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Immunological Aetiology of Major Psychiatric Disorders

Evidence and Therapeutic Implications

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Abstract

Historically, immunological research in psychiatry was based on empirical findings and early epidemiological studies indicating a possible relationship between psychiatric symptoms and acute infectious diseases. However, aetiopathological explanations for psychiatric disorders are no longer closely related to acute infection. Nevertheless, immune hypotheses have been discussed in schizophrenia, affective disorders and infantile autism in the last decades.

Although the variability between the results of the epidemiological studies conducted to date is strikingly high, there is still some evidence that the immune system might play a role in the aetiopathogenesis of these three psychiatric diseases, at least in subgroups of patients. In anxiety disorders immunological research is still very much in its infancy, and the few and inconsistent data of immune changes in these patients are believed to reflect the influence of short- or long-term stress exposure. Nevertheless, there are also some hints raising the possibility that autoimmune mechanisms could interrupt neurotransmission, which would be of significance in certain patients with anxiety and panic disorders. Drug and alcohol (ethanol) dependence are not believed to be primarily influenced by an immunological aetiology. On the other hand, immune reactions due to different drugs of abuse and alcohol may directly or indirectly influence the course of concomitant somatic diseases. In different organic brain disorders the underlying somatic disease is defined as a primary immune or autoimmune

disorder, for instance HIV infection or systemic lupus erythematosus (SLE). For other neurodegenerative disorders, such as Alzheimer's disease, immunoaetiopathological mechanisms are supported by experimental and clinical studies.

Treatment strategies based on immune mechanisms have been investigated in patients with schizophrenia and affective disorders. Furthermore, some antipsychotics and most antidepressants are known to have direct or indirect effects on the immune system. Different immunotherapies have been used in autism, including transfer factor, pentoxifylline, intravenous immunoglobulins and corticosteroids. Immunosuppressive and/or immunomodulating agents are well established methods for treating the neuropsychiatric sequelae of immune or autoimmune disorders, for example AIDS and SLE. Therapeutic approaches in Alzheimer's disease also apply immunological methods such as strategies of active/passive immunisation and NSAIDs.

Considering the comprehensive interactive network between mind and body, future research should focus on approaches linking targets of the different involved systems.

The knowledge about the immune system and its close relationship to the CNS has grown rapidly during the last decades, leading to a considerable expansion of the field of psychoneuroimmunology. It is now widely accepted that psychological stress and psychiatric illness can compromise immune function. This suggests that an individual's psychological state may influence his/her susceptibility to illness or modify the course of an illness and its prognosis (i.e. the 'brain's effect on the body'). On the other hand, psychoneuroimmunology also deals with the effects of diseases on brain functions and behaviour (i.e. the 'body's effect on the brain'). Thus, current research emphasises bi-directional communication between the CNS and the immune system. In addition, interactions between mind and body often use endocrine pathways and, therefore, at least three 'communication partners' are involved in this cross-talk.

The increased understanding of this interactive network between brain and immune structures has provoked the question of whether immunological alterations in psychiatric diseases are due to aetiological and/or pathophysiological causes or are merely secondary, not specifically disease-related, effects. In schizophrenia, affective disorders and infantile autism the aetiology is largely unknown and immunological hypotheses are still actively investigated. Searching for the reason why the immune system is addressed in aetiological considerations of these psychiatric disorders leads to the following three important observations.

1. Epidemiological studies have indicated a possible relationship between psychotic illness and acute infectious diseases. At the end of the nineteenth century a paper about the "infectio psychica" was published and, even earlier, Esquirol described an "epidemic" appearance of psychotic disorders.[1,2]
2. The chronic course of major psychoses, characterised by the typical 'waxing and waning' of symptomatology and episodic manifestations, is similar to some immune disorders, especially autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.
3. On the basis of these empirical findings scientists started to investigate immune parameters in schizophrenia as well as in patients with depression. Early studies applied simple methods such as white blood cell counts and found abnormalities, at least for subgroups of patients.[3-7]

At the beginning of the twentieth century little was known about distinct components and functions of the immune system and, therefore, results were difficult to interpret. Although immunology represents one of the fastest growing research areas and immune studies in schizophrenia, depression and

autism have since employed markedly improved techniques, results have remained controversial. Therefore, this review focuses on two major psychiatric disorders, schizophrenia and depression, as well as on autism, whereas immunological considerations in the aetiology of anxiety disorders and of substance abuse and dependence are only outlined briefly. In the area of organic brain disorders the emphasis of the review is placed on Alzheimer's disease, summarising relevant immunopathological mechanisms as well as mentioning some possible immunoaetiological aspects of the disorder.

1. Methods of Literature Review

In order to obtain data concerning possible immunoaetiological, or at least immunopathological, aspects of major psychiatric disorders we performed a literature search using PubMed and MEDLINE. With the entered keywords we covered the following psychiatric diagnoses – schizophrenia, affective disorders, autism, anxiety disorders, substance abuse and dependence, as well as organic brain disorders – and the field of immunology. We also focused on therapeutic aspects for these disorders, including immunological strategies. Data from controlled studies and supplementary information from review articles and textbooks of psychiatry pertinent to the topic were used. Additional information was collected by cross-referencing from papers found in the database. Altogether, 409 articles are included dealing with immunoaetiological aspects of major psychiatric disorders and possible immunotherapeutic concepts in this connection. These articles were published between 1846 and 2004. This review focusses on historical papers providing background on immunoaetiology in psychiatric disorders, and on literature dealing with modern laboratory techniques and newly adapted immune approaches. Only papers with valid clinical diagnosis of groups and subgroups of patients, and with a valid description of laboratory procedures were chosen. Unfortunately, many articles were found to be of poor quality in both respects.

2. A Brief Immunology Primer

Immune response always consists of two components: the recognition of the pathogenic or foreign material and a reaction to eliminate it. This can be achieved either by the innate or the adaptive immune response. Both pathways are based on the activation of leukocytes that are assisted by soluble mediators such as complement, antibodies, cytokines, etc. Most immune cells derive from pluripotent stem cells that have the ability both to self-renew and to differentiate to all blood cell lineages under the influence of different cytokines. Cytokines are produced by different immune cells and serve as a signal for communication between leukocytes. The complement system is a group of about 20 serum proteins that are mainly responsible for controlling inflammation.

Optimal function of the immune system requires that immune cells and soluble cell products interact with each other in a sequential and regulated manner. The distinction between self and nonself occurs through complex mechanisms that depend upon specific recognition molecules present on the surface of immunocompetent cells.

The innate immune system is phylogenetically older. It is characterised by a fast (within minutes) but unspecific immune response. Malfunctions are rarely seen in this type of response. The main components of the innate immune system are natural barriers of defence such as the skin and mucous membranes, phagocytic cells (e.g. monocytes, macrophages and polymorphonuclear neutrophils) and soluble mediators (e.g. the complement system, acute phase proteins and cytokines [especially interferons]).

The adaptive immune system is younger and acts very specifically but more slowly (within days). It remembers the infectious agent and repeated exposure to the same pathogen improves the adaptive immune response. B and T lymphocytes and natural killer (NK) cells are the main cellular compounds of the adaptive immune system. Antibodies, T-cell receptors, protein products of a genetic region referred to as the major histocompatibility complex and

cytokines are the soluble recognition molecules of this system (table I).

There is considerable interaction between the innate and adaptive systems, and most immune responses to infectious organisms involve a variety of components of both systems. In the earliest stages of infection, innate responses predominate and phagocytes act as a first line of defence. Later on, lymphocytes start to generate adaptive and regulatory immune responses. They remember the pathogen, and mount more effective and rapid responses if the individual becomes reinfected with the same offensive agent.

In contrast with antibody-mediated (or humoral) immunity, which is related to B-cell function, the function of T cells is sometimes referred to as cell-mediated immunity. Antigen-presenting cells (APCs), such as dendritic cells in the skin or macrophages, are critical in initiating the activation of B and T cells. Initially, APCs take up antigens and subject them to proteolytic degradation in various compartments of the cell. These events are called antigen processing and are required because T-cell receptors for antigens only recognise processed antigens that are displayed on APCs.

Each B cell is genetically programmed to encode a surface receptor specific for a particular antigen. Having recognised its specific antigen, B cells multiply and differentiate into plasma cells, which produce large amounts of the receptor molecule in a soluble form that can be secreted. These are known as antibodies. They are virtually identical to the original receptor molecule and bind specifically to the antigen that initially activated the B cells. Their aims are an inactivation of the antigen, preventing toxins and microorganisms from entering cells, and the elimination of these antigens via phagocytosis or complement activation.

The T-cell system consists of several different types of cells. One group interacts with mononuclear phagocytes and helps them to destroy intracellular pathogens; they are called T-helper (T_h1) cells. Another group interacts with B cells and induces them to divide, differentiate and produce antibodies: these are the T_h2 cells. Cytotoxic T lymphocytes (CTL) represent the third group, which is responsible for the destruction of host cells infected by viruses or other intracellular pathogens (figure 1). T cells generate their effects either by releasing cytokines or by direct cell-cell interactions. The balance in the T_h1/T_h2 system is controlled by T_h1/T_h2-specific cytokines that negatively regulate each other (table II).

NK cells arise from the same lymphoid progenitor cells as T and B cells. They are activated by cytokines and play two important roles in the immune system. They are excellent killers of cells

Table I. The innate and the adaptive immune systems

Innate system		Adaptive system	
characteristics	components	characteristics	components
Old system	Barriers such as skin, mucous, membranes	Young system	
No specific response	Cells: phagocytes – monocytes/ macrophages, polymorphonuclear neutrophils	Very specific response	Cells: B and T lymphocytes
Fast response (within minutes)	Soluble mediators: acute phase protein, complement, cytokines (interferons)	Slow response (within days)	Soluble mediators: antigen recognition molecules – antibodies, T-cell receptors, major histocompatibility complex II, cytokines
No memory: response does not change after repeated exposure		Memory with improvement abilities: faster, stronger, qualitatively different	
Rarely malfunctions		Frequently malfunctions causing autoimmunity and immunodeficiency	

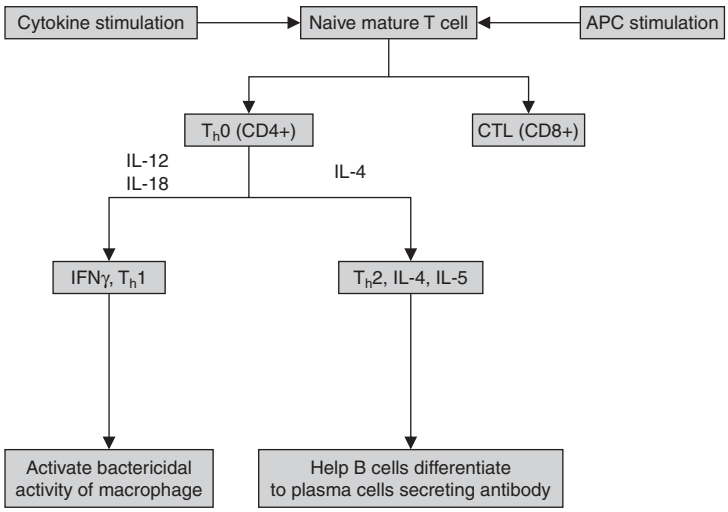

Fig. 1. The function of the T-helper (T_h) subsets (T_h0, T_h1, T_h2) of the T-cell system. **APC** = antigen-presenting cell; **IFN** = interferon; **IL** = interleukin; **CTL** = cytotoxic T lymphocytes or cells.

infected by some viruses and, like macrophages, they have a role in stimulating the adaptive immune response. NK cells are part of the innate immune system but they also fill a potential gap in the adaptive immune system.

As mentioned earlier, the immune system not only interacts with the CNS but also has a very close relationship with the endocrine system. The main facilitators of communication between the three systems are chemical messengers, such as cytokines, neurotransmitters and hormones. The influence of the autonomic nervous system on immune function is exerted primarily through sympathetic fibres that innervate the lymphoid organs[8] and through circulating catecholamines that originate in the adrenal medulla.[9] The hypothalamic-pituitary-adrenal (HPA) axis represents another important pathway mediating signals between the immune system and the nervous system. In conditions of stress the activation of the HPA axis is triggered by an increased release of corticotropin-releasing factor (CRF) that consequently stimulates the release of corticotropin (ACTH), which in turn causes an increase in the synthesis and release of glucocorticoids in the adrenal cortices. The immunosuppressive and anti-inflammatory effects of glucocorticoids are well established. Another example of glucocorticoids influencing the immune system is their ability to modulate the pattern of activation of T cells by causing a downregulation of T_h1 response and concomitantly upregulating T_h2 activity.[10] Because catecholamines exert similar effects, the dual activation of the sympathoadrenal system and the HPA axis in stress results in a pronounced shift in the balance of the T_h1/T_h2 activity towards T_h2. In the other direction, both the sympathoadrenal system and the HPA axis are highly sensitive to alterations in the immune system and respond for instance to the wide array of cytokines released from activated immune cells.[11,12]

Table II. Major immune cells and relating cytokines

Cell	Cytokines
T cell	
T_h1	IL-2, IFNγ, TNFα, TNFβ
T_h2	IL-4, IL-5, IL-6, IL-9, IL-10, IL-13
B cell	IL-3
Natural killer cell	IFNγ, IL-12
Monocyte/ macrophage	IL-1, IL-6, IL-10, TNFα, IFN, IL-15, IL-12, TGFβ, IL-18
Neutrophils	IL-8

IFN = interferon; **IL** = interleukin; **TGF** = transforming growth factor; **T_h** = T-helper; **TNF** = tumour necrosis factor.

3. Immunological Aetiology and Major Psychiatric Disorders

3.1 Schizophrenia

Schizophrenia is a vastly heterogeneous disorder and its clinical manifestations include changes in thought, emotion, behaviour and perception. Variable clinical pictures may reflect different aetiological factors. Immunological hypotheses are among the various hypotheses put forth to account for the aetiology of schizophrenia.[13,14]

Initially, the 'infection hypothesis' of schizophrenia was triggered by observing schizophrenia-like psychoses in influenza pandemics.[15,16] Antibodies against several viruses – such as herpes simplex virus, cytomegalovirus, Epstein-Barr virus, influenza virus and the Borna disease virus – were reported in schizophrenia patients. It has also been postulated that retroviruses may play a role in the aetiopathogenesis of some cases of schizophrenia. Karlsson et al.[17] have found the HERV-W retrovirus in the cerebrospinal fluid (CSF) of some patients with chronic schizophrenia.

The variability between the results of the studies is strikingly high[18-36] and up to now it was not possible to identify a specific virus as being consistently associated with the disease.[14,37,38] On the other hand, some mechanisms by which a viral hypothesis would still fit the aetiology of schizophrenia have been explained by Pearce.[39] According to this author, the aetiological process might not be restricted solely to a viral infection but additional interacting factors such as genetic, neurodevelopmental, environmental, immunological and neuropsychological conditions could be built into a comprehensive theory of schizophrenia.

Epidemiological evidence indicates that schizophrenia occurs universally,[40] with very similar incidence rates across different populations.[41] However, there are some investigations that show different prevalence rates among various geographical regions. This has been interpreted as pointing towards differences in immunity or exposure to a pathogenetic agent, possibly a virus.[42]

Epidemiology has also presented some evidence that schizophrenia patients may have a reduced risk of acquiring certain forms of cancer[43] as well as rheumatoid arthritis.[44-46] On the basis of these observations, different hypotheses were created proposing genetic vulnerability to viral infections and/or an autoimmune process.[47,48]

Another issue being addressed by epidemiological studies is seasonality of birth, reflecting a higher risk of schizophrenia in the offspring of mothers delivering in the winter and spring months, and after influenza epidemics.[49-52] Prenatal and perinatal infections may affect infant brain development, thus resulting in schizophrenia in later life, most likely in genetically susceptible individuals.[53,54]

In 1937 Lehmann-Facius[55] raised the topic of impaired autoimmunity in schizophrenic patients by publishing a report on autoantibodies in CSF against brain tissue. Recent studies have investigated antibodies against specific brain regions, etc.,[56-61] as well as a great variety of auotantibodies against other human structures in- and outside the brain.[62-64] However, despite the great number of studies, results remain controversial. Antibody titres against nonspecific antigens such as heat shock proteins[65-68] and other structures such as soluble intercellular adhesion molecules[69-71] present a more homogenous picture, with elevated antibodies in at least a subgroup of schizophrenia patients. Signs of an increased permeability of the blood-brain barrier are also in line with these findings.[65,72-74] However, all of these studies fail to identify a specific autoimmune reaction. An alternative explanation for increased antibody titres in schizophrenia is that these patients are predisposed toward more vigorous B-cell responses, and consequently prone to develop autoantibodies. Elevated numbers of B cells, as well as subsets of specific B cells, have been reported.[75-77]

Viruses or other infections are capable of triggering or promoting autoimmune diseases of the CNS.[78] Thus, it was hypothesised that schizophrenia, or at least a subtype of the disease, could be initiated by an epidemic virus that causes neuropsychiatric sequelae only in individuals who are geneti-

cally predisposed to mount an atypical immune response or even an autoimmune reaction during a critical neurodevelopmental period.[79-82] Recent studies underlined such an autoimmune pathogenesis in a subgroup of schizophrenic patients by reporting a typical cytokine pattern besides other immune alterations.[83-86]

Autoimmune and virus hypotheses have often been investigated by examining T cell-related functions. Results are inconsistent, especially those dealing with the cellular components of the T-cell system.[87-102] Influences of antipsychotic medication, the stage of the disorder and age are only some of the possible confounding variables likely to be responsible for the inconsistency of immunological findings.[103]

Despite controversial results, immune alterations in schizophrenia have been reported for more than 100 years and more recent studies have applied better laboratory methodology and more rigorous clinical research criteria. Cytokines are interesting targets for such investigations, as they not only provide communication between immune cells but also play a role in inducing neurochemical, neuroendocrine, neuroimmune and behavioural changes in the brain.[104] Cytokines are produced by many cells in the CNS[105] and can be actively transported through the blood-brain barrier. Several studies have found that schizophrenia patients have increased levels of proinflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α in the peripheral blood or the CSF.[106-111] Studies reporting increased acute phase proteins and monocytic activation support this theory of an activated inflammatory response system in at least a subgroup of schizophrenia patients.[112-115] Cytokines are involved in regulatory activation circuits of different parts of the immune system. Some of them influence the balance of the T_h1/T_h2 cell system. In this context several findings point to alterations of IL-2, either with regard to production by peripheral lymphocytes[83,109,116] or concerning plasma or CSF levels.[67,68,117] Several immunological studies showed a decreased *in vitro* production of IL-2 and interferon (IFN)-γ,[118-122] whereas others reported increased levels of IL-10 and IL-4.[114,120,123] These results provide some support for a shift of T_h1 to increased T_h2 activity in the acute state of the disease.[103,115,124] Clinically, a chronic immune response is characterised by T_h2 activation, whereas acute immune reactions are T_h1 dominated. Therefore, the discussed results in schizophrenia may support a chronic infectious process. Conversely, there have been investigations that do not or only partly support these interpretations.[109,125-127]

Cytokines are also known to modify the metabolisms of neurotransmitters and to influence neuronal development.[128-131] Several authors have suggested that increased dopaminergic transmission and abnormal brain morphology could be due to cytokine alterations.[67,132,133] Marx et al.[133] hypothesised that proinflammatory cytokines generated in response to infection, ischaemia or other stressors during neurodevelopment might constitute a final common pathway contributing to the aberrations of neuronal development in schizophrenia. They have found at least indirect evidence for cytokine-mediated decreased neuronal survival in rat-cortical cell cultures.

Cytokine aberrations in schizophrenia might be, at least partly, genetically determined. Boccio Chiavetto et al.[134] demonstrated an association between specific promoter haplotypes of the IL-10 gene and schizophrenia. These authors suggest that an abnormal secretion of IL-10, in response to infections or other stressors during critical stages of brain development and/or to imbalances in the neurotransmitter systems, could result in immune alterations linked to schizophrenia.[134] Other studies on gene polymorphisms of IL-1 and TNFα also support the idea that cytokine aberrations in schizophrenic patients could be of genetic aetiology.[135,136]

Maternal infections during pregnancy have also been seen as a potential risk for schizophrenia among offspring.[137-140] Animal models have indicated that maternal immune response can influence fetal brain development, possibly via circulating cytokines.[141,142] Immune activation due to direct fetal or early postnatal infection might cause similar

effects on the developing CNS.[143,144] Based on these primary aetiological processes, which might occur early in life or even during the prenatal period, it is possible that secondary alterations such as non-specific immune activation and/or dysfunction[113-115,145] may play a role in the clinical manifestation of psychosis. Conditions eventually triggering the advent of symptoms could be stress,[146] somatic illness or injury, or physiological changes such as hormonal influences, all of which are known to have an impact on immune reactions.[147-150]

When critically appraising reports on immune alterations in schizophrenia it should always be acknowledged that many immune aberrations can also be influenced by different confounding factors such as age, gender, smoking habits, medication, etc.[151,152]

3.2 Autism

Autism (autistic spectrum disorder) is now recognised as a heterogenous syndrome. It belongs to a group of neurodevelopmental disorders, which are classified as pervasive developmental disorders. Primarily, the diagnosis is based on clinical criteria showing a broad range of behavioural symptoms with significant deficits in social interaction and communication accompanied by stereotyped or restricted behaviours and interests,[153] and without defined biological markers of dysfunction. Since it was demonstrated by the reviews of Bayley et al.[154] and Trottier et al.[155] that autism has an organic aetiology rather than a psychological origin, numerous studies have been carried out to elucidate different aetiological aspects. Although a solid body of evidence points to genetic factors playing an important role in the aetiology of autism,[156-159] conclusive results are still missing. An exception is Rett's syndrome, which is attributable in most affected individuals to mutations of the methyl-CpG-binding protein 2 *(MeCP2)* gene.

Other current theories involved in the aetiological research of autism include immune,[160-163] environmental and neurochemical factors. Autism shares features with autoimmune disorders, such as genetic susceptibility, association with viral infection, immunological dysfunction and gender difference.[164-166]

Although there are several inconsistencies in immune alterations being reported in autistic children, recently published results can be summarised as follows: T cell-mediated immune deficiencies,[161,167] altered NK cell activity[161] and different patterns of immune system activation including an abnormal CD4 **:** CD8 ratio,[168] a higher number of DR+ (activated) T cells,[169] higher monocyte counts and an increased percentage of monocytes in relation to total leukocytes,[165,170] high urinary neopterin levels[171,172] and increased levels of immunoglobulins.[173,174] Gupta et al.[175] reported a shift in the T-helper system from T_h1 to an increased T_h2 activity evidenced by reduced production of IL-2 and IFNγ, and a concomitant increase in the production of IL-4. In another study, proinflammatory cytokine production was associated with innate and adoptive immune responses showing increased values of TNFα, IL-1β and IL-6.[176]

Immune system regulation is influenced by genetic mechanisms and, in this context, immunomodulatory genes in the human leukocyte antigen region of chromosome 6 have been implicated in autism in some studies.[165,177-179] By applying immunogenetic analyses, genes long implicated in autoimmune diseases, such as SLE and rheumatoid arthritis, have often been found to be higher in autistic populations.[177,178,180,181] As for autoimmune disorders in general, the prevalence for autoimmune phenomena is increased in family members;[182-184] this has also been reported for families with autistic children.[185] Furthermore, several studies revealed autoantibodies against different proteins of the CNS in subgroups of autistic patients, for instance autoantibodies against myelin basic protein,[186] against neurofilament proteins[187] and against serotonin 5-HT_{1A} receptors,[187,188] the latter not being confirmed by two other groups.[189,190] Connolly et al.[191] reported high rates of antibrain autoantibodies, both IgG and IgM, specific for brain-endothelial cell proteins in children with autistic disorder.

However, most of these findings are of questionable significance since often only small numbers of

individuals were analysed. Two recently published papers analysed larger samples. The first one by Silva et al.[192] investigated the autoantibody repertoires to brain tissue extract in the plasma of 171 autistic children, their parents and healthy controls by quantitative immunoblotting. The results showed a significantly higher frequency of antibodies against brain antigens in children with autism compared with controls and the possibility to discriminate between patients and controls by a certain pattern of autoantibody reactivity, but without revealing correlations between parents and offspring. Singh and Jensen[193] included 68 autistic children aged 4–12 years and 30 healthy children. They studied the distribution of antibodies to rat caudate nucleus, cerebral cortex, cerebellum, brain stem and hippocampus. Since a significant number of autistic children had antibodies to the caudate nucleus the authors proposed that an autoimmune reaction to this brain region may cause neuropsychiatric impairment in autism.

An investigation by Vojdani et al.[194] was based on previous findings in autoimmune diseases such as rheumatoid arthritis and SLE, and reported on membrane-bound peptidases, which play key roles in T cell-mediated immune responses and cytokine production.[195,196] The authors postulated the hypothesis that heat shock proteins, which are ubiquitous in human cells, produced by many infectious agents and known to modulate host immune functions, or dietary peptides such as gliadin peptides, may bind to the membrane-bound peptidases and induce autoantibody production, thus causing neuroimmune dysregulation and autoimmunity in autism.[174,194]

Besides the immunogenetic mechanisms discussed earlier playing a possible role in the aetiology of infantile autism, immunological findings – immune dysfunction and/or enhanced autoimmunity – are discussed either in relation to viral or bacterial infection in early life or even prenatal infectious exposure[139,185,193,197-200] or in connection with neurochemical abnormalities causing immune alterations.[201-203] This possibility has been considered for frequently reported changes in serotonin metabolism[204] as well as for abnormalities in oxytocin metabolism,[205,206] which were both found in some groups of autistic children. Another aetiological background that was discussed extensively was the link between vaccines and the development of autism.[207] However, this theory has found little support as epidemiological studies have failed to show a link between the measles, mumps and rubella vaccine (MMR),[153,176,178,185,208-218] as well as between other vaccines[219,220] and autism. In addition to this, the authors of the article who originally interpreted their findings as linking MMR and autism formally retracted this interpretation.[221]

Despite various hints that both immune dysfunction and enhanced autoimmunity may play an important role in the aetiopathogenesis of autism, final conclusions are still impossible because heterogenous immunological findings are probably caused by the heterogeneity of the disorder itself.

3.3 Affective Disorders

Contemporary concepts of affective disorders propose complex interacting models which involve genetic hypotheses, neurodevelopmental, neurotransmitter as well as environmental- and stress-related influences. In this context, investigating interactions between the immune, endocrine and neurotransmitter systems have received increasing attention. Although findings are rather heterogeneous and often inconsistent in depressive patients, there is some evidence for a relationship between major depression and immunological abnormalities.

Reduced NK cell cytotoxicity is one of the most consistent results in depression, as recently confirmed by a meta-analysis.[222-224] Impairments in functional assays of mitogen-stimulated lymphocyte proliferation[223,225,226] have also been replicated in a number of studies. A change in number and percentage of leukocytes indicating a neutrophilic leukocytosis[227] was one of the first observations in depressive patients. On the other hand, several reports emphasise states of immune activation such as increased levels of cells bearing activation markers, increased positive acute phase protein levels and

increased circulating soluble IL-2 receptors in major depression.[228,229]

When discussing biological alterations, which may contribute to the aetiology or at least to the pathogenesis of depression, stress, with its heterogeneous features, must be taken into account. There is wide agreement that stressful life experiences can play an important role in the aetiology of depressive disorders. There is also evidence suggesting that exposure to long-term low-grade stress may be a predisposing factor for depression.[230-232] Long-term or unavoidable/uncontrollable stress conditions induce changes in behaviour and neurotransmitters, as well as in endocrine and immune functions that are similar to those found in depression. However, it is still unclear whether the changes occurring in depressive patients are independent of the long-term stress generally accompanying such disorders. Individual coping styles may also influence the immunobiological response to depression and different kinds of stress.[233] Zorilla and colleagues[222] have shown that leukocytosis, reduced blastogenic response to phytohaemagglutinin (PHA) stimulation and reduced NK cell cytotoxicity are commonly observed in relation to both depression and short- or long-term stressors.[222] On the other hand, their meta-analysis suggests that major depression, but not stress, is associated with immune activation, namely indicators of acute phase response.[222]

Increased rates of morbidity and mortality[234,235] have been reported in patients with psychological stress and depressive symptoms, but despite the statistical relationship of depression and stressors to certain immune parameters the clinical significance of these findings remains largely unknown.

Depression has been indicated to be an independent risk factor for the development of cardiovascular disease.[236,237] Depression precedes the onset of ischaemic heart disease, is associated with a greater risk of sudden death among post-myocardial infarction patients and has been implicated in increased platelet aggregation.[238]

Other findings related to macrophage-mediated inflammatory processes have supported speculations that depression increases the susceptibility to diseases that opportunistically exploit reductions in innate and adaptive immunity.[239,240] In this context it is important to further investigate the role of stress, depression and depressive symptoms in the onset, and the progression of infectious and inflammatory diseases as well as of cancer.[241-246]

Links between the neurotransmitter systems, the endocrine system and the immune system in depression have been reported, for instance, through noradrenergic activity. For example, enhanced noradrenergic turnover in the hypothalamus leads to an increased release of CRF, which further activates the HPA axis to produce glucocorticoids.[247] Enhanced glucocorticoid production normally inhibits the immune system, but in patients with chronic depression, glucocorticoid receptors seem to be desensitised and, thus, the negative regulatory feedback mechanism between glucocorticoids and the immune system is impaired. The consequence is cytokine overproduction, prostaglandin synthesis and a further activation of the HPA axis, leading to even more glucocorticoid production. This has fueled the ongoing debate about an acquired or inherited glucocorticoid feedback resistance being responsible for depression.[248]

In 1991, Smith[249] proposed a 'macrophage theory of depression'. Since then, inflammatory processes have been increasingly investigated with respect to the aetiology of depressive disorders.[249-251] This hypothesis surmised that an excessive secretion of monocyte/macrophage cytokines, such as IL-1, TNFα and IFNα may cause symptoms of depression. Macrophages are activated, and the production and secretion of their specific cytokines are increased in many different diseases such as cancer, cardiovascular diseases[234-236,252] and autoimmune disorders such as SLE, as well as in allergic conditions caused by food. In patients with these diseases the prevalence of depressive symptoms is reported to be distinctly higher than in the general population. Maes[229] extended this aetiological approach by incorporating the inflammatory response system. Thus, additional cytokines including IL-6 were studied. This group found numerous indicators of inflammatory response system activation such as in-

creased numbers of leukocytes, monocytes, neutrophils and activated T cells, as well as increased levels of neopterin and prostaglandin, both released by activated macrophages.[229] Increased prostaglandin plasma concentrations cause immunosuppressive effects on the activities of lymphocytes, NK cells and neutrophils.[253] Prostaglandins also negatively regulate biogenic amine release, which points to a possible influence on neurotransmitter systems involved in depression.[254,255] Furthermore, increased acute phase proteins such as haptoglobin, ceruloplasmin, C-reactive protein and others, as well as lowered serum concentrations of negative acute phase proteins such as albumin and transferrin, have been reported.[229] Inflammatory response system activation is also partly confirmed by the meta-analyses mentioned earlier in this section.[222,223] On the other hand, a recently published study by Carpenter et al.[256] that measured the IL-6 concentration in CSF of depressed patients and healthy controls failed to find differences, thus not supporting an immune activation process.[256]

Cytokines facilitate communication between the immune system and CNS.[104,257] Neurotransmitter synthesis, release and metabolism can be altered by cytokines. As mentioned earlier, cytokines are also synthesised by brain cells including neurons, microglia, endothelial cells and astrocytes, and they can disrupt the blood-brain barrier. Furthermore, they penetrate in the brain through circumventricular organs in which capillaries have open junctions and abundant fenestrations, and by acting on peripheral nerves which then signal the brain.[254] In depressive patients, cytokines have been shown to influence various dysregulated CNS functions, such as sleep, food intake, cognition, behaviour, temperature control and neuroendocrine regulation. IL-1 plays a crucial role in the CNS. In the context of the inflammatory hypothesis of depression, the influence of IL-1β and IL-1 receptor antagonists have been investigated.

The earlier mentioned activation of the HPA axis during chronic stress and/or chronic depression could also be developed in disease conditions that are characterised by immune activation and inflammatory processes. It is well established that cytokines such as IL-1, IL-6 and TNFα enhance the release of glucocorticoids. An excessive production of these cytokines in disease conditions might stimulate the HPA axis continuously and, thereby, induce the negative feedback control of ACTH release. Consequently, corticosteroid receptors in the CNS would be downregulated.[258] Therefore, endocrine alterations that occur in depression, such as increased CRF, blunted ACTH response and hypercortisolaemia, might also result from increased cytokine release.

In addition to an increase of proinflammatory cytokines in depression, some T cell-derived cytokines, such as IFNγ and TNFα, and IL-2 receptors are also increased. However, it is not certain whether macrophage deriving cytokines induce T cell-mediated immunity or *vice versa*. Immune activation, mediated by IFNγ, has been shown to influence the metabolism of the essential amino acid tryptophan, which can be metabolised in two different pathways, one resulting in serotonin and the other ending up with kynurenine.[259] Consequently, immunologically induced tryptophan degradation may elicit depressive symptoms when the availability of tryptophan becomes insufficient for normal serotonin biosynthesis.[260,261] Furthermore, it has been suggested that the enzyme indoleamine 2,3-dioxygenase, which regulates tryptophan degradation to kynurenine, could represent an important link between the immunological network and the pathogenesis of depression. In this context, an activated monocyte/macrophage axis could be seen as a basis for the development of depressive symptoms in patients who have diseases with immune activation such as cancer, autoimmune diseases, infections and others.[262] In patients with infectious diseases of the CNS such as HIV encephalitis, low tryptophan levels in CSF and high values of the kynurenine/tryptophan ratio have been reported indicating an increased tryptophan degradation caused by an activated immune system.[263,264] Conversely, there are single case reports about immune activation connected with increased levels of brain tryptophan,[265] which are most probably due to an influx of trypto-

phan from the blood caused by damage to the blood brain barrier in, for example, severe states of infection. Corcos et al.[266] have recently reviewed the links between depressive illness and cytokine production.

By focusing on the connection between neurotransmitter systems and the immune system, some attention should also be paid to tetrahydrobiopterin (THB), a required co-factor for the enzymes that are involved in the biosynthesis of serotonin, noradrenaline and dopamine. As monocytes/macrophages seem to be the main sources of THB, it has been suggested that THB might represent an important link between the immune system and neuronal networks.[267] Cytokines are responsible for an increased biosynthesis of THB. In this way, the immune system regulates the mediator THB that is able to influence the biosynthesis of neurotransmitters known to play a crucial role in the development of depression. The biosynthesis of the pleiotropic neurotransmitter nitric oxide (NO) is also under the control of THB. In the CNS, NO has been shown to be involved in functions such as memory and learning behaviour, and in diseases including schizophrenia, bipolar disorder and addiction.[268] Various immunocompetent cells such as macrophages, neutrophils, microglia and astrocytes are able to produce and release NO. Furthermore, NO positively affects the release of amines (i.e. noradrenergic). This fact further strengthens the proposed links between the immune system and neuronal transmission. There is also a close relationship with the endocrine pathways as NO seems to modulate the HPA axis by stimulating CRF. Simultaneously, NO activates prostaglandin production. Although NO plays a role in stress-dependent immune alterations,[269,270] its relevance for depression still awaits clarification.

The findings in this section refer primarily to major depression generally without a more detailed clinical description. The heterogeneous nature of the clinical subtypes of affective disorders most likely contributes to controversial results. Anisman et al.[271] have reported different patterns of HPA axis regulation in melancholic and atypical depression as well as an elevated IL-1β production in patients with dysthymia. As IL-1β does not normalise after symptom improvement, these authors have suggested that IL-1β production could be a trait marker playing a role in the pathophysiology of this disorder. Different immunological findings have also been reported for depressed patients with and without melancholic symptoms,[272] as well as for pure manic compared with mixed manic patients.[273,274] Signs of an activated T-cell system, such as increased prevalence of autoantibodies, high numbers of circulating activated T cells and raised levels of serum IL-2 receptor, have been described in several studies of patients with bipolar disorder.[275-277] In patients with seasonal affective disorder immune changes following monoamine depletion as well as light therapy have been found in some studies, but were not confirmed by others.[278-280] The severity of depressive symptoms as well as the duration of illness may also have an impact on immune functions (e.g. cytokine levels).[250] Obviously, this last report appears to reflect secondary rather than causative alterations of the immune system; however, it underlines the difficulties of research in this field. Other confounding factors, such as the influence of sleep disorders, physical activity, nutrition and lifestyle, may also modulate the immune system and, thus, contribute to the complex interactive network between immune, endocrine and neurotransmitter systems, making it difficult to determine a temporal or even causal relationship of aberrations with regard to their role in the aetiopathophysiology of affective disorders.[149,281,282]

3.4 Anxiety Disorders

There have been few reports on the relationship between anxiety disorders and the immune system. Findings include an impaired lymphocyte response to mitogen stimulation, reduced IL-2 production and lower levels of circulating IL-1β in patients with anxiety than in healthy controls.[283,284] On the other hand, there are also studies indicating that anxiety disorders may be associated with increased immune function. The majority of investigations have evaluated immunological parameters in patients with panic disorder or depression with panic disorder.[285-291]

Koh[292,293] has suggested that subclinical anxiety might be associated with increased immune functions, representing a transient phenomenon which occurs prior to the downregulation of immune function. A recently published study by Atanackovic et al.[294] showed marked immunological changes, for example an elevated ratio of CD4+ : CD8+ cells in patients with anxiety disorders compared with healthy controls and those with mild depression. This high ratio was not reversible after an 8-week course of inpatient psychotherapy.

The few and inconsistent data of immune alterations in patients with anxiety are believed to reflect the influence of short- or long-term stress exposure. All anxiety disorders are associated with an overactivation of the sympathetic system, which is anatomically connected to the major immune organs and the HPA axis. Thus, many of the changes in immune function could be a consequence of the alterations in these relationships. Nevertheless, elevated anti-serotonin and serotonin anti-idiotypic antibodies, found in patients with panic disorder,[295] raise the possibility that a potential interruption of serotonin neurotransmission through autoimmune mechanisms might be of significance in certain patients with this disorder.

3.5 Substance Abuse and Dependence

Immunology is not believed to be primarily involved in the aetiology of either drug or alcohol (ethanol) dependence. On the other hand, immune reactions caused by different drugs or alcohol may directly or indirectly influence the course of concomitant somatic diseases.

There is some evidence that alcohol can have both immunosuppressive and immune-activating effects.[296-298] Immunological findings such as impaired NK cell activity, T-cell abnormalities and increased immunoglobulin levels (e.g. IgE) have been reported in some studies of patients with alcohol dependence,[299-304] whereas other studies have found no changes.[305-308] As to cytokine expression, basic observations *in vitro* and in animal studies suggest that alcohol induces a decreased secretion or production of proinflammatory cytokines such as IL-1β, TNFα, IL-6[309-313] and an increased production of T_h2-dependent cytokines, for example IL-10.[314,315] Although available clinical data are limited, a reduced production of TNFα[316,317] was reported in alcoholics without liver disease. However, another paper showed an increased production of IL-10, IL-6 and TNFα.[318] A recently published study Nicolaou et al.[319] found that serum IL-6 concentration was significantly increased in alcohol-dependent individuals without liver disease compared with healthy controls.

At this point it is important to mention that other factors such as ethnicity and behavioural mechanisms may have a significant influence on mediating the alterations of immune function in specific subgroups of persons with alcohol dependence. In this context, Irwin et al.[320-323] studied the relationship between alcoholism, sleep and immunity in several investigations over the last 5 years that focused on cytokines as a possible mediating link.

The clinical significance of immune alterations found in patients with alcohol dependence is not known, but they are thought to contribute to the increased incidence of infections that is well documented in this group.[297,324-326] Recently, Frank et al.[327] published an investigation on 36 alcoholic patients without liver disease, which pointed towards a prolonged lipopolysaccharide-mediated hypoinflammatory condition of the innate, but not of the adaptive, immune system predisposing to infections and sepsis by blunting initial response to the pathogens. Factors that contribute to this process include malnutrition, exposure to frequent different infections, high risk of aspiration and liver cirrhosis. Furthermore, the amount consumed and the type of alcoholic beverages might also influence immune response and interaction.[328] Abnormal immune function is a well recognised feature in patients with alcoholic liver cirrhosis. There is some evidence that alcohol might stimulate immune response, suggesting that it could be directly involved in the developing process of alcoholic cirrhosis.[298,329] McClain et al.[330] have reported an activation of monocytes and macrophages with subsequent proinflammatory cytokine production playing an impor-

tant role in the liver injury of alcohol-induced liver disease (ALD) as well as in certain metabolic complications of ALD, such as fever and anorexia.

The association between illegal drug use and a high incidence of infectious diseases has been documented in numerous reports.[331] *In vitro* studies with drugs of abuse leading to immune-modulating effects also support these clinical observations. In this context, drugs of abuse have been suggested as possible cofactors in AIDS progression and in an alteration of the susceptibility to other infectious diseases.[332] Mechanisms by which drugs increase susceptibility to infection seem to function directly as well as indirectly. One indirect way is a drug-induced stimulation of the HPA axis resulting in glucocorticoid production, which in turn influences the immune system.[333,334] Different drugs of abuse such as opiates and cannabinoids appear to influence immunity and infection via receptor-mediated direct action on immune cells.[335-338] Another common effect by which drugs of abuse influence the immune system is via the T_h1/T_h2 response, either by inhibition of T_h1- or activation of T_h2-associated cytokines.[339]

Furthermore, psychiatric comorbidity, such as depressive symptoms in patients with substance abuse, could be caused by immune activation either directly because of the drugs of abuse or indirectly via drug-induced somatic diseases such as inflammation or infections.

3.6 Organic Brain Disorders

The definition of acute organic brain disorders is based on an underlying causative somatic disease. Consequently, diseases of the immune system can lead to different psychiatric symptoms. SLE can be taken as an example of an immune disorder commonly presenting with psychiatric symptoms, either preceding the disease and/or developing during its course. Neuropsychiatric manifestations have been described in up to 75% of SLE patients.[340] The most frequently reported psychiatric syndromes are cognitive dysfunction, mood disorders, psychosis and acute confusional states.[341,342] Neuropsychiatric symptoms in SLE are most likely to be caused by multiple factors including autoantibody production, microvasculopathy and proinflammatory cytokines.[340] Other immune disorders with neuropsychiatric complications include, for instance, Sjögren's syndrome, primary vasculitis, primary antiphospholipid syndrome and AIDS. Mood disorders and dementia are often found in the middle to late stages of AIDS.[343] Current studies are aimed towards elucidating direct and indirect mechanisms of HIV neuropathogenesis, HIV-mediated processes of neuronal damage and apoptosis, as well as the compartmentalised evolution of the virus in the brain.[344]

In various other neurodegenerative disorders such as Alzheimer's, Huntingon's, Pick's and Parkinson's disease, immunoaetiopathological mechanisms are supported by experimental and clinical studies.[345] In patients with Parkinson's disease, alterations of the immune system might be closely related to dopamine neurotransmission which has been shown to have a regulative role in some immune functions.[253] There is also some clinical, epidemiological and experimental evidence that inflammation and even autoimmune processes could be involved in Parkinson's disease, either in its development or in its progression.[345]

In Alzheimer's disease a dysregulation in the metabolism of the β-amyloid precursor protein and consequent deposition of β-amyloid is said to be a main pathogenetic mechanism.[346,347] Amyloid deposition starts 10–20 years before the appearance of clinical dementia. During this time the brain is confronted with increasing amounts of β-amyloid. Mounting evidence suggests that both the innate and the adaptive immune system play an important role in this disorder.[348] Two inter-related mechanisms, namely inflammation and free radical-induced oxidative stress,[261] have been indicated in this context. Innate immunity in the brain is mainly represented by microglial cells, which phagocytose and degrade β-amyloid. As the catabolism of β-amyloid decreases, glial cells become overstimulated and start to produce substances that are toxic to neurons, such as NO and inflammatory proteins. Proinflammatory cytokines (IL-1, IL-6 and TNFα) can be directly

toxic or stimulate β-amyloid production and increase its cytotoxicity.[348] Of the proinflammatory cytokines involved in these processes, TNFα appears to be of crucial significance.[349] The role of adaptive immunity is mainly related to the fact that β-amyloid can be recognised as an antigen. Besides the amyloid-based hypothesis involving the immune system in Alzheimer's disease, there a several *in vitro* findings supporting a primarily increased neurotoxic inflammatory activity in the context of immune response to external organisms or enhanced autoimmune reactions.[350] For example, elevated amyloid precursor protein expression[351,352] and increased production of β-amyloid by astrocytes and neurons[353,354] have been shown to be induced by inflammatory proteins. Clinically, this neuroimmune connection was originally suggested by the observation that NSAIDs used for extended periods have been reported to reduce the risk of developing Alzheimer's disease.[355,356] In an opinion piece published recently by Itzhaki and Wozniak,[357] they suggested that peripheral infection, and probably other types of stress, lead to entry of cytokines into the brain causing reactivation of latent herpes simplex virus 1 infection, which causes inflammation- and immune-dependent mechanisms, resulting in neuronal damage. Although the immune system clearly contributes to the pathophysiology of Alzheimer's disease, its aetiological role needs further clarification.

4. Therapeutic Implications

On the basis of the evidence described in section 3, a number of treatment trials applying immunomodulating agents were carried out in patients with schizophrenia. Müller et al.[358] have recently used celecoxib, a selective cyclo-oxygenase-2 inhibitor, as an add-on to the antipsychotic risperidone. Adding celecoxib enhanced the therapeutic effects of risperidone significantly. A nonimmunological contribution to the therapeutic effect of celecoxib mediated by NMDA receptors is also mentioned by the authors. Azathioprine has also been studied in schizophrenia with some positive effects;[359] however, the experience with this drug is very limited in this indication. Antipsychotics by themselves also influence immune response in so far as second-generation or atypical agents such as clozapine, risperidone and olanzapine have been shown to have immunomodulatory effects.[150,360]

A recently published paper by Zhang et al.[361] reported that both risperidone and haloperidol may at least partially normalise abnormal immune alterations such as elevated serum IL-2 concentrations in schizophrenic patients. They also observed a possible predictive value of some immune parameters, demonstrating that patients with low concentrations of serum IL-2 or IL-8 at baseline showed greater improvement after treatment.[361] Although the authors mention several limitations of their study and, even more significantly, emphasise that the exact mechanism underlying the effects of antipsychotic drugs on the cytokine levels in schizophrenic patients is unknown, they maintain the opinion that further investigations on immune parameters, either as predictive values or as additional outcome variables, seem to be an interesting future strategy.

Different immunotherapies have been used in autism, including transfer factor, pentoxifylline, intravenous immunoglobulin and corticosteroids.[362] One of the first reports on these kinds of therapies was made by Fudenberg et al.[363] who prescribed immunostimulators such as transfer factor and isoprinosine to eight autistic children, obtaining some improvement in six of them. Therapy with pentoxifylline was also reported to be successful to a certain extent in about one-third of all treated patients. However, none of these studies included parallel control groups or placebo groups and, additionally, several studies did not even use standard behavioural measures to evaluate the severity of autistic symptoms.[364] Some mechanisms discussed for immune-based treatment in autism focus on immunomodulatory effects of cytokines such as TNFα, correction of antibody deficiency and counteraction of autoantibodies. In this context intravenous immunoglobulin therapy was used in autistic children by the group of Gupta et al.,[173] who noted clinical improvement in some patients. However, autistic features reappeared after discontinuation of

intravenous immunoglobulin in a few children. Other groups could not or only partly confirm these results.[365,366] Treatment with corticosteroids has been reported in single cases and in a small open-label trial. It appeared to be successful, especially in patients with clinical and laboratory data supporting an autoimmune process as aetiological hypothesis for the disease.[367,368] Although there have been some positive effects of immunotherapies in children with autism, it has not been possible to develop really convincing therapeutic strategies based on any kind of immunomodulation. Future research in this field needs to consider methodological aspects such as diagnostic subgroups, standardised outcome measures and control group designs. Furthermore, clinical trials with immunotherapies in autism should be hypothesis driven and focus on identifying parameters correlating clinical features with biological alterations.

Antidepressants modulate different neurotransmitter systems, which consequently cause direct and/or indirect effects on the immune system.[369] Furthermore, antidepressants affect the HPA axis and especially CRF release and, in turn, immune functions.[370,371] Different classes of antidepressants are known to inhibit the synthesis and release of proinflammatory cytokines *in vitro*.[372] Lastly, it has been reported that the concentration of the anti-inflammatory cytokine IL-10 as well as the level of IL-1 receptor antagonist are increased after treatment with different antidepressants.[373,374] These effects appear to contribute to the reduction of the proposed adverse impact of proinflammatory cytokines in the development of depression. Nevertheless, it still remains to be elucidated whether the immune effects of antidepressants are a side effect or a significant part of their clinical activity. To the best of the author's knowledge, immunomodulators have not yet been formally studied in the treatment of mood disorders, but clinical trials are planned in the future.

In the context of neuronal damage the important role of neurotrophins in the survival and development of neurons, and in the establishment and maintenance of synapses during early life stages and in adults should be mentioned.[375-377] Alterations of neurotrophins at the protein and gene level, for example of brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) or nerve growth factor, have been found in animal models of schizophrenia and depression. These findings support the hypothesis that neurotrophins might contribute to the morphological and neurobiochemical brain abnormalities reported at least in subgroups of both disorders.[378-381] Furthermore, different immune cell subpopulations express neurotrophin receptors and produce neurotrophins, particularly BDNF and NT3.[382,383] Wank[383] hypothesised that microbial factors might be involved in the pathogenesis of schizophrenia, bipolar disorder and autism and, consequently, treatment with the patient's own *in vitro* activated immune cells (adoptive immunotherapy) might support psychopharmacological treatment. The astonishing quick and positive response in three patients after adoptive immunotherapy was interpreted as "restoration of distorted cytokine levels, especially neurotrophins like BDNF and NT3, resuming the crosstalk between immune system and CNS". Some recently published data suggest that neurotrophin-induced trophic responses in neuronal connectivity and plasticity may be involved in the mechanism of action of different psychopharmacological drugs, particularly antidepressants and mood stabilisers.[381,384,385]

Omega-3 fatty acids represent another group of biological compounds that are believed to play a potential role in the pathophysiology of different neuropsychiatric disorders, especially in major depression.[249,386] The involved mechanisms seem to be due to alterations in the metabolism of fatty acids and to altered composition of phospholipids in serum and cell membranes which might be closely linked to the activation of the inflammatory response system and, in particular, may be related to increased levels of proinflammatory cytokines.[387,388] Furthermore, recent research in the field of affective disorders has provided some hints that omega-3 fatty acids may also offer a new therapeutic approach by an antidepressant and/or a mood-stabilising effect.[389-391] Animal studies showed that

dietary supplementation of omega-3 fatty acids normalised levels of BDNF and reduced oxidative damage. Consequently, theses results indicated a beneficial effect in maintaining neuronal function and plasticity in rats after traumatic brain injury.[392]

To date, immunological therapy has not been applied in anxiety disorders, although anxiolytic treatment with benzodiazepines might also influence the immune system.[393]

In patients with alcohol dependence, implications for immune-related therapy might be relevant for concomitant somatic diseases such as ALD. Although some alcohol-induced mechanisms in ALD concerning the innate immune system are better understood now, there are still critical questions that remain unanswered.[394] One possible future target for therapeutic intervention in ALD might be found in blocking monocytic activation and proinflammatory cytokine production.[322] Despite the fact that immune processes do not play a role in the aetiopathogenesis of drug addiction, a new therapeutic approach based on immune mechanisms of vaccination is currently being investigated in initial clinical trials.[395] Further clinical results are necessary to evaluate the success of this method.

According to the definition of organic brain disorders, therapeutic interventions primarily focus on the underlying somatic disease. In this context, different immunosuppressive and/or immunomodulating agents are well established methods for treating the neuropsychiatric sequelae of immune or autoimmune disorders such as AIDS, SLE, primary vasculitis, etc.

From an immunological point of view the treatment of Alzheimer's disease offers two primary approaches, both aiming at prevention and clearance of β-amyloid deposits:

- stimulating the host immune system to recognise and attack β-amyloid; and
- providing passive immunisation, intended to cause a forced clearance as well as to prevent the deposition of β-amyloid.

In accordance with these concepts, strategies of active/passive immunisation are currently under investigation for Alzheimer's disease.[346] Although preclinical studies of active vaccination provided very convincing results,[396,397] first experiences in humans have revealed serious clinical complications, namely aseptic meningoencephalitis in a small number of patients.[398,399] Despite this setback, the results of autopsy and antibody analyses have provided evidence of potential effectiveness by showing whole areas of the cerebral cortex without β-amyloid deposits.[400,401] As a result, other immunisation approaches will soon be tested in clinical trials.[399,402-404]

It has also been claimed that NSAIDs have positive effects with regard to the onset and the progression of Alzheimer's disease.[405-407] As the chronic inflammatory reaction initiated by β-amyloid deposits in the brain stimulates neurodegeneration, future studies with improved NSAIDs, which selectively decrease the inadequate activation of glial cells without influencing peripheral organs, are warranted.[348,408]

5. Conclusion and Outlook

A large body of evidence indicates an involvement of the immune system in the aetiopathogenesis of schizophrenia, autism and affective disorders, at least in subgroups of patients. Given the comprehensive network of hypotheses that has been put forward, future research should not be restricted to alterations in single systems; more attention should be drawn to approaches linking two or more targets. In this context, interactions between the cytokine – the neurotransmitter – and the hormone systems clearly deserve more attention. This could be achieved by sophisticated disease models exploring possible connections on a molecular basis as well as in clinical respects by using, for example, advanced imaging techniques, neuropsychological characterisation and comprehensive diagnosis, including information about the course of the disorder, details about treatment response, etc. As large numbers of patients are necessary to allow relevant subgroup analyses, multicentre protocols may be a helpful strategy.

Immunological research is still very much in its infancy in anxiety disorders, and the link between

immunological alteration related to stress and pathological anxiety related to the immune system has yet to be established.

The involvement of the immune system in Alzheimer's disease is no longer disputed, although the significance of these findings and their potential relevance for the development of treatment approaches needs further investigation.

As we begin to unravel the crosstalk between the CNS and the immune system, the fields of neurobiology, immunology and endocrinology have found increasing common ground. Future research needs to draw on collaborative efforts of the relevant disciplines in order to shed more light on the impact of immunological alterations on the aetiopathogenesis of psychiatric disorders. In addition, the potential therapeutic implications of these interactions need to be elucidated by clinical trials that follow rigorous scientific standards.

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