

Current Findings on the Spectrum of Neuronal Autoantibodies Associated with Psychotic Disorders – Pages 116-123

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Abstract: *Background:* Neural autoantibodies are observed in a subtype of psychotic disorders ranging from first-episode psychosis to schizophrenia. The clinical spectrum has so far been incompletely described, as new neuronal autoantibodies are emerging in the context of psychosis. This review is dedicated to describing the current spectrum of neural autoantibodies associated with psychotic disorders.

Methods: In our narrative review, we searched for neural autoantibodies addressed in the PubMed database in the last 15 years focusing on the last three years after publication of the international guidelines for autoimmune psychosis. We relied on small and large cohort studies and case series descriptions related to neural autoantibodies in psychotic disorders.

Results: Mainly neural autoantibodies against membrane surface structures such as N-Methyl-D-aspartate receptors (NMDAR) and against intracellular targets are present in psychotic disorders, but also in healthy controls. There is current suspicion that these neuronal autoantibodies (ie., NMDAR autoantibodies) play a potentially relevant role in the development of brain pathologies in psychotic disorders, especially when detected in cerebrospinal fluid. Autoantibodies against cell adhesion molecules and synaptic proteins such as neuronal cell adhesion molecule 1 (NCAM1) and antigen neurexin 1 alpha (NRXN1)-alpha occur in schizophrenia, but not in controls, suggesting that these are highly disease-specific antibodies. These lines of evidence are further supported by animal-model evidence showing a role of these autoantibodies in brain pathology and the development of schizophrenia-like symptoms.

Conclusions: In recent years, a new landscape of potentially relevant neural autoantibodies has emerged in a subtype of psychotic disorders. Their significance remains unclear. Large-scale investigations should particularly investigate what triggers the pathogenicity of these autoantibodies, as they probably do not cause the psychotic disorder per se, but might be involved as one factor in the immunopathophysiology. Psychotic disorders remain elusive, and differential diagnosis is required to determine the role neural autoantibodies play in the manifestation of psychoses.

Keywords: Autoimmunity, Neural autoantibodies, Psychotic disorder.

1. LINK BETWEEN AUTOIMMUNE ENCEPHALITIS AND NEURAL AUTOANTIBODIES IN PSYCHOTIC DISORDERS

Autoimmune psychosis is a term only coined in recent years, and it was defined in detail by an international panel of experts in immunopsychiatry until 2020 (Pollak *et al.*, 2020). The diagnosis of autoimmune psychosis has relied somewhat on the Graus criteria for autoimmune encephalitis (Graus *et al.*, 2016). Psychotic symptoms are often the main and first clinical presentation of autoimmune encephalitis (Wcislo *et al.*, 2023), as in in N-Methyl-D-Aspartate-Receptor (NMDAR) autoantibody-mediated encephalitis. However, the clinical spectrum of autoantibody-associated psychosis is much more diverse and includes various neural autoantibodies as well as heterogeneous clinical presentations. The aim of this review is to describe the clinical spectrum and thus provide a new perspective on the clinical picture,

psychotic disorders. The following definitions are important to understand the clinical picture as it is currently understood.

2. CURRENT TERMINOLOGY OF AUTOIMMUNE PSYCHOSIS

The term autoimmune psychosis refers to psychotic symptoms with a rapid onset in under three months (Pollak *et al.*, 2020). One of the following manifestations is also required for a possible autoimmune psychosis (Pollak *et al.*, 2020): they include the diagnosis of a tumor or movement disorder (catatonia or dyskinesia), adverse response to antipsychotics, a severe cognitive disorder, the occurrence of seizures, autonomic dysfunction, and/or an altered level of consciousness. Autoimmune psychosis is also likely if psychotic symptoms are present and another when another criterion is met in addition to the aforementioned factors, ie, 1) pleocytosis in the cerebrospinal fluid (CSF) or 2) bilateral signal abnormalities in the T2 magnetic resonance imaging (MRI) or in fluid attenuated inversion recovery sequences (FLAIR) MRI sequences (Pollak *et al.*, 2020). In addition, if one of these features

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as it has recently been differentiated from classic

is not present, it is probably autoimmune psychosis if two of the following anomalies are observed, eg, abnormal electroencephalography (EEG) data, intrathecal immunoglobulin G (IgG) synthesis in the CSF, or neural autoantibodies in the cell-based assay. Autoimmune psychosis should definitively be considered if neural autoantibodies are present in the CSF (Pollak *et al.*, 2020). However, this diagnosis should also be made in patients with previous psychotic or other psychiatric symptoms that have regressed (Pollak *et al.*, 2020). Autoimmune psychosis is suspected when neural autoantibodies are detected in the serum or cerebrospinal fluid. We describe below various neural autoantibodies as the spectrum to observe in autoimmune psychosis. The rationale of the review is to understand the diverse and constantly growing spectrum of neural autoantibodies and to find evidence for their pathogenicity in symptom development.

3. METHODOLOGICAL APPROACH

As a method for this narrative review, we relied on the PubMed database from 15 years ago, focusing on the last three years after the international expert consensus guidelines were published for autoimmune psychosis (Pollak *et al.*, 2020). We sought articles reporting neural autoantibodies against membrane surface and intracellular targets in psychotic disorders.

4. NEURAL AUTOANTIBODIES IN PSYCHOTIC DISORDERS

A recent large study in a schizophrenia cohort and other patients examined over 49 different neural autoantibodies in a total of over 7000 participants (Daguano Gastaldi *et al.*, 2022). Specifically, neural autoantibodies were measured in the blood of 2043 patients with schizophrenia versus healthy controls. Overall, that working group measured a frequency of 346 out of 2043 (16.94%) positive autoantibodies in patients with schizophrenia spectrum disorders. However, autoantibodies were also detected in 400 of 2748 patients (14.56%) in the healthy controls (Daguano Gastaldi *et al.*, 2022). Such autoantibodies per se cannot be disease-defining therefore, and it is unclear what causes their pathogenicity. RhoA GTPase-activating protein 26 (ARHGAP26), potassium voltage-gated channel subfamily A member 1 (KCNK1), glycine receptor alpha 1 (GLRA1b), Ma2, myelin oligodendrocytic protein (MOG), metabotropic glutamate receptors 5 (mGluR5) and Yo have been reported in patients with schizophrenia, but to a similar extent also in controls at frequencies amounting to less than 1% (Daguano Gastaldi *et al.*, 2022). This evidence

deserves further investigation in large-scale studies. While neurofascin 155 (NF155) autoantibodies have also appeared in schizophrenia and healthy controls (Daguano Gastaldi *et al.*, 2022), they are unlikely to be of pathogenically significant, as they are more likely to coincide with neuromuscular peripheral nervous system disorders (Tan *et al.*, 2022; Bai *et al.*, 2023) and are involved in impaired electrical nerve conduction. Below we discuss autoantibodies against membrane surface antigens in 4.1 and autoantibodies against intracellular antigens in 4.2 and autoantibodies against unknown not further specified antigens in 4.3 (see Table 1 for details of described studies).

4.1. Autoantibodies Against Membrane Surface Antigens

4.1.1. Alpha 7 Subunit of Nicotinic Receptor Autoantibodies

In schizophrenia, autoantibodies against nicotinic receptors' alpha-7 subunit have been detected in 23% of patients with schizophrenia (n=21), and their levels were higher than in controls (Chandley *et al.*, 2009). Muscarinic autoantibodies have also been observed in addition to nicotinic autoantibodies, in schizophrenia patients (Ryan *et al.*, 2019) and may play a role in the pathophysiology of psychotic symptoms and schizophrenia (Pechlivanidou *et al.*, 2023) due to a possible disruption in neurotransmission and altered network plasticity. They should be tested at the first episode of a psychotic episode.

4.1.2. AP3B2 Autoantibodies

A very interesting recent study delivered evidence of anti-Adaptor-Related Protein Complex 3, beta 2 Subunit (AP3B2) autoantibodies being increasingly associated with persecutory delusions as a specific psychopathology. In that investigation, IgG-AP3B2 autoantibodies were identified in the blood plasma of 461 people with psychotic disorders. The researchers examined planar protein microarrays (Falk *et al.*, 2021). This study is important because it linked AP3B2 autoantibodies to the presentation of persecutory delusions, indicating that certain autoantibodies may be involved in the development of delusional psychopathology.

4.1.3. CASPR2 Autoantibodies

Contactin associated protein 2 (CASPR2) autoantibodies were identified last year in 26/ 1816 (1.43%) of schizophrenic patients and in 35 of 2391 (1.46%) healthy control subjects in a large cohort study (Daguano Gastaldi *et al.*, 2022). It thus seems

Table 1: Spectrum of Neural Autoantibodies Involved in Psychotic Disorder

Neural Autoantibody Type	Number, Prevalence	Methods, Fluid Medium	Disorder	Reference
Target antigen of cell-surface antibodies				
nAChRalpha7	21, 23%	ELISA using recombinantly expressed $\alpha 7$ protein	Schizophrenia	Chandley <i>et al.</i> , 2009
AP3B2	23, 438, 5.2%	Blood planar protein microassays with 42100 human antigens with corresponding 18914 proteins	Psychotic disorder	Jernbom Falk <i>et al.</i> , 2021
Astrocytic	2, 100%	CSF		Endres <i>et al.</i> , 2022
CASPR2	26 / 1816, 1.43%	Blood, indirect immunohistochemistry, cell based assay	Schizophrenia	Daguano Gastaldi <i>et al.</i> , 2022
GFAP	22/ 1816, 1.21%	Blood, indirect immunohistochemistry, cell based assay	Schizophrenia	Daguano Gastaldi <i>et al.</i> , 2022
GluN2D	7, 73, 9.6%	Brain tissue lysates, planar microarrays composed of 11520 protein fragments representing 10820 unique proteins	Schizophrenia	Just <i>et al.</i> , 2020
GlycinR	75	Serum nuclear magnetic resonance (NMR) metabolite profiles	Acute psychosis	Lennox <i>et al.</i> , 2022
KCNA2	26/ 1816, 1.43%	Blood, indirect immunohistochemistry, cell based assay	Schizophrenia	Daguano Gastaldi <i>et al.</i> , 2022
MGlur5	14/ 20, 70%	CSF and serum cell based assay	Autoimmune psychosis	Guo <i>et al.</i> , 2023
NCAM	12 / 223, 5.4% (CBA), 6.7% (ELISA)	Cell based assay, ELISA	Schizophrenia	Shiwaku <i>et al.</i> , 2022
NRX1alpha	387, 2.1%	Cell based assay, ELISA	Schizophrenia	Shiwaku <i>et al.</i> , 2023
NMDAR	12 / 123, 9.8%	Cell based assay	Schizophrenia	Hinotsu <i>et al.</i> , 2022
PAGE 2,3,5	8/30, 26.7%	2304 fragments of human proteins using a multiplexed affinity proteomic technique	Schizophrenia, delusional disorder and schizoaffective disorder	Zandian <i>et al.</i> , 2017
Target antigen of intracellular antibodies				
GAD65	1/199, 0.5%	Blood, cell based assay	Schizophrenia	Hoffmann <i>et al.</i> , 2021
	8/40, 20%	Blood indirect immunohistochemistry	Schizophrenia	Keshavarz <i>et al.</i> , 2022
Amphiphysin	26/ 1816, 1.43%	Blood, indirect immunohistochemistry, cell based assay	Schizophrenia	Daguano Gastaldi <i>et al.</i> , 2022

Abbreviations: nAChRalpha7 = nicotinic receptors' alpha-7 subunit, AP3B2 = Adaptor-Related Protein Complex 3, beta 2 Subunit, CASPR2 = Contactin associated protein 2, CSF = cerebrospinal fluid, ELISA = enzyme-linked immunosorbent assay, GAD65 = glutamic acid decarboxylase 65, GFAP = glial fibrillary acid protein, KCNA2 = potassium voltage-gated channel subfamily A member 2, MGlur5 metabotropic glutamate receptors type 5, NCAM 1 neural cell adhesion molecule 1, NRX1alpha = antigen neurexin 1 alpha, NMDAR = N-Methyl-D-Aspartate receptor PAGE protein = N-terminal fragment of the PAGE protein (P antigen) family.

worthwhile to look for these autoantibodies in the context of subacute psychotic symptoms, although thorough clinical phenotyping including MRI and EEG exams should be conducted to assess their value.

4.1.4. GFAP Autoantibodies

In a large cohort study, GFAP autoantibodies were shown to be rarely present in 22/1816 (1.21%) with schizophrenia but also in healthy controls in 21 of 2391 (0.88%) (Daguano Gastaldi *et al.*, 2022). Whether these GFAP autoantibodies contribute to astroglial inflammation in patients is a tantalizing speculation, but

so far remains unclear. More studies should follow, in particular to differentiate neurodegenerative processes in chronic psychotic disorders.

4.1.5. GluN2D Autoantibodies

Another working group investigated brain sections from 73 patients with schizophrenia in comparison to controls. Microarray examinations were used to identify certain protein antigens. Among others, the GluN2D antigen was detected in this way. The GluN2D antigen is one of those NMDARs that are heterotetrameric complexes containing two obligatory GluN1 subunit and two GluN2 subunits with the subtypes GluN2A–GluN2D. GluN2D autoantibodies were identified in this way with higher IgG reactivity in schizophrenia patients than in controls (Just *et al.*, 2020). These results were validated in a larger independent cohort of diverse psychiatric disorders compared to controls; higher levels of serum GluN2D autoantibodies were detected in 395 patients compared to controls. Although these autoantibodies are rare, those findings have been replicated in an independent cohort, thereby confirming the importance of these findings.

4.1.6. Glycine Autoantibodies

The psychotic symptoms in psychotic disorders seem to be particularly pronounced in conjunction with higher positive and negative symptom score (PANSS) scores than in patients with psychotic disorders associated with autoantibodies against NMDAR1, Leucin rich glioma inactivated protein 1 (LGI1) and CASPR2 (Lennox *et al.*, 2022). Moreover, nuclear magnetic metabolites were detected in 75 patients with autoantibodies to anti-glycine, voltage gated potassium channels (VGKC), CASPR2 and NMDAR versus 70 age-, sex- and ethnicity-matched control patients. Patients with glycine-receptor antibodies were found to present reduced lipoprotein fatty acids and increased amino acid concentrations. In contrast, the metabolome of patients with NMDAR, CASPR2 and LGI1 did not differ significantly from controls. We therefore suspect that there is a different biochemical subtype of autoimmune psychosis potentially associated with increased inflammation (Lennox *et al.*, 2022). Whether the neuroinflammatory fingerprint of certain autoantibody subtypes in the context of psychotic disorders actually is evident in studies analyzing cerebrospinal fluid cells or brain tissue should be investigated.

4.1.7. KCNA2 Autoantibodies

Autoantibodies against the potassium voltage-gated channel subfamily A member 2 (KCNA2) were detected in 26 of 1816 schizophrenic patients (1.43%) and in 35 of 2391 (1.46%) (Daguano Gastaldi *et al.*, 2022). KCNA2 autoantibodies have recently become the focus of interest in the context of cognitive impairment (Timäus *et al.*, 2021), but their role in psychotic disorders is unclear and requires further investigation.

4.1.8. mGluR5 Autoantibodies

Another investigation reported on 14 out of 20 (70%) patients with autoimmune encephalitis and mGluR5 autoantibodies who exhibited psychotic symptoms including hallucinations; 85% also revealed behavioral abnormalities (Guo *et al.*, 2023). However, fewer patients with mGluR5 encephalitis (75%) had cognitive dysfunction (Guo *et al.*, 2023). Overall, the prevalence of mGluR5 autoantibodies in schizophrenia patients is less than 1% (Daguano Gastaldi *et al.*, 2022), but its frequency in psychotic disorders with hallucinations associated with autoimmune encephalitis seems to be much higher according to this preliminary study by Guo *et al.* (2022). It is therefore well worth investigating such autoantibodies in psychotic disorders.

4.1.9. NCAM 1 und NRXN1alpha Autoantibodies

The clinical spectrum of neural autoantibody associated psychotic disorders varies considerably, and many new neural autoantibodies have recently been discovered in patients with psychotic symptoms. They may not have fulfilled the criteria for autoimmune psychosis, for example because they responded to antipsychotics, or failed to meet other criteria. We therefore explain each autoantibody in its individual clinical context in this report. Two very interesting investigations (Shiwaku *et al.*, 2022, 2023) described autoantibodies against cell adhesion molecules and synaptic proteins detected in patients with schizophrenia, but not in controls. This evidence differs from that reported in many other studies, especially when neural autoantibodies were collected in large cross-sectional populations with schizophrenic symptoms. In one of Shiwaku's studies, autoantibodies against a neural cell adhesion molecule 1 (NCAM1) were found in 12 of 223 patients with schizophrenia, but not in 201 controls (Shiwaku *et al.*, 2022). The transfer of NCAM1 autoantibodies to mice was investigated by Shiwaku *et al.* (Shiwaku *et al.*, 2022) in an animal model: they observed drastic reduction in the number of spines and synapses in the frontal cortex. This reduction also led to schizophrenia-like behavior in mice characterized by impaired prepulse inhibition and

cognitive impairment (Shiwaku 2022). Another of their studies (Shiwaku *et al.*, 2023) reported on an equally interesting antibody against the antigen neurexin 1 alpha (NRXN1alpha), which they detected in 2.1% of 387 patients in a Japanese cohort; NRX1alpha autoantibodies disrupts the interaction between NRXN1alpha and neuroligin 1 and between NRXN1 and neuroligin 2 at the molecular level. Transfected human antibodies have been shown to induce schizophrenia-like behaviors such as reduced cognition, impaired prepulse inhibition, and reduced social novelty preference also in a mouse transfer model. Interestingly, those changes were reversed after removal of the anti-NRXN1alpha autoantibody-derived IgG from patients with schizophrenia. These two Japanese studies are extremely remarkable for two reasons, as their findings may prove to be very relevant a subtype of psychotic disorder. First of all, their pathogenicity has been demonstrated indirectly in animal models and beyond that, schizophrenia-like symptoms were produced. This means that they may actually be pathogenic autoantibodies in schizophrenia. Secondly, Shiwaku and his team demonstrated that these autoantibodies were only detected in schizophrenia patients, but not in control patients, thus reinforcing the pathogenic role these autoantibodies play in psychotic disorders.

4.1.10. NMDAR Autoantibodies

Most studies to date have been conducted on individual NMDAR antibodies, examining their association with the occurrence of psychotic disorders. Oddly enough, NMDAR antibodies of the IgG type have not been detected more frequently in patients who subsequently develop psychotic symptoms (Pollak *et al.*, 2021), which means that NMDARs cannot be predictive of psychotic symptoms (Pollak *et al.*, 2021). However, the presence of positive NMDAR autoantibodies in serum is an indication of functional deterioration in these patients, as there is evidence of poorer functional performance associated with the titer of NMDAR autoantibodies (Pollak *et al.*, 2021). The presence of a neural autoantibody was also associated with larger amygdala volumes in their study (Pollak *et al.*, 2021), suggesting increased inflammation in this area. Nevertheless, NMDAR antibodies are rare in schizophrenia, and were only detected in 1/ 293 serum samples from patients with schizophrenia, as a recent study showed (Zhou *et al.*, 2022) via a cell-based assay and immunostaining of primary neurons. A recent review analyzed 79 patients with NMDAR autoantibodies and psychiatric symptoms and observed that CSF NMDAR antibodies were more

common in women and in patients with a subacute symptom onset compared to those with serum antibodies (Blackman *et al.*, 2022). Psychiatric patients with CSF NMDAR antibodies were more likely to suffer psychotic symptoms and have a functional brain disorder (pathological EEG abnormalities), and present as evidence of structural CNS damage than patients with serum NMDAR autoantibodies (Blackman *et al.*, 2022). A further interesting finding is that in a study of patients with atypical psychosis, 12 of 123 (9.8%) had anti-NMDAR1/2B IgG autoantibodies (Hinotsu *et al.*, 2022) indicating that atypical psychosis might be often accompanied by anti-NMDAR1/2B antibodies. The aforementioned study by Daguano Gastaldi showed NMDAR1 antibodies in patients with schizophrenia in 158/2043 (7.73%) of patients but also in 183 out of 2735 (6.69%) in healthy controls. Because of their frequency, NMDAR1 autoantibodies play the most important role among the various autoantibody subtypes and should therefore be routinely assessed in initial investigations of patients presenting atypical or organic psychotic disorders.

4.1.11. PAGE Protein Autoantibodies

Applying an affinity proteomic technique, protein fragments were analyzed for IgG reactivity in 30 patients with psychotic disorders (schizophrenia, delusional disorder and schizoaffective disorder) (Zandian *et al.*, 2017) and autoantibodies against the N-terminal fragment of the PAGE protein (P antigen) family (PAGE2B/PAGE2/PAGE5) were identified in 8 of the patients, while no such autoantibodies were detected in the controls (Zandian *et al.*, 2017). As the patients had all suffered an initial episode of psychosis, this autoantibody could play a role in the first onset of psychosis in a subunit of schizophrenia. This antibody probably only plays a minor role in chronic psychotic disorders, but nevertheless deserves inclusion in a panel in the initial examination of a first-episode psychosis.

4.2. Autoantibodies Against Intracellular Antigens

4.2.1. GAD65 Autoantibodies

A relatively large cohort study examined GAD65 autoantibodies in 199 patients with psychotic disorders, but GAD 65 antibodies were detected in only one patient with schizophrenia and one control patient (Hoffmann *et al.*, 2021). In contrast, a meta-analysis of 17 different studies showed that GAD65 antibodies were present in 31 of 2754 patients with psychotic disorders, while that was only the case in 24 of the controls. However, the antibodies were low-titer and

failed to meet the diagnostic criteria for autoimmune encephalitis (Warren *et al.*, 2023). Another study with schizophrenic patients showed that GAD autoantibodies were present in the serum of 8 out of 40 (20%) patients (Keshavarz *et al.*, 2022). The larger cohort study by Daguano Gastaldi (Daguano Gastaldi *et al.*, 2022) demonstrated that GAD65 autoantibodies were present in both schizophrenia patients [9/2043 (0.44%)] and healthy controls [9/2735 (0.33%)]. Although rare, GAD65 autoantibodies should be investigated in conjunction with insulin autoantibodies (Melkersson *et al.*, 2023) and metabolic disorders in psychotic disorders.

4.2.2. Amphiphysin Autoantibodies

Amphiphysin autoantibodies were reported to occur in 26 of 1816 (1.43%) schizophrenic patients and in 35 of 2391 (1.46%) of controls (Daguano Gastaldi *et al.*, 2022). Amphiphysin antibodies are known to be associated with stiff person syndrome (Chia *et al.*, 2023; Dalakas *et al.*, 2022) or paraneoplastic neurological syndromes. However, their role in schizophrenia is completely unknown; it may be attributable to the effects of amphiphysin antibodies on synaptic vesicular transport dynamics via dynamin on nerve endings (David *et al.*, 1996) that interfere with synaptic transmission. Amphiphysin autoantibodies could trigger psychotic symptoms via the mechanism of synaptic maltransmission and consecutive development of psychotic symptoms.

4.3. Autoantibodies Against Unspecified Target Antigens

4.3.1. Astrocytic Autoantibodies

New target antigens have been reported on in a recently published case series in psychotic disorders: a pattern against astrocytic structures was identified in two patients with psychosis. These new autoantibodies are described as anti-astrocytic autoantibodies ("GFAP-like") in the CSF. Indirect immunofluorescence and unfixed mouse brain slices were used for visualization (Endres *et al.*, 2022). These findings highlight the importance of seeking further unknown antigens to decipher potential autoantibodies involved in subtypes of psychotic disorders.

5. DISCUSSION

As we have shown, there are several different neural autoantibodies present in psychotic disorders, but their prevalence is very low. Of particular interest are autoantibodies against NMCAM1 and

NRXN1alpha, which coincide exclusively within psychotic disorders. There are also human animal transfer models for these autoantibodies that explain how psychotic-like symptoms develop. It is pathophysiologically conceivable that many other membrane-bound autoantibodies lead to the development of psychotic disorders by interfering with excitatory or inhibitory neurotransmitters. However, although the large Daguano Gastaldi cohort study (Daguano Gastaldi *et al.*, 2022) also demonstrated that the presence of autoantibodies in psychotic disorders (with similar prevalence in healthy subjects) is not disease-defining, it is also clear that at least their overall prevalence of 17% in psychotic disorders certainly affects a considerable proportion of patients, which clearly limits the need to clarify at least theoretically conceivable pathogenicity. The second most frequent syndrome in definitive psychiatric autoimmune encephalitis was a parahallucinatory syndrome (after the most frequent psychoorganic syndrome (Hansen *et al.*, 2023) – a finding consistent with autoimmune psychosis as one of the major subtypes of autoimmune encephalitis.

5.1. Limitations

It is undoubtedly important to list the diversity of neural autoantibodies that occur in association with psychotic disorders. However, it should be made clear that it cannot be assumed that these associated autoantibodies can be pathogenic. Only for the NMCAM1 and NRXN1alpha autoantibodies was a pathogenic significance of these autoantibodies suggested by animal transfer models (Shiwaku *et al.*, 2022, 2023). Similar animal test models in mice were also able to show for the NMDAR antibodies that these autoantibodies cause "psychotic-like" symptoms when the blood-brain barrier was disturbed in the mice (Pan *et al.*, 2019). The other aspect is that it must be emphasized that neural autoantibodies may well be involved in an inflammatory subtype of psychosis. Therefore, it is of immense importance to identify novel antigen targets using different methods such as planar protein microassays, multiplexed affinity proteomic techniques and specific new cell-based assays for further implementation of potential treatment strategies.

5.2. Conclusions

Neural autoantibodies in psychotic disorders are a phenomenon that must not be ignored in the future as it will have therapeutic implications, such as the use of immunotherapies such as corticosteroids or antibody-suppressive B-cell depletion therapies such as

rituximab, which are currently under investigation (Bejerot *et al.*, 2023) when differential diagnostic investigations reveal evidence of possible autoimmunity. In addition, further studies should investigate the interesting observation that clozapine treatment can lead to a reduction in various immunoglobulins such as IgG, immunoglobulin M or immunoglobulin A with different time intervals of one to two years (Griffith *et al.*, 2023) and symptoms to assess the ability of antipsychotics to act as secondary immunomodulation. Other therapeutic approaches include the generation of autoantibody-specific chimeric autoantibody receptor (CAAR)-T cells to deplete autoantibody-producing B cells, as recently shown for NMDAR antibodies (Reincke *et al.*, 2023). The classification of potential autoimmunity is not trivial and should of course be based on international expert consensus, but criteria from regional research associations such as the CAP (Cerebrospinal fluid Analysis in Psychiatry) are also relevant (Hansen *et al.*, 2020). It will be important to study neural autoantibodies in conjunction with proteomic, lipidomic and metabolic markers to generate conclusions about the pathogenic role of neural autoantibodies in the development of psychosis.

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