



Review

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Synaptic plasticity in multiple sclerosis and in experimental autoimmune encephalomyelitis

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Approximately half of all patients with multiple sclerosis (MS) experience cognitive dysfunction, including learning and memory impairment. Recent studies suggest that hippocampal pathology is involved, although the mechanisms underlying these deficits remain poorly understood. Evidence obtained from a mouse model of MS, the experimental autoimmune encephalomyelitis (EAE), suggests that in the hippocampus of EAE mice long-term potentiation (LTP) is favoured over long-term depression in response to repetitive synaptic activation, through a mechanism dependent on enhanced IL-1 β released from infiltrating lymphocytes or activated microglia. Facilitated LTP during an immune-mediated attack might underlie functional recovery, but also cognitive deficits and excitotoxic neurodegeneration. Having identified that pro-inflammatory cytokines such as IL-1 β can influence synaptic function and integrity in early MS, it is hoped that new treatments targeted towards preventing synaptic pathology can be developed.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, demyelinating disease of the central nervous system (CNS). It is the most common cause of neurological disability in young adults, with disease onset peaking between 20 and 40 years. The disease takes three main forms: relapsing and remitting, where unpredictable acute attacks are interposed with periods of stability; primary-progressive, characterized by a gradual but steady progression of disability; and secondary-progressive, which begins with a relapsing–remitting course, and then becomes steadily progressive [1].

Clinical signs of MS are heterogeneous, reflecting the areas of the brain and spinal cord that are affected [2]. The neuropathological hallmarks of MS are demyelinating white matter lesions associated with inflammatory infiltrates, oxidative injury, excitotoxicity, astrogliosis and early axonal injury/neuronal damage, as well as disruption of the blood–brain barrier [3]. However, grey matter atrophy is also present early in the disease and worsens along with MS progression, correlating with motor, sensory, visual disability and cognitive deficits [4]. Accordingly, brain magnetic resonance imaging (MRI) studies in patients with MS have shown structural changes in both the cerebral cortex and hippocampus, with atrophy of the CA1 hippocampal subfield [5]. These data are in agreement with post-mortem studies showing demyelination and neuropathology in the hippocampus of MS patients [6], where cellular and molecular alterations affecting synaptic plasticity, axonal transport and glutamate homeostasis occur [7]. Glutamate-mediated excitotoxicity is among the key factors underlying neuronal damage in MS. Glutamate levels are significantly increased in the cerebrospinal fluid (CSF) [8] and brain of MS patients [9]. In addition, changes in the expression of glutamate transporters and receptors

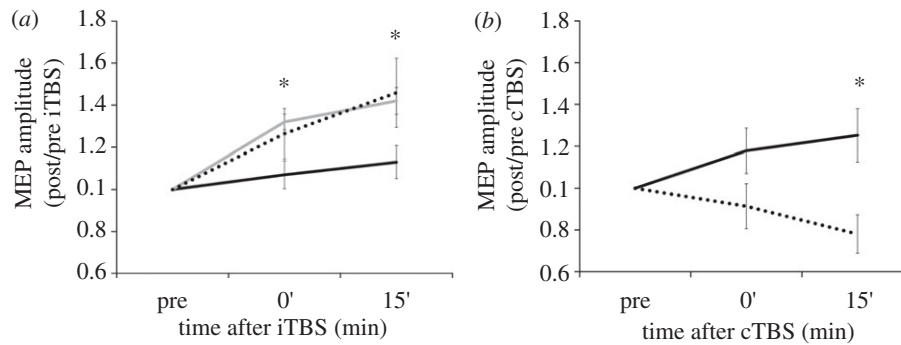


Figure 1. TBS-induced plasticity in MS and healthy controls. (a) iTBS induces the expected effects in MS Gd⁻ (grey line) patients and in healthy subjects (HS, dotted line) but is altered in MS Gd⁺ (black line) patients. Gd⁻ patients and the control group display the predictable LTP-like effect, while in MS Gd⁺ patients no plastic changes of cortical excitability are observed (adapted from [21]). (b) cTBS-induced effects diverge between MS (solid line) patients and healthy control subjects (HS, dotted line). The control group displays the predictable LTD-like effect, while MS patients manifest LTP-like changes. * $p < 0.05$, ANOVA.

have been found in MS patients [10–12] and in the experimental autoimmune encephalitis (EAE) model of MS [13–15]. These results suggest that an increased excitatory neurotransmission plays a role in the pathogenesis of MS [16]. We have recently found that synaptotoxicity might also be the result of the inflammatory damage of hippocampal inhibitory GABAergic interneurons, which shifts the inhibitory/excitatory balance towards excessive excitation [17].

In this review, we will describe abnormal patterns of cortical plasticity in a sample of MS patients and in EAE, which models MS in mice. Our central hypothesis is that enhanced long-term potentiation (LTP) during immune attacks on the CNS might on the one hand facilitate functional recovery, and on the other trigger cognitive impairment and synaptic degeneration.

2. Abnormal neuroplasticity in multiple sclerosis patients

LTP- and long-term depression (LTD)-like cortical plasticity can be explored safely and non-invasively in humans by a number of neurophysiological stimulation protocols, including intermittent (iTBS) and continuous theta-burst stimulation (cTBS), which have been developed in the attempt to mimic the physiological activity of hippocampal neurons during learning episodes [18,19].

Both forms of synaptic plasticity are altered in patients with MS, providing a plausible synaptic substrate for the cognitive deficits frequently associated with this disorder [20]. LTP induced by iTBS is absent in relapsing–remitting MS (RR-MS) patients during disease exacerbations (figure 1a) [21], probably because acute inflammation alters the metabolism of amyloid- β (A β) peptide, thereby restraining its effect on synaptic plasticity [22].

In MS, gadolinium (Gd⁺) lesions tend to be associated with an inflammatory response. In 42 MS patients stratified for the absence or the presence of acute inflammatory lesions (i.e. Gd⁺ lesions at the MRI), we found that CSF levels of A β _{1–42} were lower in Gd⁺ MS patients when compared with both Gd⁻ MS patients and non-MS controls. A striking correlation between CSF A β _{1–42} levels and LTP amplitude assessed by iTBS was also found, indicating that A β is a potent regulator of synaptic plasticity not only in animals [23] but also in the MS brain [22]. To examine whether cognitive impairment in MS patients was associated with reduced cortical LTP, we compared iTBS-induced LTP amplitude in MS patients with or

without cognitive impairment. We found that iTBS-induced LTP was lower in cognitively impaired MS patients [22], in agreement with the finding that the effects of repetitive transcranial magnetic stimulation (TMS) on synaptic plasticity are altered in patients with Alzheimer's disease (AD) [24,25]. Our results indicate that acute inflammation in MS alters A β metabolism and cognitive abilities by interfering with LTP-like, activity-dependent synaptic plasticity [22].

Recent evidence suggests that certain mechanisms of neurodegeneration are shared between MS and AD. However, the relationship between inflammatory mediators and A β metabolism in the two diseases is quite complex to define. In AD inflammatory changes, typified by activated microglia, are in close proximity to A β -containing plaques, neurofibrillary tangles and neuronal loss. It is still unclear, however, whether inflammation contributes to the pathogenesis of AD or is the consequence of the progressive neurodegenerative process [26]. A recent study showed that A β -specific Th1 cells increase microglial activation and A β deposition, changes that are associated with impaired cognitive function in a transgenic mouse model of AD. Treatment with anti-IFN- γ antibody attenuated the effects of Th1 cells, suggesting that release of IFN- γ from infiltrating Th1 cells might induce the A β misprocessing and behavioural deficits [27]. Moreover, BACE activity was found either increased in the CSF of AD patients [28] or decreased over time in the CSF of patients with RR-MS [29]. The reduction of CSF A β in AD has been postulated to reflect deposition of the aggregated insoluble fibrillar A β peptides in senile plaque, with lower levels of diffusion into the CSF [30]. There is no evidence, however, of A β tissue deposition in MS brains [31]. We cannot argue, therefore, that A β CSF levels decrease as a consequence of tissue deposition in MS.

More recently, we also explored LTD-like plasticity by using the cTBS stimulation paradigm in MS. We found that cTBS caused the expected LTD-like effect in healthy individuals, while it resulted in no effect or even in LTP in MS subjects [32] (figure 1b). These findings differ from findings in AD patients where an impairment of LTP-like together with normal LTD-like cortical plasticity was recently reported [33]. In line with these findings, altered LTD in MS was associated with IL-1 β and not with A β CSF levels, consistent with the idea that specific inflammatory processes underlie synaptic plasticity alterations in different diseases.

Together with the finding that also iTBS-induced plasticity is altered in MS [22], these results indicate a profound

subversion of plasticity rules and mechanisms in the MS brain, which is probably caused by the inflammatory milieu generated by infiltrating autoreactive T lymphocytes and by activated microglia in the CNS during immune-mediated attacks. Interestingly, a previous study reported the expected LTD-like plasticity in response to cTBS in a sample of 14 stable MS patients [34], while about half of our studied population (59 patients in total) was in the relapsing phase [32].

3. Animal models of multiple sclerosis

Two main animal model systems are used for the study of MS: EAE [35], and experimental viral infection models, exemplified by Theiler's murine encephalomyelitis virus (TMEV) [36]. Both models have significantly advanced our understanding of MS and allowed preclinical testing of disease therapies. EAE is considered to be the best model of MS, because it recapitulates the main pathological features of the human disease. EAE can be induced by immunization of susceptible animals with defined myelin antigens, including myelin basic protein [37], proteolipid protein [38] and myelin oligodendrocyte glycoprotein (MOG) [39], which determine the different disease phenotypes and pattern of lesions. Chronic progressive EAE is usually induced in six- to eight-week-old C57BL/6 female mice by subcutaneous immunization with MOG 35–55 amino acid peptide in incomplete Freund's adjuvant supplemented with *Mycobacterium tuberculosis*. Pertussis toxin is injected on the day of the immunization and again 2 days later to increase the permeability of the blood–brain barrier [40,41]. In general, EAE symptoms appear 8–12 days post-immunization, peaking 10 days later. EAE clinical course usually begins with a weakened tail, gradually followed by hind limb paralysis and rarely by front limb paralysis. After the acute clinical phase, a gradual partial recovery is usually observed, resulting in a chronic phase characterized by less severe symptoms.

Like all animal models of human disease, also EAE presents several limitations. Different experimental variables including the species, strain, sex and age of the animals used; but also the specific induction method might account for the inconsistent results. Most EAE studies are performed in genetically identical groups of animals, which exclude an important source of variation. Furthermore, genetically identical animals may differ in their susceptibility to EAE depending on environmental factors, which may not easily be controlled. Despite their intrinsic limitations, EAE models remain an important tool to understand the pathogenic cellular and molecular mechanisms of EAE and potentially of MS, as well as to assess the efficacy of novel disease-modifying therapies. Certainly, our understanding of EAE pathogenesis is still incomplete; thus caution is needed when translating the results of experimental research into clinical trials [42].

4. Long-term potentiation studies in experimental multiple sclerosis

Animal models of human diseases represent excellent tools for the investigation of pathogenic mechanisms of diseases and the identification of potential targets for pharmacological intervention [43]. Cognitive function in animal models is usually assessed by electrophysiological analysis of hippocampal

synaptic plasticity or behavioural analysis of learning and memory [44–46]. Of note, aberrant synaptic plasticity has been observed in experimental models of AD [47–49], Parkinson's disease [50], autism spectrum disorders [51] and depression [52]. Few papers have investigated so far hippocampal LTP in the EAE model. Ziehn *et al.* [53] found normal LTP at CA1 hippocampal synapses but impaired basal excitatory synaptic transmission and paired-pulse facilitation (PPF) (a presynaptic form of synaptic plasticity) at 21–45 days after induction of EAE. By contrast, two subsequent studies showed that LTP was impaired at two different time points (14–19 days and 30–35 days) after EAE induction [54,55], while excitatory basal transmission and PPF were unaltered in the acute phase of disease [55]. In the latter study, the LTP deficit was associated with a decreased expression of the NMDA receptor subunit NR2B and increased interleukin-1 β (IL-1 β) levels. Interestingly, a ketogenic diet could rescue motor disability, spatial learning and LTP impairment associated with EAE by restraining pro-inflammatory cytokines and oxidative stress [54].

Our group has recently performed a comprehensive study of bidirectional synaptic plasticity at CA3–CA1 synapses from EAE (20–25 days after disease induction) compared to their respective complete Freund's adjuvant (CFA) controls [17]. Animals were scored daily for clinical symptoms of EAE, as follows: 0, no clinical signs; 1, flaccid tail; 2, hind limb weakness; 3, hind limb paresis; 4, complete bilateral hind limb paralysis; 5, death because of EAE; intermediate clinical signs were scored adding 0.5 value. Generally, only animals with a significant clinical disability score (at least 3–4) were selected for the experiments in the EAE group.

We showed that paired-pulse low-frequency stimulation (PP-LFS) at 1 Hz for 15 min, a protocol able to induce LTD in adult rodents [56], triggered the expected LTD in control slices, but slightly potentiated synaptic transmission in slices from EAE (figure 2*a*). This trend was also maintained at a stimulation frequency of 100 Hz (1 s), with LTP being significantly higher in slices from EAE mice (figure 2*b*). Figure 2*c* summarizes the frequency–response plots using different conditioning protocols. The rightward shift in the frequency–synaptic function response observed in EAE mice resembles the plasticity subversion observed in MS patients. As the amplitude of synaptic potentiation correlates with the concentration of the pro-inflammatory cytokine IL-1 β in the CSF of MS patients [32], we tested whether the facilitated LTP in EAE mice was caused by IL-1 β . Control hippocampal slices exposed to exogenous IL-1 β showed responses similar to those seen in EAE, i.e. a moderate synaptic potentiation following PP-LFS (figure 2*d*), and a more robust LTP following high-frequency stimulation (HFS; 100 Hz, 1 s) (figure 2*e*). These data suggest that IL-1 β *per se* is capable of lowering the threshold for LTP induction (figure 2*f*), thus mimicking the abnormal frequency–response relationship observed in EAE. Differently from transgenic AD models where A β -mediated LTD facilitation might promote loss of synapses, the contribution of LTD alterations to EAE pathogenesis still requires further investigation.

Contrasting electrophysiological data in EAE models are inherent to the high variability of these models in terms of mouse strains, methods used for EAE induction and housing conditions. It is not uncommon that data of synaptic plasticity are not homogeneous in animal models of neurological disorders [57].

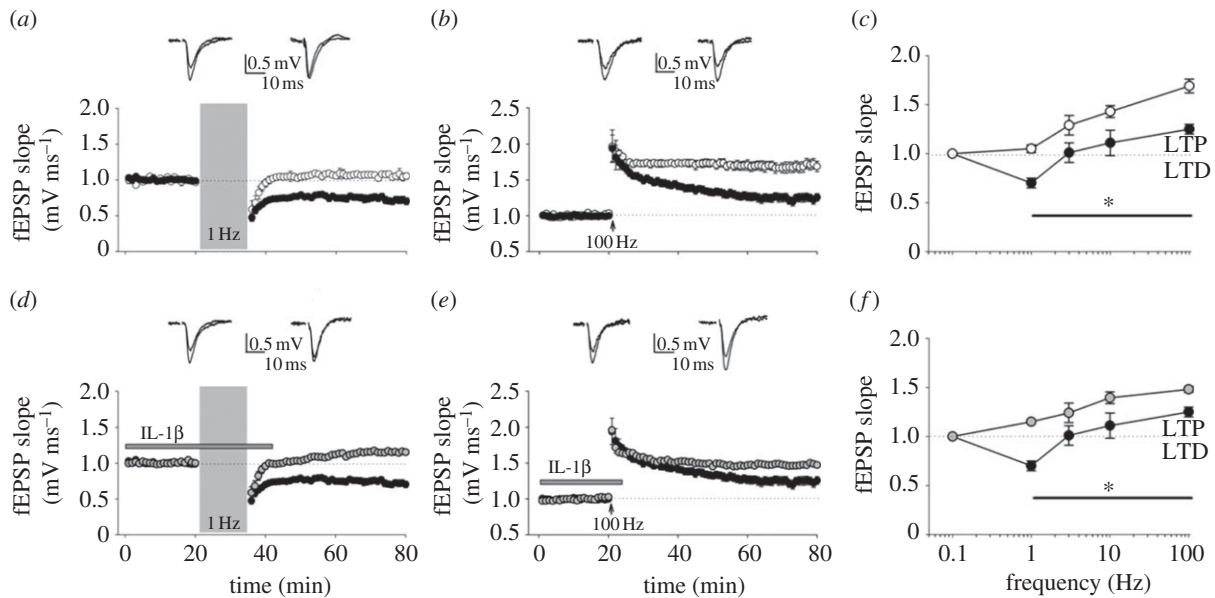


Figure 2. Shifted hippocampal frequency–response function in EAE mice and in response to IL-1 β . (a) Superimposed pooled data showing the normalized changes in field potential slope (\pm s.e.m.) (CFA, $n = 11$; EAE, $n = 12$) induced by paired-pulse low-frequency stimulation protocol (PP-LFS: 1 Hz, 15 min). Here and after, insets show field EPSPs from representative experiments during a baseline interval and 60 min after delivery of conditioning train. (b) Superimposed pooled data showing the normalized changes in field potential slope (\pm s.e.m.) (CFA, $n = 9$; EAE, $n = 12$) induced by high-frequency stimulation (HFS: 100 Hz; 1 s). (c) Frequency–response function in EAE and CFA mice. The graph shows the percentage change in synaptic strength from baseline in EAE and CFA animals at 60 min in response to a variety of conditioning trains (at least seven slices were tested for each condition). Values are mean (\pm s.e.m.). * $p < 0.05$ (t -test) at all frequencies tested. (d) Superimposed pooled data showing the normalized changes in field potential slope (\pm s.e.m.) induced by PP-LFS in CFA animals with ($n = 10$) or without ($n = 11$) IL-1 β application (30 ng ml $^{-1}$, duration of application indicated by bar). (e) Superimposed pooled data showing the normalized changes in field potential slope (\pm s.e.m.) induced by HFS in CFA animals with ($n = 9$) or without ($n = 9$) IL-1 β application. (f) Shown is a frequency–response graph of the fEPSP changes in response to a variety of conditioning trains in CFA animals with or without IL-1 β (at least seven slices were tested for each condition). Values are mean (\pm s.e.m.). * $p < 0.05$ (t -test) at all frequency tested (adapted from [17]). (a–c) Black circles, CFA; white circles, EAE and (d–f) grey circles, CFA+IL-1 β ; black circles, CFA+vehicle.

5. Role of inflammatory cytokines

In recent years, the canonical separation between inflammation and neurodegeneration has been challenged by compelling experimental evidence showing that both aspects are strictly interconnected either in neurodegenerative diseases, including AD and amyotrophic lateral sclerosis, or in traditional inflammatory disorders, such as MS [41]. Accordingly, inflammatory infiltrates with overt microglial and astroglial activation and specific neurodegenerative features have been found in discrete regions of the EAE brain, such as the cerebellum [58,59], striatum [40] and hippocampus [17,60]. In all brain regions, synaptic dysfunctions involving either glutamatergic or GABAergic neurotransmission often precede the onset of motor deficits. In general, glutamatergic transmission seems to be enhanced in EAE, while GABAergic transmission is reduced [17,40,59,61,62]. Notably, these synaptic alterations are likely to occur also in the MS brain and have been associated with the activity of pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α) and IL-1 β . We have recently demonstrated that abnormalities in both excitatory and inhibitory transmission found in the brain of EAE mice can be replicated in control brain tissue incubated with the CSF of MS patients [63,64]. Thus, these results indicate that in the course of MS, pro-inflammatory cytokines are released from infiltrating T cells and from activated microglial cells at concentrations sufficient to diffuse into the CSF and cause widespread alteration of synaptic transmission. EAE-induced alterations of synaptic transmission occurring in the hippocampus are

believed to play a crucial role in the cognitive deficits observed in EAE and also in MS patients [65]. In order to elucidate the cellular mechanisms underlying the subversion of synaptic plasticity observed in the EAE hippocampus [17], we performed immunohistochemistry and confocal imaging to analyse neuronal architecture in the CA1 region of EAE and CFA controls at 20 days after EAE induction. In line with previous observations in the striatum [61] and cerebellum [62], we observed a lower density of parvalbumin-positive (PV+) GABAergic interneurons associated with a strong microglia activation (Iba1+ cells), when compared with the hippocampus of control mice (figure 3a–d). Specifically, the density of PV+ neurons was significantly reduced in the CA1 layer and stratum oriens of EAE mice (figure 3e). A strong Iba1+ labelling was also localized in proximity of the dentate gyrus, CA3 region and fimbria of the EAE hippocampus. We also observed that IL-1 β staining was clearly evident in the lesion sites endowed with activated microglia/macrophages [17]. Besides microglia/macrophages, infiltrating T lymphocytes may represent another potential source of IL-1 β . Indeed, our immunofluorescence and confocal imaging analysis highlighted the presence of CD3+ lymphocytes in lesion sites of the EAE hippocampus [32]. Hippocampal slices incubated with preparations of either activated microglia or T lymphocytes taken from EAE mice displayed reduced GABAergic transmission, being prevented by blockade of IL-1 β signalling with IL-1ra [17,32].

As local PV+ GABAergic interneurons strongly modulate gamma oscillations in the hippocampus, regulating

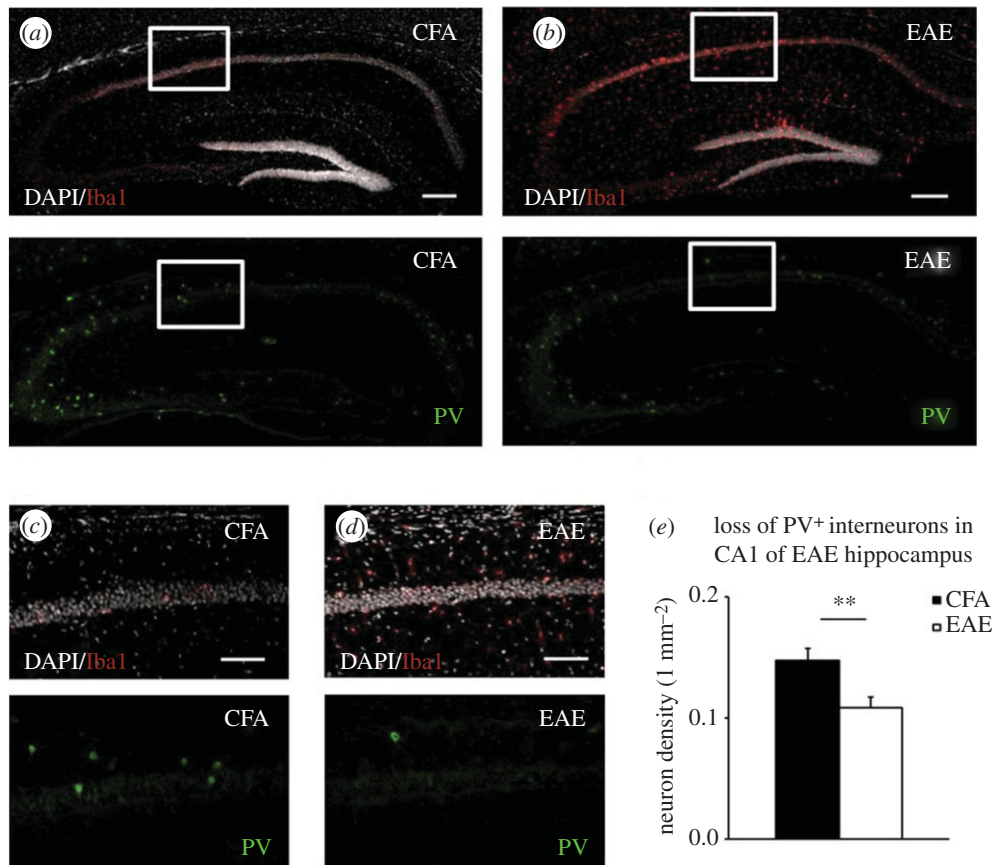


Figure 3. Loss of PV⁺ interneurons in the EAE hippocampus. (a–d) Immunostaining of Iba1⁺ microglia cells (upper panels), DAPI cell nuclei (grey, upper panels) and PV⁺ neurons (lower panels), in hippocampal coronal sections derived from CFA (a) and EAE mice at 20 d.p.i. (b), respectively. A strong microglia activation and loss of PV⁺ neurons characterize EAE hippocampus. (c) and (d) are high magnifications of the white boxes in (a) and (b), respectively. The number of PV⁺ interneurons (lower panels) in the CA1 layer and *stratum oriens* was reduced in EAE mice relative to CFA mice. (e) Histogram shows the mean percentage of the PV⁺ density interneurons (1 mm⁻²) which was significantly reduced in EAE mice by about 27% relative to CFA in the acute phase of the disease. ***p* < 0.01, *t*-test. Scale bars: (a,b) 200 μm, (c,d) 100 μm. (Online version in colour.)

synchronization of pyramidal cell firing [59], we hypothesized that degeneration of PV⁺ neurons could also affect hippocampal gamma frequency, thereby exacerbating the functional consequences of abnormal synaptic plasticity in EAE mice. Accordingly, in addition to aberrant synaptic transmission and plasticity, slices from EAE mice were characterized by reduced hippocampal gamma oscillations [17].

Overall, our data suggest that the selective vulnerability of this neuronal population to the actions of soluble mediators might contribute to sustain synaptic hyperexcitability in EAE, and possibly cognitive impairment in MS. These findings are in line with previous studies conducted in EAE mice [60] and in the frontal cortex of MS patients [65,66].

6. Concluding remarks

Our results show that TBS-induced abnormal plasticity in MS patients and changes in synaptic function and network activity in the hippocampus of EAE mice largely rely on IL-1 β -mediated suppression of GABAergic activity, at least before the degeneration of GABAergic interneurons is established. It is noteworthy that elevated IL-1 β levels during focal inflammation in MS, as well as in the acute phase of EAE, can influence in opposite directions glutamatergic and GABAergic transmission (which is increased and inhibited by pro-inflammatory cytokines, respectively) [59,61,63,64]. Thus, neuroinflammation

and IL-1 β signalling network might contribute to the high prevalence of cognitive impairment associated with MS [67] and to the spatial learning deficits in EAE [62,66]. On the other hand, we cannot discard the hypothesis that LTP-like phenomena occurring during immune attacks on the brain might represent a highly adaptive compensatory mechanism. This ‘plasticity reservoir’ may be crucial to counteract the clinical progression in MS by promoting recovery of function after a lesion. Likewise, potentiated excitatory synaptic transmission has been observed in areas surrounding a focal infarct, and this is associated with a better functional outcome [68]. Along this line, neurophysiological tools, such as repetitive TMS and transcranial direct current stimulation, have been recently introduced in the clinical setting to promote endogenous plasticity mechanisms aimed at improving functional outcome in drug-resistant neurological and psychiatric disorders [69].

Further research is required to understand the mediators and associated molecular pathways acting to preserve brain function and to limit the clinical consequences of neuronal injury in the progressive phases of MS and possibly in other acute and chronic neurological diseases.

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