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**Review: Brain immune communication psychoneuroimmunology of multiple sclerosis**

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# Brain–immune communication psychoneuroimmunology of multiple sclerosis

S Kern and T Ziemssen

The central nervous system (CNS) and the immune system are two extremely complex and highly adaptive systems. In the face of a real or anticipated threat, be it physical (eg, infection) or psychological (eg, psychosocial stress) in nature, the two systems act in concert to provide optimal adaptation to the demanding internal or environmental conditions. During instances of well being, the communication between these two systems is well tuned and balanced. However, a disturbed crosstalk between the CNS and the immune system is thought to play a major role in a wide series of disorders characterized by a hyporesponsive or hyperresponsive immune system. In multiple sclerosis (MS), a chronic inflammatory and neurodegenerative disease, an excess of inflammatory processes seems to be a hallmark and there is growing evidence for a disturbed communication between the CNS and the immune system as a crucial pathogenic factor. While the exact mechanisms for these phenomena are still poorly understood, the young discipline of psychoneuroimmunology (PNI), which focuses on the mechanism underlying the brain to immune crosstalk, might offer some insights into the existing pathogenic mechanisms. Findings from the field of PNI might also help to gain a better understanding regarding the origin and course of MS clinical symptoms such as fatigue and depression. *Multiple Sclerosis* 2008; 14: 6–21. <http://msj.sagepub.com>

**Key words:** multiple sclerosis; psychoneuroimmunology; HPA axis; ANS; cortisol; stress

## Psychoneuroimmunology

Psychoneuroimmunology (PNI) is the study of the bidirectional communication between the central nervous system (CNS) and the immune system. It reflects a young scientific discipline that overcomes traditional Cartesian dualism, which stands for a separation between the body and the mind [1], by addressing observations indicating that affective states and stressful experience are capable of influencing bodily states and reactions. *Mens sana in corpore sano—a healthy mind in a healthy body*, or the idea that the mind and the body are inseparable entities, has been around for centuries but without a solid understanding for the underlying processes. The discipline of PNI significantly picked up speed in 1970s and 1980s, when new findings indicated that the immune system is subject to classical conditioning [2,3]. Ever since, a wealth of new information on how mental processes influence bodily reactions has emerged [4,5] and more

complex models on brain and immune interaction have evolved [6,7]. In the course, it has been shown, that several psychological states such as chronic stressful experience [8], positive [9,10] or negative [9,11–13] affect and behaviour [14] influence immune function. At the same time, the immune system seems to be capable of inducing profound changes in affect and behaviour [15–17]. When it comes to the mechanisms underlying these phenomena, the hypothalamus-pituitary-adrenal (HPA) axis, and the autonomic nervous system (ANS) are regarded as crucial pathways linking the mind and the body [18,19].

The aim of this review is two-fold. In a first step (Part I), the reader is familiarized with the anatomical and physiological basis of current PNI concepts and the role of endocrine and autonomic pathways in brain to immune interaction is elucidated. In a second step (Part II), the relevance of these herein introduced concepts for MS research and treatment are highlighted.

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## Part I: brain-immune interaction

### Interaction between the immune system and the HPA axis

The HPA axis is a hierarchically organized endocrine system which responds to physical and psychological challenge in order to allow the organism to adapt to challenging internal or external circumstances.

During instances of stress, corticotropin-releasing-hormone (CRH) and arginin-vasopressin (AVP) are released from the paraventricular nucleus (PVN) of the hypothalamus. In a subsequent step, CRH and AVP are passed on to the anterior part of the pituitary (adenohypophysis) where they stimulate the release of the adrenocorticotrophic hormone (ACTH). ACTH in turn is submitted to the general blood stream and, when it reaches the adrenal cortex, stimulates the release of the glucocorticoid (GC) cortisol (corticosterone in animals).

The HPA axis and its role during stress have first been systematically studied by Hans Selye [20], who believed that activation of the axis during aversive experience reflects an innate, unspecific defense mechanism in the face of various stressors. Overactivity in the adrenal cortex was believed to be an etiologic factor in a series of disorders [20,21]. This idea was challenged when in the late 1940s growing evidence indicated strong immune suppressive action of GC [21]. In the following years, the idea was born that the release of GC does not represent a shield against the stressor itself but rather reflects a mechanism that prevents the stress-associated defense reactions from overshooting [21]. This view was further supported by work of Hugo Besedovsky and Adriana del Rey who showed that pro-inflammatory cytokines (eg, IL-1), which are released during instances of physical stress such as antigen challenge, are capable of activating the HPA axis [22]. According to Besedovsky and coworkers, the ability of IL-1 to activate the axis reflects a defense mechanism that prevents the stress-induced immune activation from overshooting [6,23]. However, research performed over the past decades has accumulated increasing evidence that GC effects on immune function should not be restricted to immune suppressive properties (for review see [19]). Instead, GC should be viewed as complex immune modulators that have enhancing as well as inhibiting influence on immune function depending on the exact domain (eg, acute versus chronic, systemic versus local) and thereby help to establish a fine tuned balance prerequisite for health and well being [19].

GC exert their influence by binding to two types of cytoplasmic receptors which are present in virtually every nucleated cell [21]. Type-I receptors,

the so-called mineralocorticoid receptors, have a high affinity for endogenous GC and are readily occupied at lower GC concentrations. Type-II receptors, the so-called GC receptors, have a low affinity to endogenous but high affinity to exogenous GC and are only readily occupied at higher endogenous GC concentrations [24]. Both receptor types have been mapped in the immune system and different immune departments (eg, spleen, thymus) and cell types (monocytes, lymphocytes) seem to vary greatly in receptor expression, which often translates into different response and sensitivity patterns [25–29]. After binding to the cytosolic receptor, the activated GC/GR complex translocates to DNA-binding sites where it causes up-regulation (transactivation) as well as down-regulation (transrepression) of protein synthesis, which in turn translates into changes in immune function (eg, synthesis of pro-inflammatory cytokines) [30]. GC signal transmission via DNA-binding sites reflects a slow, genomic pathway that takes place on a timescale of minutes, hours and even days [31]. While these genomic effects have long been thought to be the exclusive way of GC action, recent evidence such as the existence of membrane-bound GR on human peripheral blood mononuclear cells [32], point towards a more rapid, non-genomic GC dependent signal transmission [33]. As therapeutic effects of high dose GC treatment often occur rapidly (eg, within minutes), and complete cytosolic GR occupation occurs below treatment doses (eg, complete receptor occupation at 100–200 mg prednisolone vs. effective treatment doses of 1000 mg/day), rapid, non-genomic GC actions are also believed to be involved in GC treatment effects [31]. Currently, three different non-genomic GC pathways have been discussed 1) specific interaction with the cytosolic GR, 2) non-specific interactions with cellular membranes, and 3) specific interactions with membrane-bound GR (mGR) [31]. Although the precise underpinnings are still poorly understood, better understanding of these mechanisms is currently believed to open up new strategies for anti-inflammatory drug developments [34].

In rodents and humans, acute stress exposure or pharmacological GC treatment results in marked changes in leukocyte distribution, expression of cell adhesion molecules, changes in immune cell trafficking, and immune cell proliferation (for review see [35]). Upon GC exposure, pronounced initial increases followed by marked decreases in several leukocyte subsets have been observed [36]. Although initially assumed, it has now been shown that the GC mediated decrease in some leukocyte subsets does not necessarily reflect an immune suppressive action *per se*. Rather, decreased leukocyte subsets in the peripheral blood are associated with

an increased immune response in the skin (delayed type hypersensitivity) and therefore reflect an immune enhancing redistribution of relevant immune cells [37,38]. According to recent models, acute GC induced changes in immune cell circulation have therefore been regarded adaptive, in a sense that GC ensure appropriate leukocyte distribution (eg, blood stream versus lymphoid tissue, skin), which helps immune cells to be in the right place at the right time in order to initiate an optimal immune response in the face of a stress-inducing agent [19,37,39]. While an acute rise in GC, as seen during a short lasting stress encounter, seems to be adaptive, chronic stressors seem to have more deleterious effects.

In animal models it was shown, that the adaptive redistribution patterns seen during instances of an acute stress are abundant during instance of chronic stress [38,40]. In humans, similar effects have been observed. In chronic caregivers for example, enhanced cortisol concentrations [41,42] as well as reduced lymphocyte populations [43] along with a reduced vaccine response [42] have been reported.

Due to their potent anti-inflammatory actions, GC are used as a standard therapy in a wide series of inflammatory disorders [44]. In humans, inflammation is mediated, at least to some extent, by pro-inflammatory cytokines released from T helper (Th) cells. According to a popular immunological concept, Th cells can be divided into Th1 and Th2 cells [45]. Naïve CD4<sup>+</sup> cells (Th0) serve as precursors for Th1 and Th2 cells. The influence of the concurrent cytokine milieu determines the differentiation process. While IL-12 in concert with INF- $\alpha$  and INF- $\gamma$  promotes Th1 induction [46], IL-4 strongly favours the expression of Th2 cell clones [47]. Th1 cells, with a predominantly pro-inflammatory cytokine profile (IL-2, TNF- $\beta$ , IFN- $\gamma$ ) are part of the cellular immunity and are involved in the attack against intracellular pathogens and cancers cells as well as delayed type hypersensitivity skin responses [48]. In accordance, a Th1 dominance has been proposed to be an underlying factor in autoimmunity [49]. The cytokine profile of Th2 cells is characterized by IL-4, IL-10 and IL-13, which promote humoral immunity [50]. Thus, Th2 cells seem to be involved in the defense of extracellular pathogens and activate B-cell mediated antibody production as well as eosinophils and mast cells [48]. In accordance, relative Th2 dominance seems to mediate allergic disorders [51]. Apart from distinct immune functions, Th1 and Th2 cells also seem to influence each other in a reciprocal suppressive way. Th1 cytokines such as INF- $\gamma$  promote Th1 induction and oppose Th2 differentiation [52]. Th1 cells also induce IL-12 production by cell-to-cell contact with dendritic cells [53]. In contrast, Th2 cytokines such

as IL-4 and IL-10 promote Th2 induction while inhibiting the differentiation of Th1 clones [52,54].

The balance between a Th1 and a Th2 based immunity is not static and GC have been shown to be potent modulators. For example, GC inhibit IL-12 production by monocytes. As IL-12 promotes INF- $\gamma$  release and inhibits IL-4 synthesis by T cells, a GC-mediated inhibition of IL-12 reduces INF- $\gamma$  release and favors IL-4 secretion [55,56]. On the other hand, GC do not suppress IL-10 secretion [57] but rather stimulate the release of it [58]. Taken together, GC seem to promote Th2 dependent immune response while suppressing Th1 mediated immunity. GC also seem to suppress pro-inflammatory cytokines released by monocytes/macrophages such as IL-1, TNF- $\alpha$  and INF- $\gamma$  [59,60] and promote the secretion of anti-inflammatory, T cell inhibiting agents like TGF- $\beta$  [61].

The interaction between the HPA axis and the immune system during instance of stress reflects a fine tuned balance and the HPA axis plays a major inhibitory role that keeps the immune response from overshooting. By signalling to relevant brain centers, it is the immune system itself that requests restraining mechanisms reflecting a form of negative feedback regulation. Elevated levels of IL-1 have been shown to induce marked HPA axis activation [22], which results in inhibition of peripheral IL-1 and other pro-inflammatory agents [6]. IL-1 influences the corresponding brain centres via humoral or neural pathways and IL-1 dependent stimulation of the vagus, seems to mediate HPA axis activation during minor to moderate IL-1 concentrations [15,16,62,63].

Taken together, GC exert immune enhancing as well as immune suppressing effects. While acute increases in GC seem to be adaptive (eg, leukocyte distribution), chronic GC exposure might exert more deleterious effects. GC also seem to influence the fine tuned balance between a Th1 versus a Th2 mediated immunity by suppressing Th1 stimulatory cytokines and promoting a Th2 dominated immune response. GC also suppress pro-inflammatory cytokine production while promoting anti-inflammatory responses (see Figure 1).

### **Interaction between the immune system and the ANS**

While a substantial amount of brain to immune interaction is mediated by the HPA axis, the ANS serves as a second major pathway connection the CNS and the immune system (for review see [18]).

The ANS, similar to the HPA axis, reflects a highly adaptive system which promotes adaptation in situations of enhanced internal or external demands. Activation of the ANS results in a cascade

of actions which collectively aim to maintain the organism's homeostasis and promote fight or flight reactions in the face of a stressful encounter [64]. Based on functional and anatomical distinctions, the ANS constitutes of three different entities: the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS) and the enteric nervous system. The SNS and PNS are characterized by myelinated preganglionic fibres which synapse onto postganglionic fibres which then innervate the various effector organs [65]. Most organs receive fibres from the SNS and PNS, which usually exert opposing effects on the target organ [64,65]. During instances of stress, when the internal milieu is threatened, the SNS is activated in close timely proximity and provokes a series of adaptive changes like increased heart rate and blood pressure, increased blood flow to peripheral muscles and increased energy supply [64].

As part of this adaptive response, the ANS communicates with the immune system. A strong case for the ANS immune interaction was made, when anatomical findings indicated dense sympathetic nerve endings within various lymphoid organs [66–69]. During the activation of the sympathetic nervous system, catecholamines, namely norepinephrine (NE) and epinephrine (E) are released from nerve terminals and the adrenals. NE and E impact target cells via binding to two types of receptors: alpha ( $\alpha$ ) and beta ( $\beta$ ) adrenoceptors (AR).  $\beta$ -AR are subdivided into  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  receptor subclasses, whereas  $\alpha$ -AR are further differentiated in  $\alpha_1$  and  $\alpha_2$  [18]. For the brain to immune communication,  $\beta$ -AR seem to be relevant, as virtually all lymphoid cells express  $\beta$ -AR [18,70,71]. Cells greatly differ in the expression of  $\beta$ -AR, with natural killer (NK) cells expressing the highest while Th cells express the lowest density [72]. Much controversy currently exists whether Th2 function is modulated by  $\beta$ -AR agonists. While there is some evidence that Th2 cells dependent cytokine release is unaffected by  $\beta$ -AR stimulation due to a lack of  $\beta$ -AR on Th2 cells [70,71], others show a  $\beta$ -AR agonist induced modulation of Th2 cell function in the presence of the according receptor [73].

AR density on immune cells not only depends on cell types but is also influenced by other factors like pharmacological treatment [74], and disease state [75,76]. Similar to GC, catecholamines influence lymphocyte migration and circulation. Acute administration of pharmacological AR agonist result in marked increases in circulating NK cells [77]. Increases in immune subsets were prevented by a non-selective beta-adrenoceptor antagonist but not by a selective beta-1 receptor antagonist, indicating a beta-2 dependent mechanism [77]. Not only pharmacological stimulation but also confrontation with acute, short lasting stressful

circumstances results in pronounced NK cell increases [78,79]. In addition to changed distribution patterns, increased NK cell activity in acutely stressed individuals has been reported [80,81]. Increases in NK cells have also been shown in a epinephrine-based classical conditioning paradigm [82]. However, while NK cells seem to be sensitive to AR stimulation, T cells, probably due to lower AR densities, only show modest increases in response to an  $\beta$ -AR agonist [77].

While acute NE and E effects seem to exert an immune enhancing effect, chronic treatment (eg, 7 days of terbutaline) seems to result in decreased concentration of circulating NK cells [83]. Likewise, chronic life stress was associated with reduced NK cell activity during an acute stressful exposure [84] and chronic stress in older caregivers has been associated with reduced overall NK cell activity [10].

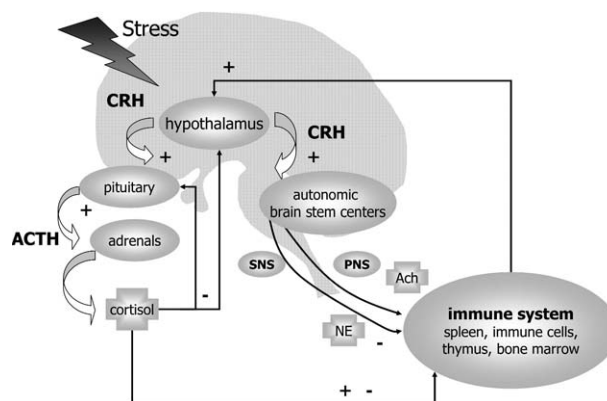
Although  $\beta$ -AR densities on T cells are comparatively low [72], E and NE have significant impact on T-cell functioning. Similar to GC, NE and E seem to inhibit Th1 mediated immunity while enhancing Th2 immune function [18,85]. As Th2 cells lack significant number of AR [70,71], NE and E seem to exert these effects via modulating Th1 function as well as antigen presenting cells. Catecholamines have been shown to profoundly inhibit IL-12 secretion [86–88], which most likely reflects a Th1 inhibiting pathway. Accordingly, administration of the  $\beta_2$  agonist salbutamol, suppressed Th1 cell clones and promoted Th2 cell development [88]. At the same time,  $\beta$ -AR agonists (eg, isoproterenol) stimulate IL-10 released by macrophages in a dose-dependent fashion [57,89] and thus most likely promote Th2 mediated immunity. Additionally, catecholamines seem to have more wide spread anti-inflammatory properties by inhibiting other pro-inflammatory agents like TNF- $\alpha$  [90,91]. However, while the majority of studies indicate a rather inhibitory effect on pro-inflammatory cytokine secretion, more recent reports show a  $\beta$ -AR mediated stress-induced increase of IL-1 and IL-6 [92].

Recently it has been shown that not only the SNS but also the PNS seems to play a major role in brain to immune interaction. Acetylcholine (ACh), the principle neurotransmitter in postganglionic parasympathic/vagal efferent neurons, inhibits the release of pro-inflammatory cytokines from macrophages [93] and this effect seems to be mediated via nicotinic ACh receptors on the surface of macrophage cells [93].

Apart from E, NE and ACh, other molecules such as adenosine, neuropeptide Y (NPY), somatostatin, nitric oxide and vasocative intestinal polypeptide (VIP) are co-released from sympathetic and parasympathetic nerve terminals [94]. While the various functions of these transmitters are still

poorly understood, increasing evidence suggests immune modulatory effects of these molecules. As in the case of NPY, immune modulatory effects through stimulation of NPY (Y1) receptors on T cells and antigen presenting cells (APC) have been described (for review see [95]). In mice lacking the NPY Y1 receptor (Y1<sup>-/-</sup>), reduced spleen size along with reductions in absolute B cell counts and impaired IgG2a production has been observed [96]. Swelling in the face of a delayed type hypersensitivity response was reduced by 55% in Y1<sup>-/-</sup> mice, which indicates an impaired Th1 immune response [96]. These findings seem consistent with *in vitro* findings showing reduced INF- $\gamma$  and increased IL-4 production in Th cells co-stimulated with NPY [97]. However, conflicting results indicate that Y1<sup>-/-</sup> T cells are hyper-responsive to activation and trigger a severe course of colitis in lymphopenic mice [96]. Further experiments indicated a bi-modal role of NPY by showing that reduced Th1 immune response in Y1<sup>-/-</sup> was due to a defect in APC function but not an intrinsic defect of Y1<sup>-/-</sup> T cells [96].

As mentioned earlier on, communication between the brain and the immune system is not a one way road and it has been shown that the ANS plays a crucial role in transmitting immune related signals to the CNS. As previously described [15], blood born soluble factors (eg, cytokines) influence central sites such as the hypothalamus and can cause activation of endocrine cascades [22] as well as changes in affect and behaviour [17,98]. Soon after it became apparent that cytokines alter neural activity, the existence of IL-1 and IL-6 as well as the corresponding receptors in the CNS were shown [99,100]. But how was it possible for these comparatively large and hydrophilic molecules to gain access to central sites? In the beginning, humoral mechanisms were regarded as most likely (eg, blood derived cytokines enter the brain in regions where the blood-brain-barrier is rather weak; activation of second messenger systems in CNS blood vessels; reviewed by [7]). However, while humoral mechanisms could not account for all the findings (eg, changes in sickness related brain function and behaviour despite low peripheral cytokine levels; reviewed by [101]), neural pathways involving the vagus nerve were taken into consideration (see [15,16,102] for review). Sickness behaviour, a set of behavioural (eg, reduction in activation, social interaction and sexual behaviour) and physiological (eg, fever, reduced appetite, increased pain sensitivity) changes in response to an antigen challenge, was shown to be sensitive to vagotomy. In response to cytokine administration or antigen challenge (LPS), lesions to this neural structure block behavioural depression (eg, social withdrawal) and neural activation (eg, c-fos expression)



**Figure 1** Endocrine and autonomic crosstalk between the brain and the immune system (SNS = sympathetic nervous system; PNS = parasympathetic nervous system; NE = nor-epinephrine; Ach = acetylcholine).

in autonomic and limbic sites but not fever [103,104]. These findings underscore the ANS' role in bidirectional brain-immune communication and at the same time support the notion of a complex interplay where neural pathways do not exclusively account for transmission of immune related signals to the CNS.

ANS dependent neurotransmitters such as NE, E and Ach are potent modulators of immune function and, similar to GC, exert suppressive as well as enhancing effects on the immune system. While acute exposure to elevated levels of catecholamines seems to be adaptive, chronically elevated levels seem to have opposite effects. Catecholamines, just like GC, also seem to favour a Th2 dominated immune response by modulating cytokine release by monocytes and dendritic cells. Although still poorly understood, ANS dependent neuropeptides, next to catecholamines, also seem to play a complex role in neuro-immune regulation. The multifaceted nature of the neuro-immune interaction is further supported by findings showing that information about the peripheral immune milieu (eg, pro-inflammatory cytokines) is transmitted to neural sites via parasympathetic branches.

### The immune system and psychosocial variables

The HPA axis, the ANS and the immune system are modulated by various psychosocial variables. Especially various forms of positive and negative affect, induced by rewarding or demanding interactions with the environment cause distinct changes within the internal milieu. Acute or longer lasting stressful encounters initiate pronounced activation of the HPA axis and the ANS which result in increased heart rate activity, elevated blood pressure

and increased levels of cortisol, NE and E [105–107]. In humans, situations that are uncontrollable or potentially threatening to the perceived self have been shown to act as major elicitors of HPA axis activation [108,109]. While perceived uncontrollability during a laboratory stressor seems to have no effects on cell distribution, proliferation or cytokine production [110–112], perceived shame results in increased levels of pro-inflammatory cytokines [113]. Other forms of negative affect such as depressed mood [114,115], anxiety [116], negative affective style [117], perceived stress [118,119], loneliness [120], and negative self-evaluation [121] are also associated with reduced immune function (eg, NK cell activity, cell proliferation, antibody status). Stressful social instances such as hostile marital interactions are also related to decreased immune function [122] and delayed wound healing [123]. Accordingly, delayed wound healing has also been reported in individuals with high actual or perceived stress [124,125].

On the protective side, perceived social support seems to promote antibody response following vaccination in young and elderly subjects [126,127]. Stress management trainings [128,129], massage therapy [130,131], and mindfulness meditation practices [132] also seem to exert immune enhancing effects.

## Part II: brain-immune interactions in multiple sclerosis

### Psychoneuroimmunology of multiple sclerosis

MS is a chronic progressive inflammatory disease characterized by inflammatory destruction of the myelin sheath throughout the central nervous system [133] as well as significant neurodegenerative processes which are believed to be responsible for the development of progressive clinical disability [134]. While the etiology of MS is still unknown, much evidence points towards the relevance of a T-cell mediated immune reaction in disease pathogenesis [135]. Another hallmark of MS is the highly unpredictable and variable course (eg, relapsing versus progressive). In the recent past, an increasing amount of research indicates that psychosocial factors might modulate the course of MS and translate into endocrine and immune changes associated with disease characteristics or disease progression [136].

### MS and life stress

Quite frequently, MS patients and their relatives report a close timely connection between stressful experiences and MS relapse and by doing so

inspired the question, whether negative affect or stressful encounters could possibly be related to MS relapse or disease progression. While this hypothesis raised considerable controversy [137], an increasing amount of prospective studies indicates that MS relapse is indeed associated with perceived stressful encounters [138]. For example, in a female study sample of 23 women with relapsing-remitting MS, 85% of MS exacerbations were associated with stressful life events in the preceding 6 weeks. On average, stressful encounters took place about 14 days before the onset of the exacerbation [139]. Another study on 36 patients with relapsing-remitting MS indicated a positive relationship between perceived conflict and disruption of routine and gadolinium-enhancing (GD+) brain lesions. Associations were found within a timeframe of 8 weeks [140]. Strong support for the association between stressful life events and disease progression comes from a meta-analysis on 14 studies investigating this topic. Meta-analytic evaluation indicated an increased risk for MS exacerbation after stressful life events (effect size  $d = 0.53$ ) [141].

However, while an increasing amount of studies indicate a positive association between stressful experience and MS relapse, others suggest an opposite view. In a prospective investigation including Israeli citizens who were immediately threatened by missile attack during the Gulf War I, a significant reduction in MS exacerbation was observed [142]. Given that findings indicating positive as well as negative associations between stressful experience and MS exacerbations are not mutually exclusive, others have suggested, that severe stressors (eg, threat to one's own life) might be protective, while more moderate stressors (eg, frustration, psychosocial issues) rather represent a risk enhancing factor [143].

While most studies clearly indicate an association between stressful life events and MS relapse, little is known about how the experience of stress or negative affect translates into pathogenic mechanisms in MS. Further research is also needed to elucidate whether aversive psychosocial factors, in the short or in the long run, not only trigger relapses but also lead to disease progression and disability.

From what is known at this point, translation occurs most likely via nervous and humoral pathways involving the HPA axis and the ANS.

### HPA axis function in MS

GC are well known for their anti-inflammatory actions and are therefore widely used as pharmacological treatment in chronic inflammatory disorders [44]. Not surprisingly, the question whether dysregulation in endogenous GC play a role in the

pathogenesis of chronic inflammatory disorders has inspired a substantial amount of research.

Studies on experimental autoimmune encephalomyelitis (EAE), a common animal model for MS, have indeed indicated a prominent role of GC in disease progression. Clinical manifestation of EAE is associated with marked increases in GC, which are mediated by disease associated elevated levels of IL-1 [144]. At the time when GC concentrations reach their maximum, clinical symptom remission sets in and is accompanied by a gradual decline in circulating GC [145]. Interestingly, different rat strains vary in regard to their susceptibility for EAE. Rat strains characterized by a hyporesponsive HPA axis (eg, Lewis rats) show higher susceptibility for EAE compared to rats characterized by a normo- or hyperresponsive HPA axis (eg, Fisher rats) [23,146,147]. Adrenalectomized rats show an earlier clinical manifestation of EAE as well as a more severe clinical course characterized by a lack of recovery and a lethal outcome [145,147]. On the other hand, corticosterone implants in adrenalectomized animals reversed the observed effects [145,147]. In EAE prone Lewis rats, administration of GC results in a marked symptom reduction. The administration of a GC antagonist causes disease exacerbation [148]. On a CNS level, stress-induced increase in CRH in combination with mast cell activation, causes increased permeability of the blood brain barrier (BBB) [149,150], which could result in increased migration of inflammatory immune agents into the CNS and hence could reflect a possible pathogenic mechanisms through which stress influences disease course.

While animal data clearly indicate the impact of a hypo-responsive HPA axis on disease progression, the role of the HPA axis in MS patients is far less clear. Some reports indicate elevated basal GC levels [151] and increased adrenal size [152] in MS patients. In post-mortem investigations, an increased density and activity of CRH positive neurons has been detected in hypothalamic areas [153,154]. During acute exacerbation, MS patients show a decreased suppression in response to the dexamethasone suppression test (DEX test) [155,156] which reflects a diminished HPA axis feedback regulation. Others report a trend towards lower basal cortisol concentrations for the primary or secondary progressive MS when compared to patients with other neurological disease [157]. In response to a pharmacological CRH challenge, secondary progressive MS has been associated with significantly lower cortisol concentrations when compared to patients with a primary progressive form or healthy controls [157]. In a synthetic ACTH test, a trend for lower cortisol concentrations for patients with relapsing-remitting MS was observed [157].

Two studies so far investigated HPA axis responses in MS patients in the face of acutely administered psychological stress. While one study failed to induce relevant stress-associated increases in endocrine measures in the control as well as the MS group [158], the other study did not find any significant differences in endocrine measures between MS patients and healthy controls [159]. On CNS level, cortisol responses to DEX/CRH test were negatively associated with the presence and number of GD+ lesions [160]. In accordance, patients with acute GD+ enhancing plaques expressed higher cortisol concentrations when compared to MS patients without GD+ enhancing plaques [156].

In respect to immune cell GC receptor density, no difference has been found between MS patients and control subjects. However, recent data indicate a decreased GC receptor sensitivity in relapsing-remitting MS patients [161,162] and a trend towards clinical worsening in association with increasing GC resistance has been observed [161].

In summary, animal data give evidence for the influence of a hyporesponsive HPA axis on disease course in EAE. Data on humans seem to be less clear and there is support for a hyperactive as well as a hypoactive HPA axis function in MS. Data also indicate that different disease forms (eg, primary progressive versus secondary progressive versus relapsing-remitting) and different disease stages (eg, exacerbation versus remission) are characterized by different HPA axis patterns. To date, little is known about whether the observed patterns play a causal role in MS pathogenesis, promote disease progression or rather reflect a consequence of neurodegenerative processes in MS (eg, disturbed HPA axis regulation due to increased lesion load in the CNS).

### **Autonomic nervous system function in MS**

Reports showing that sympathectomy results in augmentation of EAE symptoms, indicate a protective role of the ANS in EAE disease progression [163].

Accordingly, administration of the  $\beta$ -adrenergic agonist isoproterenol suppresses clinical and histological symptoms of EAE in Lewis rats [164,165]. EAE rats also show a decreased number of INF- $\gamma$  producing splenic lymphocytes in response to the  $\beta$ -adrenergic agonist isoproterenol and terbutaline [165]. In chronic/relapsing EAE, an animal model for relapsing-remitting MS, administration of the  $\beta$ -adrenergic agonist isoproterenol and terbutaline resulted in a significant suppression of an acute first attack as well as a decreased number of relapses [166]. Other reports indicate suppressed

clinical signs in EAE after treatment with prazosin, an  $\alpha$ 1-adrenoceptor antagonist due to changed function of BBB endothelium [167,168].

In MS patients, increased  $\beta$ -adrenergic receptor density on immune cells (eg, CD8+, B cells) has repeatedly been reported [75,169–171]. Interestingly, in contrast to healthy controls, MS patients do not show any significant IL-1 induced receptor density up-regulation. During acute EAE, but also during remission, a decreased suppression of pro-inflammatory cytokines (TNF- $\alpha$ , INF- $\gamma$ ) in response to stimulation with a  $\beta$ -adrenoceptor agonist has been observed [172]. Administration of the  $\beta$ -agonist terbutaline caused significantly enhanced release of IL-10 and IL-12 in healthy controls but not in MS patients [173]. Similarly, administration of isoproterenol reduces T cell proliferation and pro-inflammatory cytokine release in healthy controls but not in untreated MS patients [174]. Further analysis indicated, a reduced expression of G protein receptor coupled receptor kinase, which indicates disturbed intracellular signal processing in response to  $\beta$ -adrenergic receptor stimulation [174].

In the face of an increased  $\beta$ -adrenergic receptor density on immune cells and disturbed intracellular signal processing, little is known about basal catecholamine levels in MS patients. In chronic progressive MS, no differences in E but elevated NE levels have been detected [171]. Patients characterized by an active disease state show significantly lower NE concentrations when compared to patients characterized by a clinically stable state or healthy controls [175].

In the recent past, evidence emerged that not only catecholamines but also ANS related neuropeptides might play a role in autoimmune related pathology. It was shown, that NPY for example not only promotes a shift from a Th1 to a Th2 dominated cytokine profile, but also seems to ameliorate EAE symptoms in a dose-dependent fashion (for review see [176]).

Dysfunction in other domains of the ANS have often been reported in MS patients (eg, bladder dysfunction, cardiovascular autonomic dysfunction) [175,177,178]. However, currently little is known about whether some of these autonomic changes (eg, SNS dysregulation) reflect a predisposing, etiologic factor or rather represent a consequence of increasing CNS lesions.

Taken together, the ANS seems to have protective functions in MS. MS patients also seem to express higher  $\beta$ -adrenergic receptors on immune cells but demonstrate a disturbed intracellular signal transmission in response to  $\beta$ -adrenergic receptor stimulation.

Data also indicate that different disease forms (eg, primary progressive versus secondary progressive

versus relapsing-remitting) and different disease stages (eg, exacerbation versus remission) might go along with distinct changes in the ANS regulation. As in the case of the HPA axis, little is known about whether the observed patterns play a causal role in MS pathogenesis, promote disease progression or rather reflect a consequence of neurodegenerative processes in MS.

#### Key points: brain-immune interaction

- Under certain circumstances, psychological factors such as affective state or cognition exert a modulating tone over immune function.
- The immune system in turn is in close communication with the central nervous system and modulates endocrine function (eg, HPA axis) as well as affective states.
- Endocrine (eg, HPA axis) and autonomic pathways (eg, sympathetic tone, vagus nerve) play a major role in brain-immune interaction.
- Although the precise underpinnings are still poorly understood, dysregulation in these endocrine and autonomic pathways has been repeatedly described in MS patients.
- To date, little is known whether impaired endocrine and autonomic functioning are primary and/or secondary to MS disease progression.

#### Psychosocial and psychopathological and factors in MS

John Mason, one of the founding fathers of psychobiological stress research, pointed out that not all individuals experience the same amount of stress in a specific situation. According to him, factors such as novelty, personal relevance, anticipation or perceived controllability determine whether an individual expresses a stress related activation [179,180].

The diagnosis MS reflects a novel situation for patients as well as their social environment (eg, spouse, relatives). As disease progression is hardly predictable, MS often comes with feelings of uncontrollability and uncertainty. In many cases, MS patients are in a state of anticipatory tension in expectation of newly occurring exacerbations. As exacerbations are commonly associated with temporal or permanent physical and cognitive impairments, MS naturally comes with high personal relevance for everyone involved.

Hence, MS by itself can be regarded as a major stressor which forces patients as well as their social environment to respond with adequate strategies in order to cope with the challenging situation.

The way a person responds to stressful situations is influenced by personal and situational factors as well as previous experiences with stressful encounters [181]. Successful coping usually results in overcoming of the threatening situation or adaptation. Non-adaptive coping often leads to psychological distress and poor health outcomes.

In MS, a problem-focused coping style (eg, an active effort to change a situation) has often been associated with better adjustment [182], less disability [182] and less depressive symptoms [183]. A more passive or emotion-focused coping strategy seems to be less adaptive and often goes along with increased psychological distress [136,184], increased levels of overall stress [185] and negative mood and depression [185]. Emotion-focused coping seems to predominate during acute exacerbation [184]. Compared with healthy controls, MS patients are less likely to express active coping styles (eg, problem solving, seeking social support) [136]. Representation of the illness, which refers to the way a person thinks and feels about his or her illness also seems to impact disease adaptation and comorbid depression. For example, patients who feel that they have considerable control over their illness tend to have higher self-esteem, are less distressed and report less depressive symptoms [186]. Similarly, optimistic attitude, expressed as efficacy expectancies seem to promote self-care behaviour [187] and good social support is positively associated with quality of life in MS patients [188]. Patients with a lack of understanding regarding their illness and a psychological attribution style (eg, this illness is my fault) tended to show poor social functioning, strong emotional representations and low self-esteem [186].

While there is much data on the relationship between various coping styles and other MS relevant psychosocial factors (eg, self-esteem, self care behaviour, emotional distress), so far, only a few studies have looked at the relationship between psychological domains and neurological MS symptoms. In one investigation, small associations between active, instrumental coping and a decreased relationship between stress and new GD+ lesions was observed. On the other side, emotional preoccupation was slightly associated with an increased relationship between stress and newly occurring GD+ lesions [143]. However, at this point in time, it is completely unknown how emotional factors trigger or promote disease relevant actions. Although this has not been shown yet, one might speculate whether such effects are, at least in part, dependent on endocrine and autonomic path-

ways which in turn influence immune function in a disease relevant way.

Assuming that emotional factors are capable of influencing disease relevant actions, it seems noteworthy that depressive symptoms are very common in MS. Lifetime prevalence for Major Depression in MS patients is around 50% and is significantly higher than in the normal population or other chronically ill patients [189,190]. Accordingly, significantly elevated suicide rates have been observed in MS patients [191,192].

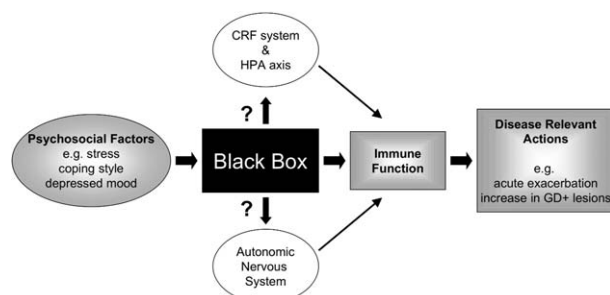
When it comes to the etiology of depression in MS, several factors have been considered: Depression in MS could result from the psychological burden such as increased cognitive and physical impairment and uncertainty [193]. Low social support and emotion-focused coping strategies have also been related to depression in MS [193,194]. On the other hand, depression in MS could be associated with an ongoing inflammatory process. Recent data indicate, that pro-inflammatory cytokines are positively associated with depressive symptoms [195] although this association has not been investigated in MS. In patients treated with interferon  $\beta$ -1a, increased depression has been a suspected side effect, although stringent data analysis did not confirm these concerns [196]. An alternative explanation comes from neuroimaging data showing that brain lesions in frontal regions and reduced temporal lobe volume have been positively associated with depressive symptoms [197,198].

To date, little is known about the impact of depressive symptoms on the course of MS but nonetheless, appropriate treatment of depression is mandatory. Symptoms of depression have been shown to have a pronounced negative impact on quality of life [199,200]. In accordance, recent reports even suggest that not so much the degree of neurological disability but rather depression, next to fatigue, accounts for the most drastic impairments in quality of life in MS patients [201,202]. However, even though depressive symptoms in MS are a well described phenomenon and dramatically impact patients overall well being, a recent study comes to the conclusion, that depression is not sufficiently treated in a US based study sample of MS patients [203].

Psychological interventions, psychotherapy and pharmacological anti-depressive treatment have proven successful in decreasing depressive symptoms and increasing quality of life and psychological well being in MS patients [204–206]. In two preliminary studies, enrolling small samples of MS patients, psychotherapeutic treatment of depression (16 weeks) was associated with decreased levels of INF- $\gamma$  [205,207] and the effect was clearly moderated by the factor social support [207].

**Key points: psychological and psychiatric symptoms and MS**

- There is evidence for a timely link between stressful experience and MS course (eg, MS relapse).
- There is a high prevalence of depressive symptoms in MS and these symptoms are predictors of poor quality life and impaired disease adaptation in MS patients.
- Depressive symptoms often go unrecognized or are insufficiently treated.
- There is evidence that treatment of depressive symptoms might have a positive impact on MS relevant immune parameters (eg, reduction in pro-inflammatory cytokines).



**Figure 2** Model for psychoneuroimmunological mechanisms in multiple sclerosis.

Taken together, psychosocial factors and psychiatric symptoms such as depressive mood seem to influence MS patients' disease adaptation and quality of life. First data indicate that some of these factors translate into disease specific processes such as immune function and directly influence the course of MS. However, further research as well as the evaluation of specifically aimed interventions (eg, stress-management) are needed.

### Summary

Over the last three decades, the field of PNI has gathered a wealth of information on the nature of mind and body interactions. According to what is known today, psychological factors such as perceived stress or threat, influence immune function via humoral and nervous pathways. For example, activation of the HPA axis or the ANS cause the release of endocrine mediators such as cortisol, E or NE, which modulate immune function by binding to immune based glucocorticoid receptors

and adrenoceptors. Simultaneously, mediators released from immune cells signal back to the brain and modulate affect, behaviour and endocrine responses.

In MS, the well described immune pathogenesis seems to be accompanied by dysregulations in these humoral and nervous pathways. At the same time, psychosocial factors capable of mounting a response from these humoral and nervous pathways seem to modulate the course of MS. However, while an increasing amount of research points towards a close relationship between the experience of stress and MS relapses, still little is known whether psychosocial factors also translate into disease progression and disability (see Figure 2).

To date, basal and acute dysregulations in humoral and nervous pathways have only poorly been characterized in MS patients and little is known about whether disturbances in these systems constitute a predisposing factor or rather reflect a consequence of ongoing inflammation and neurodegeneration.

Either way, better understanding of the brain-immune interaction in MS seems mandatory at this point in time and could lead to new perspectives in regard to pharmacological as well as psychosocial interventions in MS.

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