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Autoimmunity in psychotic disorders. Where we stand, challenges and opportunities

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ABSTRACT

Psychotic disorders are debilitating mental illnesses associated with abnormalities in various neurotransmitter systems. The development of disease-modifing therapies has been hampered by the mostly unknown etiologies and pathophysiologies.

Autoantibodies against several neuronal antigens are responsible for autoimmune encephalitis. These autoantibodies disrupt neurotransmission within the brain, resulting in a wide range of psychiatric and neurologic manifestations, including psychosis. The overlap of symptoms of autoimmune encephalitis with psychotic disorders raised the question as to whether autoantibodies against a number of receptors, ion channel and associated proteins could ultimately be responsible for some forms of psychosis. Here we review our current knowledge, on antibody mediated autoimmunity in psychotic disorders, the different diagnostic methods and their limitations, as well as on varying therapeutic approaches targeting the immune system.

Abreviations

AChR	acetylcholine receptor
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BBB	blood brain barrier
CASPR2	contactin-associated protein 2
CBA	cell-based assay
CNS	central nervous system
CSF	cerebrospinal fluid
D2DR	dopamine receptor D2
DPPX	dipeptidyl aminopeptidase-like protein 6
$GABA_AR$	*gamma*-aminobutyric acid A receptor
$GABA_BR$	*gamma*-aminobutyric acid B receptor
GAD	glutamic acid decarboxylase
GlyR	glycine receptor
Ig	immunoglobulin
IHC	immunohistochemistry
IVIG	intravenous immunoglobulin
LGI1	leucine-rich glioma inactivated protein l
MAC	membrane attack complex
NMDAR	N-methyl-D-aspartate receptor
RIA	radioimmunoassay
VGKC/C	voltage-gated potassium channel/complex

1. Introduction

Psychotic disorders like schizophrenia and bipolar disorder have been well documented in terms of prevalence, demographics and co-morbidity. The pathopysiology of these disorders, however, remains poorly understood. Robust evidence suggests that synaptic transmission within dopaminergic and glutamatergic pathways is altered, which may result in a dysequilibrium between inhibitory-excitatory mechanisms. Diminished function of neurotransmitter receptors like dopamine- and N-methyl-D-aspartate receptors (NMDAR) and dysfunction of ion channels such as voltage-gated potassium channels (VGKC), have all been shown to play an important role in the development and progression of schizophrenia [1–3]. Interestingly, antibodies and venom peptides targeting purinoceptors (P2X7), transient receptor potential cation channels (TRPC4 and TRPC5), cannabinoid receptor, nicotinic alpha-7 receptor, *gamma*-aminobutyric acid A receptor ($GABA_AR$) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) are currently approved or under clinical trial indicated for cognitive impairment, anxiety, depression and schizophrenia [4,5]. Furthermore, there are genetic risk factors: studies in large, pooled,

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cohorts have indicated that there are variations in the genetic coding for ion channels (common and rare gene variants), which thereby could increase the risk for psychotic disorders. Single nucleotide polymorphisms in genes encoding for the L-type calcium channel, affecting the gene activity of two subunits (CACNA1C and CACNB2), have been identified as risk loci, with shared effects in five major neuropsychiatric disorders, including schizophrenia and bipolar disorder [6]. Alterations in neurexin genes, coding for proteins involved in synaptic differentiation and transmission, have been associated with higher risk of developing schizophrenia [7,8] and autism [7,9–11]. Moreover, there are also genetic factors that affect the immune system. Gene variants encoding for human leukocyte antigen (HLA) regions (major histocompatibility complex (MHC) molecules), involved in building an immune response through antigen presentation, have also firmly been associated with an increased risk of schizophrenia [12,13].

The idea that autoimmunity may play a role in neuropsychiatric disorders began to take root in the last decade. Dr. Dalmau was the first to describe a group of patients with encephalitis associated with ovarian teratoma. After developing prodromal symptoms such as fever, headache and nausea, patients presented with a variety of severe psychotic and neurological manifestations, including anxiety, delusions, mania, short-term memory loss and seizures. Extensive analysis showed that serum and cerebrospinal fluid (CSF) contained antibody reactivity towards neuronal tissue, which was also present in the tumor. Autoantibodies reacted specifically against the NR1 subunits of the NMDAR. After immunosuppressive treatment and tumor resection, most of the patients recovered completely, regaining their normal social behavior and cognitive abilities in the absence of any remaining neuropsychiatric manifestations. This previously unassociated collection of symptoms was termed autoimmune encephaltitis [14].

It is not entirely unexpected, of course, that antibodies targeting neuronal receptors can cause psychotic symptoms. Neurotransmitter receptor antagonists such as phencyclidine, quinuclidinyl benzilate and lysergic acid diethylamide, that block NMDAR, muscarinic acetylcholine receptor and 5-HT receptor, respectively, are well-known to be potent hallucinogens. Agonists of the cannabinoid receptors also have the capacity to induce psychosis [15–20]. The different mechanisms by which autoantibodies alter synaptic transmission likely impacts the widespread function of neurons and neural networks, culminating in serious mental (and neurological) disturbances (Fig. 1).

This article reviews what is known about the occurrence of autoantibodies against neuronal neurotransmitter receptors, voltage-gated ion channels and associated proteins. We also summarize the effect of the autoantibodies in the pathophysiology of neuropsychiatric disorders and the corresponding treatment options.

2. Autoimmunity

Autoimmune diseases occur in 7-9% of the general population [21]. Specialized cells are generated in the adaptative response, namely T and B lymphocytes. This requires a maturation process with several built-in check points to detect and delete defective cells. One of these mechanisms is the acquisition of tolerance, which is generated centrally and peripherally in the lymphoid organs, where the lymphocytes are screened for their ability to distinguish between self and non-self-antigens [22]. Failure of this machinery can lead to autoimmunity where different cell mechanisms are involved. Autoimmune disorders can show a wide expression of phenotypes ranging from endocrine, musculoskeletal to neurological syndromes. Diseases where ion channels, on the surface of nerve or muscle membranes, are affected by autoantibodies, or altered by point mutations in the genome, have been named channelopathies [23,24].

2.1. Autoimmune mechanisms in channelopathies

Immunoglobulins (Igs) in the soluble form, commonly known as antibodies, are synthesized and released by B cells and plasma cells; differentiated B cells, developed in the lymphoid follicles, spleen and lymph nodes, are used as defence weapons in the adaptative immune response. IgM, IgD, IgG (1-4), IgA (1-2) and IgE are different Ig isotypes with a shared general structure (Fig. 2), but differ in characteristics such as size, capacity to activate complement, FcR binding and response to antigen, which is based on the heavy chain of the constant region. IgG is the most abundant and has the longest half-life; its isoforms are the most studied in autoimmune diseases [25]. IgG1 and IgG3 subclasses have the capacity to bind to protein antigens and induce endocytosis through cross-linking and can damage tissue as a result of complement activation, leading to loss of antigen function [26–28]. In contrast, the capacity to fix complement is lower or non-existent for the subclasses IgG2 and IgG4, which have higher affinity to polysaccharide antigens [29,30].

IgG-mediated autoimmune disease mechanisms against membrane receptors ion channels and their associated proteins (Fig. 3) are summarized as follows:

a) Stimulation, inhibition or blocking of receptor or channel function. This mechanism has been observed in: i) infantile-onset neuropsychiatric disorders with psychomotor retardation, cerebellar ataxia, dyskinesia and in some cases, seizures due to the blocking of the folate receptor [31]; ii) autoimmune basal ganglia disorders with altered function of the dopamine receptor D2 (D2DR), comparable to the inhibitory effect of dopamine [32]; iii) cases of autoimmune encephalitis with hyper excitability in neurons in contact with antibodies targeting dipeptidyl aminopeptidase-like protein 6 (DPPX) [33] and iv) $GABA_BR$ derived antibodies from limbic encephalitis patients which have been proposed to cause functional blockage of the receptors, seizures and memory dysfunction [34,35].
b) Antigenic modulation. The binding of IgG1 leads to cross-linking of antigens, inducing internalization or endocytosis of the antigen-antibody complex, commonly followed by the degradation of the antigen. Examples are the cross-linking and selective internalization of NMDAR [14] as shown in cultured neurons [36–38] and also in an animal model of NMDAR encephalitis where reduction of membrane-associated NMDAR is observed [39]. Reduction in the number of receptors in the synapse has also been observed *in vitro* by autoantibodies to AMPAR [40,41], $GABA_AR$ [42], IgLON5 [43], neurexin-3 [44] and glycine receptor (GlyR) [45].
c) Complement activation and inflammation. Antigen-antibody complexes (IgG1 and IgG3 isotypes) lead to the activation of the complement system [46,47]. The activation of the complement system leads to i) chemo-attraction and activation of phagocytes; ii) opsonization and engulfment by phagocytes and iii) formation of membrane attack complex (MAC) in cell membranes leading to lysis, extensive tissue damage and loss of tissue architecture. Activation of the classical complement pathway is an important mechanism in Rasmussen's encephalitis, where antibodies against the subunit 3 of the AMPAR have been detected [48]. Autoantibodies to GlyR, associated to progressive encephalomyelitis with rigidity and myoclonus (PERM), were shown to induce deposition of C3b in an *in vitro* assay with colocalization of the patient autoantibodies, which are predominantly of the IgG1 subclass [49]. Complement mediated pathology has been reported in the voltage-gated potassium channel complex (VGKCC) encephalitis with autoantibodies against contactin-associated protein 2 (CASPR2). In this case the patient presented brain atrophy detected by MRI and deposition of the final complement complex was observed in a hippocampus biopsy [50]. Complement activation in brain biopsies was studied in different subjects, including patients with anti-NMDAR and anti-VGKCC antibodies. In this study, 3 out of 4 patients with VGKCC autoantibodies, independently of the antigen specificity [leucine-rich glioma inactivated protein l (LGI1) or CASPR2], showed reactivity

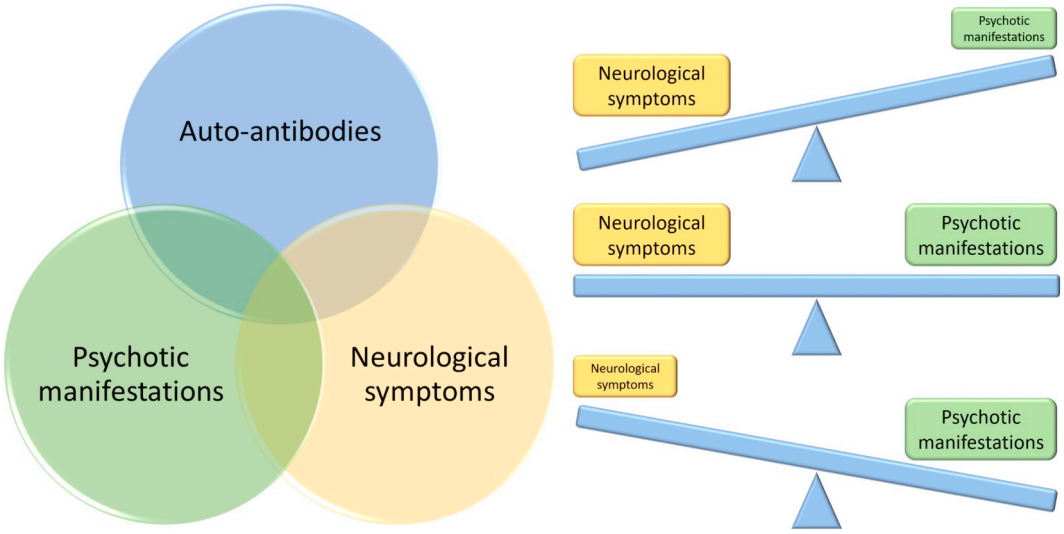

Fig. 1. Venn diagram of the relationship between neurological, psychotic and autoimmune disorders.
The overlap between the different diseases is being described in this review. Autoimmune encephalitis is a case in point, where autoantibodies (blue) and neurological symptoms (yellow) have been found with or without psychotic manifestations (green). However, the balance between the neurological symptoms and the psychotic manifestations can vary largely among the different disorders where autoantibodies are the organic cause of the pathology. These could lead in some cases to misdiagnoses and the use of anti-psychotic drugs instead of immunotherapy. This review focuses on the findings regarding the area shared by the 3 disciplines, where psychiatric and neurological manifestations are caused by the presence of autoantibodies. However, the scales represent the different expression of psychotic and neurological manifestations in different cases, raising the possibility of having a new subgroup of patients with autoimmune psychotic disorders with subtle or undetectable neurological symptoms.

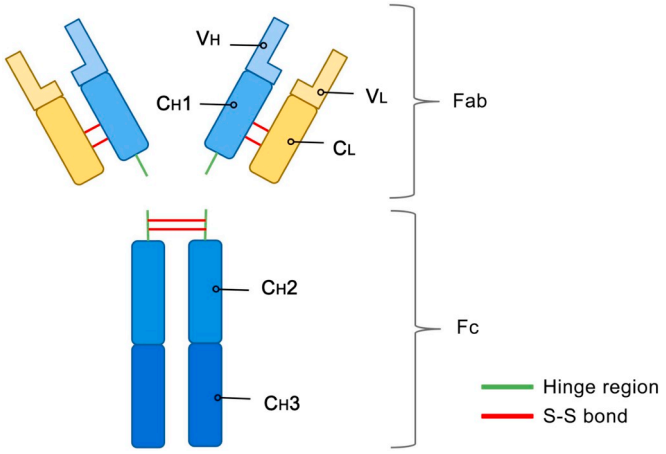

Fig. 2. General structure of an immunoglobulin.
Immunoglobulins, commonly known as antibodies, are heterodimeric glycoproteins consisting of four chains, two heavy (H) and two light (L), each of them with constant (C) and variable (V) regions. Each H chain is composed by 3 C (C_{H1-3}) and 1 V (V_H) regions, linked with a disulfide bound at the C_{H2}. The L chains are formed by a C (C_L) and a V (V_L) region and they are linked with the H chains one to one through the C_{H1}, in a "Y" shape molecule. The constant regions together form the Fc fragment, while the variable regions compose the Fab fragment.

to neurons and complement deposition on neurons in brain tissue. However, none of the 3 patients with NMDAR autoantibodies presented with complement deposition [51]. Another two studies presented similar results, with no evidence of complement deposition in brain biopsies from NMDAR encephalitis patients [52,53]. Based on the Ig isotype, complement mediated pathology could be hypothesized in $GABA_BR$, $GABA_AR$, mGluR5 and neurexin-3, where IgG1 is the most prevalent isotype described [54].

d) Loss or block of antigen-associated proteins. An important example of this is the VGKCC, where the autoantibodies are often directed against associated proteins, LGI1 and CASPR2 [55,56]. Antibodies to LGI1 can disrupt the interaction with scaffolding proteins like ADAM22 or ADAM23 [56,57]. Autoantibodies from patients with NMDAR encephalitis are found to interrupt the contact between NMDAR and Ephrin B2/EphB2 receptors, stabilizing and helping the receptor clustering in the postsynaptic membrane [58–61]. As a compensatory mechanism, increased EphB2 levels have been observed *in vitro* and *in vivo* [37]. A decrease of DPPX and Kv4.2 expression has been detected in presence of DPPX antibodies when incubated with hippocampal neurons [33,54].

3. Blood-brain-barrier

After the activation of the immune system, antibody producing cells travel in the blood to reach the organ with the targeted antigen. However, how antibodies or antibody producing cells reach the central nervous system (CNS) is still not well characterized. The blood brain barrier (BBB) unselectively prevents passage of the vast majority of molecules to the brain. The BBB is impermeable to hydrophilic substances and mostly also to large molecules such as proteins, so as to protect the CNS against the potential deleterious actions of these substances. In fact, antibodies can cross the human BBB to a limited extent [62] and reach sites in the CNS to exert pathogenic effects [63]. Diseases in which this is known to occur include paraneoplastic neurological syndromes [64], neuromyelitis optica [65], Stiff-person's syndrome [66], epilepsy with glutamic acid decarboxylase (GAD) antibodies [66,67], narcolepsy [68], dyslexia [69], Morvan's syndrome and limbic encephalitis [55].

Antibodies can be generated on both sides of the BBB, intrathecally [70] or peripherally from where they access the brain by crossing the BBB through different mechanisms. With an intact BBB, antibodies gain access to the CSF with a rate of 0.018 mg/min and have a turnover rate of five times per day, comparable to the CSF turnover itself of four times per day [62]. This very dynamic equilibrium results in brain IgG levels of around 1% of the plasma levels. Nonetheless IgG still composes 9.8% of the total protein in the CSF [62,71], whereas IgA and IgM are found only in trace amounts [72]. Following local inflammatory reactions, it is known that the BBB becomes much more permeable. For instance, in

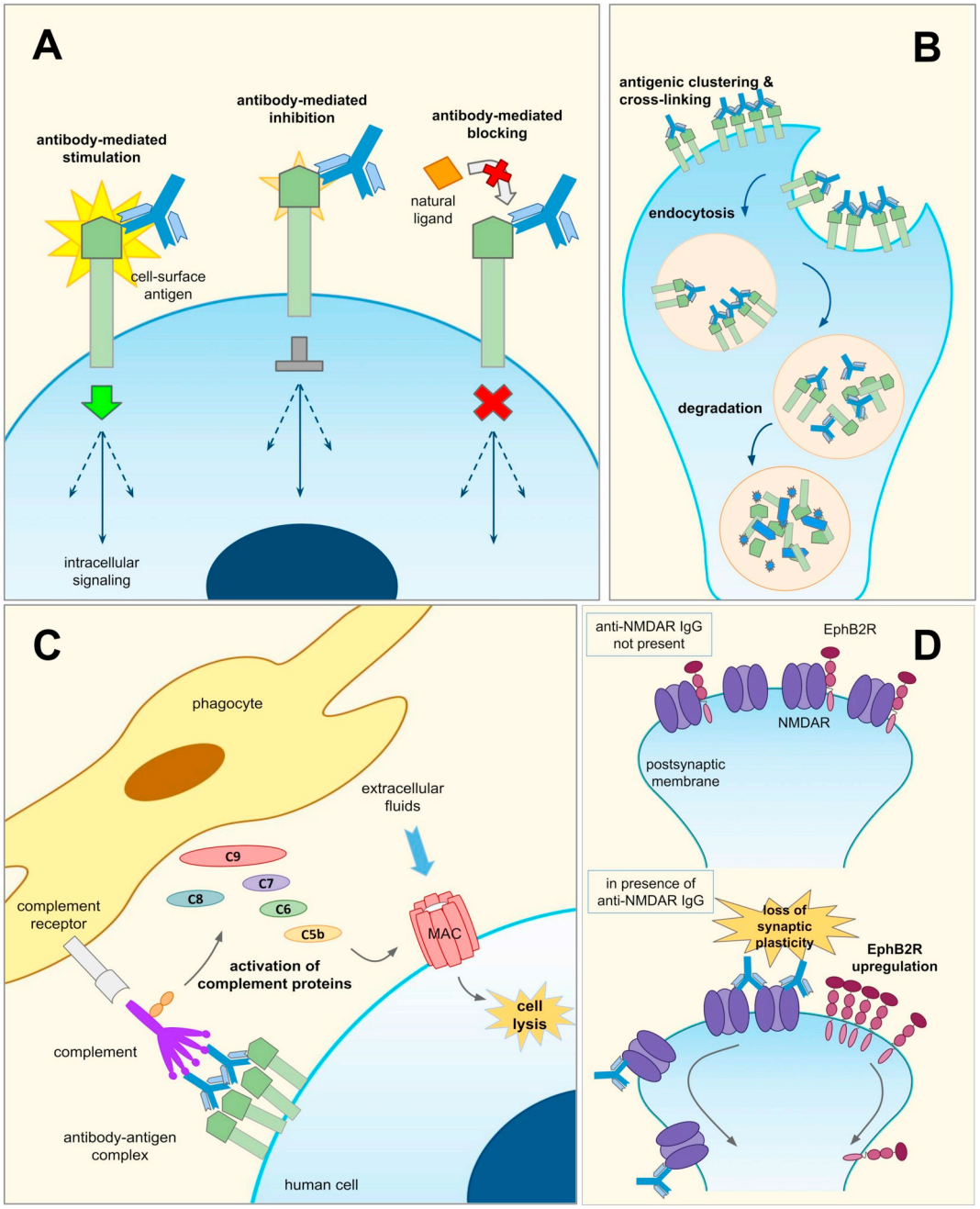

Fig. 3. IgG antibody-mediated disease mechanisms.
A) The binding of an antibody to a cell surface antigen can cause either stimulation, inhibition or blocking to the action of agonists on the antigen and its intracellular signaling pathways. B) Cross-linking or clustering of antigens can occur when one antibody binds to 2 antigens. This triggers the removal of the antibody-antigen complexes via endocytosis, after which the complexes are degraded. C) Formation of an antibody-antigen complex can activate the complement system leading to chemoattraction of phagocytes, which can bind to complement via specific receptors, initiating opsonization and engulfment. Various other complement proteins are activated as well and assembled into a membrane attack complex (MAC). This creates a pore in the cell membrane through which extracellular fluids enter the cell, eventually inducing cell lysis. D) Antibodies can interfere with the contact between the antigen and its associated membrane proteins, as is the case for NMDA and EphB2 receptors. EphB2 receptors contribute to proper clustering of NMDAR in the postsynaptic membrane, which is crucial for synaptic plasticity. Antibodies can obstruct the contact between EphB2 and NMDAR, causing impaired synaptic retention of both receptors and loss of synaptic plasticity. As compensatory mechanism, EphB2R is upregulated.

multiple sclerosis, the permeability is increased six fold [71]. Moreover, neuroinflammation may lead to local production of antibodies by B-cells or plasma cells in the brain itself, so that the concentration of antibodies there is strongly increased. A high level of antibodies in the CSF indicates an intrathecal synthesis of antibodies by migrated antibody producing cells in the brain, which is in line with the observation that the level of antibodies in CSF is more closely related with relapses in NMDAR encephalitis than in serum [73]. In psychotic disorders, the CSF analysis presented elevated white cell count as well as total protein levels and albumin quotient in 3.4, 42.2 and 21.8% respectively, concluding that Igs have been intrathecally produced in 7.2% of the cases [74].

Recent studies have shown that the deep cervical lymph nodes have an important role in the processing and presentation of antigens of the CNS for T-cell mediated responses [75] but not for antibody-mediated

Table 1
Studies on the prevalence of neuronal autoantibodies in psychotic disorders.

Targeted antigen	Disorder	Reference	Antibody source	Methods	N (patients/ controls)	Isotypes studied	IgG prevalence (patients/ controls)	Targeted antigen
VGKC complex	First episode psychosis	[94]	Serum	RIA	228/105	IgG	5	3
				Live CBA (LGI1)	228/105	IgG	1	0
				Live CBA (CASPR2)	228/105	IgG	1	3
	First episode psychosis	[93]	Serum	RIA	46/n.a.	IgG	2.2	n.a.
	Psychotic disorders*	[74]	CSF	Fixed CBA (LGI1/CASPR2)	125/n.a	IgG	2.4	n.a.
	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (LGI1) + IHC	1378/1703	IgG, IgA, IgM	0.1	0.1
				Fixed CBA (CASPR2) + IHC	1378/1703	IgG, IgA, IgM	0.4	0.3
	Affective disorders	[95]	Serum	Fixed CBA (LGI1) + IHC	310/1703	IgG, IgA, IgM	0	0.1
				Fixed CBA (CASPR2) + IHC	1378/1703	IgG, IgA, IgM	0.3	0.3
	First episode psychosis	[96]	Serum	Fixed CBA (CASPR2) + IHC	70/34	IgG	0	0
	Schizophrenia spectrum disorder	[109]	CSF	Fixed CBA (LGI1)	110/n.a.	IgG	0	n.a.
			Serum	Fixed CBA (LGI1)	81/n.a.	IgG	0	n.a.
			CSF	Fixed CBA (CASPR2)	111/n.a.	IgG	0	n.a.
			Serum	Fixed CBA (CASPR2)	81/n.a.	IgG	2.5	n.a.
	Schizophrenia	[108]	Plasma	Fixed CBA (LGI1)	78/n.a.	IgG	0	n.a.
				Fixed CBA (CASPR2)	78/n.a.	IgG	0	n.a.
	Acute schizophrenia spectrum disorder	[103]	Serum	Fixed CBA (CASPR2) + IHC***	144/n.a.	IgG, IgA, IgM	1.4	n.a.
	Acute bipolar disorder	[103]	Serum	Fixed CBA (CASPR2) + IHC***	125/n.a.	IgG, IgA, IgM	0.8	n.a.
	Acute schizophrenia spectrum disorder	[103]	Serum	Fixed CBA (LGI1)	144/n.a.	IgG, IgA, IgM	0	n.a.
	Acute bipolar disorder	[103]	Serum	Fixed CBA (LGI1)	125/n.a.	IgG, IgA, IgM	0	n.a.
	First episode psychosis	[104]	Serum	Fixed CBA (CASPR2) + IHC + neurons**	61/45	IgG	0	0
				Fixed CBA (LGI1) + IHC + neurons**	61/45	IgG	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA (CASPR2) + IHC + neurons****	96/64	IgG	0	0
				Fixed CBA (LGI1) + IHC + neurons****	96/64	IgG	0	0
NMDAR	First episode psychosis	[94]	Serum	Live CBA (NR1/2b)	228/105	IgG	3	0
	First episode psychosis	[93]	Serum	Live CBA (NR1/2b)	46/n.a.	IgG	6.5	n.a.
	Psychotic disorders*	[74]	CSF	Fixed CBA (NR1/2b)	125/n.a	IgG	0.8	n.a.
	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (NR1) + IHC	1378/1703	IgG, IgA, IgM	0.6	1.2
	Affective disorders	[95]	Serum	Fixed CBA (NR1) + IHC	310/1703	IgG, IgA, IgM	1.9	1.2
	Schizophrenia	[38]	Serum	Fixed CBA (NR1/2b) + IHC	50/n.a.	IgG, IgA, IgM	0	n.a.
	First episode psychosis	[110]	Serum	Flow/live CBA (NR1) + IHC + neurons	43/17	IgG, IgM, IgA	11.6	0
	Schizophrenia spectrum disorder	[107]	Serum/plasma	Fixed CBA (NR1/2b) + IHC	475/n.a	IgG	0	n.a.
	First episode psychosis	[106]	Serum	Fixed CBA (NR1/2b) + IHC + neurons	80/40	IgG	0	0
	First episode psychosis	[96]	Serum	Fixed CBA (NR1/2b) + IHC	70/34	IgG	0	0
	Schizophrenia spectrum disorder	[109]	CSF	Fixed CBA (NR1/2b)	119/n.a.	IgG	0	n.a.
			Serum	Fixed CBA (NR1/2b)	81/n.a.	IgG	0	n.a.
	First episode psychosis	[105]	Serum	fixed CBA (NR1/2b),	298/n.a.	IgG	0.7	n.a.
				Live CBA (NR1/2b)	298/n.a.	IgG	2.7	n.a.
	Schizophrenia	[108]	Plasma	Fixed CBA (NR1) + IHC**	312/n.a.	IgG	0	n.a.
	Treatment refractory schizophrenia spectrum disorder	[111]	Serum	Live CBA (NR1/2b)	43/n.a.	IgG	7.0	n.a.
	Acute schizophrenia spectrum disorder	[103]	Serum	Fixed CBA (NR1) + IHC	144/n.a.	IgG, IgA, IgM	0	n.a.
	Acute bipolar disorder	[103]	Serum	Fixed CBA (NR1) + IHC***	125/n.a.	IgG, IgA, IgM	1.6	n.a.
	First episode psychosis	[104]	Serum	Fixed CBA (NR1) + IHC + neurons**	61/45	IgG	3.3	0
	Post-partum psychosis	[112]	Serum	Fixed CBA (NR1/2) + IHC + neurons****	96/64	IgG	2.1	0

(*continued on next page*)

Table 1 (*continued*)

Targeted antigen	Disorder	Reference	Antibody source	Methods	N (patients/ controls)	Isotypes studied	IgG prevalence (patients/ controls)	Targeted antigen
AMPAR	First episode psychosis	[94]	Serum	Live CBA (GluR1/2)	228/105	IgG	0	0
	Psychotic disorders*	[74]	CSF	Fixed CBA (GluR1/2)	96/n.a.	IgG	0	n.a.
	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (GluR1/2) + IHC	1378/1703	IgG, IgA, IgM	0.1	0.1
	Affective disorders	[95]	Serum	Fixed CBA (GluR1/2) + IHC	310/1703	IgG, IgA, IgM	0	0.1
	First episode psychosis	[96]	Serum	Fixed CBA (AMPAR) + IHC	70/34	IgG	0	0
	Schizophrenia spectrum disorder	[109]	CSF	Fixed CBA (GluR1/2)	114/n.a.	IgG	0	n.a.
			Serum	Fixed CBA (GluR1/2)	81/n.a.	IgG	0	n.a.
	Schizophrenia	[108]	Plasma	Fixed CBA (GluR1/2)	78/n.a.	IgG	0	n.a.
	Acute schizophrenia spectrum disorder	[103]	Serum	Fixed CBA (AMPAR) + IHC***	144/n.a.	IgG, IgA, IgM	0.7	n.a.
	Acute bipolar disorder	[103]	Serum	Fixed CBA (AMPAR) + IHC	125/n.a.	IgG, IgA, IgM	0	n.a.
	First episode psychosis	[104]	Serum	Fixed CBA (GluR1/2) + IHC + neurons**	61/45	IgG	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA (GluR1/2) + IHC + neurons****	96/64	IgG	0	0
$GABA_AR$	First episode psychosis	[94]	Serum	Live CBA ($GABA_AR$, α1,γ2)	228/105	IgG	4	1
	First episode psychosis	[96]	Serum	Fixed CBA ($GABA_AR$) + IHC	70/34	IgG	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA ($GABA_AR$) + IHC + neurons****	96/64	IgG	0	0
$GABA_BR$	Psychotic disorders*	[74]	CSF	Fixed CBA ($GABA_BR$)	96/n.a	IgG	0	n.a.
	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA ($GABA_BR1/2$) + IHC	1378/1703	IgG, IgA, IgM	0	0
	Affective disorders	[95]	Serum	Fixed CBA ($GABA_BR1/2$) + IHC	310/1703	IgG, IgA, IgM	0.3	0
	First episode psychosis	[96]	Serum	Fixed CBA ($GABA_BR$) + IHC	70/34	IgG	0	0
	Schizophrenia spectrum disorder	[109]	CSF	Fixed CBA ($GABA_BR1/2$)	112/n.a.	IgG	0	n.a.
			Serum	Fixed CBA ($GABA_BR1/2$)	81/n.a.	IgG	0	n.a.
	Schizophrenia	[108]	Plasma	Fixed CBA ($GABA_BR1$)	78/n.a.	IgG	0	n.a.
	Acute schizophrenia spectrum disorder	[103]	Serum	Fixed CBA ($GABA_BR$) + IHC	144/n.a.	IgG, IgA, IgM	0	n.a.
	Acute bipolar disorder	[103]	Serum	Fixed CBA ($GABA_BR$) + IHC	125/n.a.	IgG, IgA, IgM	0	n.a.
	First episode psychosis	[104]	Serum	Fixed CBA ($GABA_BR$) + IHC + neurons**	61/45	IgG	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA ($GABA_BR$) + IHC + neurons****	96/64	IgG	0	0
D2DR	First episode psychosis	[110]	Serum	Flow/live CBA (D2DR) + IHC + neurons	43/17	IgG, IgM, IgA	7.0	0
	First episode psychosis	[96]	Serum	Fixed CBA (D2DR) + IHC	70/34	IgG, IgM, IgA	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA (D2DR) + IHC + neurons****	96/64	IgG	0	0
DPPX	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (DPPX) + IHC	1378/1703	IgG, IgA, IgM	0.1	0.1
	Affective disorders	[95]	Serum	Fixed CBA (DPPX) + IHC	310/1703	IgG, IgA, IgM	0	0.1
	First episode psychosis	[96]	Serum	Fixed CBA (DPPX) + IHC	70/34	IgG	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA (DPPX) + IHC + neurons****	96/64	IgG	0	0
Nicotinic AChR	Schizophrenia	[165]	Serum	ELISA (α7 AChR)	21/17	IgG	23.8	0
	Psychotic disorders	[166]	Serum	RIA (α7 AChR)	508/118	IgG	0.2	0
GlyR	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (GlyRα1) + IHC	1378/1703	IgG, IgA, IgM	0.1	0.1
	Affective disorders	[95]	Serum	Fixed CBA (GlyRα1) + IHC	310/1703	IgG, IgA, IgM	0	0.1
	First episode psychosis	[96]	Serum	Fixed CBA (GlyR) + IHC	70/34	IgG	0	0
	Post-partum psychosis	[112]	Serum	Fixed CBA (GlyR) + IHC + neurons****	96/64	IgG	0	0
GAD	Psychotic disorders*	[74]	CSF	immunoblot (GAD65)	142/n.a	IgG	0	n.a.
	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (GAD65) + IHC	1378/1703	IgG, IgA, IgM	0.6	0.3
				Fixed CBA (GAD67) + IHC	1378/1703	IgG, IgA, IgM	0.1	0.1
	Affective disorders	[95]	Serum	Fixed CBA (GAD65) + IHC	310/1703	IgG, IgA, IgM	0.3	0.3
				Fixed CBA (GAD67) + IHC	1378/1703	IgG, IgA, IgM	0.3	0.1
	First episode psychosis	[96]	Serum	Fixed CBA (GAD65) + IHC	70/34	IgG	0	0
	Acute schizophrenia spectrum disorder	[103]	Serum	Fixed CBA (GAD65) + IHC***	144/n.a.	IgG, IgA, IgM	0.7	n.a.
	Acute bipolar disorder	[103]	Serum	Fixed CBA (GAD65) + IHC***	125/n.a.	IgG, IgA, IgM	2.4	n.a.

(*continued on next page*)

Table 1 (*continued*)

Targeted antigen	Disorder	Reference	Antibody source	Methods	N (patients/ controls)	Isotypes studied	IgG prevalence (patients/ controls)	Targeted antigen
Amphiphysin	Psychotic disorders*	[74]	CSF	Immunoblot (amphiphysin)	142/n.a	IgG	0	n.a.
	Schizophrenia/schizoaffective disorder	[95]	Serum	Fixed CBA (amphiphysin)	1378/1649	IgG, IgA, IgM	1.7	1.7
	Affective disorders	[95]	Serum	Fixed CBA (amphiphysin)	310/1649	IgG, IgA, IgM	2.3	1.7
	Schizophrenia spectrum disorder	[96]	CSF	Fixed CBA (amphiphysin)	93/n.a.	IgG	0	n.a.
			Serum	Fixed CBA (amphiphysin)	81/n.a.	IgG	0	n.a.

AChR: acetylcholine receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2: contactin-associated protein 2; CBA: cell based assay; CSF: cerebrospinal fluid; D2DR: dopamine receptor 2; DPPX: dipeptidyl aminopeptidase-like protein 6; $GABA_AR$: *gamma*-aminobutyric acid A/B receptor; GAD: glutamic acid decarboxilasa; GlyR: glycine receptor; Ig: immunoglobulin; IHC: immunohistochemistry; LGI1: leucine-rich glioma inactivated protein 1; NMDAR: N-methyl-D-aspartate receptors; RIA: radioimmunoassay; VGKC: voltage gated potassium channel.

* Some patients were selected based on suspicion of organic brain disease.

** Only CBA positive samples were tested by IHC/neurons.

*** Positive CBA results were negative when tested by IHC.

**** Only IHC positive were tested by neurons/CBA.

disorders. However, in NMDAR encephalitis, antibodies seem to occur earlier in CSF than in peripheral blood [76,77]. Moreover NMDAR antibodies have been cloned from CSF-derived cells [78], which indicates an intrathecal synthesis of autoantibodies [70]. This is usually accompanied with inflammatory changes such as pleocytosis and increased protein levels [73,74,79]. Furthermore, levels of the B cell attracting chemokine C-X-C motif chemokine 13 -CXCL13-, associated with plasma cells in the CNS, have been correlated with the intrathecal synthesis of NMDAR antibodies and with limited response to treatments and relapses [80].

It is important to note that in spite of the dynamic turnover of antibodies between the periphery and the brain, well-defined autoantibodies of peripheral diseases, like the Lambert-Eaton myasthenic syndrome and neuromyotonia, do not have central effects. This is remarkable because calcium $Ca_v2.1$ (P/Q-type) channels and VGKCC proteins are also present in the brain and could therefore be targeted by these antibodies. Thus, in some cases, CNS autoimmune channelopathies occur only when the integrity of the BBB is disrupted and antibodies gain access to the brain at a higher rate. From this point of view, it might be argued that CASPR2 limbic encephalitis, Morvan's syndrome and acquired neuromyotonia harbor the same or similar disease aspects of pathophysiology and immunological pathogenesis, but that there is a relative difference in permeability of the BBB to the antibodies in these disorders [55].

In line with this, mice immunized with a peptide producing both antibodies to DNA and NMDAR did not show brain pathology unless the integrity of the BBB was challenged [63]. It is unlikely that the BBB is equally permeable to antibodies or antibody-producing cells throughout the brain. Factors affecting the BBB integrity with respect to the transport of antibodies may show regional specificity. This would explain why the "phenotype" of the antibody effect may well depend on the location where the antibody enters the brain and why the same autoantibody might have substantially different pathological effects between different groups of patients. After lipopolysaccharide treatment, NMDAR antibodies derived from systemic lupus erythematosus patients attack channels in hippocampal neurons [81], while the same antibodies damage channels in other regions of the brain, after treatment with adrenaline -which is known to breach BBB integrity [82] (see ref. [63] for a review on BBB and antibodies).

4. Antibody-mediated channelopathies in neuropsychiatric disorders

Over two-thirds of patients with autoimmune encephalitis have marked psychotic symptoms that can prevail in periods without obvious neurological manifestations; before onset of encephalitis or as a relapse. Around 45% of pediatric [83] and 16.5% of adults with limbic encephalitis [84] and antibodies to VGKCC presented with psychotic manifestations [85]. Many patients have their initial presentation at psychiatric services with more than 60% being first admitted to a psychiatric unit [86–88]. The psychotic manifestations are similar to those seen in schizophrenia including delusional and delirious thinking, anxiety, insomnia, paranoid thoughts, manic and aggressive behaviour, hallucinations and catatonic movement disorder [70,83,89–92]. In VGKCC antibody-associated encephalopathy, cognitive impairment is an important feature but other neuropsychiatric symptoms occur in various degrees, mainly characterized by personality changes, depression and anxiety (see ref. [85] for review including single case studies). These findings indicate that some cases with underlying encephalitis could be mistaken for a primary psychotic disorder.

4.1. Incidence of autoantibodies in psychotic disorders

In the past 10 years, numerous cohorts of patients with mental disorders have been tested for the presence of specific neuronal autoantibodies, with those against the NMDAR and the VGKCC being the

most well-described. Outcomes of these studies are variable, as are the detection methods applied. This section summarizes these findings. Details of relevant studies are shown in Table 1.

An initial study reported serological prevalence of antibodies to VGKCC in first episode psychosis (2.2%) [93], tested by radioimmunoassay (RIA), but lacked a control group. A recent study also using VGKCC RIA reported a similar prevalence of autoantibodies both in first episode psychosis (5%) as well as controls (3%) [94]. Importantly, the same and other studies find much lower prevalences when studying specific IgG autoantibodies targeting LGI1 and CASPR2 by cell based assay (CBA) (0-1%) [95–97]. Antibodies to LGI1 but not to CASPR2 were also detected in 2 out of 144 (1.4%) patients with actute schizophrenia disorders and in 1 out of 125 patients (0.8%) with acute bipolar disorder in serum by CBA. However this study lacked a control group and CBA positive sera gave negative results by immunohistochemistry (IHC) [103]. However, it is important to keep in mind that autoantibodies against VGKCC but not directed against LGI1 or CASPR2, have no clinical relevance in cases of autoimmune encephalitis [98–100].

Variable results have been reported for the prevalence of autoantibodies to NMDAR in patients with psychotic disorders. Several studies have shown high prevalence (~10%) of autoantibodies when including IgG, IgA, and IgM isotypes. However, there were no differences in the distribution of Igs among psychotic patients, other neuropsychiatric disorders and healthy controls; indicating that these isotypes are not disease specific [95,101,102]. When studying only the IgG isotype, these and other studies reported much lower NMDAR prevalences in psychotic patients (0.7-3.3%) [74,94,103–105] or complete absence of these autoantibodies [96,103,106–109]. A recent study also analyzed the three Ig isotypes in serum of different disease cohorts (NMDAR encephalitis, suspected autoimmune encephalitis, schizophrenia, stroke, and dementia), and found that the IgG NMDAR autoantibodies were disease specific for NMDAR encephalitis, with no antibodies present in 50 schizophrenia subjects nor in the other disease groups. In addition, IgG but not IgA or IgM had pathogenic effects *in vitro* [38].

Higher prevalence of NMDAR IgG autoantibodies have been, however, found in special cohorts of psychotic disorders: The first group included children with first episode of acute psychosis. Using a combination of NR1 and D2DR flow cytometry, CBA and primary neuronal cell culture, Pathmanandavel and colleagues found serum NMDAR IgG antibodies in 5 out of 43 of these children (one of the patients had IgG + IgM autoantibodies targeting NR1, one had IgG to NR1 + D2DR IgG autoantibodies, and another one had IgA but not IgG to NR1) [110]. The second group consisted of a cohort of 43 refractory patients with schizophrenia or schizoaffective disorder (with a mean duration of more than 15 years). IgG autoantibodies to NMDAR were found in 7% of the cases by live CBA. None of the patients had MRI abnormalities, nor neurological signs including seizures [111]. However, the lack of a control group, together with the exclusive use of live CBA, known to give higher detection rates [105], make these results difficult to interpret. The third group consisted of patients with post-partum psychosis. Neuronal surface reactivity was detected by brain IHC in serum in 4 out of 96 post-partum patients with psychosis. Two of these patients specifically presented IgG against the NMDAR by CBA. However, all the patients recovered without any immunotherapy [112]. Effects of the maternal antibodies in the offspring have been so far only described in cases of autism spectrum disorder, mental retardation and/or disorders of psychological development [113], specific language difficulties and dyslexia [69,114–117], all of them disorders wich develop early in life.

The detection of autoantibodies have proven to be more sensitive in CSF compared to serum in cases of NMDAR encephalitis [73,118,119]. However, in psychotic disorder cohorts, there is limited access to CSF samples. NMDAR and VGKCC (LGI1 and CASPR2) autoantibodies were detected in CSF (not tested in serum) in 0.8% for NMDAR antibodies and 2.4% for VGKCC antibodies in psychotic disorder patients [74]. Another study with a similar cohort showed comparable percentages of VGKCC autoantibodies in CSF (2.5% positive for CASPR2) but no antibodies were detected for NMDAR. No neuronal autoantibodies were found in the serum from the same patients [109]. The difficulty of interpreting studies where CSF has been analyzed, is that there are no control cohorts available, and the results have not been cross-validated.

Antibodies against other neuronal antigens have been described for autoimmune encephalitis and are associated with psychotic manifestations. To date autoantibodies to AMPAR, $GABA_BR$, $GABA_AR$, D2DR, GlyR, mGluR1/mGluR5, alpha7 AChR, GAD67/GAD67, amphiphysin, neurexin, etc. have been reported as absent or at low prevalence among psychotic disorders (reviewed by [54]).

Interestingly, some studies have reported presence of autoantibodies against unkonwn neuronal antigens. This is the case of 2 out of 96 post-partum psychosis patients, who showed reactivity by brain immunohistochemistry and immunocytochemistry using live hippocampal neurons [112]. In 17 out of 925 cases, patients admitted to acute psychiatric care, presented immunofluorescence staining on rat and monkey brain sections, without corresponding to a specific antigen [103]. A cohort from the Netherlands Study of Depression and Anxiety (NESDA) revealed that 8 out of 1739 patients but none of the 492 controls, presented with strong hippocampal patterns by rat brain IHC. Five of the positive patients were confirmed by primary hippocampal neurons and all of them shared common clinical manifestations, characterized by anxiety (Zong et al., manuscript in preparation). Similar results have been observed in a cohort of neuropsychiatric disorders, where autoantibodies against neuronal antigens have been detected by brain IHC in 14 out of 621 patients with psychosis, in 1 out of 70 patients with affective disorders and in 5 out of 259 non-disease controls (Hoffmann et al., manuscript in preparation).

4.2. Case reports of patients with strong psychotic manifestations

The increasing awareness of autoimmune encephalitis clinical presentation among clinicians and especially psychiatrists has led to early diagnoses of autoimmune encephalitis with psychotic manifestations. However, there are still a number of case reports with NMDAR autoantibodies predominantly with psychotic symptoms, where a correct diagnosis was complicated. These patients were given provisional diagnoses such as dissociative disorder, or psychotic disorder for several weeks or even years, until the presence of antibodies was finally discovered and treated accordingly with immunosuppression [90,120,121]. A recent case reported a misdiagnosed autoimmune encephalitis with VGKCC antibodies in a 16-year old girl, acutely presenting with isolated psychotic symptoms characterized by mania, psychosis and various behavioral and personality changes with no evidence of any neurological abnormality. Psychotropic medication only aggravated some of the symptoms and resulted in a minimal overall improvement. After 2 weeks, high levels of anti-VGKCC antibodies (but not specifically against LGI1 or CASPR2) were detected in serum (methodology not clearly specified). The patient received several courses of intravenous immunoglobulin (IVIG) and methylprednisolone and gradually recovered to normal status, 6-9 months after the psychotic episode [122,123].

Yet, despite the presence of neurological symptoms, an autoimmune condition can be misdiagnosed as psychotic disorder. Especially, after initiation of antipsychotic medication, typical autoimmune symptoms such as dyskinesias are often assumed to be extrapyramidal side effects [5]. Also, epilepsy patients have shown increased risk of psychosis and psychotic illness [124,125], whilst schizophrenic patients are also more likely to suffer from epilepsy [126]. Therefore, it is not surprising that psychotic manifestations are accompanied in many cases by neurological abnormalities, including seizures and therefore the diagnosis of autoimmune encephalitis can be delayed.

A case of a 17-year old male was reported with acute behavioral and mental disturbances characterized by psychosis, agitation,

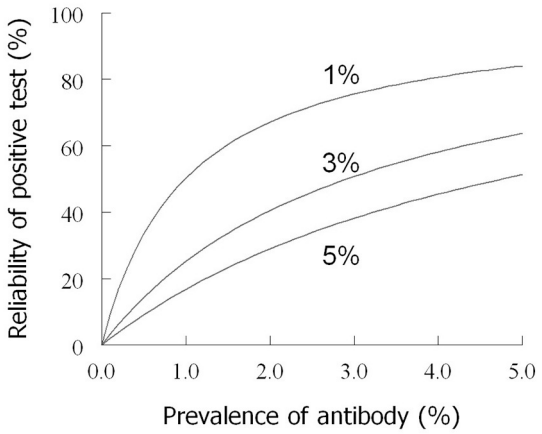

Fig. 4. Relation between reliability of positive outcomes of antibody tests as a function of the prevalence of the antibody within the targeted group with psychosis.
The fractions are expressed as percentages. For specificity three conditions are shown, corresponding to 1%, 3% and 5% false positives assumed for the group of healthy controls. The graph is a hyperbole according to the equation Reliability = Pr/((Pr + (1 – Sp)(1 – Pr)), where Pr is prevalence of the autoantibody within the psychosis group and Sp the specificity of the antibody assay in the control group. For the equation it is assumed that the likelihood for yielding false positives in the psychosis patients without the antibody is the same as in the healthy control group. The figure shows that the antibody test becomes very unreliable when the prevalence is low in combination with a high percentage of false positives in the human control group. For example, with a prevalence of 1% and a specificity of 95%, only 17% of all positive outcomes are expected positive whereas 83% of them are expected to be false. With 99% specificity, the outcomes are expected to be 50% correct and 50% false positives, respectively.

disorganization in behavior and thought processes, hypermetabolism and catatonia, together with seizures. Upon unresponsiveness to antipsychotic agents, the patient underwent electroconvulsive therapy with a remarkable improvement. After a period of four weeks, CSF analysis revealed the presence of anti-NMDAR antibodies (methodology not specified). IVIG immunosuppressant therapy was started, showing a noteworthy improvement [127]. After a long history of alcohol excess consumption, depression and self-harm, a 58-year old male was admitted to the hospital after presenting with seizures, confusion, slurred speech and ataxia. After psychiatric assessment he was diagnosed with paranoid schizophrenia and given antipsychotic medication. Further tests were performed after a deterioration of his symptoms and epileptic onset. Antibodies to VGKCC were detected in serum but not in CSF (detection assay not specified) and the patient underwent plasmapheresis, in combination with IVIG and corticosteroids, which caused a substantial improvement of the seizures but with only a minor gain of his cognitive abilities [128].

Post-partum psychosis cases include: i) a 21-year old female presented with psychotic symptoms four weeks after giving birth. After a few weeks, she suffered generalized seizures and had high anti-nuclear antibody levels but no abnormalities in the CSF. A substantial improvement resulted from plasmapheresis and steroids treatment. Later, serum IgGs against VGKCC, specifically targeting LGI1 were identified by RIA and live CBA respectively. The patient recovered completely after immunosuppressive treatment [129]; ii) three months after a normal delivery, a 25 year old female developed insomnia, agitation and thanatophobia (fear of death). Antipsychotic treatment, including electroconvulsive therapy, resulted in generalized seizures. After aggravation of the psychotic symptoms and a suicidal attempt, laboratory tests were performed. No abnormalities were detected in serum but in CSF, where antibodies to NMDAR were found (detection assay not specified). Forthwith she was diagnosed with an ovarian teratoma. Repeated IVIG and intravenous methylprednisolone did not show any relieve of symptoms. However, after tumor resection, the patient had a dramatic and stable improvement with minimal behavioural changes at 6 months after surgery [119]; iii) similarly, three women were hospitalized during pregnancy presenting with headache and malaise; followed by bizarre behavior, anxiety, paranoid delusions, seizures and a decreased level of consciousness. Ovarian teratoma was diagnosed in 2 cases (resulted in pregnancy termination in one of the cases). After the identification of NMDAR antibodies in serum and CSF by CBA, the patients were treated with methylprednisolone, plasmapheresis and/or IVIG, together with ovarian teratoma resection in 2 of the cases. The babies showed no abnormalities after birth [130].

Tumor resection and immunotherapy using first line treatment usually results in partial or complete disappearance of the symptoms. However, in some cases, second line immunosuppressive therapies are required. This is also described in two independent case reports of young women, who developed post-partum psychosis followed by typical signs of NMDAR encephalitis. One was diagnosed with ovarian teratoma and both had NMDAR autoantibodies in the CSF. Tumor removal, intravenous methylprednisolone and plasmapheresis resulted in little improvement, but subsequent rituximab therapy improved the clinical manifestations of both women dramatically [131,132].

All in all, autoimmune encephalitis is estimated to have an annual incidence of around 1.2 per 100,000 cases [133]. In many case reports describing patients with pronounced psychotic manifestations, the methodology used to detect autoantibodies is not carefully detailed, making it very difficult to interpret results. Although we do not expect a higher incidence rate in the psychiatric population, we would still like to highlight the importance of considering the diagnosis of autoimmune encephalitis in patients presenting with psychosis and seizures. This is especially vital in those with no previous history of psychotic disorders, a rapid progression of the disease, or resistance to antipsychotic medication since the majority of the patients respond well to readily available immunotherapy.

5. Sensitivity and specificity

The interpretation of the results in the literature regarding patients with pronounced psychotic manifestations is, unfortunately, difficult. As described through this review, lack of specified methodological strategies and the choice of the different assays, together with the absence of control groups reduces the impact of the findings.

In a group of patients with psychosis, it is likely that the prevalence of neuronal surface antibodies will be below 1% per specific neuronal antibody, making the reliability of a positive outcome rather small. Thus, the outcome of individual tests would be a poor guidance for counseling immunotherapy and certainly would make simple screening for antibodies in psychosis unfeasible. False results can pose a considerable problem for its interpretation, especially when the probability of specific neuronal antibodies in the test group is low. This is because the reliability of a positive assay outcome is influenced by the prevalence and the number of false positives of the test, as depicted in Fig. 4: the lower the prevalence, the poorer is the reliability with a concomitant increase of the chance of obtaining false positive results.

5.1. Sensitivity and false negatives

The fraction of disease cases that an assay correctly predicts, defines the clinical sensitivity of the assay in question [134,135]. A clinical assay should have around 70% or higher sensitivity to be useful. There are several reasons why an assay could result in negative outcomes for patients genuinely suffering from an autoimmune disease (i.e. with a sensitivity of 70% this would be 30% of all cases);

1) Low (undetectable) antibody concentration in blood
2) Low affinity of the antibody to the antigen
3) High affinity and avidity of the antibody for the antigen *in vivo*,

leading to reduced antibody levels in blood (immunoabsorption effect [136])
4) Interference between the protein in the sample and the assay (i.e. absence of the antibody in the membrane due to antibody internalization and resulting in unclear or ambiguous results)
5) Lack of recognition caused by conformational epitope changes (denaturalization or non-native conformations) or by absence of receptor-associated proteins, required for the original exposure of the antigen (i.e. anchoring the receptor to the membrane and keeping it in its native conformation) [137]
6) Hook or prozone effect, caused by the excess of antibodies or the lack of agglutination and formation of immunocomplexes

5.2. Specificity and false positives

The fraction of individuals with absence of disease that an assay correctly predicts defines the clinical specificity of an immunological assay. Clinical specificity should be preferably 95% or higher to be useful. However, there are at least three reasons why a test might not be fully specific (95% specificity implies that there are 5% false positives in the control group). "False positive" outcomes may arise because:

1) The test sample does indeed contain an antibody that is directed to the antigen used in the test; but apparently non-pathogenic (e.g. by not reaching the CNS)
2) The test sample contains an (non-pathogenic) antibody that is directed to a "related" antigen which cross-reacts with the antigen used in the test (e.g. a similar receptor or ion channel)
3) A different protein in the sample interferes with the antigen staining so that an incorrect positive result is read in the laboratory

Is has been reported that positive results for NMDAR antibodies obtained by a commercial kit were not confirmed through cross-validation in two other independent laboratories using commercial and in-house CBA as well as IHC [107]. This example highlights the importance of considering the variation across tests (including vatiability between different batches of the same test), which will result in differences in sensitivity, specificity, or background signal and supports the need for expert and independent approaches evaluating the results in order to reduce variability and inconsistent results [105,107,138].

Changes in sensitivity and, specifically, in specificity between different laboratories (including companies), variations in the protein homology between species used in the assays and conformational modifications by the pre-treatment such as fixation of the tissue are all possible causes for incoherent or false positives/negatives to occur. Although the homology between human and rodent proteins reaches 95% in most cases, some differences in the extracellular regions can lead to false results, both positive and negative. It has also been observed that embryonic and adult forms of some subunits may differ [139] (i.e. the *gamma* subunit of the AChR is present in embryonic tissue but is replaced by a homologous *epsilon* subunit in adult tissue [140]). Different autoantibodies can coexist in the same patient and this phenomenon may occur in up to 10% of the patients with an autoimmune disease. This raises the possibility that part of the false responses are due to the presence of autoantibodies against a variety of antigens, some of which happen to cross-react with the antigen used in the assay.

5.3. Considerations for combining diagnostic assays

Cellular and tissue based techniques are used to diagnose the presence of autoantibodies. However, it is important to mention that when approaching psychotic disorder cohorts where the expected prevalence of autoantibodies is quite low, the methods likely require optimization.

Results from the different assays can be complementary but may not always be comparable. CBA for example is a very specific but not especially sensitive technique [105]. Within this method, variations exist in the experimental conditions, which will highly influence the results. Live CBA is known to better preserve the epitopes which can be damaged when applying fixatives and permeabilizing agents. Live assays, however, not withstanding the technical disadvantage that they can not be prepared as a kit in advance, have higher rates of positivity [105]. Variable results can also be dependent on the species origin from which the cells in the test are derived and also on the expression of the antigens when composed of different subunits (e.g. the NMDAR CBA can be set up with the NR1 or the NR1 + NR2a/b or the NR2 subunit alone). The choice of antigen fragments used can also affect the validity of the CBA results e.g. i) the use of synthetic peptides, ii) parts or the complete antigen and iii) the incorporation of carrier proteins to detect secreted proteins that are naturally anchored to the membrane. This is highly relevant, since most of the antibodies have been shown to target the antigen when expressed in the native conformation *in situ*.

Whether one or another subunit is targeted can matter as this may be translated into different clinical manifestations For example, the NR1 subunit plays a pathogenic role in NMDAR encephalitis [141] whereas the second subunit of the receptor, NR2a/b, has been related with neuropsychiatric systemic lupus erythematosus [142].

A source of confusion has been the detection of different antibody isotypes and their subtypes. Some studies only report the presence of Igs without any distinction of which type and moreover, the pathogenic relevance of some of the isotypes is disputed [38,143]. Comparative studies in different disease cohorts showed that IgG was the most prevalent, pathogenic (validated using 3 different methods) and disease specific isotype for NMDAR. Furthermore, the experimental results, due to differences in sample dilution used in the separate assays (i.e. from 1:10 to 1:320 in CBA) are thus of limited comparability across experiments [38].

Some differences could stem from the type of body fluids that are tested, serum, plasma or CSF. Such differences have been reported in the literature, since there is no clear consensus on the most relevant fluid for diagnosis among the different types of encephalitis. Antibodies to $GABA_AR$ were detectable in CSF samples from all patients using live or fixed CBA, while antibodies in serum were mostly visible only with the live version of the CBA [42]. In psychotic disorders where autoimmunity in the CNS could be responsible for the pathology, the analysis of the CSF is a critical point, since a role for Igs in neuropsychiatric disorders is doubtful when autoantibodies cannot be demonstrated in the CSF [144].

A minimum of two different tests in tandem should be used in order to decrease the likelihood of false outcomes. For example, it is recommended to use a combination of CBA's, IHC and/or primary hippocampal cell culture assays or comparing similar tests between different laboratories. At the same time of course, it is also necessary to analyze a group of control samples to confirm that the antibodies are truly disease specific and so the number of "false positives" are reduced to negligible low levels. Screening of autoantibodies in these cases should be done in a panel rather than for individual antigens due to probable coexistence of different target antigens because of the overlap of symptoms in different cohorts [145] and in individual patients [146–148]. Lastly, it is very important to include an exhaustive psychiatric and neurological examination to preselect the patients to be tested, by recognizing particular symptoms that can be associated with specific autoimmune variants of the disease. Discovering such relevant clinical details is therefore the main challenge before we can start treating patients on the basis of individual test assays.

6. Effect of immunosuppression and new therapeutic approaches

When it is not too late, immunosuppressive intervention after immuno-diagnosis might avoid possible brain damage as a result of prolonged exposure of the target to the autoantibodies. Based on the evidence from autoimmune encephalitis, psychotic disorders caused by

autoimmunity are expected to be similarly treatable by diminishing the level of the autoantibodies. First line immunotherapy may consist of high intravenous steroid (methylprednisolone), high-dose IVIG and/or plasma exchange. A substantial proportion of autoimmune encephalitis patients improve with these treatments. The non-responders have to follow second line immunotherapies, based on cell therapy, including rituximab and cyclophosphamide [149]. Innovative therapies such as proteasome inhibitors, targeting plasma cells involved in the production of antibodies with a secretion of more than 10,000 molecules/cell/second [150] have been used to treat autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and myasthenia gravis [151]. Bortezomib, a first generation proteasome inhibitor, has been used as therapy in a small group of patients with treatment-resistant NMDAR encephalitis, showing a potential therapeutic effect of this drug in refractory patients [85]. A period of 4–8 months is required in most cases to recover completely, starting with a normalization of the autonomic dysfunctions, seizures and abnormal movements, followed by the recovery of the memory and attention deficits and of the behavior and executive impairment functions [73]. The effect of prolonged exposure to the autoantibodies synthesized by plasma cells within the CNS and the effect of these antibodies in the synapse can explain why the recovery in patients with encephalitis is slow. Infiltration of plasma cells and autoantibody production in NMDAR encephalitis [52,152] and the observation of the long white matter tracts degeneration, neuronal loss, antibody deposits and decreased expression of the target antigen, support the notion of an effect of plasma cells within the CNS [36,52].

NMDAR encephalitis cases with first episode isolated psychotic symptoms are treatable by immunotherapy and the majority of patients showed a good response [87], with early treatment predicting a better outcome [149]. However, it should be noted that upon recovery the CSF antibody levels decreased but still tested positive in most cases (i.e. 24 out of 28 patients with NMDAR antibodies) [73]. Plasmapheresis, IVIG and corticosteroids have shown good efficacy in autoimmune encephalitis patients with psychotic symptoms, leading to gradual improvement in all cases [90,92,120,121,153,154]. Second line immunosuppressants have been applied in an acute psychotic episode, after NMDAR antibodies were detected. A combination of intravenous steroids and IVIG together with cyclophosphamide and rituximab were administered and showed a slow but almost complete progressive recovery after a period of four months [155]. Immunotherapy in VGKCC antibody-associated encephalopathy, including IVIG or plasma exchange, effectively reduces antibody levels and showed an improvement of cognitive functions, although memory deficits are usually not fully reversible [118,128,129,156–161] which likely implicates some damage to the hippocampus. Complement activation could be responsible for this damage or, alternatively, calcium overload-induced neuronal cell death due to overstimulation, as inhibition of potassium current causes spontaneously high frequency firing. Such firing is observed in neuromyotonia, a peripheral disease with antibodies to VGKCC [162]. Whether or not immunotherapy would be equally beneficial in terms of efficacy and recovery in all autoimmune patients purely with psychotic symptoms is still unclear, since only a few cases (VGKCC and NMDAR positive) have been described up to now (see section on cases report).

7. Conclusions

It is conceivable that an antibody against a neurotransmitter receptor or an ion channel evokes recognizable neurological symptoms in some way. In some cases these symptoms can be subtle and almost insignificant, tending to be overlooked when patients are first seen in psychiatry rather than in neurology departments [5]. It is also possible that a higher level of autoantibodies or a longer exposure time is necessary for neurological symptoms to surface in a patient.

Patients with neuronal autoantibodies diagnosed with a psychotic disorder, although rare, are now recognized primarily due to increasing awareness. However, to date only a few articles have described the presence of these autoantibodies (Table 1). Sample cohorts are usually small and heterogeneous, with an unclear distinction between the different mental disorders and the stage of the disease (especially in psychotic disorders, where the symptoms overlap among the different disorders). It is also clear that in many cases there is a superposition of clinical manifestations between autoimmune encephalitis and psychotic disorders [86]. There is a need to include neurological evaluation and CSF analysis in psychotic patients, since these symptoms can be easily misinterpreted. The use of more sensitive scales for mild symptoms such as the neurological soft signs examination, is intended to detect subtle but observable abnormalities in motor and sensory functions not associated with specific brain regions. Interestingly, several studies have reported lower neurological soft signs scores in healthy controls compared to patients with schizophrenia and bipolar disorder. This makes this scale very promising to identify neurological signs in specific cohorts where these manifestations are not very prominent, such as psychotic disorders [163,164].

The identification of neurological manifestations could serve to better characterize this specific subgroup of autoimmune mediated mental disorder patients where psychotic manifestations are very pronounced, masking the neurological abnormalities. It is also important to mention that several neurological side effects including parkinsonism, akathisia, tardive syndromes, seizures and cerebrovascular events are often observed in patients on antipsychotic drugs. These neurological complaints can overlap with neurological symptoms due to an autoimmune reaction and be mistaken as purely side effects of the drugs.

The methodological differences of the diagnostic assays reviewed are a limiting factor, due to their specificity and sensitivity. There is a need to analyze the prevalence of antibodies targeting novel antigens that are not currently detectable, e.g. those that are not specifically targeting defined antigens, those that are not sufficiently homologous between rodent and human or antigens present on other cell types such as astrocytes and glial cells.

The study of the autoantibodies using *in vivo* and *in vitro* techniques is essential to understand the pathogenic mechanisms underlying these rare autoimmune psychotic cases. This will help to create better diagnostic tools and more specific therapeutic strategies.

In the future, large systematic studies of psychotic patients are needed in order to examine the occurrence of autoimmune-related pathology such as antibody-mediated channelopathies. It is very important to learn how to select clinical phenotypes that help to identify certain patients as a group that runs an increased risk for an autoimmune pathology. Early diagnosis and treatment will reduce the possible sequels generated by the presence of autoantibodies in the target organ and will cut the recovery time of the patients.

Take home message

To date, pathogenic autoantibodies targeting neuronal surface antigens are very rare in psychotic disorders without any form of neurological manifestation.

It is essential that psychiatrists are aware of the existence of symptoms which overlap between autoimmune encephalitis and psychotic disorders in order to prompt early diagnosis and intervention for cases with an atypical disease course.

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Statement of author contributions

All authors participated in the drafting of the manuscript and provided approval of the final submitted version.

Declarations of Competing Interest

None.

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