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Current concepts of autoantibodies in mood disorders

Niels Hansen and Berend Malchow

Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany.

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Corresponding author:
Niels Hansen; Email: niels.hansen@med.uni-goettingen.de

Abstract

Research into the causes of mood disorders has been going on for decades. However, most of the hypotheses put forward have been insufficiently substantiated by living biomarkers. Much research is therefore being conducted into biomarkers that help us better assess the diagnosis and course of mood disorders. Neural autoantibodies are one such biomarker potentially appearing in a subgroup of mood disorders. The aim of this narrative review is to describe the spectrum of autoantibodies in mood disorders while substantiating their prevalence, about which there is very inconsistent evidence. In addition, we discuss autoantibodies in the context of systemic autoimmune diseases associated with depressive symptoms. The pathogenicity of individual autoantibodies has occasionally been demonstrated in animal models, and there is evidence that the severity of depressive symptoms correlates with certain autoantibodies. Possible models of autoimmunity are also explained, such as involvement of the B-cell system, the complement system, and systemic inflammation in autoimmune processes. Nevertheless, note that the mere presence of autoantibodies does not justify the assumption of an autoimmune genesis, as more evidence is needed. The aim of this review is to describe the concepts behind targeting autoantibodies in mood disorders.

1. Linking autoimmunity and mood disorders

The evidence in recent years has been growing (Yirmia et al., 2015; Rege & Hodgkinson, 2013; León-Caballero et al., 2015; Leite Dantas et al., 2021) that autoimmune processes play an important role in affective disorders (Arnaud et al., 2022, Sarno et al., 2021; Siegmann et al., 2018; Yirmiya et al., 2015; Maes et al., 1993) at least in a subset of patients. Autoimmunity is an immunological term meaning that the body and parts of it such as the central nervous system show an immune reaction against the body's own antigens through the loss of self-tolerance. The loss of immune tolerance involves so-called B and T cells and their interaction; the passage of immune cells from the blood into the brain is an essential aspect of the initiation of autoimmunity (Ramanathan et al., 2023). Mood disorders are a heterogeneous psychiatric disease entity that encompasses cardinal features such as a loss of drive, mood disturbances, the inability to experience joy, and a loss of interest. Mood disorders are widespread and among the most common mental impairments; they therefore constitute an important disease entity to investigate to improve diagnosis and treatment. An important goal when studying autoantibody-mediated mood disorders is to optimize phenotype fingerprinting to identify subgroups so that affected patients can benefit from individualized medicine such as specific immunotherapy. Immunotherapy is a treatment mode aiming to inhibit or suppress the immune system's functions; it can be applied to reduce or weaken these immune responses, particularly in the case of excessive immune responses in autoimmune processes. Autoantibodies are small molecules and a manifestation of autoimmunity, as they are formed after the breakdown of self-tolerance and attack the body's own antigens. A distinction is made between different types of autoantibodies that can affect neuronal structures but also other cell surfaces or intracellular structures. Autoantibodies form immune complexes with their target antigens. These immune complexes activate microglia, which release cytokines that can trigger neuronal dysfunction (Schilling et al., 2021; Nestor et al., 2016). Various autoantibody subgroups potentially associated with depressive symptoms are described in Section 2. In Section 2, we focus on neural autoantibody subgroups in terms of their prevalence (2.1), on a detailed description of the spectrum of neural autoantibodies (2.2), on the psychopathological characterization of patients with neural autoantibodies (2.3), phenotypes (2.4) and mechanisms (2.5) of autoantibody-associated mood disorders.

2. Neural autoantibodies associated with mood disorders

2.1. Prevalence of neural autoantibodies in mood disorders

Neuronal and glial, also termed neural autoantibodies, are less frequently suspected in mood disorders than in psychotic disorders. However, they form a relevant group among mental illnesses alongside cognitive and psychotic disorders, in which a certain patient subgroup

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presents neural autoantibodies (Luykx et al., 2024; Hansen et al., 2024). Neuronal autoantibodies can be divided into several groups, e.g. autoantibodies against ion channels such as anti-N-Methyl-D-aspartate receptor (NMDAR) autoantibodies, against metabotropic receptors such as anti-metabotropic glutamate receptors type 5 (mGluR5) autoantibodies, against receptor-associated regulatory proteins such as anti-contactin-associated protein-like 2 (CASPR2) autoantibodies, and against intracellular antigens such as anti-Hu autoantibodies. There are various detection methods to search for autoantibodies, i.e., cell-based assays with very high sensitivity and specificity (Kerstens et al., 2024), or indirect immunohistochemistry to assess initial autoantibody detection in cell-based assays or immunoblots. Other testing methods include immunoblots with recombinant target antigens in test strips or in combination with applying cell-based assays accompanied by indirect immunohistochemistry to achieve a higher positive predictive value. There are further methods to detect membrane surface autoantibodies such as live cell immunoassays. Live cell immunoassays are, for example, cell cultures of living hippocampal neurons in which the sera containing patient autoantibodies are incubated with the cultures and later visualized by fluorescently labeled immunoglobulin G (IgG) antibodies. A large study of patients with affective disorders demonstrated that a total of 23% (n = 62/267) of the cohort had positive autoantibodies in their serum (Daguano Gastaldi et al., 2023). Twelve percent of these patients with affective disorders had NMDAR antibodies (Daguano Gastaldi et al., 2023) (Table 1). The second most frequently reported autoantibodies were antibodies against Rho GTPase activating protein 26 (ARHGAP26) and Amphiphysin (6 of 264 patients, 2%) (Table 1) (Daguano Gastaldi et al., 2023). An enormous number of autoantibody types (n = 49) were examined in their study. Ultimately, however, the significance of these autoantibodies remains unclear, as they were also detectable in 400 of 2748 (15%) of healthy controls. This means that neural autoantibodies are present in the serum of healthy as well as sick people. It is unclear whether these neural autoantibodies are pathogenically relevant in patients and are partly responsible for the development of depressive symptoms. It is therefore important to identify biomarkers that verify autoimmune inflammation. Criteria for autoimmune psychiatric syndromes, including depressive symptoms, have been published (Hansen et al., 2020) that report on additional diagnostic examinations of the cerebrospinal fluid and imaging to confirm such autoimmune inflammation. Clinical items such as a poor response to standard antidepressants have also been postulated to make an autoimmune genesis of depressive symptoms potentially indicating an inflammatory immune response. Another study demonstrated that the prevalence of neuronal autoantibodies did not differ between patients with depressive symptoms and anxiety and controls. That study (Table 1) examined blood samples from 819 patients with depression or anxiety, and blood samples from 912 patients with these diseases in remission, as well as 492 controls without these disorders d (Zong et al., 2020). Novel neuronal surface antibodies were detected in a total of 50 (2.2%) patients, but the groups did not differ significantly in the presence of neuronal antibodies in plasma samples (22/819 vs. 18/920 and 11/492). However, the authors found more prevalent autoantibodies in depressive patients than in controls when applying the live cell immunoassay method as described above. Significant numbers of neuronal autoantibodies were detected in 7/819 (0.85%) of depressed and anxious patients via live cell immunoassay compared to remitted patients (0/920, 0%) and controls (1/492, 0.2%) (Zong et al., 2020). In patients with affective disorders, therefore, a specific live cell immunoassay test can serve to filter out those patients whose disease may have an autoimmune genesis, as antibodies play a key role in a probable autoimmune origin according to current guidelines for classifying affective psychosis (Pollak et al., 2020) or depressive syndrome (Hansen et al., 2020). In a heterogeneous cohort of patients with various psychiatric disorders, however, we identified a subgroup with affective disorders in whom we detected neural autoantibodies in 25% of CSF samples and 36% of serum samples (Hansen et al., 2022). One study showed that serum autoantibodies are detected similarly often in psychiatric patients as a whole and in those with affective disorders (26%) (Saether et al., 2019). The prevalence of neural autoantibodies in mood disorders varies widely, ranging from 0.85% to 36% in blood samples when including several types of neural autoantibodies, but they are much less prevalent when considering individual autoantibody subtypes. This considerable variance is due to various factors, i.e., different studies applying diverging test methods, the varied sensitivity and specificity of the immunoblot or cell-based assays, or of the criteria assessing the positivity of autoantibodies, as well as different study populations presenting heterogeneous phenotypes. Note that the medium plays a major role in determining autoantibodies, as autoantibodies in serum are less diagnostically relevant, as CSF autoantibodies are among the criteria defining autoimmune based depressive syndrome (Hansen et al., 2020). Autoantibodies detectable in the CSF are also an indirect indication of inflammation in the CNS. Furthermore, the mere presence of serum autoantibodies is not per se disease-defining, and autoimmune-based criteria must be applied to classify the autoimmune genesis of psychiatric disorders (Hansen et al., 2022). Therefore, to determine an autoimmune pathogenesis, patients presenting neural autoantibodies should always be diagnosed by relying on additional criteria.

2.2. Spectrum of neural autoantibodies associated with mood disorders

Neural autoantibodies have been studied in cohorts of patients with depression (Sørensen et al., 2023) to determine the prevalence of neural autoantibodies. It is important to note that these are not depressive symptoms in an autoimmune encephalitis context, but rather depressive disorders. A recent study reported that serum autoantibodies to NMDAR were detected in 0.9% of depressed patients and in 0% of controls via a cell-based assay, whereas GAD65 serum autoantibodies were found in 0% of depressed patients and in 0.9% of control patients via a cell-based assay (Sørensen et al., 2023) (Table 1). However, these autoantibodies were not verified in tissue-based assays. Note that their study investigated seven autoantibody types in serum and CSF probes [0% anti-Leucine-rich Glioma Inactivated 1 (LGI1), 0% anti-CASPR2, 0% anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1/2 (AMPAR1/2) and 0% anti-γ-aminobutyric acid B1/2 receptor (GABABR B1/B2) antibodies] (Sorensen et al., 2023). In another study, we detected mood disorders associated with neural autoantibodies in 8 of 12 (67%) patients with autoantibodies in the cerebrospinal fluid. These prevalence data are not representative because they were examined in a very small cohort of depressive patients that included patients with depressive disorders who had undergone a lumbar puncture test for organic etiology. This is an example of how prevalence numbers can differ considerably from the prevalence figures mentioned in the paragraph above. In contrast, affective symptoms were observed

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Table 1. Spectrum and prevalence of neural autoantibodies in mood disorders

Abs type	Number of Abs+ patients/all patients, %	CSF	Serum	Detection method	Specification of mood disorder	Reference
Alpha7 nicotinic acetylcholine	Unclear, 256	–	+	ELISA and immunostaining	Bipolar disorder	Darrau et al., 2024
Amphiphysin	6/264, 2.27	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
AP3B2	2/267, 0.75	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
ARHGAP26	6/264, 2.27	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
Astrocytic pattern	1/1	+	–	Indirect immunofluorescence on unfixed murine brain sections	Depressive disorder	Endres et al., 2022a
Bergmann glia	1/1		+	Indirect immunofluorescence on unfixed murine brain sections	Treatment resistant depression	Endres et al., 2023
CASPR2	3/264, 1.14	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
CASPR2	1/920, 0.1	–	+	IHC and fixed CBA	Depressive disorder in remission	Zong et al., 2020
CASPR2	1/819, 0.1	–	+	IHC and live CBA	Depressive disorder	Zong et al., 2020
CASPR2	5/920, 0.5	–	+	IHC and live CBA	Depressive disorder in remission	Zong et al., 2020
CASPR2	2/492, 0.4	–	+	IHC and live CBA	Depressive disorder in remission	Zong et al., 2020
GABAAR	2/819, 0.2	–	+	IHC and live CBA	Depressive disorder	Zong et al., 2020
GABAAR	1/920, 0.1	–	+	IHC and live CBA	Depressive disorder in remission	Zong et al., 2020
GAD65	1/106, 0.9	–	+	CBA	Healthy controls	Sørensen et al., 2023
GAD65	1/819, 0.1	–	+	Positive IHC and fixed CBA	Depressive disorder, current	Zong et al., 2020
GFAP	4/267, 1.5	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
Homer 3	1/267, 0.37	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
KCNA1	2/267, 0.75	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
KCNA2	5/267, 1.87	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
KCNA2	1/112, 0.89	–	+	Anti-neural IgG IFT	Depressive disorder	Hansen et al., 2022
LGI1	1/920, 0.1	–	+	IHC and live CBA	Depressive disorder in remission	Zong et al., 2020
Ma2	1/112, 0.89	+	+	Immunblot (Euroline)	Bipolar disorder	Hansen et al., 2022
Ma2	1/41, 2.4	+	+	Immunblot (Euroline)	Bipolar disorder	Hansen et al., 2024
Neuropil	1/112	+	+	Anti-neural IgG IFT	Depressive disorder	Hansen et al., 2022
NMDAR	1/106, 0.9	–	+	CBA	Recent onset depression	Sørensen et al., 2023
NMDAR	1/112, 0.89	+	+	Anti-neural IgG IFT	Depressive disorder	Hansen et al., 2022
NMDAR	1/41	+	+	Anti-neural IgG IFT	Depressive disorder	Hansen et al., 2024

(*Continued*)

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Table 1. (*Continued*)

Abs type	Number of Abs+ patients/all patients, %	CSF	Serum	Detection method	Specification of mood disorder	Reference
NMDAR1	31/264, 11.74	–	+	BIOCHIP mosaics	Affective disorders	Daguano Gastaldi et al., 2023
Novel neuronal Abs	7/819, 0.9	–	+	Positive by IHC and staining on live neurons	Depressive disorder	Zong et al., 2020
Novel neuronal Abs	7/819, 0.9	–	+	Positive by IHC and staining on live neurons	Controls	Zong et al., 2020
Recoverin	1/112	–	+	Immunblot (Euroline)	Depressive disorder	Hansen et al., 2022
Recoverin	1/41	+	+	Immunblot (Euroline)	Depressive disorder	Hansen et al., 2024
Yo	2/112, 1.78	+	+	Immunblot (Euroline)	Depressive disorder	Hansen et al., 2022
Yo	3/41, 2.4	+	+	Immunblot (Euroline)	Depressive disorder	Hansen et al., 2024

Abbreviations: Abs+ = positive, AP3B2 = adaptor related protein complex 3 subunit beta 2, ARHGAP26 = RhoA GTPase-activating protein 26, ELISA = enzyme linked immunosorbent assay, GAD65 = glutamic acid decarboxylase 65, GFAP = glial fibrillary acid protein, IFT = immunofluorescence test, IgG = immunoglobulin G, KCNA1 = potassium voltage-gated channel subfamily A member 1, KCNA2 = potassium voltage-gated channel subfamily A member 2, NMDAR = N-methyl-D-aspartate receptor.

in 13 of 25 (52%) antibody-positive patients with serum autoantibodies (Hansen et al., 2022). The types of autoantibodies were Ma2, Yo, Recoverin, potassium voltage-gated channel subfamily A member 2 (KCNA2), NMDAR and neuropil in the serum in affective disorders, while Ma2 and neuropil autoantibodies were found in the CSF in affective disorders (Table 1) (Hansen et al., 2022). Mood disorders were diagnosed more frequently in psychiatric patients without neural autoantibodies than in those with them (Hansen et al., 2022). These studies show that neural autoantibodies can be detected more frequently than expected in affective disorders provided one is looking out for them. Psychotic disorders and cognitive disorders are not only associated with neural autoantibodies. Cerebrospinal fluid antibodies such as the paraneoplastic Ma2 antibodies or unknown target antigens of neuropil antibodies exist in depressive disorders. However, the vast majority of depressed patients reveal no neural autoantibodies. There is a working group that has repeatedly reported novel autoantibodies in association with depression, such as autoantibodies against Bergmann glia (Endres et al., 2023), autoantibodies with an anti-astrocytic pattern in CSF (Endres et al., 2022a) (Table 1), antibodies against myelin (Endres et al., 2024) and against central nervous system IgG in 22 of 119 patients (2022b) (Table 1). These results indicate that it is important to screen patients with depressive syndromes by using new methods such as mass spectrometry, protein microarrays (Ehtewish et al., 2013), yeast-based rapid extracellular antigen characterization (Talucci and Maric, 2024) and phage immunoprecipitation sequencing (Gilligan et al., 2024) to better identify high throughput capacity in the future. Autoantibodies against acethlcholine receptors in the blood have also been investigated, as there is evidence of cholinergic regulation of mood (Sitaram et al., 1982). The presence and role of peripheral AAbs to the α7-nicotinic acetylcholine receptor (nAChR) in inflammatory subgroups of psychiatric patients with bipolar disorder or schizophrenia and healthy controls were therefore investigated: rarer autoantibodies such as alpha7 nicotinic acetylcholine antibodies in serum were identified more frequently and were more optically dense in their immunostaining in bipolar patients (Darrau et al., 2024) than in controls (Table 1). In particular, this study identified a subgroup with high levels of acetylcholine receptor antibodies, an inflammatory profile, and severe psychiatric symptoms (Darrau et al., 2024). Both autoantibodies against nAChR) are found in patients with affective disorders, as well as other autoantibodies with potential influence on the GABAergic inhibitory system in the CNS, e.g., GAD autoantibodies. Higher titers of GAD antibodies are often found in patients suffering acute depressive episodes, for example, than in patients already in remission (Ferensztajn-Rochowiak et al. 2019). These findings suggest that a merely acute depressive episode might be associated with GAD autoantibody-mediated inflammation. The spectrum of autoantibodies that can be potentially associated with depressive symptoms in connection with a depressive illness is therefore very diverse, but it is partly attributable to changes in cholinergic or GABAergic mechanisms.

2.3. Psychopathology of mood disorders associated with neural autoantibodies

To determine whether a particular clinical phenotype is characteristic of autoantibody-associated specific psychiatric syndromes such as depressive syndrome, we conducted a study with detailed examination of psychopathology. A depressive syndrome incorporates several depressive symptoms constituting a syndrome occurring in patients with a depressive episode. According to AMDP, it can be characterized by, for example, rumination, feeling of loss of feeling, loss of vitality, depressed mood, hopelessness or feelings of inadequacy (Broome et al., 2017), to name a few symptoms, while depressive symptoms are mainly those symptoms belonging to a depressed mood, loss of drive or loss of pleasure. We examined the psychopathology in 35 of 154 psychiatric patients with autoantibodies via two measurement methods: the more traditional categorical description of psychopathology according to the AMDP (Working Group for Methodology and Documentation in Psychiatry), and the more dimensional psychopathology classification via HiTOP (hierarchical taxonomy of psychopathology)] in a study (Grenzer et al., 2022). Researchers found that patients with serum autoantibodies presented a blunted affect less

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often and affective rigidity assessed by the AMDP system compared with psychiatric patients without proof of serum autoantibodies (Grenzer et al., 2022). Blunted affect, according to the AMDP system, refers to a reduced spectrum of affective states, whereas the term affective rigidity describes a reduced capacity for emotion modulation (Broome et al., 2017). Thus, in autoantibody-positive psychiatric patients, the capacity for modifying emotion and the spectrum of affect are less frequently impaired than in autoantibody-negative psychiatric patients, suggesting that the spectrum and modulation capacity of affect may be preserved in autoantibody-positive patients. This could mean that autoantibody-positive patients experience less affective stress. Surprisingly, however, loss of vitality was more common in patients with CSF autoantibodies than in those without them (also according to the AMDP system) (Grenzer et al., 2022). A loss of vitality refers to reduced perception of strength, power and a lower energy level according to AMDP (Broome et al., 2017). Applying the HiTOP classification revealed no relevant differences in antibody-positive and negative patients (Grenzer et al., 2022). Ultimately, the phenotype of patients with neural autoantibodies is thus characterized by less affective distress, but by a significant loss of vitality. In another study, we investigated the question of how frequently a depressive syndrome is associated with psychiatric autoimmune encephalitis (Hansen et al., 2023). In a psychiatric autoimmune encephalitis diagnosis based on moderate evidence (possible psychiatric autoimmune encephalitis), a depressive syndrome was the second most common (65%) after a psycho-organic syndrome. In contrast, the depressive syndrome corresponded roughly to the paranoid-hallucinatory syndrome in patients with possible psychiatric autoimmune encephalitis (Hansen et al., 2023). The most common autoantibody, namely NMDAR, is also frequently associated with depressive symptoms (Arinuma et al., 2008; Al-Diwani et al., 2019) and coexists with psychotic symptoms (Al-Diwani et al., 2019). NMDAR autoantibodies are probably moderately associated with depressive symptoms, as shown in a study by Lapteva et al. (2006), as this association persisted even after correcting for the influence of cognitive variables. There are thus indications of a direct relationship between the development of depressive symptoms and NMDAR autoantibodies.

2.4. Phenotypes of autoantibody-associated mood disorders

Summarizing the psychopathology in autoantibody-associated mood disorders, we maintain that antibody-positive patients more often sense a loss of energy but continue to reveal their full spectrum of affects and continue exhibiting modifiable affects. Depressive syndrome is second only to psycho-organic syndrome in autoantibody-associated mood disorders. The most common neural membrane surface autoantibody is also found in mood disorders and is closely associated with depressive symptoms independent of cognitive impairment with NMDAR.

2.5. Potential mechanisms of autoantibody-associated mood disorders

Several pathogenic mechanisms have been reported and identified in the context of neural autoantibody-associated diseases. To understand these mechanisms, examples of basic pathogenic mechanisms are briefly outlined in this section. An important mechanism already identified in animal models and in cell cultures is the internalization of receptors on the membrane surface after membrane surface autoantibodies have docked to the receptors on the membrane surface. Evidence from NMDAR autoantibodies indicates that after the formation of the antigen-antibody complex with NMDAR on the membrane surface, these receptors become internalized (Moscato et al., 2014. Hughes et al., 2010). As a result, if fewer NMDARs are present on the membrane surface, information transmission between the synapses becomes irregular, which can trigger symptoms. There are also serotonergic and noradrenergic receptors on the synaptic surface that frequently interact with NMDAR, making an influence on depressive symptoms also conceivable. Internalization after blocking a receptor's antibodies is conceivable not only for NMDAR, but also for mGluR5 receptors and the corresponding antibodies (Spatola et al., 2018). Another mechanism is a synergistic aspect of antibody action on the acetylcholine receptor with acetylcholine receptor autoantibodies and simultaneous complement activation, demonstrated in vitro (Rose et al., 2022). Thus, a secondary strong complement activation in acetylcholine receptor autoantibodies is conceivable as a mechanism for the expression of the inhibition of cholinergic transmission and its effect on the development of depressive symptoms, but this has not yet been demonstrated.

3. Systemic autoantibodies and mood disorders

In the following section, we report on systemic autoantibodies as part of existing autoimmune diseases associated with affective symptoms that may affect CNS function and suggest CNS involvement. Autoantibodies that are systemic are those that can be measured in the blood and occur in autoimmune diseases that affect several parts of the body. We do not describe the occurrence of autoantibodies in systemic autoimmune diseases in detail here, but these autoantibodies also play an important role in our topic, so they are also described briefly. Systemic autoantibodies are found in the blood serum in association with various autoimmune diseases. Depression coexists more frequently in patients with autoimmune diseases than in control subjects (Iseme et al., 2014). We focus on different autoantibodies in this section on systemic autoantibodies such as anti-endothelial cells, anti-gliadin, anti-16alpha-hydroxyestrone-albumin complex, anti-dsDNA, anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH), anti-cardiolipin and anti-thyroid autoantibodies. There is also evidence that specific autoimmune disease such as celiac disease that present serum anti-gliadin antibodies are associated with higher rates of depression than in control subjects (5 vs. 2.5%) (Ruuskanen et al., 2010). Much more frequent are anti-nuclear antibody titers in blood associated with depression, which are in themselves non-specific, in 16% of subjects (Iseme et al., 2015). There is therefore a lot of evidence of autoimmune diseases caused by autoantibodies that can also be associated with depressive symptoms. However, lupus erythematosus in particular is a systemic autoimmune disease in which autoantibodies are frequently reported. In addition, lupus erythematosus is an autoimmune disease that can also involve the CNS. In patients with lupus erythematosus and CNS involvement, it is conceivable that autoantibodies may be associated with affective symptoms. An association between an affective syndrome in patients with lupus erythematosus and CNS involvement is briefly reported in the form of recent studies in the section below

3.1. Lupus erythematosus and depression

Lupus erythematosus is a systemic disease characterized by a dysfunction of the immune system presenting a variety of clinical features such as cardiac, neuropsychiatric or dermatological symptoms (Yu et al., 2021). There are autoantibodies to endothelial

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cells in lupus erythematosus in conjunction with depression, which play an important role due to their involvement in blood-brain barrier integrity (Iseme et al., 2014). Autoantibodies also potentially associated with depression are anti-dsDNA antibodies in blood samples from lupus erythematosus patients (Iseme et al., 2014). Other rarer serum autoantibodies have proven to be associated with depressive symptoms in lupus erythematosus such as autoantibodies against 16alpha-hydroxyestrone-albumin complex (Khan et al., 2019) and anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Delunardo et al., 2016). Furthermore, the depression level measured via CES-D (Center for Epidemiologic Studies Depression Scale, CES-D) was observed to be independently associated with anti-P ribosomal autoantibody serum level (Chessa et al., 2023). There is therefore a lot of evidence of autoimmune diseases and in particular lupus erythematosus in which autoantibodies can have an important influence on the development and course of the disease that can also be associated with depressive symptoms.

3.2. Cardiolipin autoantibodies and depression

There are various other autoantibodies against antigens that are not primarily associated with the nervous system, but which can also influence CNS functions due to various mechanisms.

Inflammatory processes are often suspected in the pathogenesis of depression. Autoantibodies against cardiolipin are a promising inflammatory biomarker, as cardiolipin as a phospholipid plays a role in the dysregulation of CNS functions (Falabella et al., 2021). Other human autoantibodies include antibodies against cardiolipin, which appears to be relevant in depression. Plasma levels of cardiolipin antibodies are higher in patients with major depressive disorder than in controls (Costa et al., 2022). These antibodies also correlate with the HAM-D17 depression scale score (Costa et al., 2022). These findings show that these antibodies are relevantly associated with depressive symptoms and therefore make an autoimmune genesis of depressive symptoms likely.

3.3. Thyroid autoantibodies and depression

There is a form of autoimmunity directed against thyroid tissue that is caused by autoantibodies targeting thyroid hormone enzymes. In addition, thyroid autoantibodies such as TPO autoantibodies are also important for the validation of autoantibodies in connection with depressive symptoms, as they correlate with depression in adult women and in young adults, as a recently published study demonstrated (Ma et al., 2024). As summarized in a review, thyroid autoantibodies may predispose individuals for major depressive disorder (Iseme et al., 2014). Thus, there are other human autoantibodies against endocrine gland proteins potentially associated with depressive symptoms that might be involved in the pathophysiology of depressive symptoms.

4. Animal models testing autoantibody transfer from humans to animals

Animal models are particularly suitable for investigating the pathogenicity of certain autoantibodies through transfer models from humans to animals. By transferring the autoantibodies in the animal model, both the development of depression-like symptoms and as well as the pathomechanisms of depressive symptoms can be observed. Below we describe two different antibody classes in animal models, namely anti-ribosomal autoantibodies and anti-NMDAR autoantibodies, each of which is briefly outlined in an animal model entailing effects on depressive-like behavior.

4.1. Anti-ribosomal autoantibodies and an animal model of depression-like behavior

An animal model yielded evidence that the intracerebroventricular infusion of anti-ribosomal antibodies can induce depression (Katzav et al., 2014; Katzav et al., 2007). Anti-ribosomal autoantibodies are antibodies that are essentially directed against carboxy 22 amino acids of PO, P1 and P2 ribosomal phosphoproteins (Shoenfeld, 2007). These antibody-antigen complexes are capable of penetrating living cells and triggering apoptotic processes (Shoenfeld, 2007). These autoantibodies can also lead to the failure of cytokine secretion. There is a general correlation between autoantibodies and disease activity (Shoenfeld, 2007). A humanized mouse model refers to when anti-ribosomal autoantibodies were derived from patients with lupus erythematosus and transferred to a mouse via intracerebroventricular transfer. Anti-ribosomal antibodies are frequently detected as a neuropsychiatric manifestation in lupus erythematosus. A mouse model demonstrated that intracerebroventricular injections with human anti-P ribosomal autoantibodies as mentioned above led to depressive-like behavior, which was reversed by applying fluoxetine (Katzav et al., 2008). However, the olfactory dysfunction after administering the fluoxetine, which had developed in the mice after transfer of the autoantibodies, was not reversible (Katzav et al., 2008). It could thus be shown that anti-ribosomal autoantibodies can contribute to the development of depression in animal models.

4.2. Anti-NMDAR autoantibodies and animal model of depressive-like behavior

It has also been demonstrated for NMDAR autoantibodies in an animal model that they can play an important role in the pathogenesis of depressive symptoms. In a humanized mouse model of NMDAR encephalitis demonstrated a disrupted blood-brain barrier, and NMDAR autoantibodies were produced, leading to depressive-like behavior (Pan et al., 2021). These studies thus prove that human antibodies such as anti-P ribosomal antibodies and NMDAR antibodies can induce depressive-like symptoms and thus fulfill an essential condition for defining an autoimmune disease.

5. Concepts of autoimmunity in mood disorders

It could thus be shown that both neural autoantibodies and systemic autoantibodies are reported in the context of depressive symptoms. Ultimately, however, this is initially an association and not a causal link between the autoantibodies and the development of depressive symptoms. However, we were able to show via the animal models that at least anti-NMDAR and anti-ribosomal autoantibodies can induce depressive symptoms after they have been transferred from humans to animals. This therefore fulfills part of the requirements for proving autoimmunity. In addition to this mechanistic evidence for the inducibility of depressive-like behavior, however, there are also other concepts for the development of autoimmunity, which we will discuss below. The risk of mood disorders is increased in conjunction with autoimmune diseases (Benros et al., 2013) possibly indicating that autoimmune conditions pave the way for depressive symptoms. Autoimmunity can be caused by altered cell sets such as altered B-cell densities in mood disorders (Schlaaff et al., 2020). B cells are key to the

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maintenance of autoimmunity in autoimmune diseases, as they produce autoantibodies, secrete pro-inflammatory cytokines, and are involved in antigen presentation to T cells and in T-cell stimulation. In addition, B cells are involved in the body's immune response through the secretion of autoantibodies, which are also referred to as antibody-dependent functions. Binding of the Fc region of the antibody to the Fcγ receptors of natural killer cells can result in antibody-dependent cellular cytotoxicity, which can directly target neurons. Furthermore, they have antibody-independent effects such as pro-inflammatory and anti-inflammatory functions. Activated B cells are also responsible for plasma cell differentiation, and are increased in autoimmune diseases. Autoimmunity is ultimately caused by the faulty recognition of self-antigens by B and T cells, which subsequently trigger the production of autoantibodies. Thus, the importance of B cells for the development of autoimmunity has been emphasized and it is obvious that B-cell-associated concepts can also promote autoimmune processes in the development of depressive symptoms. In the next section, the B-cell activating factor is presented as an example of such a B-cell associated concept (5.1). In this section, we would also like to mention other concepts of autoimmunity such as complement-mediated cytotoxicity (5.2) or slow smoldering inflammation (5.3).

5.1. B-cell activating factor and depression

B-cell activating factor (BAFF) is a ligand for receptors on B cells and is important in maintaining inflammation, lymphocyte activation, B-cell maturation, and survival. BAFF belongs to the family of tumor necrosis factors (Krivosikova et al. 2009). In particular, it is essential for B-cell tolerance, which plays an important role in the development of autoimmunity, as explained above. As a trigger factor, it also leads to the production of autoantibodies in autoimmune processes (Krivosikova et al. 2009). A study by Boukouaci (Boukouaci et al., 2024) demonstrated that serum levels of BAFF in patients with bipolar disorder and schizophrenia were elevated in those carrying the Herpes simplex virus 1 IgG as opposed to those who tested negative for it. This could indicate that its increased activation of the immune system is taking place. Moreover, serum BAFF levels were lower in patients with systemic or central nervous system (CNS) autoantibodies (Boukouaci et al., 2024), suggesting a differential modulation of BAFF in bipolar disorder and thus mood disorders. CNS autoantibodies led to lower BAFF levels in their study, suggesting the downstream regulation of autoimmune conditions, as BAFF is normally elevated in a large proportion of immune-derived disorders (Cheema et al., 2001). There is also evidence that serum BAFF levels correlate significantly with several inflammatory markers such as tumor necrosis factor α, interleukin-6, interleukin 10, interferon-γ or C reactive protein in patients with bipolar disorder (Boukouaci et al., 2024), supporting the relevant importance of BAFF in key parts of the immune system. Ultimately, however, the significance of this transdiagnostic marker has not been clarified, attributable to the lack of studies on unipolar depression. There is thus evidence of inflammatory processes in bipolar disorder that are related to the level of BAFF in the blood.

5.2. Complement dependent cytotoxicity and depression

The complement system is an important part of the humoral immune defense belonging to the innate immune system and essentially serving to eliminate cellular antigens. The complement system can induce tissue injury in autoimmune conditions (Vignesh et al., 2017). The so-called classical pathway of complement activation is caused by antibody-antigen complexes (Porter and Reid, 1979). It is important in autoimmune diseases, as activation of the complement system by the immunoglobulin G1 (IgG1) subclass binds the classical C1q component to the Fc region of autoantibodies that have found their specific antigen and can ultimately lead to lysis of the neurons. The role of the C1q component is diverse, as it also has a preventive effect in autoimmune conditions, i.e., animal models with a C1q deficiency could cause autoimmunity in Lupus erythematosus (Botto and Walport, 2002). This is referred to as complement dependent cytotoxicity and often coincides with antibody-dependent cellular toxicity (ADCC) (Duan et al., 2019) leading to tissue damage by injuring adjacent cells called "ADCC bystander mechanism." The complement system is thus an important player in causing neuronal damage in autoimmune conditions. A small pilot study demonstrated that patients with residual disability due to past depression differ in their serum proteomic plasma markers from patients who have fully recovered (Lee et al., 2024). The complement C1q subcomponent subunit B and serum amyloid P component, both markers of inflammation and immune response, were markedly higher in relative expression in patients with residual disability than in those experiencing full remission of their depressive episode (Lee et al., 2024). They found that the patients with depression did not differ significantly in their relative expression levels of these proteins from those patients who were still residually impaired, but rather from those already in remission (Lee et al., 2024). In particular, C1q plays an important role in preventing autoimmune diseases by maintaining tissue homeostasis. This prevention of autoimmunity may also result from the fact that C1q crucially has an impact on the immune response to self-antigens involving less consecutive tissue damage. There is thus an indication that depressive episodes can persist if such a pathway is not adequately deactivated, or is continuously reactivated after an episode has passed.

5.3. Low-threshold systemic inflammation and depression

There is a group of autoimmune diseases called systemic auto-inflammatory diseases that are characterized by a dysregulation of the innate immune system generating intermittent systemic inflammation (Krainer et al., 2020). Low-threshold systemic inflammation can also play a role in the pathogenesis of depressive disorders. This is supported by a recently published study showing that the inflammatory marker c-reactive protein (CRP) was elevated in n = 55,098 individuals in the Dutch Lifelines cohort via non-genetic analyses for any depression form and especially lower positive and higher negative affect scores (Giollabhui et al., 2024). The relationship between a higher negative affect score (meaning more depressive symptoms) and higher CRP was confirmed in CRP analyses, but not in conjunction with the depressive episode as such (Giollabhui et al., 2024). These results suggest that low-threshold inflammation may be present in depressions that can represent the systemic inflammation component in a subset of depressed patients. At the same time, this systemic inflammation may also be part of a potential auto-inflammation in depression. This is particularly relevant, as it could potentially play a therapeutic role, i.e., via anti-inflammatory therapies such as non-steroidal anti-inflammatory agents (Kohler et al., 2016; Cavanagh, 2024) if this proves to be crucial in large cohorts. However, this is only speculative, and auto-inflammation markers such as phagocyte-derived S100 protein

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(Kessel et al., 2013) should be investigated in patients with depressive disorders compared to controls.

5.4. Synopsis regarding mechanistic clues for autoimmunity in depression

The concepts of autoimmunity in depression just presented can suggest autoimmunity such as altered BAFF activity, activation of the complement system with complement dependent cytotoxicity, or low-threshold systemic inflammation besides the presence of neural autoantibodies, at least in a subgroup of patients with mood disorders. Pathophysiological proof of the pathogenicity of human antibodies in an animal is necessary, as pathogenicity can be specifically investigated in animal models at the behavioral and molecular level. There is already animal model evidence supporting such autoantibody-pathogenicity. Moreover, the severity of depressive behavior in the animal model and severity of depressive symptoms in humans correlate with autoantibodies, putting the decisive prerequisites in place to prove the pathogenicity of autoantibodies in depressive illnesses as well. At the same time, as this is not provable for all antibodies, it should be examined on a case-by-case basis. This presentation reveals that there is solid evidence from individual cases for a potential autoimmune process underlying depressive symptoms. There are many concepts on how to proceed therapeutically with such autoimmune processes in the CNS, many of which can be derived from the field of neuroimmunology. The next section therefore briefly describes the immunotherapeutic approaches that are available.

6. Immunotherapeutic approaches

These considerations are therapeutically highly relevant in the context of newer promising therapies also being discussed in conjunction with autoimmune encephalitis and other autoimmune diseases, such as the depletion of B cells with novel chimeric antigen receptor (CAR) T cells (Abeles et al., 2024). CAR-T cell therapy has several advantages but is also associated with severe life-threatening toxicities. A complex work-up is required to carry out CAR T-cell therapy. Meanwhile, CAR-T cell therapy has expanded its focus from cancer therapy to include autoimmune diseases (Kong et al., 2025). New concepts include specialized CAR T cell therapies or involve the novel use of different CAR cells such as CAR regulatory cells (Treg), CAR natural killer cells (NK) (Kong et al., 2025) to modulate other cell populations. Such different CAR cell approaches can also be combined with each other. It would therefore also be interesting and worth investigating in clinical studies as to whether such CAR-T cell therapy can also succeed in neural autoantibody-associated mood disorders, which has not yet been investigated. To make matters worse, however, anxiety and depression in particular are risk factors that can cause long-term neuropsychiatric problems (Ruark et al., 2020). It is therefore still too early to propose treatment guidelines for our patient group with mood disorders and possible autoimmune involvement. Monoclonal antibodies are also being discussed as therapeutically effective in inflammatory disorders with depression, i.e., ixekizumab and dupilumab, provided they are proven to be safe (Rizk et al 2024). There are therefore many new approaches, apart from the standard therapies for autoimmune encephalitis applied to date, which are indicated in parallel with standard antidepressant therapy if psychiatric autoimmune encephalitis (Hansen et al., 2023) is detected, which can also present with a primary affective syndrome.

7. Concluding remarks

These hints suggest that autoantibodies in depression are an important target for future research to make more personalized medicine in psychiatry possible. Nevertheless, we emphasize that the mere association of autoantibodies in no way establishes causality. Therefore, to demonstrate an autoimmune genesis, we also call for more investigations that could prove organically-induced CNS damage or inflammation. We have published examples of such possible criteria (Hansen et al., 2020) to enable such an approach in a simplified manner. It is therefore particularly important in mood disorders to seek markers of inflammation, neuronal cell damage, and autoantibodies in combination to prove such potential autoimmunity. Several neuronal autoantibodies are associated with depressive disorders. It is not only psychotic or cognitive syndromes that are associated with neuronal autoantibodies, as a recent study of ours showed (Hansen et al., 2024). Animal models have delivered evidence that autoantibodies can play a pathogenic role in depression-like symptoms, thus making it important to pursue this avenue and provide more evidence for a causal role of autoantibodies in depressive disorders. However, note that only a minority of depressed patients show neural autoantibodies (Hansen et al., 2024). The phenotypes of such depressive disorders associated with autoantibodies might differ in their affective manifestation involving a more pronounced loss of vitality and less affective emotional regulation capacity. This topic is attracting increasing attention, and new autoantibody techniques will enable the subentities of mood disorders to be delineated more specifically. Criteria such as concomitant tumor, altered consciousness, visual hallucinations, severe cognitive impairment, movement disorders, seizures or adverse response to antidepressants (Hansen et al., 2020) have been established to select patients with possible underlying autoantibodies; they appear to be relevant. A higher rate of autoantibodies is to be expected in such cohorts, than in those without these features. We strongly recommend that the search for autoantibodies in mood disorders be included in the national and international guidelines for depressive disorders, similar to the national schizophrenia guideline as in Germany. It could prove useful to require this especially in case of a first manifestation or treatment refractoriness. It is also important to take a lumbar puncture and look for other aspects of inflammation such as intrathecal IgG synthesis or pleocytosis. Such inflammatory findings could trigger the decision to initiate early immunotherapy in addition to standard antidepressive therapy.

Data availability statement. The authors confirm that the data supporting the findings of this study are available within the article.

Author contributions. NH concepted and wrote the article. BM revised the article critically for important intellectual content. NH and BM approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Connections references

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