multiple studies show that core can have far reaching effects on the broader landscape of cognitive ability. Core training involves repetition of demanding working memory tasks that are created to target domain-general working memory structures (Klingberg & Westerberg, 2002). This has, for example, been found in a study that studied the effects of core working memory training with a computer program on the working memory and other cognitive domains in healthy adults and patients with mild cognitive impairment. This study found that both groups improved on the trained, but also untrained working memory tasks (Vermeij et al., 2016). Furthermore, training with a computer program that contains different visuospatial working memory tasks improved cognitive function in patients with dysfunctional working memory after brain injury (Åkerlund et al., 2013).

The effect of cognitive training on cognition has also been examined in MS patients in a meta-analysis by Lampit et al. (2019) which analyzed twenty randomized controlled trials. In this meta-analysis, it was proven that cognitive training is valuable for cognitive performance as they found a significant positive effect on attention and processing speed, executive functions, verbal memory, and visuospatial memory. The overall effect of the randomized controlled trials was also significant and positive. However, there were no long-term effects of cognitive training on the cognition of MS patients as the outcomes from longitudinal follow-ups revealed a small and nonsignificant effect size on overall cognition. The duration of the short- and long-term effects are not mentioned in the article.

A possible mechanism that could contribute to the cognitive enhancement following working memory training is increased cortical dopamine D1 receptors signaling. Multiple articles show that these D1 receptors are involved in cognition. For example, administering a D1 agonist in aged rhesus monkeys enhances working memory performance (Castner & Goldman-Rakic, 2004). Furthermore, fourteen hours of cognitive training over 5 weeks caused prefrontal and parietal binding potential to decrease and a larger decrease in D1 binding potential is associated with a larger improvement in working memory. Cognitive training might increase working memory by recruiting D1 receptors from the interior of the cell to the plasma membrane by the activation N-methyl-D-asparate receptors (McNab et al., 2009). Another possible mechanism through which cognitive training can enhance cognition is the neurotoxic 3-hydroxykynurenine (3-HK) which is the neuroactive metabolite of Kynurenic Acid. The kynurenine pathway is a major route of tryptophan metabolism which could be involved in the

cognitive enhancing effect of cognitive training (Gulaj et al., 2010). A study found that cognitive training of older adults significantly decreased the neurotoxic 3-hydroxykynurenine (3-HK) (Figure 16) (Küster et al., 2017). Additionally, Platzer et al. (2017) showed that a higher ratio of 3-HK to kynurenic acid is associated with a worse cognitive performance in mice with bipolar disorder. As cognitive training can decrease 3-HK levels, and because lower 3-HK levels are associated with better cognitive functioning, decreased 3-HK levels could underly the positive effect of cognitive training on cognition.

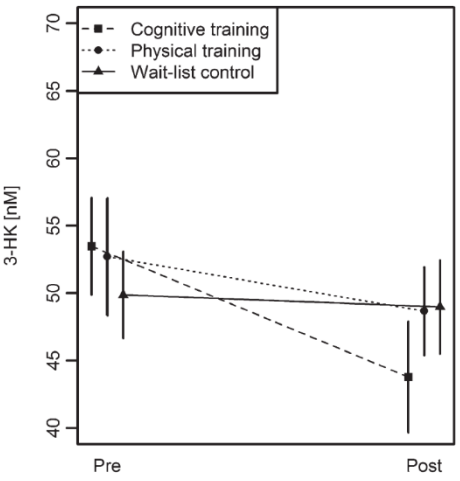

Figure 16. Pre to post changes in irisin, 3-HK and BDNF serum levels of older adults who received cognitive training, physical training or no training (Taken from Küster et al., 2017)

Cognitive enhancement and myelination

A beneficial effect of cognitive training on myelination can also be found. One study showed that spatial learning increases oligodendrogenesis and de novo myelination in adult mice in areas that have been previously associated with spatial information (Figure 17) (Steadman et al., 2020). This oligodendrogenesis is regulated by neuronal activity and these new oligodendrocytes preferentially myelinate active neurons (Geraghty et al., 2019; Mitew et al., 2018). This suggests that cognitive training causes myelination in active neurons. Furthermore, more neuronal activity causes more myelination, cognitive training could do the same. Additionally, it was found that, in the prefrontal cortex, fear learning activates oligodendrocytes to start myelinating and that neuronal activity instructs the formation of new myelin (Pan et al., 2020).

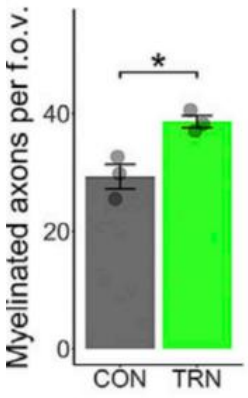

Figure 17. The number of myelinated axons increased in the corpus callosum/cingulum after spatial learning (Steadman et al., 2020)

Neuronal activity is able to induce myelination because of adenosine signaling through its receptors at oligodendrocyte progenitor cells (OPCs). Adenosine is the active axon-glial signaling molecule in the CNS that inhibits OPC proliferation, stimulates differentiation, and promotes the formation of myelin (Figure 18) (Stevens et al., 2002). This is supported by the fact that an adenosine A1 receptor agonist protects myelin and induces remyelination (Asghari et al., 2013). Overall, cognitive training can promote myelination of activated neurons because of adenosine release.

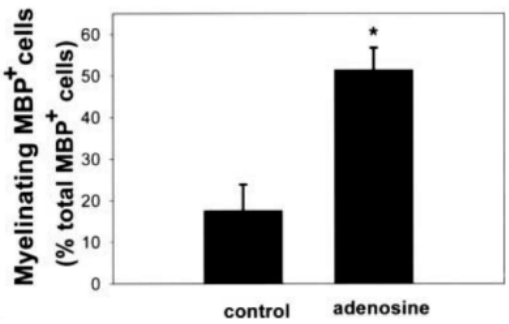

Figure 18. The number of MBP oligodendrocytes with multiple parallel processes in adenosine-treated cultures increased significantly as compared with controls (Taken from Stevens et al., 2002)

Cognitive enhancement and the immune system

Lastly, there is a connection between cognitive training and the immune system. Cognitive training increases neuronal activity which is induces beneficial neuroimmune interactions that helps promote homeostasis of the nervous system (Kipnis et al., 2004). For example, with learning, long-term potentiation (LTP) is induced which causes the up-regulation of IL-1β. This is a proinflammatory cytokine but is also necessary for the learning potentiation (Schneider et al., 1998). The same was shown in patients with MS as a study showed that the amplitude of the LTP shows a positive correlation with the concentration of IL-1β (Figure 19) (Mori et al., 2014). Additionally, similar results were found for IL-1α, which is very robustly up-regulated during LTP protocols (Ross et al., 2003). Next to this, TNF signaling through the TNFR1 receptor can module synaptic strength by influencing AMPA receptor expression (Dummer et al., 2002).

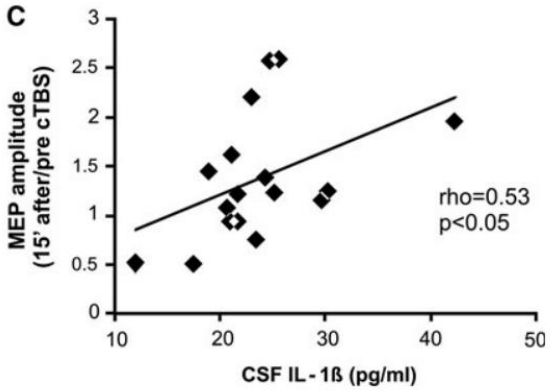

Figure 19. IL-1b levels in the CSF of 17 MS subjects and the MEP amplitude changes show that LTP-like changes in MS patients correlate with IL-1b (Taken from Mori et al., 2014))

The release of these cytokines IL-1α an IL-1β is necessary for proper cognitive performance, but an excess of these cytokines is also associated with memory deficits and decreased synaptic strength (Matsumoto et al., 2004; Ikegaya et al., 2003). Overall, this means that cognitive training causes an increase in specific pro-inflammatory cytokines which is necessary for proper learning but might be harmful for MS patients as it might exacerbate inflammatory lesions. This would be disadvantageous for MS patients as the severity inflammatory lesions correlates with physical disability and cognitive impairment (Rinaldi et al., 2010). All in all, cognitive training may increase cognitive performance, possibly by increasing specific inflammatory cytokines that induce LTP. The effect of cognitive training beyond this necessary release of different pro-inflammatory cytokines for learning has not been studied and therefore cannot be described in this chapter.

In summary, cognitive training is beneficial for cognitive performance and myelination, but its effect on inflammation is questionable. Cognitive training might have cognitive enhancing effects through activation of the dopamine D1 receptor or by increasing 3-hydroxykynurenine through the release of IFN-α. Myelination is improved by cognitive training by increasing neuronal activity.

Environmental enrichment in MS patients

As discussed before, the three different components of environmental enrichment (cognitive training, physical exercise, and social enrichment) all have benefits for MS patients. Most studies that were previously mentioned, studied the effect of the different components separately. However, what is the effect of the components combined and what underlying mechanisms can explain these effects?

Can EE benefit MS patients?

Although most studies look at the effect of the individual components of EE, there are a few studies that investigated physical exercise and cognitive training together. The combination of these enrichment components proved beneficial effect for cognition and motor functioning in MS patients was found. For example, one study found that a combination of exercise and cognitive rehabilitation can improve motor and cognitive symptoms in MS patients (Jimenez-Morales et al., 2017). Another study showed that cognitive and neuromotor training improves motor functioning and cognition in MS patients (Barbarulo et al. 2018). This shows that the combination of motor and cognitive training can be very beneficial for cognition and motor skills of MS patients. There are no studies that assess the combined effect of social interaction with either cognitive training or physical activity in MS patients.

Although, so far, no studies have been performed investigating the effect of all EE components on MS patients, there is one study that looked at the effect of EE on an animal model for MS. The study of Silva et al. (2020) looked at the effect of EE on different pathophysiological features of MS such as expression of IL-1β, cognitive impairment, anxiety-like symptoms, neuroinflammation, demyelination and neurodegeneration in an animal model for MS. The animals were socially enriched by group housing, cognitively enriched by exposure to novel stimulation and experiential learning (toys and tunnels), and physically enriched by voluntary exercise (access to a running wheel). The results showed that EE was very beneficial for inflammation, cognition, neurodegeneration, and myelination. In short, the researchers found an attenuated inflammatory response to the pro-inflammatory agent IL-1β with animals in the EE group. Neuroinflammation was reduced as EE caused the inflammatory cortical lesions that develop during MS to go towards a less inflammatory infiltrate. This was concluded as they observed decreased microglial activation and decreased astroglia activation in the lesions. Demyelination was also decreased in the EE group eighter by improving remyelination or decreasing demyelination. This was concluded as the intensity of MAG and MBP was increased in the EE group compared to control. Next, cognitive deficits were improved as time spent at a novel object in the novel object recognition test increased and the discrimination index was also improved.

How EE can benefit MS patients

The same article of Silva et al. (2010) also investigated possible mechanisms involved in the beneficial effect of EE on cognition, inflammation and myelination. As explained before, they exposed an adult rat animal model for MS to physical exercise and cognitive and social stimulation. They propose different molecular pathways through which a beneficial effect on cognition, inflammation and myelination can be achieved.

Inflammation

First of all, Silva et al (2010) investigated if EE had an effect on inflammation. They did this by measuring serum pro- and anti-inflammatory molecules in the cortex. First of all, they found diminished expression of the pro-inflammatory cytokines IL-1β, TNF-α and IL-6 in the EE group. Additionally, anti-inflammatory molecules were more highly expressed in the EE group compared to the control group as the EE group had an enhanced expression of TGF-β and BDNF. Furthermore, there was an increased expression of Arginase-1, which is a marker for the M2 phenotype of alternatively activated macrophages. The M2 phenotype of macrophages is characterized by the increased production of anti-

inflammatory cytokines (Pusic et al., 2014b). This further shows the anti-inflammatory effect of EE. Silva et al (2010) concluded that the increase of anti-inflammatory cytokines combined with the decreased expression of pro-inflammatory cytokines is possibly the underlying mechanism of the anti-inflammatory effect of EE.

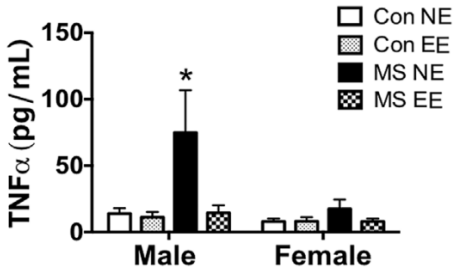

Figure 20. TNF-α levels after maternal separation in male rats with or without EE (Taken from do Prado et al., 2016)

do Prado et al. (2016) has also tried to examine the effects of environmental enrichment in rats who suffered from early life stress by maternal separation. These early life stress animals suffered from cognitive disfunction, and this paper found that EE could prevent this cognitive dysfunction. Animals that were maternally separated had higher pro-inflammatory cytokine levels. When the animals were exposed to both maternal separation and EE, this increase of pro-inflammatory cytokines was not present. This was seen in for example TNFα (Figure 20). From this, they concluded that EE was able to prevent cognitive deficits through protection against inflammatory processes.

Another study that proves the connection between EE and inflammatory activity is the study of Xiao et al. (2019). They exposed mice to an enriched environment and studied thymus and thymocyte development. They studied the thymus specifically because it is the primary organ for maturation of lymphocytes into functional T cells (Fink, 2013). They found that EE induced an increased proportion of CD8+ cytotoxic T lymphocytes and reduced the CD4:CD8 ratio. This further suggests that EE can have an immunomodulatory effect.

Overall, these three studies provide evidence that environmental enrichment can be beneficial for MS patients as it can prevent high levels of pro-inflammatory cytokines, promotes the production of anti-inflammatory cytokines and has a general immunomodulatory effect on the thymus.

Cognition

Next, BDNF is a proposed mechanism through which EE could influence cognition. The study of Joushi et al. (2021) investigated if and how environmental enrichment could influence cognitive ability of rats who went through early life stress because of maternal separation. They housed the animals in larger groups, gave them accessibility to a running wheel or climbing ladder and gave them toys for cognitive stimulation. This study found that early life EE can overcome cognitive defects induced by maternal separation as it enhanced LTP-induction impairment and BDNF levels (Figure 21). This provides evidence that EE can enhance cognition by increasing BDNF levels.

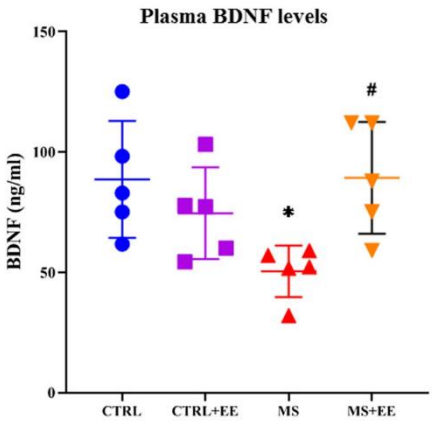

Figure 21. Effect of MS on the brain-derived neurotrophic factor (BDNF) protein levels in plasma (ng/ml) in animals that were either control or MS and with or without EE (Taken from Joushi et al., 2021)

The same connection between EE and cognition and increased BDNF levels was observed in a study by Guilarte et al. (2003). This study investigated the effect of environmental enrichment on animals that were exposed to lead (Pb^{2+}) as it was found that exposure to lead in children caused long-term cognitive deficits. Here, EE reversed spatial learning deficits and increased levels of BDNF.

The theory that increased BNDF levels underlies the beneficial effect of EE on cognition is further supported by the study of do Prado et al (2016). As previously explained, this study investigated the effect of EE

on animals who experienced early life stress by maternal separation. They concluded that the protective effect of EE against cognitive dysfunction was due to protection against inflammatory processes.

Overall, EE could benefit cognition by increasing BDNF levels, but an anti-inflammatory effect could also underly the beneficial influences of EE on cognition.

Myelination

Lastly, a mechanism through which EE can impact myelination can be found by looking at two studies that investigated EE serum exomes. Exomes are naturally occurring nanovesicles that contain mRNA, miRNA, and proteins. They play important roles in cell function, disease, and immunomodulation (Kooijmans et al., 2012). The study of Pusic et al. (2016) applied EE serum exomes to hippocampus cultures or administered exomes nasally to naïve rats and investigated CNS myelination. They showed that these EE serum exosomes significantly reduces oxidative stress and increases myelin content, oligodendrocyte precursor (OPC) levels and neural stem cell levels. Furthermore, several miRNA species that are involved in the regulation of inflammatory responses were detected in EE exomes. Pusic et al. (2016) further observed that rat EE exomes were enriched in miR-219, which is essential for oligodendrocyte progenitor cell differentiation into myelinating cells. Additionally, miR-219 inhibits inflammation and oxidative stress (Zhu et al., 2019). Because of this, Pusic et al. (2019) suspected that EE can increase myelination by modifying immune function.

The study by Pusic & Kraig (2014) also investigated EE serum exomes and found similar results as Pusic et al. (2016). Pusic & Kraig (2016) showed that EE serum-derived exomes had a promyelinating effect and that the exomes were enriched in miR-219. Moreover, they transfected the exomes with an miR-219 inhibitor which prevented the increase in myelin basic protein (MBP) that is normally observed in animals that have been exposed to EE. As MBP is essential for myelin formation, the effect of miR-219 on this protein could be a possible mechanism (Gupta et al., 2005). This result suggests that EE can be beneficial for myelination because of high miR-219 levels. Since the subject of environmental enrichment and the effect on MS is not very widely studied, more research is needed to further explore the mechanism behind the effect of EE on myelination.

In summary, in an animal model for MS, a beneficial effect of EE was found for myelination, cognition and inflammation. EE is anti-inflammatory by decreasing pro-inflammatory cytokine levels and increasing anti-inflammatory cytokine levels. The anti-inflammatory effect of EE could also be the mechanism behind the beneficial effect on myelination. The cognitive enhancing effect of EE could be caused by increased BDNF levels or protection against inflammation.

Discussion

In conclusion, environmental enrichment is beneficial for MS patients as it increases myelination, decreases inflammation, and improves cognition primarily by decreasing inflammation and increasing BDNF levels. This is concluded as the three components of EE (social interaction, physical exercise and cognitive) can separately and combined (as EE) produce these beneficial effects for MS patients. EE is beneficial for MS patients through anti-inflammatory pathways as both social interaction and physical exercise are able to decrease pro-inflammatory cytokine levels. Additionally, the same is found when looking at EE (when the animals are exposed to all three components). This improved immune functioning due to EE is beneficial for myelination, cognition and inflammation and could therefore help MS patients. The same is true for BDNF. Both social interaction and physical exercise increase BDNF levels. Furthermore, when social interaction, physical exercise and cognitive training are combined as EE, higher BDNF levels are found. The elevated BDNF levels can, partly, be the mechanism through which EE could be beneficial for MS patients.

The anti-inflammatory effect of EE can be seen by investigating the effect of the components of EE separately and together. EE improves cognition, inflammation, and cognition by anti-inflammatory pathways. Physical activity improves inflammation and social interaction improves myelination and inflammation by decreasing pro-inflammatory cytokine levels. Only cognitive training does not decrease inflammation. It increases pro-inflammatory cytokines. This could be potentially harmful for MS patients. However, a higher level of pro-inflammatory cytokines has also been proven to be necessary for proper long-term memory. Cognitive training has not been found to negatively affect inflammatory lesions in MS patients and therefore the effect of cognitive training on inflammation might not be substantial enough to be harmful for MS patients. More research should be done to investigate if cognitive training can negatively influence inflammation in MS.

Most studies presented in this essay show that EE could help MS patients as it improved myelination, cognition, and decreased inflammation by elevating BDNF levels and decreasing the levels of pro-inflammatory cytokines. However, as concluded before, cognitive therapy is more weakly connected to these anti-inflammatory and BDNF pathways. This gives the impression that cognitive training might not provide a big contribution to the beneficial effects of EE. Additionally, one study studied the effect of physical exercise, cognitive training and physical exercise and cognitive training combined on the memory of healthy young adults. They found and both the exercise and combined training group had a similar effect on memory performance, hinting that cognitive training might not contribute as much to the cognitive improvements as physical exercise (Heisz et al., 2017). A reason for this could be that cognitive training only benefits individuals with cognitive impairments because a meta-analysis has found that cognitive training can provide positive effects on cognition for healthy individuals, but cognitively impaired individuals did not experience the same beneficial effects (Karr et al., 2014). No studies have compared the effect of the EE components separately and if and how they contribute to a positive effect on MS patients. This should be focused on in future research to further elucidate how different components of EE can contribute to MS patients.

One of the main limiting factors in this essay is the limited research about the specific effect of environmental enrichment on MS patients. Although environmental enrichment is getting more attention because of its therapeutic potential for different disorder such as Alzheimer's disease and Parkinson's disease, only one research paper has investigated its effects on an animal model for MS. Moreover, no research has been performed investigating the effect of social enrichment on pathophysiological features associated with MS. This further emphasizes the lack of knowledge. More research about how EE can help MS patients can also help point in new pathways where treatment can be used to help MS patients.

Another limiting factor in this essay is that most research used to explore the effect of EE on cognition, myelination and inflammation have been performed on rodents. Because of this, the results of these studies are not completely translatable to humans. Furthermore, many of the studies that have been used investigated diseases or disorders that are not translatable to MS. For example, several papers investigated rodents that experiences an ischemic stroke. More research has to be performed on specific MS animal models or on MS patients to draw further conclusions on the beneficial effect of EE.

A third limiting factor of this essay is that there is a lack of research about social enrichment. Because of this, the effect of social enrichment on, for example, myelination, had to be inferred from the effect of social isolation. Because of this, it is not completely certain if the social enrichment would have the opposite effect from social isolation. Additional research about the effect of social enrichment on cognition, inflammation and myelination is needed to resolve this.

The implications of this essay are that more information about possible treatment strategies can help MS patients who are faced with many debilitating symptoms. Understanding how EE can improve the trajectory and life of MS patients contributes to the knowledge about the main underlying pathways that can be targeted for treatment. Although it is already well known that MS is a disease that involves the immune system, the results of this essay further prove the importance of this system in MS. Furthermore, understanding that EE is able to decrease inflammation strengthens its possibility to become an additional treatment strategy for MS.

References

Acuña, J. M., de la Cruz, M. H., Ros, A. L., Tapia, S. P., Ginés, M. L. M., & de Andrés Frutos, C. D. (2017). Elevated plasma fibrinogen levels in multiple sclerosis patients during relapse. *Multiple Sclerosis and Related Disorders*, *18*, 157-160.

Adilakshmi, T., Ness-Myers, J., Madrid-Aliste, C., Fiser, A., & Tapinos, N. (2011). A nuclear variant of ErbB3 receptor tyrosine kinase regulates ezrin distribution and Schwann cell myelination. *Journal of Neuroscience*, *31*(13), 5106-5119.

Aguiar Jr, A. S., Araújo, A. L., da-Cunha, T. R., Speck, A. E., Ignácio, Z. M., De-Mello, N., & Prediger, R. D. (2009). Physical exercise improves motor and short-term social memory deficits in reserpinized rats. Brain research bulletin, 79(6), 452-457.

Ahn, J. H., Choi, J. H., Park, J. H., Kim, I. H., Cho, J. H., Lee, J. C., ... & Won, M. H. (2016). Long-term exercise improves memory deficits via restoration of myelin and microvessel damage, and enhancement of neurogenesis in the aged gerbil hippocampus after ischemic stroke. *Neurorehabilitation and neural repair*, *30*(9), 894-905.

Åkerlund, E., Esbjörnsson, E., Sunnerhagen, K. S., & Björkdahl, A. (2013). Can computerized working memory training improve impaired working memory, cognition and psychological health?. Brain Injury, 27(13-14), 1649-1657.

Amato, M. P., Langdon, D., Montalban, X., Benedict, R. H., DeLuca, J., Krupp, L. B., ... & Comi, G. (2013). Treatment of cognitive impairment in multiple sclerosis: position paper. Journal of neurology, 260(6), 1452-1468.

An, D., Chen, W., Yu, D. Q., Wang, S. W., Yu, W. Z., Xu, H., ... & Yin, S. M. (2017). Effects of social isolation, re-socialization and age on cognitive and aggressive behaviors of Kunming mice and BALB/c mice. Animal science journal, 88(5), 798-806.

Asghari, A. A., Azarnia, M., Mirnajafi-Zadeh, J., & Javan, M. (2013). Adenosine A1 receptor agonist, N6-cyclohexyladenosine, protects myelin and induces remyelination in an experimental model of rat optic chiasm demyelination; electrophysiological and histopathological studies. Journal of the neurological sciences, 325(1-2), 22-28.

Ashizawa, T., & Xia, G. (2016). Ataxia. Continuum: Lifelong Learning in Neurology, 22(4 Movement Disorders), 1208.

Babinski, J. (1885). Recherches sur l'anatomie pathologique de la sclerose en plaque et étude comparative des diverses variétés de la scleroses de la moelle. Arch Physiol (Paris), 5(6), 186-207.

Barbarulo, A. M., Lus, G., Signoriello, E., Trojano, L., Grossi, D., Esposito, M., ... & Conchiglia, G. (2018). Integrated cognitive and neuromotor rehabilitation in multiple sclerosis: a pragmatic study. *Frontiers in behavioral neuroscience*, *12*, 196.

Baroncelli, L., Braschi, C., Spolidoro, M., Begenisic, T., Sale, A., & Maffei, L. (2010). Nurturing brain plasticity: impact of environmental enrichment. Cell Death & Differentiation, 17(7), 1092-1103.

Belviranli, M., Okudan, N., Kabak, B., Erdoğan, M., & Karanfilci, M. (2016). The relationship between brain-derived neurotrophic factor, irisin and cognitive skills of endurance athletes. The Physician and sportsmedicine, 44(3), 290-296.

Benatti, F. B., & Pedersen, B. K. (2015). Exercise as an anti-inflammatory therapy for rheumatic diseases—myokine regulation. Nature reviews rheumatology, 11(2), 86-97.

Bendszus, M., & Storch-Hagenlocher, B. (2013). Multiple sclerosis and other demyelinating diseases. In Inflammatory Diseases of the Brain (pp. 3-18). Springer, Berlin, Heidelberg.

Bernardes, D., Oliveira-Lima, O. C., da Silva, T. V., Faraco, C. C. F., Leite, H. R., Juliano, M. A., ... & Carvalho-Tavares, J. (2013). Differential brain and spinal cord cytokine and BDNF levels in experimental autoimmune encephalomyelitis are modulated by prior and regular exercise. Journal of neuroimmunology, 264(1-2), 24-34.

Bobinski, F., Martins, D. F., Bratti, T., Mazzardo-Martins, L., Winkelmann-Duarte, E. C., Guglielmo, L. G. A., & Santos, A. R. S. (2011). Neuroprotective and neuroregenerative effects of low-intensity aerobic exercise on sciatic nerve crush injury in mice. Neuroscience, 194, 337-348.

Briken, S., Rosenkranz, S. C., Keminer, O., Patra, S., Ketels, G., Heesen, C., ... & Gold, S. M. (2016). Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. Journal of neuroimmunology, 299, 53-58.

Brombin, C., & Di Serio, C. (2016). Evaluating treatment effect within a multivariate stochastic ordering framework: Nonparametric combination methodology applied to a study on multiple sclerosis. Statistical methods in medical research, 25(1), 366-384.

Calabresi, P. A. (2004). Diagnosis and management of multiple sclerosis. American family physician, 70(10), 1935-1944.

Cassilhas, R. C., Viana, V. A., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S. E. R. G. I. O., & Mello, M. T. (2007). The impact of resistance exercise on the cognitive function of the elderly. Medicine and science in sports and exercise, 39(8), 1401.

Castner, S. A., & Goldman-Rakic, P. S. (2004). Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D1 receptor stimulation. *Journal of Neuroscience*, *24*(6), 1446-1450.

Chekroud, S. R., Gueorguieva, R., Zheutlin, A. B., Paulus, M., Krumholz, H. M., Krystal, J. H., & Chekroud, A. M. (2018). Association between physical exercise and mental health in 1· 2 million individuals in the USA between 2011 and 2015: a cross-sectional study. The Lancet Psychiatry, 5(9), 739-746.

Cheng, J., Shen, W., Jin, L., Pan, J., Zhou, Y., Pan, G., ... & Chen, X. (2020). Treadmill exercise promotes neurogenesis and myelin repair via upregulating Wnt/β-catenin signaling pathways in the juvenile brain following focal cerebral ischemia/reperfusion. International journal of molecular medicine, 45(5), 1447-1463.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. The Lancet Neurology, 7(12), 1139-1151.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. The Lancet Neurology, 7(12), 1139-1151.

Clemenson, G. D., Deng, W., & Gage, F. H. (2015). Environmental enrichment and neurogenesis: from mice to humans. Current Opinion in Behavioral Sciences, 4, 56-62.\ Woo, C. C., Donnelly, J. H., Steinberg-Epstein, R., & Leon, M. (2015). Environmental enrichment as a therapy for autism: a clinical trial replication and extension. Behavioral neuroscience, 129(4), 412.

De la Cruz, J., & Kupersmith, M. J. (2006). Clinical profile of simultaneous bilateral optic neuritis in adults. British journal of ophthalmology, 90(5), 551-554.

Déry, N., Pilgrim, M., Gibala, M., Gillen, J., Wojtowicz, J. M., MacQueen, G., & Becker, S. (2013). Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. Frontiers in neuroscience, 7, 66.

Dinarello, C. A. (2000). Proinflammatory cytokines. Chest, 118(2), 503-508.

do Prado, C. H., Narahari, T., Holland, F. H., Lee, H. N., Murthy, S. K., & Brenhouse, H. C. (2016). Effects of early adolescent environmental enrichment on cognitive dysfunction, prefrontal cortex development, and inflammatory cytokines after early life stress. Developmental psychobiology, 58(4), 482-491.

Dobson, R., & Giovannoni, G. (2019). Multiple sclerosis–a review. European journal of neurology, 26(1), 27-40.

Doi, H., Matsushita, T., Isobe, N., Matsuoka, T., Minohara, M., Ochi, H., & Kira, J. I. (2009). Hypercomplementemia at relapse in patients with anti-aquaporin-4 antibody. *Multiple Sclerosis Journal*, *15*(3), 304-310.

Dummer, W., Niethammer, A. G., Baccala, R., Lawson, B. R., Wagner, N., Reisfeld, R. A., & Theofilopoulos, A. N. (2002). T cell homeostatic proliferation elicits effective antitumor autoimmunity. The Journal of clinical investigation, 110(2), 185-192.

Durkheim in the new millennium. Social science & medicine, 51(6), 843-857.

Duzova, H., Karakoc, Y., Emre, M. H., Dogan, Z. Y., & Kilinc, E. (2009). Effects of acute moderate and strenuous exercise bouts on IL-17 production and inflammatory response in trained rats. Journal of sports science & medicine, 8(2), 219.

Eisenberger, N. I., & Cole, S. W. (2012). Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health. Nature neuroscience, 15(5), 669-674.

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. (1999). Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *Journal of experimental psychology: General*, *128*(3), 309.

Faherty, C. J., Shepherd, K. R., Herasimtschuk, A., & Smeyne, R. J. (2005). Environmental enrichment in adulthood eliminates neuronal death in experimental Parkinsonism. Molecular brain research, 134(1), 170-179.

Fang, X. X., Jiang, X. L., Han, X. H., Peng, Y. P., & Qiu, Y. H. (2013). Neuroprotection of interleukin-6 against NMDA-induced neurotoxicity is mediated by JAK/STAT3, MAPK/ERK, and PI3K/AKT signaling pathways. Cellular and molecular neurobiology, 33(2), 241-251.

Ferguson, B., Matyszak, M. K., Esiri, M. M., & Perry, V. H. (1997). Axonal damage in acute multiple sclerosis lesions. Brain: a journal of neurology, 120(3), 393-399.

Feter, N., Freitas, M. P., Gonzales, N. G., Umpierre, D., Cardoso, R. K., & Rombaldi, A. J. (2018). Effects of physical exercise on myelin sheath regeneration: A systematic review and meta-analysis. Science & Sports, 33(1), 8-21.

Fink, P. J. (2013). The biology of recent thymic emigrants. *Annual review of immunology*, *31*, 31-50.

Finsterer, J. (2012). Biomarkers of peripheral muscle fatigue during exercise. BMC musculoskeletal disorders, 13(1), 1-13.

Fredholm, B. B., Chen, J. F., Cunha, R. A., Svenningsson, P., & Vaugeois, J. M. (2005). Adenosine and brain function. Int Rev Neurobiol, 63(1), 191-270.

Friedler, B., Crapser, J., & McCullough, L. (2015). One is the deadliest number: the detrimental effects of social isolation on cerebrovascular diseases and cognition. Acta neuropathologica, 129(4), 493-509.

Galetta, S. L., Markowitz, C., & Lee, A. G. (2002). Immunomodulatory agents for the treatment of relapsing multiple sclerosis: a systematic review. Archives of internal medicine, 162(19), 2161-2169.

Ganança, L., Oquendo, M. A., Tyrka, A. R., Cisneros-Trujillo, S., Mann, J. J., & Sublette, M. E. (2016). The role of cytokines in the pathophysiology of suicidal behavior. Psychoneuroendocrinology, 63, 296-310.

Geraghty, A. C., Gibson, E. M., Ghanem, R. A., Greene, J. J., Ocampo, A., Goldstein, A. K., ... & Monje, M. (2019). Loss of adaptive myelination contributes to methotrexate chemotherapy-related cognitive impairment. Neuron, 103(2), 250-265.

Goldenberg, M. M. (2012). Multiple sclerosis review. Pharmacy and Therapeutics, 37(3), 175.

Goldhammer, E., Tanchilevitch, A., Maor, I., Beniamini, Y., Rosenschein, U., & Sagiv, M. (2005). Exercise training modulates cytokines activity in coronary heart disease patients. International journal of cardiology, 100(1), 93-99.

Golzari, Z., Shabkhiz, F., Soudi, S., Kordi, M. R., & Hashemi, S. M. (2010). Combined exercise training reduces IFN-γ and IL-17 levels in the plasma and the supernatant of peripheral blood mononuclear cells in women with multiple sclerosis. International immunopharmacology, 10(11), 1415-1419.

Gómez-Pinilla, F., Ying, Z., Roy, R. R., Molteni, R., & Edgerton, V. R. (2002). Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. Journal of neurophysiology, 88(5), 2187-2195.

Guilarte, T. R., Toscano, C. D., McGlothan, J. L., & Weaver, S. A. (2003). Environmental enrichment reverses cognitive and molecular deficits induced by developmental lead exposure. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 53(1), 50-56.

Guillén, J. (Ed.). (2017). *Laboratory animals: regulations and recommendations for the care and use of animals in research*. Academic Press.

Gulaj, E., Pawlak, K., Bien, B., & Pawlak, D. (2010). Kynurenine and its metabolites in Alzheimer's disease patients. Advances in Medical Sciences, 55(2), 204-211.

Gupta, R., Truong, L., Bear, D., Chafik, D., Modafferi, E., & Hung, C. T. (2005). Shear stress alters the expression of myelin-associated glycoprotein (MAG) and myelin basic protein (MBP) in Schwann cells. *Journal of orthopaedic research*, *23*(5), 1232-1239.

Handschin, C., Chin, S., Li, P., Liu, F., Maratos-Flier, E., LeBrasseur, N. K., ... & Spiegelman, B. M. (2007). Skeletal muscle fiber-type switching, exercise intolerance, and myopathy in PGC-1α muscle-specific knock-out animals. Journal of Biological Chemistry, 282(41), 30014-30021.

Heisz, J. J., Clark, I. B., Bonin, K., Paolucci, E. M., Michalski, B., Becker, S., & Fahnestock, M. (2017). The effects of physical exercise and cognitive training on memory and neurotrophic factors. Journal of cognitive neuroscience, 29(11), 1895-1907.

Henze, T., Rieckmann, P., & Toyka, K. V. (2006). Symptomatic treatment of multiple sclerosis. European neurology, 56(2), 78-105.

Hu, D., Notarbartolo, S., Croonenborghs, T., Patel, B., Cialic, R., Yang, T. H., ... & Weiner, H. L. (2017). Transcriptional signature of human pro-inflammatory TH 17 cells identifies reduced IL10 gene expression in multiple sclerosis. Nature communications, 8(1), 1-14.

Huang, H. J., Liang, K. C., Ke, H. C., Chang, Y. Y., & Hsieh-Li, H. M. (2011). Long-term social isolation exacerbates the impairment of spatial working memory in APP/PS1 transgenic mice. Brain research, 1371, 150-160.

Ikegaya, Y., Delcroix, I., Iwakura, Y., Matsuki, N., & Nishiyama, N. (2003). Interleukin-1β abrogates long-term depression of hippocampal CA1 synaptic transmission. Synapse, 47(1), 54-57.

Janardhan, V., & Bakshi, R. (2002). Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. Journal of the neurological sciences, 205(1), 51-58.

Jankowsky, J. L., Melnikova, T., Fadale, D. J., Xu, G. M., Slunt, H. H., Gonzales, V., ... & Savonenko, A. V. (2005). Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. Journal of Neuroscience, 25(21), 5217-5224.

Janssen, H., Ada, L., Karayanidis, F., Drysdale, K., McElduff, P., Pollack, M., ... & Spratt, N. J. (2012). Translating the use of an enriched environment poststroke from bench to bedside: study design and protocol used to test the feasibility of environmental enrichment on stroke patients in rehabilitation. International Journal of Stroke, 7(6), 521-526.

Janssens, K., Slaets, H., & Hellings, N. (2015). Immunomodulatory properties of the IL-6 cytokine family in multiple sclerosis. *Annals of the New York Academy of Sciences*, *1351*(1), 52-60.

Jimenez-Morales, R. M., Herrera-Jimenez, L. F., Macias-Delgado, Y., Perez-Medinilla, Y. T., Diaz-Diaz, S. M., & Forn, C. (2017). Cognitive training combined with aerobic exercises in multiple sclerosis patients: a pilot study. Revista de neurologia, 64(11), 489-495.

Joushi, S., Esmaeilpour, K., Masoumi-Ardakani, Y., Esmaeili-Mahani, S., & Sheibani, V. (2021). Effects of short environmental enrichment on early-life adversity induced cognitive alternations in adolescent rats. Journal of neuroscience research, 99(12), 3373-3391.

Karr, J. E., Areshenkoff, C. N., Rast, P., & Garcia-Barrera, M. A. (2014). An empirical comparison of the therapeutic benefits of physical exercise and cognitive training on the executive functions of older adults: a meta-analysis of controlled trials. Neuropsychology, 28(6), 829.

Kipnis, J., Cohen, H., Cardon, M., Ziv, Y., & Schwartz, M. (2004). T cell deficiency leads to cognitive dysfunction: implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. Proceedings of the National Academy of Sciences, 101(21), 8180-8185.

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Training of working memory in children with ADHD. *Journal of clinical and experimental neuropsychology*, *24*(6), 781-791.

Komulainen, P., Pedersen, M., Hänninen, T., Bruunsgaard, H., Lakka, T. A., Kivipelto, M., ... & Rauramaa, R. (2008). BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA Study. Neurobiology of learning and memory, 90(4), 596-603.

Kooijmans, S. A., Vader, P., van Dommelen, S. M., van Solinge, W. W., & Schiffelers, R. M. (2012). Exosome mimetics: a novel class of drug delivery systems. *International journal of nanomedicine*, *7*, 1525.

Küster, O. C., Laptinskaya, D., Fissler, P., Schnack, C., Zügel, M., Nold, V., ... & von Arnim, C. A. (2017). Novel blood-based biomarkers of cognition, stress, and physical or cognitive training in older adults at risk of dementia: preliminary evidence for a role of BDNF, irisin, and the kynurenine pathway. Journal of Alzheimer's Disease, 59(3), 1097-1111.

Lampit, A., Heine, J., Finke, C., Barnett, M. H., Valenzuela, M., Wolf, A., ... & Hill, N. T. (2019). Computerized cognitive training in multiple sclerosis: a systematic review and meta-analysis. Neurorehabilitation and neural repair, 33(9), 695-706.

Laske, C., Stellos, K., Hoffmann, N., Stransky, E., Straten, G., Eschweiler, G. W., & Leyhe, T. (2011). Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. *International Journal of Neuropsychopharmacology*, *14*(3), 399-404.

Lassmann, H. (2013). Pathology and disease mechanisms in different stages of multiple sclerosis. Journal of the neurological sciences, 333(1-2), 1-4.

Lazic, S. E., Grote, H. E., Blakemore, C., Hannan, A. J., Van Dellen, A., Phillips, W., & Barker, R. A. (2006). Neurogenesis in the R6/1 transgenic mouse model of Huntington's disease: effects of environmental enrichment. European Journal of Neuroscience, 23(7), 1829-1838.

Lee, I. M., Shiroma, E. J., Lobelo, F., Puska, P., Blair, S. N., Katzmarzyk, P. T., & Lancet Physical Activity Series Working Group. (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The lancet, 380(9838), 219-229.

Liu, J., Dietz, K., DeLoyht, J. M., Pedre, X., Kelkar, D., Kaur, J., ... & Casaccia, P. (2012). Impaired adult myelination in the prefrontal cortex of socially isolated mice. Nature neuroscience, 15(12), 1621-1623.

Loucks, E. B., Sullivan, L. M., D'Agostino Sr, R. B., Larson, M. G., Berkman, L. F., & Benjamin, E. J. (2006). Social networks and inflammatory markers in the Framingham Heart Study. *Journal of biosocial science*, *38*(6), 835-842.

Lovera, J., & Reza, T. (2013). Stress in multiple sclerosis: review of new developments and future directions. Current Neurology and Neuroscience Reports, 13(11), 1-5.

Lundgaard, I., Luzhynskaya, A., Stockley, J. H., Wang, Z., Evans, K. A., Swire, M., ... & Káradóttir, R. T. (2013). Neuregulin and BDNF induce a switch to NMDA receptor-dependent myelination by oligodendrocytes. PLoS biology, 11(12), e1001743.

Lyons, D. A., Pogoda, H. M., Voas, M. G., Woods, I. G., Diamond, B., Nix, R., ... & Talbot, W. S. (2005). erbb3 and erbb2 are essential for schwann cell migration and myelination in zebrafish. Current Biology, 15(6), 513-524.

Makinodan, M., Ikawa, D., Miyamoto, Y., Yamauchi, J., Yamamuro, K., Yamashita, Y., ... & Kishimoto, T. (2016). Social isolation impairs remyelination in mice through modulation of IL-6. The FASEB Journal, 30(12), 4267-4274.

Makinodan, M., Rosen, K. M., Ito, S., & Corfas, G. (2012). A critical period for social experience–dependent oligodendrocyte maturation and myelination. science, 337(6100), 1357-1360.

Matsumoto, Y., Yamaguchi, T., Watanabe, S., & Yamamoto, T. (2004). Involvement of arachidonic acid cascade in working memory impairment induced by interleukin-1 beta. Neuropharmacology, 46(8), 1195-1200.

McLennan, H. (1983). Receptors for the excitatory amino acids in the mammalian central nervous system. Progress in neurobiology, 20(3-4), 251-271.

McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., & Klingberg, T. (2009). Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science, 323(5915), 800-802.

Menec, V. H. (2003). The relation between everyday activities and successful aging: A 6-year longitudinal study. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 58(2), S74-S82.
Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. The Lancet Neurology, 3(6), 343-353.

Metsios, G. S., Moe, R. H., & Kitas, G. D. (2020). Exercise and inflammation. Best Practice & Research Clinical Rheumatology, 101504.

Metsios, G. S., Moe, R. H., & Kitas, G. D. (2020). Exercise and inflammation. *Best Practice & Research Clinical Rheumatology*, *34*(2), 101504.

Miller, D. H., Ormerod, I. E. C., Rudge, P., Kendall, B. E., Moseley, I. F., & McDonald, W. I. (1989). The early risk of multiple sclerosis following isolated acute syndromes of the brainstem and spinal cord. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 26(5), 635-639.

Mitew, S., Gobius, I., Fenlon, L. R., McDougall, S. J., Hawkes, D., Xing, Y. L., ... & Emery, B. (2018). Pharmacogenetic stimulation of neuronal activity increases myelination in an axon-specific manner. Nature communications, 9(1), 1-16.

Mora, E., Portella, M. J., Piñol-Ripoll, G., López, R., Cuadras, D., Forcada, I., ... & Mur, M. (2019). High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. *European Psychiatry*, *60*, 97-107.

Mori, F., Nistico, R., Mandolesi, G., Piccinin, S., Mango, D., Kusayanagi, H., ... & Centonze, D. (2014). Interleukin-1β promotes long-term potentiation in patients with multiple sclerosis. Neuromolecular medicine, 16(1), 38-51.

Morrison, A. B., & Chein, J. M. (2011). Does working memory training work? The promise and challenges of enhancing cognition by training working memory. Psychonomic bulletin & review, 18(1), 46-60.

Niessner, A., Richter, B., Penka, M., Steiner, S., Strasser, B., Ziegler, S., ... & Huber, K. (2006). Endurance training reduces circulating inflammatory markers in persons at risk of coronary events: impact on plaque stabilization?. Atherosclerosis, 186(1), 160-165.

O'Keefe, L. M., Doran, S. J., Mwilambwe-Tshilobo, L., Conti, L. H., Venna, V. R., & McCullough, L. D. (2014). Social isolation after stroke leads to depressive-like behavior and decreased BDNF levels in mice. *Behavioural brain research*, *260*, 162-170.

Olek, M. J. (2011). Epidemiology, risk factors and clinical features of multiple sclerosis in adults. Epidemiology and clinical features of multiple sclerosis in adults. Accessed October, 31.

Pan, S., Mayoral, S. R., Choi, H. S., Chan, J. R., & Kheirbek, M. A. (2020). Preservation of a remote fear memory requires new myelin formation. Nature neuroscience, 23(4), 487-499.

Petersen, A. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. Journal of applied physiology, 98(4), 1154-1162.

Platzer, M., Dalkner, N., Fellendorf, F. T., Birner, A., Bengesser, S. A., Queissner, R., ... & Reininghaus, E. Z. (2017). Tryptophan breakdown and cognition in bipolar disorder. *Psychoneuroendocrinology*, *81*, 144-150.

Prineas, J. W., Kwon, E. E., Cho, E. S., Sharer, L. R., Barnett, M. H., Oleszak, E. L., ... & Morgan, B. P. (2001). Immunopathology of secondary-progressive multiple sclerosis. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 50(5), 646-657.

Pusic, A. D., & Kraig, R. P. (2014a). Youth and environmental enrichment generate serum exosomes containing miR-219 that promote CNS myelination. Glia, 62(2), 284-299.

Pusic, K. M., Pusic, A. D., & Kraig, R. P. (2016). Environmental enrichment stimulates immune cell secretion of exosomes that promote CNS myelination and may regulate inflammation. Cellular and molecular neurobiology, 36(3), 313-325.

Pusic, K. M., Pusic, A. D., Kemme, J., & Kraig, R. P. (2014b). Spreading depression requires microglia and is decreased by their M2a polarization from environmental enrichment. *Glia*, *62*(7), 1176-1194.

Qiu, Z., Sweeney, D. D., Netzeband, J. G., & Gruol, D. L. (1998). Chronic interleukin-6 alters NMDA receptor-mediated membrane responses and enhances neurotoxicity in developing CNS neurons. Journal of Neuroscience, 18(24), 10445-10456.

Rabin, B. S., Cunnick, J. E., & Lysle, D. T. (1988). Alteration of the immune system by housing. Advances.

Ramagopalan, S. V., Dobson, R., Meier, U. C., & Giovannoni, G. (2010). Multiple sclerosis: risk factors, prodromes, and potential causal pathways. The Lancet Neurology, 9(7), 727-739.

Rinaldi, F., Calabrese, M., Grossi, P., Puthenparampil, M., Perini, P., & Gallo, P. (2010). Cortical lesions and cognitive impairment in multiple sclerosis. *Neurological sciences*, *31*(2), 235-237.

Ross, F. M., Allan, S. M., Rothwell, N. J., & Verkhratsky, A. (2003). A dual role for interleukin-1 in LTP in mouse hippocampal slices. Journal of neuroimmunology, 144(1-2), 61-67.

Rutherfurd-Markwick, K. J., & Gill, H. S. (2004). Probiotics and immunomodulation. In *Diet and human immune function* (pp. 327-344). Humana Press, Totowa, NJ.

Sanchez, M. M., Hearn, E. F., Do, D., Rilling, J. K., & Herndon, J. G. (1998). Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. Brain research, 812(1-2), 38-49.

Scaccianoce, S., Del Bianco, P., Paolone, G., Caprioli, D., Modafferi, A. M., Nencini, P., & Badiani, A. (2006). Social isolation selectively reduces hippocampal brain-derived neurotrophic factor without altering plasma corticosterone. Behavioural brain research, 168(2), 323-325.

Schapiro, S. J., Nehete, P. N., Perlman, J. E., & Sastry, K. J. (2000). A comparison of cell-mediated immune responses in rhesus macaques housed singly, in pairs, or in groups. Applied Animal Behaviour Science, 68(1), 67-84.

Schneider, H., Pitossi, F., Balschun, D., Wagner, A., Del Rey, A., & Besedovsky, H. (1998). A neuromodulatory role of interleukin-1β in the hippocampus. Proceedings of the National Academy of Sciences, 95(13), 7778-7783.

Schwarcz, R., & Pellicciari, R. (2002). Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. Journal of Pharmacology and Experimental Therapeutics, 303(1), 1-10.

Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., ... & Suzuki, T. (2014). A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. *Frontiers in aging neuroscience*, *6*, 69.

Silva, B. A., Leal, M. C., Farías, M. I., Erhardt, B., Galeano, P., Pitossi, F. J., & Ferrari, C. C. (2020). Environmental enrichment improves cognitive symptoms and pathological features in a focal model of cortical damage of multiple sclerosis. Brain research, 1727, 146520.

Simpson, R., Booth, J., Lawrence, M., Byrne, S., Mair, F., & Mercer, S. (2014). Mindfulness based interventions in multiple sclerosis-a systematic review. BMC neurology, 14(1), 1-9.

Singhal, G., Jaehne, E. J., Corrigan, F., & Baune, B. T. (2014). Cellular and molecular mechanisms of immunomodulation in the brain through environmental enrichment. Frontiers in cellular neuroscience, 8, 97.

Sithanandam, G., & Anderson, L. M. (2008). The ERBB3 receptor in cancer and cancer gene therapy. *Cancer gene therapy*, *15*(7), 413-448.

Siuda, J., Patalong-Ogiewa, M., Żmuda, W., Targosz-Gajniak, M., Niewiadomska, E., Matuszek, I., ... & Rudzińska-Bar, M. (2017). Cognitive impairment and BDNF serum levels. Neurologia i neurochirurgia polska, 51(1), 24-32.

Skurkovich, S., Boiko, A., Beliaeva, I., Buglak, A., Alekseeva, T., Smirnova, N., ... & Gusev, E. (2001). Randomized study of antibodies to IFN-g and TNF-a in secondary progressive multiple sclerosis. Multiple Sclerosis Journal, 7(5), 277-284.

Smith, K. J., Gavey, S., RIddell, N. E., Kontari, P., & Victor, C. (2020). The association between loneliness, social isolation and inflammation: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, 112, 519-541.

Soave, O. A. (1962). Reactivation of rabies virus in a guinea pig with adrenocorticotropic hormone. The Journal of infectious diseases, 129-131.

Sobocki, P., Pugliatti, M., Lauer, K., & Kobelt, G. (2007). Estimation of the cost of MS in Europe: extrapolations from a multinational cost study. Multiple Sclerosis Journal, 13(8), 1054-1064.

Stampanoni Bassi, M., Iezzi, E., Landi, D., Monteleone, F., Gilio, L., Simonelli, I., ... & Buttari, F. (2018). Delayed treatment of MS is associated with high CSF levels of IL-6 and IL-8 and worse future disease course. *Journal of neurology*, *265*(11), 2540-2547.

Steadman, P. E., Xia, F., Ahmed, M., Mocle, A. J., Penning, A. R., Geraghty, A. C., ... & Frankland, P. W. (2020). Disruption of oligodendrogenesis impairs memory consolidation in adult mice. Neuron, 105(1), 150-164.

Stevens, B., Porta, S., Haak, L. L., Gallo, V., & Fields, R. D. (2002). Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials. Neuron, 36(5), 855-868.

Templer, V. L., Wise, T. B., & Heimer-McGinn, V. R. (2019). Social housing protects against age-related working memory decline independently of physical enrichment in rats. Neurobiology of aging, 75, 117-125.

Trapp, B. D., Peterson, J., Ransohoff, R. M., Rudick, R., Mörk, S., & Bö, L. (1998). Axonal transection in the lesions of multiple sclerosis. New England Journal of Medicine, 338(5), 278-285.

van Meeteren, N. L., Brakkee, J. H., Hamers, F. P., Helders, P. J., & Gispen, W. H. (1997). Exercise training improves functional recovery and motor nerve conduction velocity after sciatic nerve crush lesion in the rat. Archives of physical medicine and rehabilitation, 78(1), 70-77.

Venna, V. R., Xu, Y., Doran, S. J., Patrizz, A., & McCullough, L. (2014). Social interaction plays a critical role in neurogenesis and recovery after stroke. Translational psychiatry, 4(1), e351-e351.

Vermeij, A., Claassen, J. A., Dautzenberg, P. L., & Kessels, R. P. (2016). Transfer and maintenance effects of online working-memory training in normal ageing and mild cognitive impairment. *Neuropsychological rehabilitation*, *26*(5-6), 783-809.

Wake, H., Lee, P. R., & Fields, R. D. (2011). Control of local protein synthesis and initial events in myelination by action potentials. Science, 333(6049), 1647-1651.

Walker II, W. H., Meléndez-Fernández, O. H., Pascoe, J. L., Zhang, N., & DeVries, A. C. (2020). Social enrichment attenuates chemotherapy induced pro-inflammatory cytokine production and affective behavior via oxytocin signaling. Brain, behavior, and immunity, 89, 451-464.

Wang, K., Song, F., Fernandez-Escobar, A., Luo, G., Wang, J. H., & Sun, Y. (2018). The properties of cytokines in multiple sclerosis: pros and cons. The American journal of the medical sciences, 356(6), 552-560.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine Dl receptors in prefrontal cortex. Nature, 376(6541), 572-575.

Xiao, R., Bergin, S. M., Huang, W., Mansour, A. G., Liu, X., Judd, R. T., ... & Cao, L. (2019). Enriched environment regulates thymocyte development and alleviates experimental autoimmune encephalomyelitis in mice. Brain, behavior, and immunity, 75, 137-148.

Yang, T., Nie, Z., Shu, H., Kuang, Y., Chen, X., Cheng, J., ... & Liu, H. (2020). The role of BDNF on neural plasticity in depression. Frontiers in cellular neuroscience, 14, 82.

Zhu, Y., Xu, Q., Sha, W. P., Zhao, K. P., & Wang, L. M. (2019). MiR-219-5p promotes spinal cord injury recovery by inhibiting NEUROD2-regulated inflammation and oxidative stress. Eur Rev Med Pharmacol Sci, 23(1), 37-43.

Zhu, Y., Xu, Q., Sha, W. P., Zhao, K. P., & Wang, L. M. (2019). MiR-219-5p promotes spinal cord injury recovery by inhibiting NEUROD2-regulated inflammation and oxidative stress. *Eur Rev Med Pharmacol Sci*, *23*(1), 37-43.